PAEDIATRIC PROTOCOLS

For Malaysian Hospitals

5th Edition

Hussain Imam Hj Muhammad Ismail
Ng Hoong Phak
Sabeera Begum Kader Ibrahim
Muhammad Ghazali bin Ahmad Narihan
Janet Hii Lin Yee
Tan Yuong Chin



Kementerian Kesihatan Malaysia

2025

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FOREWORD
DIRECTOR-GENERAL OF HEALTH



I am honoured to be given the opportunity to provide the foreword for the 5th edition of Paediatric Protocols for Malaysian Hospitals.

In this edition, the authors and contirbutors, many of whom are respected experts in the the field of paediatrics, have once again delivered an outstanding publication. The book has broadened its scope, encompassing topics that range from fundamental aspects of paediatric care to the latest advancements and innovations in chlid health. It stands as a comprehensive and authoritative refence, reflecting the remarkable growth and maturity of paediatric expertise in Malaysia.

This compact guide is designed for medical professionals and healthcare workers involved in the care of infants, children, adolescents. The protocols serve as practical guides for clinical practice, based on the best available evidence at the time of its development.

Its is essential that frontline medical practitioners are well-prepared to manage common paediatric emergencies, enabling timely and appropriate care based on clinical presentations right form the start.

I am confident that this 5th edition will significantly contribute to enhancing the quality of paediatric care across Ministry of Health facilities throughout the country.

The collaborative efforts of all involved are truly commendable. I extend my sincere thanks to the Editors for their commitment in bringing this important edition for fruition.



Datuk Dr. Mahathar bin Abd Wahab
Director General of Health Malaysia

FOREWORD
TO THE 5TH EDITION

At the 2004 annual meeting of Paediatric Heads of Departments, it was decided to produce a national protocol book based on the Sarawak model. The first edition was ready in time for the 2005 annual meeting of HODs. However, there were a few hiccups in that production largely because the text was sent to the printers as a Word document. Many tables and algorithms were distorted in the final product. Learning from this, all subsequent editions were sent in PDF format with the help of Dr. Terrance, who joined the editorial board for the 2nd Edition.

This 5th Edition comes after a seven-year lapse. In many ways, this is a transitional edition. Dr. Terrance has migrated to Singapore and for the two remaining senior members, HIMI and NHP this will be their final production. Three young paediatricians and the current head of service have joined the editorial board and will hopefully go on to produce the 6th Edition when the time comes. This is also the first time that the officers from the Medical Development Division of the Ministry of Health have been involved in formatting the text and the result is a much more elegant product.

From the beginning, the primary aim of the protocol book has been to improve the care of children in primary and secondary care settings within the Ministry of Health. Over time, colleagues in private practice and medical students have also benefited from it. This has been made possible by the Malaysian Paediatric

Association's willingness to print and distribute additional copies at close to cost price. Most of the contributors are tertiary specialists. Despite their busy schedule, they once again volunteered to update the material in keeping with new developments and guidelines since the last edition. It is this teamwork and collaboration at all levels between members of the fraternity that has contributed to the progress of the paediatric services in the country to the current level. We pray that this spirit persists in the years to come.

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Section I

GENERAL PAEDIATRICS

Chapter 1:
Normal Values in Children

VITAL SIGNS

Normal Values for Respiratory Rate (RR) and Heart rate (HR).[1]			
Age	**Guide weight (kg)**	**RR at rest (Breaths per minute) 5th to 95th Centile**	**HR (Beats per minute) 5th to 95th Centile**
Birth	3.5	25 - 50	120 - 170
1 months	4		
3 months	5	25 - 45	115 - 160
6 months	8	20 - 40	110 - 160
12 months	10		
2 years	12	20 - 30	100 - 150
3 years	14		90 - 140
4 years	16		80 - 135
5 years	18		
6 years	20		80 - 130
7 years	22		
8 years	25	15 - 25	70 - 120
9 years	28		
10 years	32		
11 years	35		
12 years	43	12 - 24	65 - 115
14 years	50		60 - 110
Adult	70		

Estimation of Blood Pressure (BP).[1]	
Age	**5th centile Blood Pressure**
< 1 year	65 - 75
1-2 years	70 - 75
2-3 years	70 - 80
4-11 years	80 - 90
≥12 years	90 - 105
The calculation for expected systolic blood pressure is: **65 + (2 x age in years) mmHg for 5th centile**	
Blood pressure <5th centile is a DANGER SIGN!	

Blood Pressure (BP) Levels in Girls for Age and Height Percentile.[2]							
Age (Yr)	BP Percentile	SBP (mmHg)			DBP (mmHg)		
		Height Percentile or cm			Height Percentile or cm		
	Height Percentile	5%	50%	95%	5%	50%	95%
1	Height (cm)	75.4	80.8	86.1	75.4	80.8	86.1
	50%	84	86	88	41	43	46
	90%	98	100	102	54	56	58
	95%	101	103	105	59	60	62
2	Height (cm)	84.9	91.1	97.4	84.9	91.1	97.4
	50%	87	89	91	45	48	51
	90%	101	103	106	58	60	62
	95%	104	106	109	62	64	66
3	Height (cm)	91	97.6	104.6	91	97.6	104.6
	50%	88	90	93	48	50	53
	90%	102	104	107	60	62	65
	95%	106	108	110	64	66	69
4	Height (cm)	97.2	104.5	112.2	97.2	104.5	112.2
	50%	89	92	94	50	53	55
	90%	103	106	108	62	65	67
	95%	107	109	112	66	69	71
5	Height (cm)	103.6	111.5	120	103.6	111.5	120
	50%	90	93	96	52	55	57
	90%	104	107	110	64	67	70
	95%	108	110	113	68	71	73
6	Height (cm)	110	118.4	127.7	110	118.4	127.7
	50%	92	94	97	54	56	59
	90%	105	108	111	67	69	71
	95%	109	111	114	70	72	74
7	Height (cm)	115.9	124.9	134.7	115.9	124.9	134.7
	50%	92	95	99	55	57	60
	90%	106	109	112	68	70	72
	95%	109	112	115	72	73	75

Blood Pressure (BP) Levels in Girls for Age and Height Percentile (cont.)							
Age (Yr)	BP Percentile	SBP (mmHg)			DBP (mmHg)		
		Height Percentile or cm			Height Percentile or cm		
	Height Percentile	5%	50%	95%	5%	50%	95%
8	Height (cm)	121	130.6	140.9	121	130.6	140.9
	50%	93	97	100	56	59	61
	90%	107	110	113	69	72	73
	95%	110	113	117	72	74	75
9	Height (cm)	125.3	135.6	146.6	125.3	135.6	146.6
	50%	95	98	101	57	60	61
	90%	108	111	114	71	73	73
	95%	112	114	118	74	75	75
10	Height (cm)	129.7	141	152.8	129.7	141	152.8
	50%	96	99	103	58	60	62
	90%	109	112	116	72	73	73
	95%	113	116	120	75	76	76
11	Height (cm)	135.6	147.8	160	135.6	147.8	160
	50%	98	102	106	60	61	64
	90%	111	114	120	74	74	75
	95%	115	118	124	76	77	77
12	Height (cm)	142.8	154.8	166.4	142.8	154.8	166.4
	50%	102	105	108	61	62	65
	90%	114	118	122	75	75	76
	95%	118	122	126	78	78	79
13	Height (cm)	148.1	159.2	170.2	148.1	159.2	170.2
	50%	104	107	109	62	64	66
	90%	116	121	123	75	76	76
	95%	121	124	127	79	79	81
14	Height (cm)	150.6	161.3	172.1	150.6	161.3	172.1
	50%	105	108	109	63	65	66
	90%	118	122	123	76	76	77
	95%	123	125	127	80	80	82

Blood Pressure (BP) Levels in Boys for Age and Height Percentile.[2]							
Age (Yr)	BP Percentile	SBP (mmHg)			DBP (mmHg)		
		Height Percentile or cm			Height Percentile or cm		
	Height Percentile	5%	50%	95%	5%	50%	95%
1	Height (cm)	77.2	82.4	87.9	77.2	82.4	87.9
	50%	85	86	88	40	41	42
	90%	98	100	101	52	53	54
	95%	102	103	105	54	55	57
2	Height (cm)	86.1	92.1	98.5	86.1	92.1	98.5
	50%	87	89	91	43	44	46
	90%	100	102	104	55	56	58
	95%	104	106	108	57	59	61
3	Height (cm)	92.5	99	105.8	92.5	99	105.8
	50%	88	90	92	45	47	49
	90%	101	103	105	58	59	61
	95%	106	107	109	60	62	64
4	Height (cm)	98.5	105.9	113.2	98.5	105.9	113.2
	50%	90	92	94	48	50	52
	90%	102	105	107	60	62	64
	95%	107	108	110	63	66	68
5	Height (cm)	104.4	112.4	120.3	104.4	112.4	120.3
	50%	91	94	96	51	53	55
	90%	103	106	108	63	65	67
	95%	107	109	112	66	69	71
6	Height (cm)	110.3	118.9	127.5	110.3	118.9	127.5
	50%	93	95	98	54	56	58
	90%	105	107	110	66	68	69
	95%	108	111	114	69	71	73
7	Height (cm)	116.1	125.1	134.5	116.11	125.1	134.5
	50%	94	97	99	56	58	59
	90%	106	109	111	68	70	71
	95%	110	112	116	71	73	74

Blood Pressure (BP) Levels in Boys for Age and Height Percentile (cont.)							
Age (Yr)	BP Percentile	SBP (mmHg)			DBP (mmHg)		
		Height Percentile or cm			Height Percentile or cm		
	Height Percentile	5%	50%	95%	5%	50%	95%
8	Height (cm)	121.4	131	141	121.4	131	141
	50%	95	98	100	57	59	60
	90%	107	110	112	69	71	73
	95%	111	114	117	72	74	75
9	Height (cm)	126	136.3	147.1	126	136.3	147.1
	50%	96	99	101	57	60	62
	90%	107	110	114	70	73	74
	95%	112	115	119	74	76	77
10	Height (cm)	130.2	141.3	152.7	130.2	141.3	152.7
	50%	97	100	103	59	62	63
	90%	108	112	116	72	74	76
	95%	112	116	121	76	77	78
11	Height (cm)	134.7	146.4	158.6	134.7	146.4	158.6
	50%	99	102	106	61	63	63
	90%	110	114	118	74	75	76
	95%	114	118	124	77	78	78
12	Height (cm)	140.3	152.7	165.5	140.3	152.7	165.5
	50%	101	104	109	61	62	63
	90%	113	117	122	75	75	76
	95%	116	121	128	78	78	79
13	Height (cm)	147	160.3	173.4	147	160.3	173.4
	50%	103	108	112	61	62	65
	90%	115	121	126	74	75	77
	95%	119	125	131	78	78	81
14	Height (cm)	153.8	167.5	180.1	153.8	167.5	180.1
	50%	105	111	113	60	64	67
	90%	119	126	129	74	77	80
	95%	123	130	134	77	81	84

ANTHROPOMETRIC MEASUREMENTS

Age	Weight	Height	Head circumference
Birth	3.5 kg	50 cm	35 cm
6 months	7 kg	68 cm	42 cm
1 year	10 kg	75 cm	47 cm
2 years	12 kg	85 cm	49 cm
3 years	14 kg	95 cm	49.5 cm
4 years		100 cm	50 cm
5-12 years		5 cm/year	0.33 cm/ year

Points to Note

Weight

- In the first 7 to 10 days, babies lose 10% of their birth weight.
- Babies gain their birth weight by the second week.
- In the first 3 months of life, the rate of weight gain is 25 g/day
- Babies double their birth weight by 5 months old and triple by 1 year old
- Weight estimation for children (in Kg):
  Infants: (Age in months X 0.5) + 4
  Children 1 – 10 years: (Age in yrs + 4) X 2

Head circumference

- Rate of growth in preterm infants is 1 cm/week, but reduces with age.
- Head growth follows that of term infants when chronological age reaches term
- Head circumference increases by 12 cm in the 1st year of life (6 cm in first 3 months, then 3 cm in second 3 months, and 3 cm in last 6 months)

Other normal values are found in the relevant chapters of the book.

References:

1. Advanced Life Support Group (ALSG). 2023. *Advanced Paediatric Life Support: A Practical Approach to Emergencies, 7th Edition*. Wiley-Blackwell
2. Robert M. Kliegman; MD, Richard E. Behrman; MD, Hal B.J. 2007. N*elson textbook of Pediatrics, 18th edition*. Elsevier, Saunders.

HAEMATOLOGICAL PARAMETERS

Age	Hb	PCV	Retics	MCV *fl*	MCH *pg*	TWBC	Neutrophil	Lymphocyte
	g/dl	%	%	Lowest	Lowest	*x1000*	Mean	Mean
Cord Blood	13-7-20.1	45-65	5.0	110	-	9-30	61	31
2 weeks	13.0-20.0	42-66	1.0	-	29	5-21	40	63
3 months	9.5-14.5	31-41	1.0	-	27	6-18	30	48
6 mths - 6 yrs	10.5-14.0	33-42	1.0	70-74	25-31	6-15	45	38
7 - 12 years	11.0-16.0	34-40	1.0	76-80	26-32	4.5-13.5	55	38
Adult male	14.0-18.0	42-52	1.6	80	27-32	5-10	55	35
Adult Female	12.0-16.0	37-47	1.6	80	26-34	5-10	55	35
Differential counts					**Points to note**			
< 7 days age	neutrophils > lymphocytes				• Differential WBC: eosinophils: 2-3%; monocytes: 6-9 %			
1 wk - 4 years	lymphocytes > neutrophils				• Platelets counts are lower in first months of age; but normal range by 6 months			
4 - 7 years	neutrophils = lymphocytes				• Erythrocyte sedimentation rate (ESR) is < 16 mm/hr in children, provided PCV is at least 35%.			
> 7 years	neutrophils > lymphocytes							

NATIONAL IMMUNISATION SCHEDULE FOR MALAYSIA (MINISTRY OF HEALTH, MALAYSIA)

	Age in MONTHS												Age in YEARS		
Vaccine	**Birth**	**1**	**2**	**3**	**4**	**5**	**6**	**9**	**12**	**15**	**18**	**21**	**7**	**13**	**15**
BCG	1														
Hepatitis B	1														
6 in 1 (Hexaxim) DTaP-IPV-Hep B-Hib			1	2		3					4		DT (B)		T (B)
Pneumococcal					1		2			3(B)					
Measles							Sabah								
MMR								1	2						
JE (Sarawak)								1				2			
HPV														2 doses	

Legend:

BCG, *Bacille Calmette-Guerin;*

DTaP, *Diphteria, Tetanus, acellular Pertussis; IPV, Inactivated Polio Vaccine; Hib, Haemophilus influenzae type B;*

DT, *Diphtheria, Tetanus; T, Tetanus; (B), Booster doses;*

MMR, *Measles, Mumps, Rubella; JE, Japanese Encephalitis; HPV, Human Papilloma Virus;*

General Notes[2]

- Vaccines (inactivated or live) can be given simultaneously (does not impair antibody response or increase adverse effect). Administer at different sites unless using combined preparations.
- Sites of administration
  - Oral – rotavirus, live typhoid vaccines
  - Intradermal (ID) - BCG. Left deltoid area (proximal to insertion of deltoid muscle)
  - Intramuscular (IM) - 6 in 1 DTaP-hepB-IPV-Hib (Hexaxim)
  - Deep SC, IM injections. (ALL vaccines except the above)
- Anterolateral aspect of thigh – preferred site in children
- Upper arm – preferred site in adults
- Upper outer quadrant of buttock - associated with lower antibody level production

Immunisation: General contraindications

- Absolute contraindication for any vaccine: severe anaphylaxis reactions to previous dose of the vaccine or to a component of the vaccine.
- Postponement during acute febrile illness
- Live vaccines: Absolute contraindications
  - *Immunosuppressed children* - malignancy; irradiation, leukaemia, lymphoma, post-transplant, primary immunodeficiency syndromes (but NOT asymptomatic HIV): **need to defer (see below)**
  - Pregnancy (live vaccine - theoretical risk to foetus) UNLESS there is significant exposure to serious conditions like polio or yellow fever in which case the importance of vaccination outweighs the risk to the foetus.
  - Live vaccines may be given together. If not administering simultaneously then an interval ≥ 4 weeks is required.
  - Tuberculin skin test (Mantoux test) and MMR: after a Mantoux test, MMR should be delayed until the skin test has been read.
  - There should be ≥ 4 weeks interval for Mantoux test after MMR given.
- **Killed vaccines are safe**. Absolute contraindications: SEVERE local induration (involving > 2/3 of the limbs) or severe generalised reactions in previous dose.

The following are not contraindications to vaccination

- Mild illness without fever e.g. mild diarrhoea, cough, runny nose
- Asthma, eczema, hay fever, impetigo, heat rash (avoid injection in affected area)
- Treatment with antibiotics, locally acting steroids or inhaled steroids
- Child's mother is pregnant.
- Breastfed child (does not affect polio uptake)
- Neonatal jaundice
- Underweight or malnourished
- Over the recommended age
- Past history of pertussis, measles or rubella (unless confirmed medically)
- Stable neurological conditions: cerebral palsy, mental retardation, febrile convulsions, stable epilepsy
- Family history of convulsions
- History of heart disease, acquired or congenital
- Prematurity (immunise according to schedule irrespective of gestational age)

IMMUNISATION: SPECIAL CIRCUMSTANCES[4,5]

Immunisation of the Immunocompromised child:

Includes malignancy; leukaemia, lymphoma, post-transplant, congenital immunodeficiency syndromes (but NOT asymptomatic HIV), immunosuppressive therapy:

- BCG is contraindicated
- Non-live vaccines can be given but may need to be repeated depending on underlying condition and individual vaccine due to suboptimal response
- For oncology patients on chemotherapy:
  - Avoid live vaccines for two weeks before, during and for 6 months after completion of chemotherapy
  - Safe to give influenza and pneumococcal vaccines, if indicated
- For post- Haematopoeitic Stem Cell Transplant (HSCT) and Solid Organ Transplant (SOT):
  - Non-live vaccines can be given 6 months after HSCT or SOT
  - Live vaccines to be given at least 2 years after HSCT and no graft versus host disease and not on immunosuppressive therapy (and acceptable CD4 count and IgM levels)
  - Live vaccines contraindicated in SOT as most likely on immunosuppressive therapy
- Patients on Corticosteroid Therapy:
  - On high-dose steroids i.e. Prednisolone ≥2 mg/kg/day for >14 days, delay live vaccines for at least 1 month after cessation of steroids
  - On low-dose systemic steroids of 1mg/ kg/day <2 weeks or EOD for >2 weeks, can administer live vaccines
  - Any dose for ≥28 days, delay live vaccines for at least 1 month after cessation of steroids.

Immunisation of children with immunomodulatory & biologics therapy[6,7]

- Vaccination with non-live, attenuated vaccines in children on immunomodulation therapies and biologics is safe.
- It is recommended to withhold live-attenuated vaccines for these patients on immunomodulatory therapies and biologics. However, vaccination can be considered on a case-to-case basis weighing the benefit of vaccination against the risk of inducing infection through vaccination.
- Live-attenuated booster vaccinations against Varicella Zoster Virus and MMR can be considered in patients on low dose immunosuppressive drugs.
- For vaccination against HPV in patients with Rheumatic Diseases. Given the higher risk of HPV infection in female SLE patients, these patients should be advised to be vaccinated in the adolescence. However, physicians should be vigilant on potential thromboembolic events.

Immunisation of children with HIV infection

(Please refer to Paediatric HIV section)

Immunisation with Antibody-containing preparation:[8,9]

- Immunoprophylaxis against viral illness provide susceptible individuals with immunologic protection against it.
- Palivizumab is a humanized monoclonal antibody against the RSV F glycoprotein, used for the prevention of serious RSV lower respiratory tract disease in specialized group of children at high risk of RSV infection. It does not interfere with response to routine immunization with live virus vaccines (eg, measles, mumps, rubella, varicella)

Interval between administration of Immunoglobulins or blood products and measles- or varicella-containing vaccine[4]

Recommended interval	Product	Dosage
3 months	Hepatitis B IG	0.06ml/kg; (10mg IgG/kg) IM
	Tetanus IG (TIG)	250u; (10mg IgG/kg) IM
4 months	Rabies IG (RIG)	20 IU/kg; (22mg IgG/kg) IM
5 months	Varicella IG	125u/10kg IM
6 months	Packed RBC	10ml/kg (60mg IgG/kg) IV
	Whole blood	10ml/kg (80-100 mg IgG/kg IV
	Measles Prophylaxis IG	0.5ml/kg; (80mg IgG/kg) IM
7 months	Plasma/platelet product	10ml/kg (160mg IgG/kg) IV
8 months	IV Immunoglobulin	300-400 mg/kg IV
10 months	IV Immunoglobulin	1g/kg IV (eg: ITP)
11 months	IV Immunoglobulin	2g/kg IV (eg: Kawasaki)
Note: If measles- or varicella-containing vaccine is given <2 weeks before administration of Immunoglobulins or blood products, then repeat immunisation.		
Does not include Zoster vaccine. It may be given with antibody-containing product		

Children with bleeding disorders including persistent thrombocytopenia, haemophilia or patients on anti-coagulant therapy[10]

- Children with bleeding disorders or on long term anti-coagulant therapy may develop haematoma at intramuscular vaccine injection sites
- Thus, it is preferred to use the subcutaneous route instead of the intramuscular route
- Seek expert advice before using an alternative route.

Immunisation of Children with Egg Allergy[11]

- Egg allergy is not a contraindication to immunization with MMR.

Measures to protect inpatients exposed to another inpatient with measles

- Protect all **immunocompromised children** with Immunoglobulin (NHIG) 0.25-0.5 mls/kg. (Measles may be fatal in children in remission from leukaemia)
- Check status of measles immunisation in the other children. Give measles specific Immunoglobulin, if none available to give IVIG to **unimmunised children** within 24 hrs of exposure. Immunisation within 72 hours aborts clinical measles in 75% of contacts.
- Discharge the inpatient child with uncomplicated measles.
- Do not forget to notify the Health Office.

Close contacts of immunodeficient children and adults

- Must be immunized, particularly against measles, polio (IPV), varicella.

Children with Asplenia (Elective or emergency splenectomy; asplenic syndromes; sickle cell anaemia) are susceptible to encapsulated bacteria and malaria.

- Pneumococcal, Meningococcal A, C, Y & W-135, Haemophilus influenza b vaccines should be given.
- For elective splenectomy (and also chemotherapy or radiotherapy): give the vaccines preferably 2 or more weeks before the procedure. However, they can be given even after the procedure.
- Penicillin prophylaxis should continue ideally for life. If not, until 16 years old for children or 5 years post splenectomy in adults.

In patients with past history or family history of febrile seizures, neurological or developmental abnormalities that would predispose to febrile seizures:

- Febrile seizures may occur 5 - 10 days after measles (or MMR) vaccination or within the first 72 hours following pertussis immunisation.
- Paracetamol prophylaxis following immunisation is not recommended.

Maternal Chicken Pox during perinatal period

(Please refer to Perinatally acquired varicella section)

In contacts of a patient with invasive Haemophilus influenzae B disease

- Immunise:
  - Index case irrespective of age.
  - All household, nursery or kindergarden contacts < 4 years of age.
- Chemoprophylaxis: Rifampicin at 20 mg/kg once daily (Maximum 600 mg) for 4 days (except pregnant women - give one IM dose of ceftriaxone)
  - All household < 4 years who is unimmunised or incompletely immunised
  - For preschool and child care facility should be at the discretion of local health department

Babies born to mothers who are Hbe Ag OR Hbs Ag positive should be given Hepatitis B immunoglobulin (200 IU) and vaccinated with the Hepatitis B vaccine within 12 hours and not later than 48 hours. Given in different syringes and at different sites

Premature infants may be immunised at the same chronological age as term infants. **(Please refer The Premature Infant section).**

VACCINES, INDICATIONS, CONTRAINDICATIONS, DOSES AND SIDE EFFECTS[12]

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
BCG	To be given at birth.[14]	Not to be given to symptomatic HIV infected children. Can be given to newborns of HIV infected mother as the infant is usually asymptomatic at birth.	BCG adenitis may occur.	Intradermal. Local reaction: a papule at vaccination site may occur in 2 - 6 weeks. This grows and flattens with scaling and crusting. Occasionally a discharging ulcer may occur. This heals leaving a scar of at least 4 mm in successful vaccination.
Hepatitis B	All infants, including those born to HBsAg positive mothers All health care personnel.	Severe hypersensitivity to aluminium. The vaccine is also not indicated for HBV carrier or immuned patient (i.e. HBsAg or Ab positive)	Local reactions. Fever and flu-like symptoms in first 48 hours. Rarely, erythema multiforme or urticaria.	Intramuscular. Give with Hep B immunoglobulin for infants of HBsAg positive mothers at contralateral limb.
Diphtheria, Tetanus (DT)	All infants should receive 5 doses including booster doses at 18 months and Standard 1	Severe hypersensitivity to aluminium and thiomersal	Swelling, redness and pain A small painless nodule may develop at injection site – harmless. Transient fever, headaches, malaise, rarely anaphylaxis. Neurological reactions rare.	Intramuscular

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Pertussis	All infants should receive 4 doses including booster at 18 months It is recommended that booster doses be given at Std 1 and at Form 3 due to increased cases of Pertussis amongst adolescents in recent years.	Anaphylaxis to previous dose; encephalopathy develops within 7 days of vaccination Precautions: severe reaction to previous dose (systemic or local) and progressive neurological diseases.	Local reaction. Severe if involve 2/3 limbs Severe systemic reaction: Anaphylaxis (2 per 100 000 doses), encephalopathy (0 – 10.5 per million doses), high fever (fever>40.5), fits within 72 hours, persistent inconsolable crying (0.1 to 6%), hyporesponsive state. Acellular Pertussis vaccine associated with less side effects.	Intramuscular. Static neurological diseases, developmental delay, personal or family history of fits are NOT contraindications.
Inactivated Polio Vaccine (IPV)	All infants to be given 4 doses including booster at 18 months.	Allergies to neomycin, polymyxin and streptomycin Previous severe anaphylactic reaction.	Local reactions.	Intramuscular.
Haemophilus Influenzae type B (Hib)	All infants should receive 4 doses including booster at 18 months. Patients with splenic dysfunction, and post splenectomy.	Confirmed anaphylaxis to previous Hib and allergies to neomycin, polymyxin and streptomycin	Local swelling, redness and pain soon after vaccination and last up to 24 hours in 10% of vaccinees Malaise, headaches, fever, irritability, inconsolable crying. Very rarely seizures.	Intramuscular.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Measles, Mumps, Rubella (MMR)	All infants (9 and 12 months). Measles vaccine at 6 month old for Sabah, and Orang Asli population.	Avoid in patients with hypersensitivity to neomycin and polymyxin. Pregnancy. Children with immunodeficiency.	Transient rash in 5%. May have fever between D5-D12 post vaccination. URTI symptoms. Febrile convulsions (D6-D14) in 1:1000 – 9000 doses of vaccine. (Natural infection 1:200) Encephalopathy within 30 days in 1:1,000,000 doses. (Natural infection 1:1000 - 5000)	Intramuscular. Can be given irrespective of previous history of measles, mumps or rubella infection. Long term prospective studies have found no association between measles or MMR vaccine and inflammatory bowel diseases, autism or SSPE.
Mumps			Rarely transient rash, pruritus and purpura. Parotitis in 1% of vaccinees, > 3 weeks after vaccination. Orchitis and retro bulbar neuritis very rare. Meningoencephalitis is mild and rare. (1:800,000 doses). (natural infection 1:400).	Intramuscular.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Rubella			Rash, fever, lymphadenopathy, thrombocytopenia, transient peripheral neuritis. Arthritis and arthralgia occurs in up to 3% of children and 20% of adults.	Given as MMR.
Japanese Encephalitis (JE)	Given in Sarawak at 9 and 21 months.	Immunodeficiency and malignancy, diabetes , acute exacerbation of cardiac, hepatic and renal conditions.	Local redness, swelling, pain, fever, chills, headache, lassitude.	Live attenuated vaccine. Subcutaneous. Protective efficacy > 95%.
Human Papilloma Virus (HPV)	Indicated for females aged 9-45 years.	Not recommended in pregnancy.	Headache, myalgia, injection site reactions, fatigue, nausea, vomiting, diarrhoea, abdominal pain, pruritus, rash, urticaria, myalgia, arthralgia, fever.	2 vaccines available: • Cervarix (GSK): bivalent. • Gardasil (MSD): quadrivalent. - 3 dose schedule IM - (0, 1-2month, 6 month). Recombinant vaccine. Protective efficacy almost 100% in preventing vaccine type cervical cancer in first 5 years.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Pneumococcal (conjugate) vaccine[1] • PCV 13 or • PCV 7	For children aged 6 weeks through 5 years. A four-dose series at 2, 4, 6 and 12-15 months of age. 0.5 ml suspension for IM injection.	Children who have severe allergic reaction to previous pneumococcal vaccine or any diphtheria toxoid containing vaccine.	Decreased appetite, irritability, drowsiness, restless sleep, fever, injection site erythema, induration or pain, rash.	Immunogenic in children < 2 years Inactivated vaccine. High risk children: Sickle cell disease, haematopoeitic stem cell transplant, prematurity, immunosuppression (including asymptomatic HIV), asplenia, nephrotic syndrome and chronic lung or heart disease.
Pneumococcal (polysaccharide vaccine)	Recommended for children at high risk. > 2 years old. Single dose. Booster at 3-5 years only for high risk patients.	Age < 2 years old. Revaccination within 3 years has high risk of adverse reaction; Avoid during chemotherapy or radiotherapy and less than 10 days prior to commencement of such therapy – antibody response is poor. Pregnancy.	Hypersensitivity reactions.	Intramuscular, Subcutaneous Immunogenic in children ≥2 years. Against 23 serotypes. High risk: immunosuppression, asymptomatic HIV, asplenia, nephrotic syndrome, chronic lung disease. If these children are <2 years old, they should first receive pneumococcal conjugate vaccine; when > 2 years, then the polysaccharide vaccine is used.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Rotavirus	First dose given to infants ≥ 6 wks old. Rotateq (3 doses) Subsequent doses given at 4-10 wks interval. 3rd dose given ≤ 32 weeks age. *Rotarix* (2 doses). 2nd dose to be given by 24 weeks age. Interval between doses should be > 4 weeks.	Prior hypersensitivity to any vaccine component. Uncorrected congenital GIT malformation, e.g. Meckel's diverticulum. Severe combined immunodeficiency disease (reported prolonged shedding of vaccine virus reported in infants who had live Rotavirus vaccine) .	Loss of appetite, irritability, fever, fatigue, diarrhoea, vomiting, flatulence, abdominal pain, regurgitation of food.	Oral live-attenuated vaccine. Protective efficacy 88-91% for any rotavirus gastroenteritis episode; 63-79% for all causes of gastroenteritis.
Cholera	Children 2-6 years: 3 doses at 1-6 week interval. Children > 6 years: 2 doses at 1-6 weeks interval. Booster dose >2 years.		Gastroenteritis	Oral inactivated vaccine. Protective efficacy 80-90% after 6 months waning to 60% after 3 years.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Varicella Zoster	*12 months to 12 years:* 2 doses at least ≥ 4 weeks apart. Non immune susceptible health care workers who regularly come in contact with VZV infection Asymptomatic/mildly symptomatic children with HIV (with CD4% > 15%); 2 doses at 3 months interval. Children in remission from leukemia for ≥1 yr, have >700/ml circulating lymphocytes may receive vaccine under paediatrician supervision (2doses).	Pregnant patients. Patients receiving high dose systemic immunosuppression therapy. Patients with malignancy especially haematological malignancies or blood dyscrasias. Hypersensitivity to neomycin.	Occasionally, papulovesicular eruptions, injection site reactions, headache, fever, paresthesia, fatigue.	Live attenuated vaccine. Subcutaneous. 70 – 90% effectiveness.
Hepatitis A	For children >1 yr. 2 doses, given 6-12 months apart.	Severe hypersensitivity to aluminium hydroxide, phenoxyethanol, neomycin.	Local reactions. Flu-like symptoms lasting 2 days in 10% of recipients	Intramuscular. Inactivated vaccine. Protective efficacy 94%.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Influenza	Single dose. Min age 6 months. Unprimed individuals require 2nd dose 4 - 6 wks after 1st dose. Recommended for children with: chronic decompensated respiratory or cardiac disorders, e.g. cyanotic heart diseases, chronic lung disease, and HIV infection. In advanced disease, vaccination may not induce protective antibody levels.	Hypersensitivity to egg or chicken protein, neomycin, formaldehyde. Febrile illness, acute infection.	Transient swelling, redness, pain and induration locally. Myalgia, malaise and fever for 1 – 2 days starting within a few hours post vaccination. Very rarely, Guillain-Barre syndrome, glomerulonephritis, ITP or anaphylactic reaction may occur.	Intramuscular. Inactivated vaccine. Protective efficacy 70-90% Require yearly revaccination for continuing protection.
Meningococcus A, C, Y & W-135	Single dose. Immunity up to 3 years.		Local reactions. Irritability, fever and rigors for 1-2 days. Very rarely, anaphylaxis.	Intramuscular.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Rabies	Pre-exposure: 3 doses at Day 0, 7, 28. Booster every 2-3 years. Post-exposure treatment: Fully immunised: 2 doses at Day 0, Day 3. Rabies Immune Globulin (RIG) unnecessary. Unimmunised: 5 doses at Day 0, 3, 7, 14 and 28. RIG (20 IU/kg given half around the wound and the rest IM.		Headache, dizziness, malaise, abdominal pain, nausea, myalgia. Injection site reactions such as itching, swelling, pain.	Inactivated vaccine. (Available in Malaysia as Purified Vero Cell Rabies Vaccine (PVRV). Intramuscular.
Typhoid (Typhim Vi)	Single dose. Seroconversion in 85-95% of recipients; confers 60-80% protection beginning 2 wks after vaccination. Boosters every 3 yrs.	Children < 2 years. (Immunogenicity < 2 yrs of age has not been established).	Local reactions. Myalgia, malaise, nausea, headaches and fever in 3% of recipients.	Intramuscular. Polysaccharide vaccine
Typhoid (Ty21a vaccine)	Three doses two days apart. Effective 7 days after last dose. Booster every 3 years.	Infant <6 mth. Congenital or acquired immunodeficiency. Acute febrile illness & acute intestinal infection.	Very rarely: mild GIT disturbances or a transitory exanthem.	Oral. Live attenuated vaccine.

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
6 in 1 Hexaxim (DTaP-hepB-IPV-Hib)	Indicated for infants from 6 weeks - 24 months of age. 3 doses at 2, 3, and 5 months and booster dose at 18 months. 0.5ml, suspension for injection.	Severe anaphylactic reaction to previous dose. Encephalopathy unknown aetiology develops within 7 days of vaccination. Progressive neurological diseases, or uncontrolled epilepsy.	Very common: Injection site reactions, irritability, fever > 38°C. Common: Anorexia, crying, somnolence, vomiting, diarrhea Uncommon: hypersensitivity reaction, injection site nodule, fever > 39.6°C Rare: rash, hypotonic reactions, extensive limb swelling	Intramuscular Postpone vaccine during acute febrile illness Separate injection sites for concomitant vaccine
MMRV14 (ProQuad)	Age range: 12 months through 12 years, usually • 1st dose at 12-15 months • 2nd dose at 4-6 years 0.5 ml dose subcutaneously Interval: • ≥1 month after MMR/ measles vaccine • ≥3 months after Varicella vaccine	Previous allergic reaction to MMRV, MMR or Varicella vaccine Immunocompromised On salicylates Recent blood transfusion / blood product Has tuberculosis.	Fever, rash,swelling of lymph nodes,pain and stiffness of joints Seizure often associated with fever post injection Adverse reaction: transient low platelet count causing bleed Life threatening infection in immunocompromised patient	Live, attenuated virus The risk of seizure is higher after MMRV than separate MMR and Varicella vaccination Immunocompromised individual should not receive MMRV, need to confirm immunocompetent status in individual with family history of congenital/hereditary immunodeficiency

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Covid-19 (Comirnaty 10mcg/ dose)15 (Pfizer-BioNTech)	Active immunization to prevent Covid-19 infection caused by SARS-CoV-2, for children 5–11 years. 10 mcg (0.2ml), two doses, 3 weeks apart.	Hypersensitivity to the active substance (tozinameran) or to any of the excipients (ALC-0315, ALC-0159, DSPC, cholesterol, trometamol, trometamol hydrochloride, sucrose, water for injections)	Hypersensitivity and anaphylaxis Myocarditis and pericarditis Anxiety-related reaction e.g. syncope, hyperventilation or stress-related reactions, e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating	Intramuscular Risk of myocarditis and pericarditis following vaccination, no different from myocarditis and pericarditis in general. Vaccine should be postponed during acute febrile illness Caution for individuals with thrombocytopenia or bleeding disorder Efficacy may be lower in immunocompromised state
Covid-19 (Comirnaty Tris/Sucrose) 30mcg/dose (Pfizer-BioNTech)	Active immunization to prevent Covid-19 infection, for children ≥12 years. 30 mcg (0.3ml), two doses, 3 weeks apart 3rd dose, at least 28 days after the 2nd dose, may be given for children with immunocompromised. Booster at least 6 months after the primary course.			

Vaccine	Indication/Dose	Contraindication	Possible Side Effects	Notes
Palivizumab[16] (Synagis) 50mg per 0.5 ml vial/ 100 mg per 1ml	Prevention of RSV infection in premature infants with/ without bronchopulmonary dysplasia. Congenital heart disease. Special consideration in infants with pulmonary abnormalities, neuromuscular disorder, immunocompromised host and Down syndrome. 15 mg/kg IM once per month typically for a maximum of five doses, with a maximum interval between doses of 35 days.	Severe anaphylactic reaction to previous dose	Rare cases of severe hypersensitivity reactions itchy rash; swelling of the face; difficulty swallowing; difficulty breathing; bluish color of the skin; muscle weakness or floppiness; unresponsiveness).	Timing of first dose – administered before the RSV season begins. Hospitalized infant due for when first dose may receive it 48 to 72 hours before discharge home or promptly after discharge.

IMMUNISATION FOR CHILDREN WHO HAVE DELAYED FIRST VISIT TO THE CLINIC (NOT GIVEN IMMUNISATION)[17,18]

Immunisation should be started on the first visit for children who have delayed visit to the clinic for immunisation.
Below is the suggested schedule according to age for these children:

Immunisation Visits	Age			
	< 2 Months	2 – 8 months	9 – 12 months	> 1 year and < 7 years
1st visit	BCG Hep B (1)	BCG *Hexaxim (1) **	BCG Hexaxim (1) MMR (1)	BCG Hexaxim (1) MMR (1)
2nd visit (≥4 weeks interval)	follow immunisation schedule	Hexaxim (2)	Hexaxim (2) MMR (2)	Hexaxim (2) MMR (2)
3rd visit (≥4 weeks interval)	follow immunisation schedule	Hexaxim (3)	Hexaxim (3)	
18 months of age or 6 months after the last Hexaxim dose	follow immunisation schedule	Hexaxim (B)	Hexaxim (B)	Hexaxim (B)

*Hexaxim = 6 in 1 Hexaxim (DTaP-IPV-Hib-HepB)
**follow immunization schedule for measles/MMR and JE

SUGGESTED SCHEDULE FOR DELAYED OR MISSED PNEUMOCOCCAL IMMUNISATION[1]

Immunisation Visits	Age			
	6 weeks to 6 months	7 – 11 months	12 – 23 months	2 - 5 years
1st visit	*PnC (1)	PnC (1)	PnC (1)	PnC (1)
2nd visit	PnC (2) (8 weeks interval)	PnC (2) (4 weeks interval)	PnC (2) (8 weeks interval)	
15 months of age or 6 mths after the 2nd dose	PnC (B)	PnC (B)		
Total	3	3	2	1

*PnC = Pneumococcal conjugate vaccine

SUGGESTED IMMUNISATION SCHEDULE FOR VACCINES NOT LISTED IN NATIONAL IMMUNISATION PROGRAM

Vaccines listed below are available in private hospitals or clinics

Meningococcal	• Recommended for children travelling to high risk area. • Single dose provides immunity up to 3 years
Rotavirus	• Recommended first dose to be given after 6 weeks of age. • Consult your doctor for the subsequent doses and intervals according to the manufacturer recommendation.
Varicella / chicken pox	• For children 12 months and above: 2 doses more than 4 weeks apart
Hepatitis A	• For children above 1 year : 2 doses given 6-12 months apart.
MMRV	• First dose is administered at 12 to 15 months of age but may be given anytime through 12 years of age. • The second dose is administered at 4 to 6 years of age. • At least 1 month should elapse between a dose of a measles-containing vaccine and a dose of MMRV

Section 2

DEVELOPMENTAL PAEDIATRICS

Chapter 3:
Developmental Milestones in Normal Children

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
6 weeks	Pulled to sit: Head lag and rounded back. Ventral Suspension: Head held up momentarily in same plane as body. Prone: Pelvis high but knees no longer under abdomen. Chin raised intermittently off couch. Head turned to one side.	Fixates on objects. In supine, follows object from side to midline (90°).	Quietens to sound at 4 weeks. Vocalises when talked to at 8 weeks.	Social smile.
3 months	Pulled to sit: Only slight head lag. Ventral Suspension: Head held up above plane of body. Prone: Pelvis flat. Lifts head up 45° - 90°, weight supported on forearms.	Hand regard. Follows dangling toy from side to side (180°) Hands loosely open. Holds rattle placed in hand momentarily.	Squeals of pleasure. Says 'aah' or 'naah' when spoken to. Turns head to sound at the same level.	Sustained social contact. Responds with pleasure to friendly handling.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
6 months	*Pulled to sit*: Lifts head off couch. Sits with support. Bears full weight on legs when held in standing position. *Prone*: Supports weight on hands with chest and upper part of abdomen off couch. Rolls from prone to supine.	Palmar grasp of cube. Drops one cube when another is offered. Follows activities across room with alertness.	Vocalises tunefully to self and others. Laughs, chuckles, and squeals aloud in play. Screams with annoyance. Turns to source when hears sounds at ear level.	Mouthing. Beginning to take smooth semi-solids. Shows delighted response to rough-and-tumble play. Manipulates objects attentively, passing them frequently from hand to hand.
9 months	Sits unsupported. Leans forward to pick toy without losing balance. Progresses on floor by rolling, wriggling on abdomen or crawling. Pulls to standing, holding on to support for a few moments.	Inferior pincer grasp. Release toy from grasp by dropping or pressing against a firm surface. Looks in correct direction for fallen toys. (permanence of object). Plays with cause-and-effect toys and pulls on a string to get the connected toy (causal understanding).	Babbles loudly in long repetitive syllables. Responds to name. Understands 'no' and 'byebye'. Imitates playful sounds e.g. cough, 'brrr'.	Mouthing. Holds, bites and chews a small piece of food. Shakes a rattle, explores it with a finger and bangs on floor. Plays Peek-a-boo, imitates hand-clapping. Watches toy being partially hidden under a cover and promptly finds it.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
12 months	Crawls on hands and knees, shuffles on buttocks or 'bear walks' rapidly about the floor. Cruises, holding onto furniture. Stands alone for a few moments. Walks with one hand held.	Neat pincer grasp. Points with index finger at objects of interest. Bangs 2 cubes together to make noise.	Knows and responds to name. Babbles loudly and incessantly. Vocalisation contains most vowels and many consonants. 2 or 3 words with meaning. Imitates adult playful vocalisations e.g., 'uh-oh' and may use a few words. Understands simple instructions. Will follow the gaze of an adult (joint visual attention). Points to objects and then looks back to the adult for a reaction, for the purposes of requesting or eliciting a comment from the adult.	Drinks from cup with assistance. Helps with dressing. Plays 'pat-a-cake' and waves 'good-bye'. Enjoys joint play with adults, actively switching attention between objects and adult (co-ordinated joint attention). Quickly finds toys hidden from view.
15 months	Walks alone, feet apart, arms assisting balance Creeps up stairs.	Build tower of 2 cubes. Imitates to-and-fro scribble using palmar grasp.	Says 2- 6 recognizable words. Understands and obeys simple instructions. Points to familiar persons, toys when requested.	Holds and drinks from cup, attempts to hold spoon. Functional play e.g. pushing toy car or pretends to drink from an empty cup. Repeatedly casts objects to floor in play or rejection and watches where things fall.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
18 months	Walks well with feet only slightly apart, starts and stops safely. Runs rather stiffly. Walks up and down stairs with help. Squats to pick up toy.	Builds tower of 3 cubes. Spontaneous to-and-fro scribble. Enjoys picture books, turns several pages at a time. Beginning to show preference for using one hand.	Uses between 6 and 20 recognisable words. Echoes prominent or last word in short sentences addressed to self. Obeys simple instructions. Points to 2 - 3 body parts.	Holds spoon and gets food safely to mouth. Holds cup between both hands and drinks without much spilling. Assists with dressing and undressing. Imitates simple, everyday activities. Plays contentedly alone but likes to be near familiar adult.
2 years	Runs safely, avoiding obstacles. Walks upstairs and downstairs holding on to rail, two feet to a step.	Build tower of 6 - 7 cubes. Spontaneous circular scribble. Enjoys picture books and turns pages singly. Can match square, circular and triangular shapes in a simple jigsaw.	Uses 50 or more words. Uses 2 - 3 word phrases. Names familiar objects and pictures. Follows a series of 2 simple but related commands.	Feeds self competently with a spoon. Lifts cup and drinks well without spilling and replaces cup on table. Puts on shoes. Engages in make-believe play. Parallel play present.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
2.5 years	Jump with 2 feet together from a low step. Stand on tiptoe if shown. Kicks large ball gently.	Build tower of 7 plus cubes. Imitates horizontal line and vertical line.	Uses 200 or more recognizable words. Knows full name. Can select pictures of actions, e.g., 'Which one shows eating?' Frequently asks questions (what? who?). Uses pronouns (I, me, you) correctly.	Eats skillfully with spoon. More sustained role play, such as putting dolls to bed. Tantrums when thwarted and is less distracted.
3 years	Goes up stairs one foot per step and down stairs 2 feet per step. Stands on 1 foot for seconds. Rides tricycle, using pedals. Can throw a ball overhand and catch large ball on or between extended arms. Kicks ball forcibly.	Build tower of 9 - 10 cubes. Builds three-block bridges from a model. Threads large wooden beads on shoelace. Copies circle. Imitates a cross. Draws person with head and usually adds one or two other features. Matches two or three primary colours. Cuts with toy scissors.	Gives full name, gender, sometimes age. Uses personal pronouns and most prepositions correctly. Ask many questions (what? where? who?) Identify objects by function e.g. which one do we eat with? Counts by rote up to 10 or more.	Eats with a fork and spoon. Washes hands but requires supervision for drying. Can pull pants down and up. May be dry by night. Joins in make-believe play with other children. Understands sharing toys.

Age	Gross Motor	Fine Motor	Speech/Language	Self-care, Social Behaviour & Play
4 years	Walks or runs up and down stairs one foot per step. Stand, walk and run on tiptoe. Stands on one foot for 3-5 seconds and hops on preferred foot.	Builds tower of ten or more cubes. Builds 3 steps with 6 cubes after demonstration. Holds pencil with dynamic tripod grasp. Copies cross. Draws a person with head, legs and trunk and usually, arms and fingers. Matches and names 4 primary colours.	Speech grammatically correct and completely intelligible. Gives full name, address and age. Listens to and tells long stories. Counts by rote up to 20 or more. Eternally asking questions 'why?', 'when?', 'how?', and meanings of words. Knows several nursery rhymes.	Eats skillfully with spoon and fork. Washes and dries hands. Brushes teeth. Can undress and dress except for laces, ties and back buttons. Imaginative dressing up and make believe play. Understands taking turns as well as sharing.
5 years	Walks on narrow line. Skips on alternate feet. Stands on one foot for 8-10 seconds with arms folded. Can hop 2 or 3 metres forwards on each foot separately. Can bend and touch toes without flexing knees. Throws and catches a ball well.	Copies square at 5 years and a triangle at 51/2 years. Writes a few letters spontaneously. Draws a man with head, trunk, legs, arms and features. Draws house with door, windows, roof and chimney. Cuts a strip of paper neatly. Colours pictures neatly, staying within outlines.	Gives full name, age, birthday and home address. Defines nouns by use. Understands time and sequence concepts and uses terms such as 'first', 'then', 'last'.	Washes and dries face and hands. Undresses and dresses alone. Plays imaginatively, creating scenes using miniatures. Chooses own friends. Cooperative with peers and understands need for rules and fair play.

Chapter 4:
Global Developmental Delay (GDD)

- Global developmental delay (GDD) is defined as a delay in two or more developmental domains of gross/fine motor, speech/language, cognition, social/ personal and activities of daily living, affecting children under the age of 5 years.

History

- *Family history:* three-generations review exploring recurrent miscarriages, birth defects, infant deaths, neurologic conditions, genetic conditions, ethnic background and consanguinity.
- *Psychosocial history*: parental education, employment, parental drug or alcohol abuse, child care arrangements and history of abuse/ neglect, involvement of child protective services.
- *Prenatal history*: prenatal ultrasound, maternal smoking, illness, diabetes or hypertension, infections, exposure to medications or toxins
- *Birth history*: Growth parameters (weight and height, head circumference), significant events at birth and/or perinatal period, Apgar score, length of hospitalization.

Developmental milestones

- Current functioning of the child across the various developmental domains (gross motor, fine motor and vision, language and hearing, personal-social skills including activities of daily living).
- Play (solitary vs. parallel vs. interactive play, choice of toys).
- Atypical development, e.g. perseverance/obsessions/ compulsions, rigidity, motor mannerisms, sensory issues, atypical language (echolalia, odd prosody).
- Behaviour in different settings, e.g. home vs. play school.
- Play school/preschool performance, e.g. academics, behaviour, socialisation skills with peers, reports from teachers.
- Reports from professionals working with the child, e.g. therapists.
- Early temperament in infancy, e.g. social responsiveness, feeding, sleeping, crying.
- History of any developmental regression.
- Dietary history, sleep habits.

Physical examination

- Growth parameters, head shape, fontanelle, dysmorphic features, congenital abnormalities, cutaneous stigmata, spine.
- Neurological, cardiac, abdomen, limb and genital abnormalities.
- Current developmental level.
- Observation of behaviour in different settings (eg home vs playschool), social interaction and play (solitary/parallel/interactive play, choice of toys)

Investigations

A stepwise approach to investigations following clinical evaluation is recommended.

- Formal vision and hearing testing must be done.
- Blood: full blood count, renal profile-electrolytes (to calculate anion gap), AST, ALT, thyroid function test, creatine kinase, ammonia, lactate, amino acids, acylcarnitine profile, homocysteine, ferritin, vitamin B12 when dietary restriction or pica are present, lead level when risk factors for exposure are present.
  - Selection of tests should be tailored to the history, examination and developmental diagnosis of a given child.
  - Avoid "routine metabolic screening".
- Urine: organic acid, creatine metabolites, glycosaminoglycans, purines and pyrimidines.
- Genetic testing - molecular karyotyping, specific tests eg Fragile X (FRAXA/ FRAXE PCR), Prader Willi or Angelman syndrome.
- Refer to Clinical Geneticist (where services are available) if patient is syndromic.
- MRI brain is recommended for patients with microcephaly, macrocephaly, seizures or abnormal neurological findings.
- EEG if history of seizures.

Management

- Family counselling.
- Refer to rehabilitation services (ie occupational therapy, speech therapy, physiotherapy) while awaiting formal diagnosis/ results of investigations.
- Emphasize on the importance of early intervention programme.
- Provide parents/ caregivers with online links and local support available.
- Follow up 4-6 monthly to review progress.
- Initiate registration as a child with special needs when appropriate.

Note: Refer *Clinical Practice Guidelines on Management of Autism Spectrum Disorder in Children and Adolescents*[3] for children who are suspected/ diagnosed with autism.

Chapter 5:
Communication Disorders and Sensory Impairment

- Disorders of communication include deficits in language, speech and communication.
- Sensory impairment includes hearing and visual impairment.

1. Speech and Language Impairment

Speech and language delay is associated with difficulty in learning, attention and socialization. In children with delayed speech and language, a comprehensive developmental evaluation is important as presentation may be part of other developmental problems manifesting as language problems.

Component	Assessment
Speech	*Expressive production of sounds and includes articulation, fluency, voice and resonance quality.*
Language	*Form, function, and use of conventional system of symbols (i.e. spoken words, sign language, written words, pictures) for communication.*
Expressive Language	*Production of vocal, gestural or verbal signals.*
Receptive Language	*Receiving and comprehending language messages.*
Assessments of speech, language and communication abilities must take into account both expressive and receptive component and the child's spoken language at home.	

Language Disorder (DSM-5-TR Diagnostic Criteria)

A. Persistent difficulties in language (spoken, written, sign language) due to deficits in comprehension or production that include:

   - Reduced vocabulary
   - Limited sentence structure
   - Impairments in narrating an event or having a conversation.

B. Language abilities are below those expected for age, limiting effective communication, social participation and/or academic achievement.

C. Onset of symptoms is in the early developmental period.

D. Not attributed to hearing/sensory impairment, motor dysfunction, medical/neurological condition. Not due to intellectual disability or global developmental delay.

Managing children with language impairment

History

- Identify risk factors. Positive family history of language disorders is often present.
- Rule out hearing or other sensory impairment.
- Intellectual disability (ID). Language delay can be presenting feature of ID. A separate diagnosis is not given unless language deficits clearly exceed intellectual limitations.
- Neurological disorders. Language disorder can be acquired in association with neurological disorders, including epilepsy (e.g. acquired aphasia or Landau-Kleffner syndrome).
- Language regression. Loss of speech and language in a young child maybe a sign of Autism Spectrum Disorder (ASD) or a neurodegenerative disorder (e.g. adrenoleukodystrophy).
- Look for comorbidities especially specific learning disorder, ADHD, ASD and developmental coordination disorder.

Physical Examination

- Growth parameters & general examination.
- Hearing impairment.
- Complete neurological examination.
- Developmental assessment.

Management

- Hearing assessment
  (even if hearing impairment is not suggestive in history).
- Referral to speech therapist .
- Parental education to focus on language stimulation activities, Early Intervention Program options.
- Will require follow up to monitor progress and to rule out Learning Disorders in an older child.

2. Hearing Impairment

History

- Parental concern on hearing or speech.
- Quality, quantity of speech.
- Congenital infection (e.g. rubella, CMV).
- Perinatal medications.
- Severe neonatal jaundice.
- Meningitis.
- Head trauma.
- Family history of deafness or speech delay.
- Chronic ear infections.
- Genetic syndromes, neurodegenerative disorders.

Physical Examination

- Examine ears.
- Look for dysmorphic features, craniofacial anomalies.
- Distraction test.
- Assess expressive and receptive speech.
- Neurological / developmental assessment.

Management

- Formal hearing assessment.
- Speech-language assessment and intervention.

Audiological test for infants and children	
Physiological test	• Evoked or automated otoacoustic emissions (OAE) • Automated brainstem responses (ABR) *Measure cochlear/brainstem responses to sounds.*
Behavioural Test (7-18 months)	• Distraction test *Developmental age of 7 months is optimum for distraction test.* • Visually reinforced audiometry • Play audiometry *Child attention span may limit success.*
(2-4 years)	• Conventional audiometry
3.5 years onwards	Speech and frequency-specific stimuli presented through earphones.

3. Visual Impairment

Common visual disorders among children are squint, amblyopia and optical problems impairing visual acuity. Poor visual behaviour or presence of squint or abnormal eye movements can be presenting features of cataract, glaucoma or retinoblastoma.

Children at risk for visual impairment

- Prematurity.
- Intrauterine infection (TORCHES).
- Family history of cataract, squint or retinoblastoma.
- Previous history of meningitis or asphyxia.
- Syndromic children.

Warning signs for visual impairment

- Does not fix on carer's face by 6 weeks.
- Wandering or roving eyes by 6 weeks.
- Abnormal head postures.
- White eye reflex (leukocoria).
- Holds objects very close to eyes.
- Squint after 6 months of age.

Detailed history eliciting parental concerns, examination of children's eyes and vision and observation of visual behaviour of children presenting with neurodevelopmental problems is essential for early identification of visual impairments.

Children with suspected visual impairment require early referral to an ophthalmologist, developmental guidance with appropriate early intervention and school placement.

Chapter 6:
Specific Learning Disorder

- Specific learning disorder is a neurodevelopmental disorder diagnosed by the following criteria based on DSM-5-TR.

DSM-5-TR Diagnostic Criteria

A. Difficulties learning and using academic skills as indicated by the presence of at least 1 of the following for at least 6 months, despite provision of adequate intervention:
   1. Inaccurate or slow and effortful word reading.
   2. Difficulty understanding the meaning of what is read.
   3. Difficulties with spelling.
   4. Difficulties with written expression.
   5. Difficulties mastering number sense, number facts, or calculation.
   6. Difficulties with mathematical reasoning.

B. The affected academic skills are below expected for the individual's chronological age and cause significant interference with academic performance or ADL as confirmed by standardized achievement measures and comprehensive clinical assessment.

C. May begin during school-age years but may not become fully manifest until later, when the academic requirements exceed the child's limited capacities.

D. Not better accounted for by intellectual disability, sensory impairments, mental or neurological disorders, psychosocial adversity or inadequate educational exposure.

In Specific Learning Disorder, more than one domain may be affected:

1. Impairment in reading which affects word reading accuracy, reading rate or fluency and reading comprehension. Dyslexia is an alternative term used. Dyslexia is characterized by problems with accurate or fluent word recognition, poor decoding and poor spelling abilities.
2. Impairment in written expression which affects spelling accuracy, grammar and punctuation accuracy and clarity or organization of written expression.
3. Impairment in mathematics which affects number sense, memorization of arithmetic facts, accurate calculation and reasoning. Dyscalculia is an alternative term used.

Commonly co-occurs with other neurodevelopmental/psychiatric disorders
- Attention Deficit Hypersensitivity Disorder (ADHD).
- Language Impairment, Speech Sound Disorder.
- Developmental Coordination Disorder.
- Autism Spectrum Disorder.
- Anxiety disorders.

Note: Please refer to Malaysian CPG for information on Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder.

Signs and symptoms of Specific Learning Disorder
Preschool/Kindergarten
Specific learning disorder is frequently preceded by delays in attention, language or motor skills in preschool years. • May have difficulty pronouncing words and history of speech delay. • Difficulty with nursery rhymes or playing rhyming games. • Difficulty remembering alphabets, numbers or days of the week. • Difficulty remembering rote information (name, phone number, address). • Difficulty in writing alphabets, spelling or may use invented spelling. • Difficulty in breaking down spoken words into syllables and recognizing words that rhyme. • Difficulty connecting letters with their sounds and may be unable to recognize phonemes.
Primary School
• Difficulty with fluent word decoding, spelling or math facts. • Reading aloud is slow, inaccurate and effortful. • Poor reading comprehension and written work. • May mispronounce or skip parts of long, multi-syllable words. • Have trouble remembering dates, names and telephone numbers and completing schoolwork on time.
Secondary School
• Reading remains slow and effortful. • Difficulties in comprehension and written expression. • Poor mastery of math facts or mathematical problem solving. • May avoid activities that demand reading or arithmetic (reading for pleasure, reading instructions).

MANAGING CHILDREN WITH SPECIFIC LEARNING DISORDER

History

- What are the learning problems, when they were noted?
- Current problems faced at school.
- Behavioural problems (esp. inattention)
- Developmental history (esp. speech and language, fine motor).
- Family history (esp. speech delay and learning disorders).
- Significant birth and medical history (prematurity, low birth weight, perinatal asphyxia).
- Assessment of school work (esp. exam papers and teacher's report).
- Interventions and extra support received.

Physical Examination

- Growth parameters, microcephaly.
- Visual and Hearing impairment.
- Syndromic facies, Neurocutaneous stigmata.
- Complete neurological examination.
- Developmental assessment: Look for difficulties in coordination, motor sequencing and balance, fine motor (handwriting, copying shapes and patterns), receptive and expressive language, reading, and comprehension of written instructions, phonological awareness, verbal short term and verbal working memory and observation of behaviour (attention, task avoidance).

Investigations

- Depends on clinical presentation. Most children with Specific Learning Disorders do not require any investigations.
- Specific assessment (Dyslexia Early Screening Test) if available.
- Standardized Cognitive Assessment (Wechsler Intelligence Scale for Children) and adaptive function assessment (Vineland Adaptive Behaviour Scales) when diagnosis is unclear.

Differential Diagnosis

- Intellectual Disability.
- Inadequate academic exposure.
- Learning difficulties due to neurological or sensory disorders. (paediatric stroke, traumatic brain injury, hearing or visual impairment).
- Neurocognitive disorders where difficulties manifest as regression from a former state.
- Attention-deficit/hyperactivity disorder. ADHD can co-occur with specific learning disorder.

Management

- School placement: Discuss with parents on placement in mainstream/ inclusive/integrated class, registration as a child with special needs.
- Extra support: Tuition, intervention centres depending on availability. Most effective when provided in one-to-one or small-group setting.
- Occupational therapy for fine motor and visual perceptual training.
- Speech therapy for speech and language impairments.

Suggestions for School Based Interventions

- Phonics-based reading program, teaching link between spoken and written sounds.
- Multi-sensory approach to learning.
- Learning via audiotape or videotape.
- Supported reading of increasingly difficult text, writing exercises and comprehension strategies.
- Arrange for readers and extra time for exams (will need letter to school).

Refer to Table 1 for simple assessment to elicit features of Specific Learning Disorder at a general paediatric clinic. Important to note that assessment needs to be done in accordance to the child's level of cooperation (may require more than 1 visit). This is not a standardized, validated assessment. When in doubt refer to a Developmental Paediatrician or Clinical/Educational Psychologist, depending on availability of services.

Table 1: Simple Assessment to elicit features of Specific Learning Disorder

Skill	Features	How to Test?
Letter Identification	Difficulty in naming letters.	Ask child to read out letters pointed in random order.
Reading	Unable to read appropriately for age. Reading will be slow, laboured, inaccurate. Unable to read unfamiliar words or pseudo words.	Ask child to read syllables, followed by simple words. Listen to child reading aloud from his/her own grade level reader.
Comprehension	Unable to understand what has been read.	Ask child to read a short story and ask questions regarding the story.
Writing	Letter reversal, omission. Confusion with lowercase and capital letters. Poor spelling. Poor handwriting. Difficulty in writing on a straight line. Unusual spatial organization.	Ask to write alphabets/numbers in sequence. Ask to spell simple words. Ask to write a short paragraph. Observe school workbook for writing problems.
Mathematics	Unable to perform simple addition and subtraction.	Ask child to perform simple addition and subtraction.
Rote memory	Difficulty in memorizing facts.	Ask child to recite days of the week or months of the year, simple multiplication table.

Section 3

ADOLESCENT PAEDIATRICS

Chapter 7:
The H.E.A.D.S.S. Assessment

A Psychosocial Interview for Adolescents

Introduction

Adolescence is the developmental phase between childhood and adulthood and is marked by rapid changes in physical, psychosocial, sexual, moral and cognitive growth.

Dr. Cohen refined a system for organizing the developmentally-appropriate psychosocial history that was developed in 1972 by Dr. Harvey Berman. The approach is known by the acronym HEADSS (Home, Education / employment, peer group Activities, Drugs, Sexuality, and Suicide/depression). It was subsequently expanded to HEEADSSS by adding Eating and Safety.

Preparing for the Interview

Parents, family members, or other adults should not be present during the HEADSS assessment unless the adolescent specifically gives permission, or asks for it.

Starting the interview

1. Introduction
   Set the stage by introducing yourself to the adolescent and parents. If the parents are present before the interview, always introduce yourself to the adolescent first.

2. Understanding of Confidentiality
   Ask the adolescent to explain their understanding of confidentiality.

3. Confidentiality Statement
   After the adolescent has given you his/her views, acknowledge his/her response and add your views accordingly (confidentiality statement), based on the particular situation.

The HEADSS assessment Items are in listed in the following pages

Suggestions for ending interviews with adolescents

- Give them an opportunity to express any concerns you have not covered, and ask for feedback about the interview.
- Ask if there is any information you can provide on any of the topics you have discussed. Try to provide whatever educational materials young people are interested in.

Item	Examples of Questions
Home	• Who lives at home with you? Where do you live? Do you have your own room? • How many brothers and sisters do you have and what are their ages? • Are your brothers and sisters healthy? • Are your parents healthy? What do your parents do for a living? • How do you get along with your parents, your siblings? • Is there anything you would like to change about your family?
Education	• Which school do you go to? What grade are you in? Any recent changes in schools? • What do you like best and least about school? Favourite subjects? Worst subjects? • What were your most recent grades? Are these the same or different from the past? • How much school did you miss last/this year? Do you skip classes? Have you ever been suspended? • What do you want to do when you finish school? • How do you get along with teachers? How do you get along with your peers? • Inquire about "bullying".
Employment	• Are you in any full time or part time job?
Eating	• What do you like and not like about your body? • Has there been any recent change in your weight? • Have you dieted in the last one year? How? How often? • How much exercise do you get on an average day? Week? • Do you worry about your weight? How often? • Does it ever seem as though your eating is out of control? • Have you ever made yourself throw-up on purpose to control your weight?
Activities	• Are most of your friends from school or somewhere else? Are they the same age as you? • Do you hang out with mainly people of your same sex or a mixed crowd? • Do you have a lot of friends? • Do you see your friends at school and on weekends, too? • Do you do any regular sport or exercise? Hobbies or interests? • How much TV do you watch? What are your favourite shows? • Have you ever been involved with the police? Do you belong to a group or gang?

Item	Examples of Questions
Drugs	• When you go out with your friends, do most of the people that you hang out with drink or smoke? Do you? How much and how often? • Have you or your friends ever tried any other drugs? Specifically, what? • Do you regularly use other drugs? How much and how often?
Sexuality	• Have you ever been in a relationship? When? • Have you had sex? Number of partners? Using contraception? • Have you ever been pregnant or had an abortion? • Have you ever been checked for a sexually transmitted infection (STI)? • Knowledge about STIs and prevention? • For females: Ask about menarche, last menstrual period (LMP), and menstrual cycles. Also inquire about breast self examination (BSE) practices. • For males: Ask about testicular self-examination (TSE) practices.
Suicide, Depression	• Do you have difficulties to sleep? Has there been any change in your appetite recently? • Do you mix around well with others? Do you have hopeless or helpless feelings? • Have you ever attempted suicide?
Safety	• Have you ever been seriously injured? Do you always wear a seatbelt in the car? • Do you use safety equipment for sports and or other physical activities (for example, helmets for biking)? • Is there any violence in your home? Does the violence ever get physical? • Have you ever been physically or sexually abused? • Have you ever been bullied? Is that still a problem? • Have you gotten into physical fights in school or your neighborhood? Are you still getting into fights?

Section 4

PALLIATIVE CARE

Chapter 8:
End of Life Care in Children

Introduction

Paediatric palliative care is an active and total approach to care embracing physical, emotional and spiritual elements. It focuses on quality of life for the child and support for the family and includes management of distressing symptoms, provision of respite and care through death and bereavement.[1]

When the disease trajectory of the child has reached the final days, actively dying is generally defined as the hours or days preceding imminent death during which time, the patient's physiologic functions wane.[2]

Signs and symptoms that a child is actively dying: [3,4,5,6]	
Behaviour and mental state	profound tiredness and weakness, reduced interest towards surroundings, feeling irritable, hallucination, lack of concentration, restlessness.
Breathing	changes in breathing pattern or noisy breathing
Circulation	signs of reduced peripheral circulation (skin colour and capillary refill time)
Oral intake and elimination	difficulty in swallowing medicine, reduced interest in food and fluid intake, reduced urine and stool output.

During this phase, the principles of care are tailored for:

- The Child
- The Parents/Carers/Family Members
- The Child's and Carer's Environment

For the Child

- Aim to provide good symptom management.
  refer to *Table 1: Symptom Control in Dying Children*.
- Symptom Care Plan
  - An individualized step-approached care plan based on distress symptoms which may occur during the active dying phase, with steps of symptom management for family or local medical team and contact information for further consultation with key palliative care providers.
- Communication
  - Provides clear, understandable, consistent, up-to-date, either verbally or in written form for the child based on topics important to them, by taking into account their age and level of understanding, and the concerns of parents or carers. If possible, the child should be involved in all aspects of decisionmaking, including Advanced Care Planning.
- Provides regular opportunity to discuss with the children about their emotional, psychological and spiritual concerns[13] either by direct discussion, or through play, art and music activities.
- Discontinuation of unnecessary interventions such as routine observations, routine blood tests, and the use of intravenous or subcutaneous fluids and rationalisation of prescribed medicines.

For Parents/Carers/Family members

- Revision of Advance Care Planning – the care plan should be reviewed regularly, at appropriate intervals. It should contain:
  - Demographic information about the children and their family.
  - Up-to-date contact information of both parents/carers and key involved professionals.
  - A statement about who has the responsibility for giving consent.
  - Discuss and provide information about funeral arrangements.
  - Provide parents/carers the information of professional contacts (including ambulance services and key palliative care providers) in the event of further deterioration and death at home.
  - Revisit the parents/carers' understanding of the methods of home medication administration.
  - Offer parents/carers the support and guidance of how to talk about the impending death of their child with other siblings.
  - Provides parents/carers the access to respite care, if available.
  - Offer school visit to meet with the staff of the school of the children and their siblings if necessary. It provides the chance for school staff to address their concerns regarding their care and support for the child or siblings in the educational setting.
  - Based on availability of resources and parents/carers concerns, they should be provided with financial support, spiritual or chaplaincy support and emotional support by the named key providers.
  - After the death of the child, parents/carers should be provided information and support regarding process of transferring home (if died in hospital), registration of death, organ donation, and the subsequent plan for bereavement support.

For the Child's and Carer's Environment

- The child and their parents/carers should be offered hospice referral (if available and agreed by the child and the parents/carers), as well as the continued communication with local shared care hospital or community teams if their preferred place of care and death is at home.
- Ambience, private room /environment should be provided (if available) which allow the family members to have free access to visit the child in hospital.

TABLE 1: SYMPTOM CONTROL IN DYING CHILDREN[3,4,5,7,10,11,12,13,14]

Pain - Nociceptive		

Signs and Symptoms
• Somatic pain – well localized, deep or superficial, may described as aching, stabbing, throbbing or pressure.
• Visceral pain – poorly localized, may described as cramping, aching, sharp, referred pain to shoulder tip.
	Possible Causes /Issues
	• Somatic pain: stimulation of skin, muscle or bone receptors (eg: pressure sores, muscle spasm, bone metastasis).
	• Visceral pain: from infiltration, distension or compression of thoracic or abdominal viscera (eg: liver capsule, bowel colic).
	• Various contributing factors:
	  • Biological (eg: musculoskeletal).
	  • Environmental (eg: noise).
	  • Psychological (eg: anxiety, depression).
	  • Social, spiritual, cultural (eg: loneliness).
		Management
		Pain assessment tool[15] and pain diary according to child's developmental ability.
		Non-Pharmacology
		• Relaxation (reduce noise, music, guided imagery, physical contact e.g. hold, touch, massage).
		• Local hot/cold applications.
		• Comfort measures (e.g. sucrose for neonates).
		Pharmacology
		• Analgesia: Following WHO Guideline14.
		• Adjuvant- Steroids, NSAIDs, radiotherapy, palliative chemotherapy, biphosphonate.

Pain - Neuropathic		
Signs and Symptoms • Paresthesia, altered sensation e.g. shooting, sharp intense, burning. • Temperature irregulation. • Pain to light touch (allodynia).	Possible Causes /Issues • Treatment related neuropathy. • Infiltrating malignancy.	Management Pain assessment and non-pharmacology management: same as nociceptive pain *Pharmacology* • Anticonvulsant: Gabapentin/Pregabalin. • Anti-depressant: Amitriptyline. • Capsaicin cream 0.075%/Menthol aqueous cream. • Lidocaine 5% transdermal patch. • Corticosteroids e.g. Dexamethasone (tumour infiltrate).

Agitation		
Signs and Symptoms • Agitated (restless, irritability, aggressive behaviour, crying). • Delirium (confusion, disrupted attention, disordered speech, hallucinations).	Possible Causes /Issues • Medical disorders (disease related, pain, hypoxia, electrolyte imbalance, dehydration, urinary retention, constipation). • Psychology (fear, anxiety, depression). • Side effects of medication (e.g. ketamine).	Management *Non-Pharmacology* • Reassure patient and their family. • Promote calm and peaceful environment. • (e.g. reduce noise and lighting, provide familiar objects/ people) *Pharmacology* • Treat the reversible causes. • Benzodiazepines (e.g. midazolam, lorazepam). • Neuroleptics (e.g. Haloperidol, Levomepromazine).
Seizure		
Signs and Symptoms • Episodes of vacant attacks. • Facial or eye twitching. • Loss of consciousness. • Bradycardia,apnoea, cyanosis. • Aura(e.g. unusual smell/ feeling). • Loss of bladder/bowel control. • Post-ictal sleep.	Possible Causes /Issues • Disease related. • Raised intracranial pressure. • Fever. • Drug reactions. • Sleep deprivation. • Pain. • Electrolyte imbalance. • To differentiate from abnormal non-seizure movements (e.g. dystonic spasms).	Management *Non-Pharmacology* • Include seizure management in ACP. • Explain to parents on identification of seizure and home management (written guideline). • Maintain airway. *Pharmacology* • Treat reversible causes. • Short acting benzodiazepine (if seizure >5 mins) e.g. buccal midazolam/rectal diazepam IV lorazepam. • Consider PR paraldehyde if seizure does not stop. • To review/consider start regular anticonvulsant (e.g. levetiracetam/phenytoin). • For refractory terminal seizures, consider midazolam or phenobarbitone infusion.

Excessive Airway Secretions	
Signs and Symptoms • Excessive swallowing. • Drooling. • Noisy Breathing. • Recurrent chest infections.	Possible Causes /Issues • Swallow impairment due to disease. • Excessive hypotonia (disease, medication). • Reduced level of consciousness. • Pneumonia. • Side effects of medication (e.g. ketamine)
	Management *Non-Pharmacology* • Semi-recumbent positioning. • Effective oral care including cleaning teeth. • Use barrier cream to protect lower chin (e.g. Vaseline). • Consider oral suction and postural drainage.Pharmacology • Consider treat pneumonia with oral antibiotic. • Consider antimuscarinic agents if secretions not thick (e.g. Scopolamine patch, Glycopyrronium bromide). • For thick secretions, consider nebulised saline.
Difficulty in Breathing	
Signs and Symptoms • Tachypnoea, chest recession. • Tracheal tug. • Cyanosis, tachycardia. • Tired /Fatigue. • Laboured breathing.	Possible Causes /Issues • Lung: Infection, malignancy, effusion, pneumothorax, upper airway obstruction. • Cardiac: failure, SVC obstruction, embolism. • Extrathoracic: massive ascites, anaemia. • Psychology: Anxiety/Panic.
	Management *Non-Pharmacology* • Position: Sit upright /leaning forward over pillow. • Air: open window, use fan (blow to face). • Relaxation techniques. • Distraction and mirroring (face to face support • slowing of breathing). • Pacing in walk /activities (more rest). *Pharmacology* • Treat reversible causes: Infection, anaemia, ascites, pleural effusion, pneumothorax (chest tube). • Secretion management (see symptom above). • Consider anxiolytics/sedative agents for anxiety: midazolam, lorazepam. • Consider trial of oxygen supplementation (if SPO_2<92%). • Low dose opioids to relieve dyspnoea sensation (15%-30% of pain dosage). • Keep mouth moist. • Diuretics for heart failure.

Nausea and Vomiting		
Signs and Symptoms • Signs of raised Intracranial pressure (eg: headache, sleepy). • Abdominal: No bowel open, bile vomitus, abdominal pain. • Dehydration (dry mouth, reduce urine output, sunken eye).	Possible Causes /Issues • Disease or treatment related. • Constipation/intestinal obstruction. • Raised Intracranial pressure. • Infection. • GORD. • Trigger: cough, movement, food, smells, anticipatory.	Management *Non-Pharmacology* • Assess trigger factors. • Hot /cold packs for abdominal pain. • Encourage small amount of diet /fluid as tolerable. • Consider nasogastric tube if indicated. *Pharmacology* • Pharmacology • Treat reversible causes (reduce or change causative treatment /medicine, laxative for constipation). • Regular anti-emetics (choice guided by causes) and review symptoms by 24-48 hours. • Consider intravenous/subcutaneous fluid if dehydrated. • Consider anti-reflux medication. • Consider Dexamethasone (post chemo/tumour control).

Bleeding		
Signs and Symptoms • Pallor, bruises, lethargy, agitated, dehydration, confusion. • Haematemesis. • Haemoptysis. • Epistaxis. • Malaena. • Bleeding from stoma, drains, gums.	Possible Causes /Issues • Disease /treatment related (e.g. malignancy). • Clotting deficiency or DIVC (sepsis).	Management *Non-Pharmacology* • Use soft tooth brush for teeth brushing. • Nose bleed: pinch nose + cold compression, consider refer ENT for packing. • Use dark coloured towels for large amounts of vomit orcoughed-out blood. • Haemostatic dressing (e.g. Alginate) for skin trauma. *Pharmacology* • Bleed may be exacerbated by fever: consider antipyretics. • Anti-fibrinolytic : e.g. Tranexamic acid. • Vasoconstrictor: e.g. topical Adrenaline. • Catastrophic /terminal bleed: consider sedation and analgesia (e.g.: midazolam /opioid) for pain, agitation, restlessness distress. • Consider blood products transfusion if indicated. • Consider radiotherapy for solid tumour bleeding.

Section 5

INTENSIVE CARE

Chapter 9:
Paediatric Fluid and Electrolyte Guidelines

Well children with Normal hydration

- Children who are well rarely require intravenous fluids (IV). Whenever possible, use an enteral (oral or nasogastric/orogastric tube) route for fluids.
- These guidelines apply to children who are unable to tolerate enteral fluids.
- The safe use of IV fluid therapy in children requires accurate prescribing of fluids and careful monitoring because incorrectly prescribed or administered fluids are hazardous.
- If IV fluid therapy is required then maintenance fluid requirements should be calculated using the Holliday and Segar formula based on **ideal body weight**.
- However, the above calculation should serve as an initiation volume and adjusted according to individual's response to fluid therapy. Patient should be monitored closely by clinical observation, fluid balance, weight and regular electrolyte profile.

Prescribing Intravenous fluids

Fluids are given intravenously for the following reasons:
- Fluid resuscitation.
- Replacement of
  - previous fluid and electrolyte deficit due to dehydration.
  - ongoing losses.
- Maintenance of daily fluid requirement.

Prescribing Intravenous Fluids	
For Resuscitation	• Bolus. • *Crystalloids*: 0.9% Sodium chloride, balanced solution e.g. Hartmann's solution or Sterofundin. • *Colloids*: e.g. 5% Albumin can be considered after 20-40ml/kg of crystalloids. (Evidence against usage of starch-based fluids).
For Replacement	• Dehydration or ongoing losses. • 0.9% Sodium chloride. • Hartmann's solution /Ringer's lactate or Sterofundin if there is hyperchloremic acidosis.
For Maintenance	• 0.9% Sodium chloride + 5% Dextrose • +/- Potassium chloride • Alternatively in special circumstances: • 0.45% Sodium chloride + 5% Dextrose +/- Potassium chloride OR • Balanced solution +/- glucose

- A balanced solution is made to a physiological pH and isotonic salt concentration.
- If electrolytes are outside the normal range, discuss with a specialist as necessary.
- 0.45% Saline +/- Glucose should be used in special circumstances with close sodium monitoring to avoid hyponatremia.
- Electrolyte composition may vary slightly between different IV solution brands.

Electrolyte Composition (mmol/l), Osmolarity and Tonicity of commonly used intravenous solution. (Crystalloid)							
Electrolyte	**Plasma**	**0.9% NaCL**	**0.45% NaCL + Dextrose 5%**	**Ringer's Lactate/ Hartmann's**	**Sterofundin**	**Plasmalyte 148**	**0.9%NaCl + Dextrose 5%**
Sodium	140	154	77	131	145	140	154
Potassium	5	0	0	5	4	5	0
Chloride	100	154	77	111	127	98	154
Calcium	2.2	0	0	2	2.5	0	0
Magnesium	1	0	0	1	1	1.5	0
Bicarbonate	24	0	0	0	0	0	0
Lactate	1	0	0	29	0	0	0
Acetate	0	0	0	0	24	27	0
Gluconate	0	0	0	0	0	23	0
Maleate	0	0	0	0	5	0	0
Glucose g/L		0	50	0	0	0	50
Osmolarity (mosm/L)	275-295	308	406	273	309	294	560
Sodium	Isotonic	Hypotonic	Isotonic	Isotonic	Isotonic	Isotonic	Isotonic

Electrolyte Composition (mmol/l), Osmolarity and Tonicity of commonly used intravenous solution. (Colloid)		
Electrolyte	**Albumin 5%**	**Albumin 5%**
Sodium	140	150
Potassium	0	0
Chloride	125	120
Octanoate	8	0
Calcium, Magnesium, Bicarbonate, Lactate, Acetate, Gluconate, Maleate	0	0

Resuscitation

Fluids appropriate for bolus administration are:	
Crystalloids	• 0.9% Normal Saline • Ringer's Lactate /Hartmann's solution • Sterofundin • Plasmalyte
Colloids	• 5% albumin solution • Gelafundin
Blood products	• Whole blood • Blood components
**Do not use starch based solution e.g. Voluven as resuscitation fluid.*	

- Fluid deficit severe enough to cause **impaired tissue oxygenation (clinical shock)** should be **corrected with a fluid bolus of 10-20 mls/kg over 10-20 minutes**.
- **Always reassess circulation and look for signs of fluid overload after each fluid bolus** - give repeat boluses if indicated and no signs of fluid overload.
- **Look for the cause of circulatory collapse** - blood loss, sepsis, etc. This helps to decide on the appropriate choice of resuscitation fluid.
- **Smaller fluid boluses of 5 mls/kg in selected situations** - e.g. cardiac illness.
- Fluid bolus should be given over 30 minutes to 1 hour in specific conditions, e.g. Diabetic ketoacidosis and Dengue Shock.
- Consider 5% albumin as 1st choice in resuscitation of patient with extremely low albumin e.g. nephrotic syndrome.
- **Avoid low sodium-containing (hypotonic) solutions and glucose-containing solutions** for resuscitation as these may cause hyponatraemia and cerebral oedema.
- **Measure blood glucose: treat hypoglycaemia with bolus 2-3mls/kg of 10% Dextrose solution** followed by dextrose containing solutions (5-10%) as maintenance fluid.
- **Measure Na, K and glucose** at the beginning and at least 24-hourly (more frequent testing is indicated for ill patients or patients with co-morbidities). Rapid electrolyte values can be obtained from blood gases.
- **Consider septic work-up and broad-spectrum antibiotic coverage or surgical consult** in severely unwell patients with abdominal symptoms to rule out acute surgical conditions, e.g. perforated viscus.

Maintenance

- Maintenance fluid is the volume of daily fluid intake. It includes insensible losses (from breathing, perspiration, and in the stool), and allows for excretion of the daily production of excess solute load (urea, creatinine, electrolytes) in the urine.
- Most children will tolerate standard fluid requirements using the Holliday and Segar formula. However, some acutely ill children with inappropriately increased anti-diuretic hormone secretion (SIADH) may benefit from their maintenance fluid requirement being restricted to two-thirds of the normal recommended volume.
- Children should be monitored for hyponatremia or hypernatremia. These include children with the following conditions:
  - Peri-or post-operative state
  - Require replacement of ongoing losses
  - A plasma Na+ at lower range of normal (definitely if < 135mmol/L)
  - Intravascular volume depletion or hypotension
  - Central nervous system (CNS) infection
  - Head injury
  - Diabetic ketoacidosis
  - Bronchiolitis
  - Sepsis
  - Excessive gastric or diarrheal losses
  - Salt-wasting syndromes
  - Chronic conditions such as cystic fibrosis and pituitary deficits.

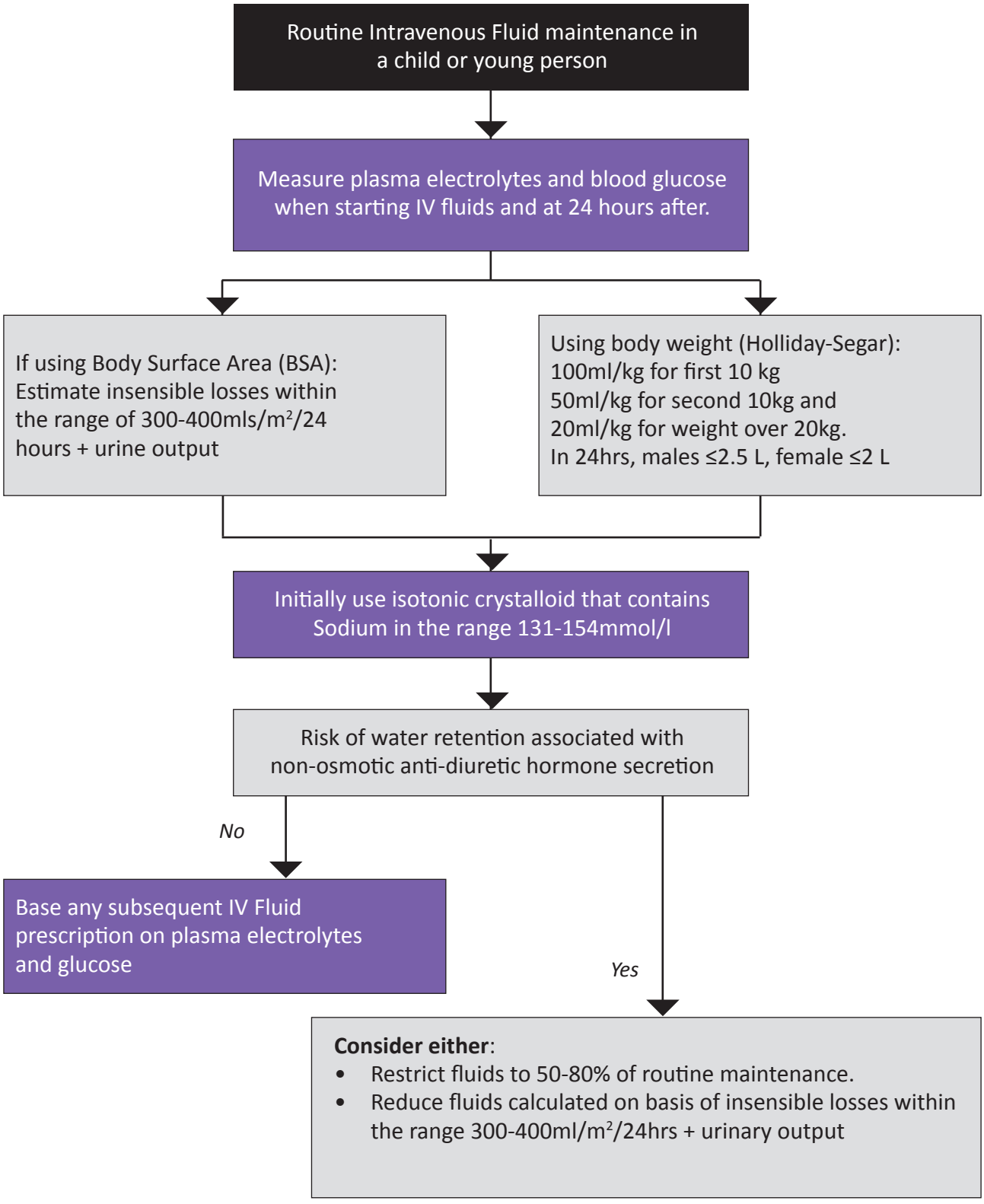
Calculation of Maintanence Fluid Requirements

The following calculations approximate the maintenance fluid requirement of well children according to weight in kg (Holliday-Segar calculator). Use ideal weight for calculation in obese children.

Weight	Total fluids	Infusion rate
First 10 Kgs	100 ml/kg	4 ml/kg/hour
Subsequent 10 Kgs	50 ml/kg	2 ml/kg/hour
All additional Kg	20 ml/kg	1 ml/kg/hour

Example: A Child of 29 kg will require:		
100ml/kg for first 10kg of weight	10 x 100	= 1000 ml
50ml/kg for second 10kg of weight	10 x 50	= 500 ml
20ml/kg for all additional weight	9 x 20	= 180 ml
	Total	= 1680 ml
	Rate	Rate = 1680/24 = 70ml/hour

Flow Chart for Maintenance Intravenous Fluid Prescription



Deficit

- A child's water deficit in mls can be calculated following an estimation of the degree of dehydration expressed as % of body weight.

Example: A 10kg child who is 5% dehydration has a water deficit of 500mls.		
Maintenance		
100mls/kg for first 10 kg	= 10 × 100	= 1000ml
Infusion rate/hour	= 1000ml/24 hr	= 42ml/hr
Deficit (give over 24hours)		
5% dehydration (5% of body water): 5/100 × 10kg × 1000ml		= 500ml
Infusion rate/hour (given over 24 hrs)	= 500ml/24 hr	= 21ml/hr

- The deficit is replaced over a time period that varies according to the child's condition. Precise calculations (e.g. 4.5%) are not necessary. The rate of rehydration should be adjusted with ongoing clinical assessment.
- Use an isotonic solution for replacement of the deficit, e.g. 0.9% saline or balanced solutions.
- Reassess clinical status and weight at 4-6hours, and if satisfactory continue. If child is losing weight, increase the fluid and if weight gain is excessive, decrease the fluid rate.
- Replacement may be rapid in most cases of gastroenteritis (best achieved by oral or nasogastric fluids), but should be slower in diabetic ketoacidosis and meningitis, and much slower in hypernatremic states (aim to rehydrate over 48-72 hours, the serum Na should not fall by >0.5mmol/l/hr or >10-12 mmol/L per 24 hours).

Ongoing losses (e.g. from drains, ileostomy, profuse diarrhoea)

- These are best measured and replaced. Any fluid losses > 0.5ml/kg/hr needs to be replaced.
- Calculation may be based on each previous hour, or each 4-hour period depending on the situation. E.g., a 200mls loss over the previous 4 hours will be replaced with a rate of 50mls/hr for the next 4 hours).
- Ongoing losses can be replaced with 0.9% Normal Saline or balanced solution. Fluid loss with high protein content leading to low serum albumin can be replaced with 5% Human Albumin.

SODIUM DISORDERS

- The daily sodium requirement is 2-3mmol/kg/day.
- **Normal serum sodium is between 135-145mmol/l**.

Hypernatraemia

- **Hypernatraemia is defined as serum Na^+ > 150mmol/l**, moderate hypernatraemia = serum Na^+ is 150-160mmol/l, and severe hypernatraemia = serum Na^+ > 160mmol/l.
- It can be due to:
  - water loss in excess of sodium (e.g. diarrhoea)
  - water deficit (e.g. diabetes insipidus)
  - sodium gain (e.g. large amount of $NaHCO_3$ infusion or salt poisoning).

Clinical signs of Hypernatraemic dehydration
Irritability
Skin feels "doughy"
Ataxia, tremor, hyperreflexia
Seizure
Reduced awareness, coma

- Children **may appear sicker than expected for degree of dehydration.**
- **Shock occurs late because intravascular volume is relatively preserved**.
- Signs of hypernatraemic dehydration tend to be predominantly that of intracellular dehydration and neurological dysfunction.
- In hypernatraemia due to **central diabetes insipidus**, consult Endocrinology.

Management

For hypernatraemic dehydration with Na+> 150mmol/l:

- **If the patient is in shock, give volume resuscitation with 0.9% Normal saline as required with bolus/es.**
- **Avoid rapid correction** (may cause cerebral oedema, convulsion and death).
- Aim to correct deficit over 48-72 hours and fall of serum $Na^+ \leq 0.5$mmol/L/hr.
- Give 0.9% Sodium chloride to ensure the drop in sodium is not too rapid (<10-12mmol/L per day).
- Remember to give maintenance fluids and replace ongoing losses.
- **Repeat blood urea and electrolytes** every 6 hours until stable.
- If hypernatraemia worsens or is unchanged after replacing deficit, review fluid type and consider changing to a hypotonic solution (e.g. 0.45% Sodium chloride with dextrose).
- If no evidence of dehydration and an isotonic fluid is being used, consider changing to a hypotonic fluid (e.g. 0.45% Sodium chloride with dextrose).
- If the fluid status is uncertain, measure urine sodium and osmolality. When correcting hypernatraemia, ensure that the rate of fall of plasma sodium < 12 mmol/litre in a 24-hour period (0.5mmol/l/hour).
- Measure plasma electrolytes every 4–6 hrs for the first 24 hrs, and the frequency of further electrolyte measurements depends on response.

Special considerations

- Use a slower rate in chronic Hypernatraemia (present for > 5 days).
- Measure **calcium and glucose**. Hypernatraemia can be associated with hypocalcaemia and hyperglycaemia, which need to be corrected concurrently.

Hyponatraemia

- **Hyponatraemia is defined when serum Na^+ < 135mmol/l.**
- **Hyponatraemic encephalopathy** is a medical emergency that requires rapid recognition and treatment to prevent poor outcome.
- **Symptoms** associated with acute hyponatraemia during IV fluid therapy: Headache, nausea, vomiting, confusion, disorientation, irritability, lethargy, reduced consciousness, convulsions, coma, apnoea.

Calculating sodium correction in acute hyponatremia	
mmol of sodium required	= (135-present Na level)× 0.6 × weight(kg)
The calculated requirements can then be given from the following available solutions dependent on the availability and hydration status:	
0.9% sodium chloride contains **154 mmol/l of Sodium**	
3% sodium chloride contains **513mmol/l of Sodium**	

- In acute symptomatic hyponatraemia in term neonates and children, review the fluid status, seek immediate expert advice (for example, from the paediatric intensive care team) and consider taking action as follows:
  - A 2 ml/kg bolus (max 100 ml) of 3% Sodium chloride over 10–15 mins.
  - A further 2 ml/kg bolus (max 100 ml) of 3% Sodium chloride over the next 10–15 mins if symptoms are still present after the initial bolus.
  - If symptoms are still present after the 2nd bolus, check plasma sodium level and consider a third 2ml/kg bolus (max 100 ml) of 3% Sodium Chloride over 10–15 mins.
  - Measure the plasma sodium concentration at least hourly.
  - As symptoms resolve, decrease the frequency of plasma sodium measurements based on the response to treatment.
  - Do not manage acute hyponatraemic encephalopathy using fluid restriction alone.
  - After hyponatraemia symptoms have resolved, ensure that the rate of increase of plasma sodium does not exceed 12 mmol/l in a 24-hr period.
- Children with a**symptomatic hyponatremia** do not require 3% sodium chloride treatment and if dehydrated may be managed with oral fluids or intravenous rehydration with 0.9% sodium chloride.
- Children who are hyponatremic and have a normal or raised volume status should be managed with fluid restriction to half or 2/3rd maintenance.
- For Hyponatraemia secondary to **diabetic ketoacidosis**; refer DKA protocol.

POTASSIUM DISORDERS

- The daily potassium requirement is 1-2mmol/kg/day.
- **Normal values of potassium are:**
  - **Birth - 2 weeks: 3.7 - 6.0mmol/l**
  - **2 weeks – 3 months: 3.7 - 5.7mmol/l**
  - **3 months and above: 3.5 - 5.0mmol/l**

Hypokalaemia

- **Hypokalaemia is defined as serum K^+ < 3.4 mmol/l**
  (Treat if < 3.0mmol/l or clinically symptomatic and < 3.4 mmol/l)
- Causes are:
  - Sepsis
  - Gastrointestinal losses - diarrhoea, vomiting
  - Iatrogenic- e.g. diuretic therapy, salbutamol, amphotericin B.
  - Diabetic ketoacidosis
  - Renal tubular acidosis
- Hypokalaemia is often seen with chloride depletion and metabolic alkalosis
- Refractory hypokalaemia may occur with hypomagnesaemia.

ECG changes of Hypokalemia
These occur when K^+ < 2.5mmol/l
Prominent U wave
ST segment depression
Flat, low or diphasic T waves
Prolonged PR interval (severe hypoK^+)
Sinoatrial block (severe hypoK^+)

Treatment

- Identify and treat the underlying condition.
- **Unless symptomatic, a potassium level of 3.0-3.4 mmol/l is generally not supplemented** but rather monitored.
- The treatment of hypokalaemia will need to be individualized for each patient.

Oral Supplementation

- Oral Potassium chloride (KCL), to a maximum of 2 mmol/kg/day in divided doses is common but more may be required in practice.

Intravenous Supplementation (1gram KCL = 13.3 mmol KCL)

- **Potassium chloride is always given by IV infusion, NEVER by bolus injection**.
- **Maximum concentration via a peripheral vein is 40 mmol/l** (concentrations of up to 60 mmol/l can be used with specialist advice).
- **Maximum infusion rate is 0.2mmol/kg/hour** (in non-ICU setting).

Intravenous Correction (1gram KCL = 13.3 mmol KCL)

- K^+ < 2.5 mmol/L may be associated with significant cardiovascular compromise. In the emergency situation, an IV infusion KCL may be given
  - Dose: initially 0.4 mmol/kg/hr into a central vein, until K+ level is restored.
  - Ideally this should occur in an intensive care setting.

POTASSIUM DISORDERS

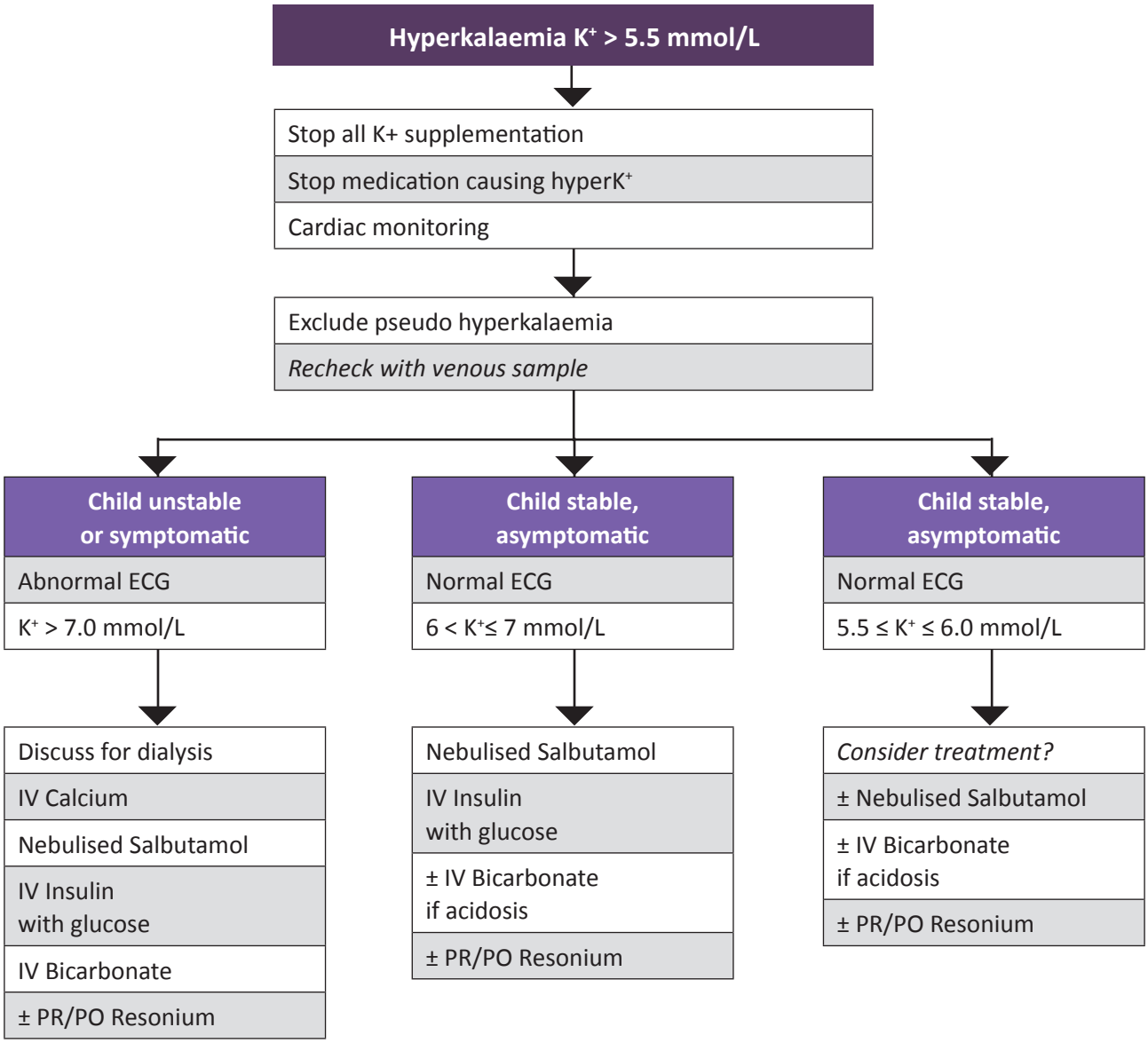
Hyperkalaemia

- Causes are:
  - Dehydration
  - Acute renal failure
  - Diabetic ketoacidosis
  - Adrenal insufficiency
  - Tumour lysis syndrome
  - Drugs e.g. oral potassium supplement,
  - K^+ sparing diuretics, ACE inhibitors.
- Symptoms of Hyperkalaemia:
  - Nausea and vomiting
  - Fatigue
  - Paraesthesia, muscle weakness, paralysis
  - Respiratory distress and failure
  - Palpitations, syncope, cardiac arrest

ECG changes in Hyperkalaemia
Tall, tented T waves. Prolonged PR interval. Prolonged QRS complex. Loss of P wave. Wide biphasic QRS.

Treatment: *Refer to Hyperkalaemia Treatment Algorithm on the next page*

HYPERKALAEMIA TREATMENT ALGORITHM



Drug doses:

- IV Calcium 0.1 mmol/kg (IV Calcium gluconate 10% 0.5ml/kg - Max 20 ml or IV Calcium chloride 0.2ml/kg - Max 10ml). Give over2-5 minutes if unstable or 15-20 minutes if stable under cardiac monitoring.
- Nebulised Salbutamol: 2.5-5mg, repeat as necessary.
- IV Insulin with Glucose:
  - Start with IV Glucose 10% 5ml/kg/hr (or 20% at 2.5 ml/kg/hr). Once Blood sugar level >10mmol/l and the K^+ level is not falling, add IV Insulin 0.05 units/kg/hr and titrate according to glucose level.
- IV Sodium Bicarbonate: 1-2 mmol/kg over 5 minutes if severe or over 30 minutes in mild to moderate hyperkalaemia.
- Calcium polystyrene sulfonate (Calcium Resonium) 0.3-0.6g/kg (Adult 15-30g) 6 hourly to be given rectally or orally.

MEDICATIONS FOR HYPERKALAEMIA

Medication	Response type	Onset of action (minutes)	Duration of action (hours)	Mechanism of action	Expected decrease in potassium level
Calcium gluconate	rapid	1-2	0.5-1	Protect cardiomyocytes	0.5-1.5 mEq/L
Glucose + insulin	intermediate	10-20	2-6	Shift potassium intracellularly	0.5-1.5 mEq/L (dose dependent)
Beta-agonists		3-5	1-4	Shift potassium intracellularly	
Sodium bicarbonate (only in patients with metabolic acidosis, bicarbonate <22mEq/L)		30-60	2-6	Shift potassium intracellularly (questionable effect)	
Exchange resin	delayed	120-360	4-6	Elimination of potassium from the body	
Furosemide		5-30	2-6		
Haemodialysis		immediate			1mmol/L in the first 60 minutes and total of 2 mmol/L by 180 minutes.

Chapter 10:
Acute Gastroenteritis

Introduction

- Acute gastroenteritis (AGE) is a leading cause of childhood morbidity and mortality and an important cause of malnutrition.
- Many diarrhoeal deaths are caused by dehydration and electrolytes loss.
- Dehydration can be safely and effectively treated with Oral Rehydration Solution (ORS) but severe dehydration may require intravenous fluid therapy.

First assess the state of perfusion of the child.

Is the child in shock?

- Signs of shock include tachycardia, weak peripheral pulses, delayed capillary refill time >2 seconds, cold peripheries, depressed mental state with or without hypotension.

For any child with shock go straight to Treatment Plan C.

You can also use the WHO chart below to assess the degree of dehydration and then choose the treatment plan A, B or C, as needed.

Assess:			
Look at child's general condition	Well, alert.	Restless or irritable.	Lethargic or unconscious.
Look for sunken eyes	No sunken eyes.	Sunken eyes.	Sunken eyes.
Offer the child fluid	Drinks normally.	Drinks eagerly, thirsty.	Not able to drink or drinks poorly.
Pinch skin of abdomen	Skin goes back immediately.	Skin goes back slowly.	Skin goes back very slowly (> 2 secs).
Classify	**Mild Dehydration** <5% Dehydrated* IMCI: No signs of Dehydration	≥ 2 above signs: **Moderate Dehydration** 5-10% Dehydrated IMCI: Some signs of Dehydration	≥ 2 above signs: **Severe Dehydration** > 10% Dehydrated
Treat	**Plan A** Give fluid and food to treat diarrhoea at home	**Plan B** Give fluid and food for some dehydration	**Plan C** Give fluid for severe dehydration. Provide food as soon as child tolerates.

**% of body weight (in g) loss in fluid (Fluid Deficit)*
e.g. a 10 kg child with 500g weight loss is estimated to have 5% dehydration.
Fluid deficit = 5/100 x 10000g = 500 mls.

PLAN A: TREAT DIARRHOEA AT HOME

Counsel the caretaker on the 3 rules of home treatment:
Give Extra Fluid, Continue Feeding, When to return.

1. Give Extra Fluids (as much as the child will take)

- Tell the mother:
  - Breastfeed frequently and for longer at each feed.
  - If exclusively breastfed, give Oral Rehydration Solution (ORS) or cooled
  - boiled water in addition to breastmilk.
  - If the child is not exclusively breastfed, give one or more of the following: ORS, food-based fluids (soup and rice water) or cooled boiled water.
- • It is especially important to give ORS at home when:
  - The child has been treated with Plan B or Plan C during this visit.
- • Provide 8 sachets of ORS to be used at home with these advice:
  - How to mix ORS.
  - To give small sips from cup or spoon.
  - If child vomits, wait for 10 minutes then continue but more slowly.
  - Amount of ORS to be given in addition to the usual fluid intake:
    - Up to 2 years : 50 to 100ml after each loose stool.
    - 2 years or more : 100 to 200ml after each loose stool.
    - If weight is available, to give 10ml/kg of ORS after each loose stool
- • To continue to give extra fluid until diarrhoea stops.

2. Continue Feeding

- Breastfed infants should continue nursing on demand.
- Formula fed infants should continue their usual formula immediately on rehydration.
- Lactose-free or lactose-reduced formula are usually unnecessary.
- Children receiving semi-solid or solid foods should continue to receive their usual food during the illness.
- Foods high in simple sugar should be avoided as the increased osmotic load may worsen diarrhoea.

3. When to Return (to clinic/hospital)

- When the child:
  - Is not able to drink or breastfeed or drinking poorly.
  - Becomes sicker.
  - Develops a fever.
  - Has blood in stool.

PLAN B: TREAT SOME DEHYDRATION WITH ORS

Give the recommended amount of ORS over 4-hour period:

Determine the amount of ORS to be given in the first 4 hours.				
Weight	**Up to 4 months**	**4 - 12 mths**	**12 mths - 2 yrs**	**2 - 5 yrs**
Weight	Less than 6 kg	6 to 10 kg	10-12 kg	12 to 19 kg
Volume	200-400 ml	400-700 ml	700-900 ml	900-1400 ml

1. Use the child's age only when you do not know the weight. The approximate amount of ORS required (in ml) can be calculated by multiplying the child's weight (in kg) x 75.
2. If the patient wants more ORS than shown, give more.

Show the mother how to give ORS solution

- Give frequent small sips from cup or spoon.
- If the child vomits, wait 10 minutes, then continue but more slowly (i.e. 1 spoonful every 2 - 3 minutes).
- Continue breastfeeding whenever the child wants.

After 4 hours

Reassess the child and classify the child for dehydration.
Select the appropriate plan to continue treatment (Plan A, B or C).
Begin feeding the child.

If the caretaker must leave before completing treatment

- Show him/her how to prepare ORS solution at home.
- Show him/her how much ORS to give to finish the 4-hour treatment at home.
- Provide enough ORS packets to complete rehydration. Also provide 8 additional packets as recommended in Plan A.
- Explain the 3 Rules of Home Treatment (Plan A):
  1. GIVE EXTRA FLUID
  2. CONTINUE FEEDING
  3. WHEN TO RETURN.

Important!

- If possible, observe the child at least 6 hours after re-hydration to be sure the caretaker can maintain hydration giving the child ORS solution by mouth.
- If there is an outbreak of cholera in your area, give an appropriate oral antibiotic after the patient is alert.

PLAN C: TREAT SEVERE DEHYDRATION QUICKLY

- Airway, Breathing and Circulation (ABCs) should be assessed and established quickly. Provide supplemental oxygen for all children in shock, and ventilatory support if the need arises.
- Start intravenous (IV) or intraosseous (IO) fluid immediately. If patient can drink, give ORS by mouth while the drip is being set up.
- Initial fluids for resuscitation of shock: 10 ml/kg of 0.9% Normal Saline (NS) or Hartmann's solution as a rapid IV bolus.
- Serum electrolytes, blood urea nitrogen, creatinine and glucose should be obtained for all children needing IV fluid therapy.
- Repeat fluid boluses as needed, until the patient's intravascular volume is restored adequately. Stop boluses if fluid overload is suspected.
- Observe the patient closely. Review patient during and after each bolus and consider other causes of shock if the child is not responding to fluid bolus, e.g. septicaemia, metabolic and cardiac disorders.
- Once shock is corrected, commence rehydration, provide maintenance fluids and replace ongoing losses.
- For rehydration use an isotonic solution, e.g. 0.9% NS or Hartmann's solution. May consider 0.45% NS in neonates.
- Fluid deficit: Percentage dehydration X body weight in grams (**to be given over 12-24 hours**).
- Beware of hypernatraemic dehydration (serum sodium ≥ 150 mmol/L), and give fluid correction over a longer duration, e.g. over 48 - 72 hours, aiming to correct sodium gradually, ≤ 0.5 mmol/L/h.
- Maintenance fluid (See *Chapter 9: Paediatric Fluid And Electrolyte Guidelines*).

Example:

A 12-kg child is clinically shocked and 10% dehydrated as a result of gastroenteritis.
Initial therapy: To establish ABCs.

- 10 ml/kg for shock = 12× 10 = 120 ml of 0.9% NS given as a rapid intravenous bolus. Repeat if necessary.
- Fluid for Rehydration/Fluid deficit: 10/100 x 12000 = 1200 ml
- Daily maintenance fluid = 1st 10 kg 100 × 10 = 1000 ml
  Subsequent 2 kg 2 x 50 = 100 ml
  Total = 1100 ml/day
- To rehydrate (1200 ml over 12 hours) 0.9% NS or Hartmann's solution + maintenance (1100 ml over 24 hours) with 0.9% NS D5%.
- Replace on going diarrhoea/vomiting losses orally whenever possible:
- ORS 5- 10ml/kg for each episode.

The cornerstone of management is to reassess the hydration status, vital signs and clinical condition frequently (e.g. at 1-2 hourly), and adjust the infusion and other support /therapies accordingly.

- Caution - more judicious fluid administration rate will be required in certain situations:
  - Children less than 6 months age.
  - Children with co-morbidities i.e. cardiac or renal diseases, severe anaemia, severe malnutrition (See *Chapter 80 Approach To Severely Malnourished Children*).
  - Children with severe hyponatraemia /hypernatraemia (See *Chapter 9 Paediatric Fluids and Electrolyte Guidelines*).
- Hypernatraemia should be suspected in a child if the degree of dehydration on clinical assessment is less severe than would have been expected from clinical history. However, this can be difficult to detect clinically.
- Serum electrolytes need to be checked from time to time to adjust the rate of rehydration and choice of fluid accordingly.
- Start giving more of the maintenance fluid as oral feeds e.g. ORS (about 5ml/kg/hour) as soon as the child can drink, usually after 3 to 4 hours for infants, and 1 to 2 hours for older children. This fluid should be administered frequently in small volumes.
- Generally normal feeds should be administered in addition to the rehydration fluid, particularly if the infant is breastfeeding.
- Once a child is able to feed and not vomiting, oral rehydration according to Plan A or B can be used, and the IV drip reduced gradually and stopped.
- If you are unable to gain IV or IO access, arrange for the child to be sent to the nearest centre that can do so immediately.
- Meanwhile as arrangements are made to send the child (or as you make further attempts to establish IV or IO access),
  - Try to rehydrate the child with ORS orally (if the child can drink) or by nasogastric or orogastric tube. Give ORS 20 ml/kg/hour for 6 hours. Continue to give the ORS along the journey.
  - Reassess the child every 1-2 hours.
  - If there is repeated vomiting or increasing abdominal distension, give the fluid more slowly.
  - Reassess the child after six hours, and classify dehydration.
  - Then choose the most appropriate plan (A, B or C) to continue treatment.

- ***If there is an outbreak of cholera in your area, give an appropriate oral antibiotic after the patient is alert.***

Role of nasogastric rehydration

- When oral rehydration is not feasible, enteral rehydration by the nasogastric (NG) route is the preferred method of rehydration, and should be proposed before IV rehydration.
- Enteral rehydration is associated with significantly fewer major adverse events and a shorter hospital stay than IV rehydration and is successful in most children.
- The rapid (40–50 mL/kg within 3–6 hours) and standard (24 hours) NG rehydration regimens are equally effective and either may be used.

Other indications for intravenous therapy

- Unconscious child.
- Failed ORS treatment due to continuing rapid stool loss (>15-20ml/kg/hr).
- Failed ORS treatment due to frequent, severe vomiting, drinking poorly.
- Abdominal distension with paralytic ileus, usually caused by some antidiarrhoeal drugs (e.g. codeine, loperamide) and hypokalaemia
- Glucose malabsorption, indicated by marked increase in stool output and large amount of glucose in the stool when ORS solution is given (uncommon).

Indications for admission to Hospital

- Shock or severe dehydration.
- Failed ORS treatment and need for intravenous therapy.
- Concern for other possible illness or uncertainty of diagnosis in the presence of red flags:
  - Vomiting without diarrhoea
  - Infant under 6 months old
  - Bilious vomiting
  - Past gastrointestinal / surgical history (e.g. short gut, Hirschsprung's disease, ileostomy) or complex medical history
  - Signs of shock
  - Presence of pallor, irritability, altered consciousness or activity level
  - Abnormal abdominal examination e.g. focal abdominal tenderness, guarding, significant distension, absent or high-pitched bowel sounds.
- Caregivers not able to provide adequate care at home.
- Social or logistical concerns that may prevent return for evaluation if needed.

* Lower threshold for admitting children with obesity/undernutrition due to possibility of underestimating degree of dehydration.

Other problems associated with diarrhoea

- Fever
  - May be due to another infection or dehydration.
  - Always search for the source of infection if there is fever, especially if it persists after the child is rehydrated.

- Seizures
  - Consider:
    - Febrile convulsion (assess for possible meningitis)
    - Hypoglycaemia
    - Hyper/hyponatraemia

- Lactose intolerance
  - Usually in formula-fed babies less than 6 months old with infectious diarrhoea.
  - Clinical features:
    - Persistent loose/watery stool
    - Abdominal distension
    - Increased flatus
    - Perianal excoriation
  - Making the diagnosis: compatible history; check stool for reducing sugar (sensitivity of the test can be greatly increased by sending the liquid portion of the stool for analysis simply by inverting the diaper).
  - Treatment: If diarrhoea is persistent and watery (over 7-10 days) and there is evidence of lactose intolerance, a lactose free formula (preferably cow's milk based) may be given.
  - Normal formula can usually be reintroduced after 3-4 weeks.

- **Cow's Milk Protein Allergy**

  - A known potentially serious complication following acute gastroenteritis.
  - To be suspected when trial of lactose free formula fails in patients with protracted course of diarrhoea.
  - Children suspected with this condition should be referred to a paediatric gastroenterologist for further assessment.

Nutritional Strategies

- Usually no necessity to withold feeding.
- Feeding fortification can be withheld temporarily until recovery.
- Undiluted vs diluted formula
  - No dilution of formula is needed for children taking milk formula.
- Lactose free formula(cow's milk-based or soy based)
  - Not recommended routinely. Indicated only in children with lactose intolerance.
  - Cow's milk based lactose free formula is preferred.

PHARMACOLOGICAL AGENTS

Antimicrobials

- Antibiotics should not be used routinely.
- They are reliably helpful only in children with bloody diarrhoea, probable shigellosis, and suspected cholera with severe dehydration.

Antidiarrhoeal medications

- Racecadotril and Diosmectite (Smecta®, only in children >2 years old) has been shown to be safe and effective in reducing stool output and duration of diarrhoea. It can be used as an adjunct in the management of AGE. It acts by restoring integrity of damaged intestinal epithelium, and can also bind to selected bacterial pathogens and rotavirus.
- Other antidiarrhoeal agents like kaolin (silicates), loperamide (anti-motility) and diphenoxylate (anti motility) are not recommended.

Antiemetic medication

- Not recommended, potentially harmful.

Probiotics

- Probiotics have been shown to reduce duration of diarrhoea in several randomized controlled trials. However, the effectiveness is very strain an dose specific. Therefore, only probiotic strain or strains with proven efficacy in appropriate doses can be used as an adjunct to standard therapy.

Zinc supplements

- It was found that zinc supplements during an acute episode of diarrhoea may be of benefit in children aged 6 months or more in areas where the prevalence of zinc deficiency or the prevalence of malnutrition is high.
- In Malaysia, it is likely that zinc supplement is not indicated in majority of cases of children with acute diarrhoea.
- Dosage for age 6 months and above 20mg/day, for 10-14 days.

Prebiotics

- Not recommended.

Chapter 11:
Sepsis and Septic Shock

- **Sepsis**
  - is a clinical syndrome characterized by **life-threatening organ dysfunction** caused by a dysregulated host response to infection.

- **Septic shock**
  - is sepsis with **profound circulatory and cellular/metabolic abnormalities** associated with a **higher risk of mortality**.

If a child with suspected or proven infection has ≥2 of these clinical signs:
- Core temperature <36.0°C or >38.5°C (38.0°C if immunocompromised),
- Leucocyte count elevated or depressed for age,
- Inappropriate tachycardia and /or tachypnoea,
- Altered mental state (e.g. irritability /lethargy /floppiness),
- Reduced peripheral perfusion /prolonged capillary refill, he /she should be treated as having sepsis or septic shock, as defined above.

Key Points

- Sepsis and septic shock are medical emergencies hence early recognition by clinician is paramount. It is important to understand that vital signs are dynamic and require frequent assessment.
- Hypotension is a late sign, and shock can be present without hypotension. (see *Chapter 12 Hypotension in Children*)
- Clinical signs can be unreliable in differentiating 'warm' versus 'cold' shock in children.
- Initial management includes securing intravenous /intraosseus access, obtaining blood culture, blood gas and lactate (if available), and early administration of empiric intravenous antibiotics.
- Fluid boluses should NOT be given in sepsis without signs of shock.
- Initial fluid resuscitation for septic shock should be with 10ml/kg boluses of balanced crystalloid, or if unavailable, 0.9% saline. Reassess child post fluid bolus, and consider additional boluses if needed.
- Inotropes should be considered if signs of shock persist after 40ml/kg fluids, or earlier if there are any concerns of fluid intolerance or overload.
- Central access is preferred, however if unavailable, it is safe to use peripheral intravenous line for inotropes and vasopressors during initial phase of resuscitation.
- Ideally blood cultures should be taken before antibiotic administration, but antibiotics must NOT be delayed (give as soon as possible, and within 1 hour of diagnosis in septic shock).

Empirical Antibiotics: Give broad spectrum antibiotics as soon as possible.

- Age < 3months: Cefotaxime 50mg/kg and C-Penicillin 50 000u/kg.
- Age > 3months: Ceftriaxone 50mg/kg or Cefotaxime 50mg/kg.
- Oncology /immunocompromised patients: follow local hospital protocol.
- To tailor /de-escalate antibiotics accordingly once organism identified.
- Identify and control source of infection, e.g. drainage of abscess.

Inotropes/ vasopressors

- 1st line inotropes in septic shock should be adrenaline or noradrenaline.
- Target a Mean Arterial Pressure between the 5th and 50th centile for age.
- Adrenaline may be preferred in children with cold shock (low cardiac output, high systemic vascular resistance), whereas noradrenaline may be chosen in warm shock (high cardiac output, widened pulse pressure, low systemic vascular resistance).
- Echocardiography and haemodynamic monitoring should be used when available, to help guide choice and titration of inotropes.
- Dopamine is no longer recommended, but may be used if adrenaline and noradrenaline are not available.
- Inotrope administration via central or intraosseous route is preferred.
- Avoid concurrent administration of other IV medication when possible.
- For peripheral administration; adrenaline and noradrenaline should be in a more dilute concentration (e.g. 1ml/hr = 0.01mcg/kg/min).
- It is preferable to have invasive arterial BP monitoring.
- Dobutamine or milrinone (inodilators) may be considered in patients with evidence of persistent hypoperfusion and cardiac dysfunction despite other vasoactive agents, to improve coronary and systemic perfusion.
- Vasopressin may be considered in vasodilatory shock refractory to noradrenaline and adrenaline (*please consult Paediatric Intensivist*).

Inotrope	Diluent	Central Dilution	Infusion Rate
Dopamine	D5% / NS	<30kg: 30mg/kg in 50ml, 1ml/hr =10mcg/kg/min >30kg: 7.5mg/kg in 50ml, 1ml/hr=2.5mcg/kg/min	5-20mcg/kg/min
Dobutamine			
Adrenaline	D5% / NS	0.3mg/kg in 50ml, 1ml/hr =0.1mcg/kg/min	0.05-1.5mcg/kg/min
Noradrenaline	D5%	0.3mg/kg in 50ml, 1ml/hr =0.1mcg/kg/min	0.02-2mcg/kg/min

Respiratory support depends on the conscious state of the patient.

- For children with septic shock, ensure airway patency and give oxygen to improve tissue oxygen delivery, aim SpO_2 >94%.
- If normal conscious level: consider NIV (HFNC, CPAP or BIPAP).
- If abnormal conscious level or refractory shock: consider intubation and invasive ventilation, to reduce metabolic demand.
- Intubation: Caution during induction and to consider Ketamine for sedation, if available (as sedation may result in crash of blood pressure).
- Cardiovascular instability is less likely during intubation after appropriate resuscitation.
- Avoid etomidate in children with sepsis (risk of adrenal suppression).
- Consider starting inotropic support early prior to intubation.
- In children with sepsis and Paediatric ARDS, consider using moderately elevated PEEP (up to 10-15 cmH20), controlled tidal volumes (4-8ml/kg) and keep Peak Inspiratory Pressure <32 cmH20 / Plateau Pressure <30 cmH_20. Titrate FiO_2 to achieve SpO_2 >94% (may need to accept lower SpO_2 in severe PARDS).

Further management

- Serial lactate levels may be used as a surrogate for tissue hypoperfusion and to guide resuscitation; aiming for serum lactate <2mmol/L.
- Maintain blood glucose between 4-10mmol/L. Avoid hypoglycaemia.
- Echocardiography may help in assessment of fluid status and cardiac function, and in guiding fluid, inotrope and vasoactive therapy.
- Titrate fluids and inotropes to achieve the therapeutic endpoints below:

System	Features of compromised end organ perfusion	Therapeutic end point
Cardiovascular	Tachycardia Poor perfusion Hypotension	Normal HR and BP for age CRT < 2sec Normal pulse volume Warm extremities
Neurology	Altered sensorium, irritability, confusion, agitation	Normal mental status
Respiratory	Tachypnoea, increase work of breathing, apnoea, cyanosis (late sign)	Improvement of work of breathing, normal SpO_2 and respiratory rate
Renal	Oliguria: urine <0.5ml/kg/hr Anuria (late sign)	Urine output >1ml/kg/hr

Supportive therapy

- Steroids may be considered in refractory septic shock, especially in children with suspected or confirmed adrenal insufficiency.
- For acute adrenocortical insufficiency, give IV hydrocortisone 2-4mg/kg STAT and QID, adjusted to clinical response. When stable, reduce over 4-5 days to oral maintenance dose.
- IV Clindamycin is recommended for toxic shock syndrome (TSS). IV Immunoglobulin may be beneficial, especially in streptococcal TSS.
- Bicarbonate therapy is not recommended for hypoperfusion induced lactic acidaemia with pH ≥ 7.15.
- Consider packed cell transfusion if Hb < 7g/dL. Children with symptomatic anaemia/ haemodynamic instability may need higher Hb targets.
- Routine prophylactic platelet and plasma transfusions in non-bleeding children with platelets > 20 x 10^3/ mm^3 are NOT recommended.
- Continuous Renal Replacement Therapy (CRRT) is recommended for haemodynamically unstable patients with AKI or fluid overload, who are unresponsive to fluid restriction and diuretic therapy.
- Therapeutic plasma exchange may be considered in children with sepsis and thrombocytopenia-associated multiorgan failure (TAMOF).
- Stress ulcer prophylaxis is recommended for patients with high risk for gastrointestinal bleeding (multiorgan dysfunction, prolonged ventilation, treated with steroids /NSAIDs, coagulopathy, persistent shock).
- Early enteral nutrition within 48 hours reduces risk of GI bleeding, and is recommended for patients without contraindications to feeding, on stable or weaning doses of vasoactive agents.
- Routine Deep Vein Thrombosis (DVT) prophylaxis is NOT recommended in critically ill children with sepsis or septic shock, but may be considered in children at high risk of DVT (e.g. obesity, adolescence, cancer).
- Clear communication and family conferences are recommended to update family members on patient's condition and progress, as well as to determine goals and direction of care.

INITIAL MANAGEMENT OF SEPSIS AND SEPTIC SHOCK

TIME

RECOGNITION OF SEPSIS AND SEPTIC SHOCK

0 MINS

Apply oxygen, continuous cardiorespiratory monitoring

<15 MINS

INTRAVENOUS /INTRAOSSEUS ACCESS
Blood investigations (e.g. FBC, **Blood C&S**, Lactate, Blood Sugar. Blood gas, RP, LFT, Coagulation Profile).

<30 MINS

Fluid resuscitation:
10ml/kg isotonic crystalloid IV bolus over 10-15 min
(Hartmann's, Sterofundin or 0.9% Saline).
Reassess after each bolus, stop once perfusion improves or signs of fluid overload (hepatomegaly, lung base crepitations). Max 40-60 ml/kg.
If signs of fluid overload develop, stop boluses and start inotropes.

Antibiotics:
Give **broad spectrum antibiotics as soon as possible**, within 1 hour of diagnosis.
Seek and aggressively control any infection source.

Call for **senior help early**.
Correct hypoglycaemia and electrolyte abnormalities.

<60 MINS

Inotropes/ vasopressor
Consider if persistent shock after 40ml/kg of fluids, or earlier if any signs of fluid intolerance or overload.
First line:
Adrenaline or Noradrenaline (0.05-0.2 mcg/kg/min)

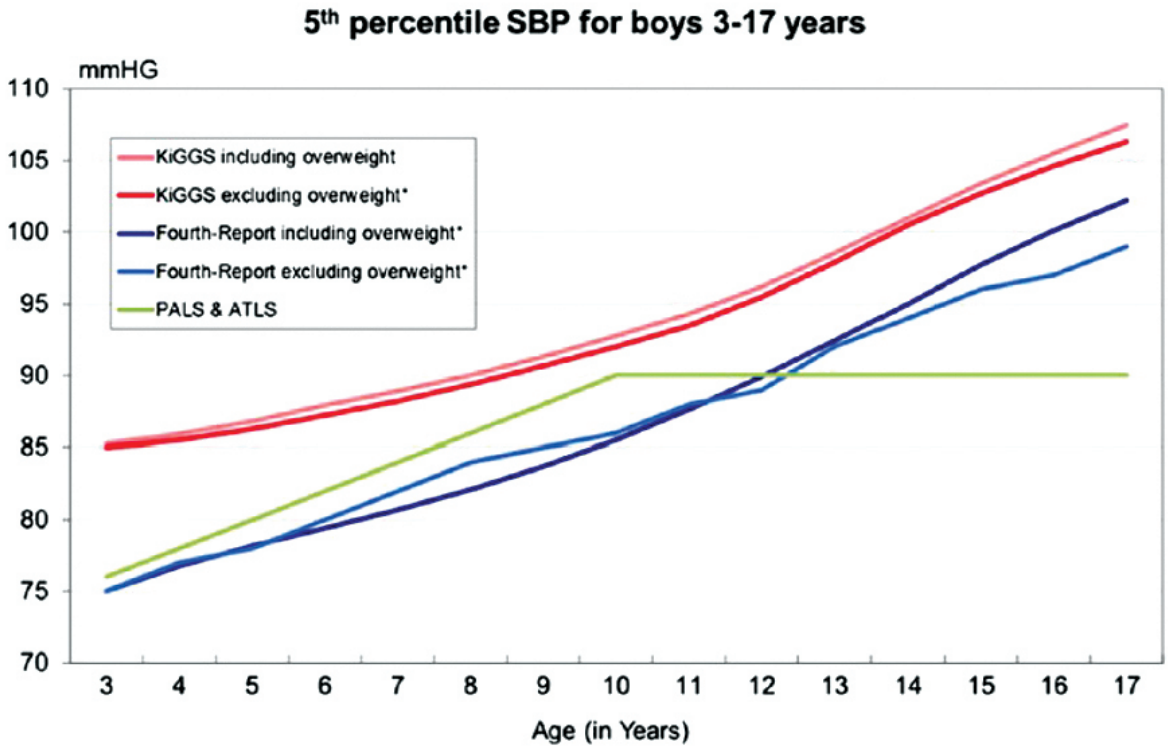
Titrate inotropes upwards according to clinical response and haemodynamic effects, using haemodynamic monitoring when possible (e.g. invasive arterial blood pressure, Echocardiography).
Children requiring >40mls/kg of fluid resuscitation or inotropic /vasopressor support should be managed in a PICU /PHDU setting.

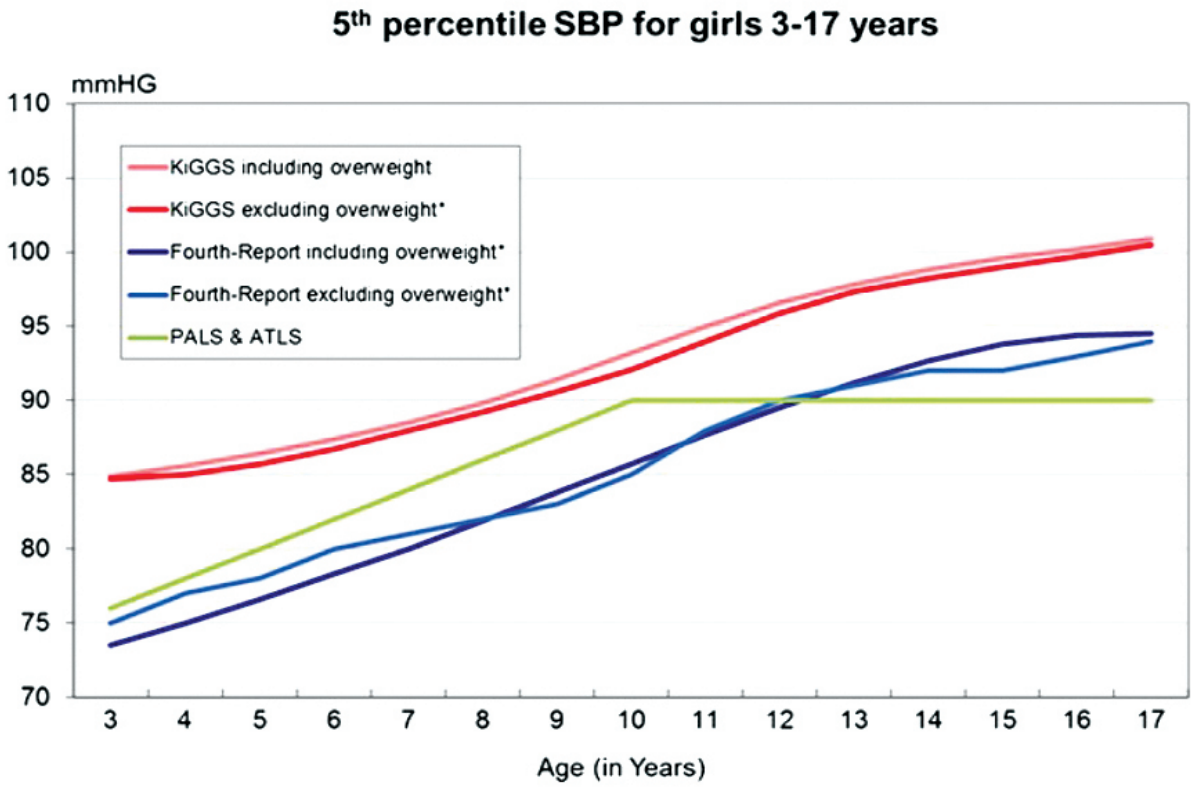
Chapter 12:
Hypotension in Children

- Definition of hypotension varies with population, age, weight and height.
- Multiple paediatric critical care guidelines define hypotension as either:
  - SBP less than 60mmHg in term neonates
  - SBP less than 70mmHg in infants 1-12 months of age
  - less than the 5th percentile for age or
  - less than 90/50 mmHg for children aged ≥10 years
- Clinical formulas for calculation of Systolic Blood Pressure (SBP) and Mean Arterial Pressure (MAP) in normal children above 1 year of age are as follows (all values in mmHg):

Measurement	Measurement Percentile	Height Percentile	Clinical Formula
SBP	5th	50th	2 x age in years + 70
MAP	5th	50th	1.5 x age in years + 40
MAP	50th	50th	1.5 x age in years + 55

- Comparison between normal population-based cut-offs including fifth percentile of systolic blood pressure (P5-SBP) in children and adolescents from the German Health Examination Survey for Children and Adolescents (KiGGS), US population data (Fourth Report), and cut-offs from PALS and ATLS guidelines.





- In conclusion, the lower limits of normal blood pressure in children are variable based on population weight, height and age.
- The PALS cut-off values for hypotension show good agreement with population data for children <12 years of age, but may underestimate hypotension in children above 12 years old.
- Data on reference values for hypotension in critically ill children are extremely limited, and require further study.
- The clinically acceptable ranges defined above should be used in correlation with other markers of end organ perfusion, such as urine output, lactate levels and cerebral function, to determine appropriate blood pressure targets in critically ill children.
- For guidance on proper blood pressure measurement technique please refer to *Chapter 71: Hypertension in children*.
- Please refer to the following chapters for management of specific types of shock:
  - Hypovolemic shock: Chapter 9 (*Paediatric Fluid and Electrolyte Guidelines*)
  - Septic shock: Chapter 11 (*Sepsis and Septic Shock*)
  - Cardiogenic shock: Chapter 41 (*Heart Failure*)
  - Anaphylactic shock: Chapter 116 (*Anaphylaxis*)

Section 6

NEONATOLOGY

Chapter 13:
Principles of Transport of the Sick Newborn

Introduction

The availability of a neonatal transport system and its effective implementation has been shown to reduce the morbidity and mortality of newborns compared to minimal or non-existent transport services.

Mode of transport

The best mode of transfer is "in utero". It is the best and safest option

The advantages and disadvantages of the different modes of transport (road/ air/ riverine) must be considered in each infant.

Pre-transport Stabilization

- Transport is a significant stress and the infant may easily deteriorate during the journey. Hypothermia, hypotension and metabolic acidosis has a significant negative impact on the eventual outcome.
- Procedures are difficult to do during the actual transport. Therefore, pre-transport stabilization is critical.

The principles of initial stabilization of the neonate

(see tables on following pages)

Airway
Breathing
Circulation
Communication
Drugs
Documentation
Environment
Equipment
Fluids – electrolytes, glucose
Gastric decompression

The principles of initial stabilization of the neonate
Airway
Establish a patent airway Evaluate the need for oxygen, frequent suction (Oesophageal atresia) or an artificial airway (potential splinting of diaphragm). Security of the airway – The endotracheal tubes (ETT) must be secured to prevent intra-transport dislodgement Chest X-ray – to check position of the ETT Blood gas analysis

Breathing

Assess the need for intra-transport ventilation. Indications of need for ventilation:

- Requirement of $FiO_2 \geq 60\%$ to maintain adequate oxygenation.
- ABG – $PaCO_2 > 60$mmHg.
- Tachypnoea and expected respiratory fatigue.
- Recurrent apnoeic episodes.
- Expected increased abdominal/bowel distension during air transport.

If there is a possibility that the infant needs mechanical ventilation during the transfer, it is safer to electively intubate and ventilate before transport.

Check the position of the endotracheal tube before setting off.

If in doubt, the receiving surgeon/paediatrician should be consulted.

If manual ventilation is to be performed throughout the journey, possible fatigue and the erratic nature of ventilation must be considered.

Circulation

Assess:

- Heart rate, Urine output,
- Current weight compared to birth weight - are good indicators of hydration status of the newborn infant.

Also note that:

- Minimum urine output should be 1-2 ml/kg /hr.
- The infant can be catheterized or the nappies weighed (1g = 1 ml urine)
- Ensure reliable intravenous access (at least 2 cannulae) before transport.
- If the infant is dehydrated, the infant must be rehydrated before leaving

Communication

Good communication between referring doctor, transport team and neonatologist / paediatric surgeon aids proper pre-transfer stabilization, coordination, timing of transfer, and preparedness of receiving hospital.

- Inform receiving specialist, emergency department of receiving hospital.
- Provide name and telephone contact of referring doctor and hospital
- Provide patient details
- Give a clear history, physical findings, provisional diagnosis, investigations
- Detail current management and status of the infant
- Discuss mode of transport, expected departure time, arrival at referral centre
- Decide on destination of the infant (e.g., A&E, NICU, Ward)

Drugs as required

- Antibiotics – needed in most sick neonates
- Analgesia or Sedation
- Inotropes
- IV fluids
- Pre-draw fluids, medication into syringes if required during the journey

Documentation

- History including antenatal and birth history, physical findings, diagnosis
- Previous and current management
- Previous operative and histopathology notes, if any
- Input/output charts
- Investigation results, X-rays
- Consent – informed and signed by parents for high-risk infants and especially if parents are not accompanying child.
- Parents' contact address, telephone numbers, if not accompanying infant.
- 10 ml of Mother's blood for cross match, if she is not accompanying infant.

Environment

Maintain a **Neutral Thermal Environment**
Optimal temperature for the neonate (axilla) – 36.5 ^{0}C– 37.0 ^{0}C. Prevention of heat loss involves maintaining an optimal ambient temperature as well as covering the exposed surfaces.

- Transport Incubator – would be ideal.
- Wrap limbs of the infant with cotton, metal foil or plastic.
- Do not forget a cotton-lined cap for the head.
- Remove all wet linen as soon as possible.
- Warm intravenous fluids.
- ELBW newborn infants placed in polyethylene bags to prevent heat loss by evaporation.
- **Special Consideration:**

- In **Hypoxic Ischaemic Encephalopathy**, *therapeutic hypothermia* may be indicated. Please discuss with receiving neonatal team prior to transfer.

Equipment *(see Table at end of chapter)*

Check all equipment: completeness and function before leaving hospital.

- Monitors- Cardiorespiratory monitor/ Pulse oximeter for transport.

If unavailable or affected by vibration, a stethoscope and a finger on the pulse and perfusion will be adequate.

- Syringe and/or infusion pumps with adequately charged batteries
- Intubation and ventilation equipment;
- Endotracheal tubes of varying sizes.
- Oxygen tanks – ensure adequacy for the whole journey.
- Suction apparatus, catheters and tubings.

Fluid therapy

Resuscitation Fluid
IV Fluids and Resuscitation fluids as per clinical status

- Monitor for hypoglycemia. Always check glucose level via a bedside glucometer before transport and regularly if indicated.

Gastric decompression

- An orogastric tube is required in most surgical neonates, especially in intestinal obstruction, congenital diaphragmatic hernia or abdominal wall defects.

Immediately before Departure

- Check vital signs and condition of the infant.
- Check and secure all tubes.
- Check the equipment.
- Re-communicate with receiving doctor about current status and expected time of arrival.
- Ensure parents are updated on their infant's condition pre transport and emotional support is offered during and post transport.

Intra-transport Care

- **Transport Team**. Ideally, there should be a specialized neonatal transport team. Otherwise, a neonatal-trained doctor with/without a neonatal trained staff nurse should escort the infant.
- A minimum of 2 escorts will be required for a ventilated/critically ill infant. The team should be familiar with resuscitation and care of a neonate.
- **Safety of the team must be a priority.**
- **Monitoring**. Regular monitoring of vital signs, oxygenation and perfusion of the infant should be performed.
- **Fluids.** Ensure that the intravenous fluids is monitored and infused according to the prescribed volume. Losses are replaced as required.
- **Temperature Regulation**. Check temperature intermittently. Wet clothes should be changed especially in the infant with abdominal wall defects.

Arrival at the Receiving Hospital

- Reassessment of the infant
- Handover to the resident team

Pre-Departure Checklist	
Equipment	
	Transport incubator (if available)
	Airway and intubation equipment are all available and working (ET tubes of appropriate size, laryngoscope, Magill forceps)
	Batteries with spares
	Manual resuscitation (Ambu) bags, masks of appropriate size
	Suction apparatus
	Oxygen cylinders-full and with a spare
	Oxygen tubing
	Nasal oxygen catheters and masks, including high-flow masks
	Infusion pumps
	Intravenous cannulae of various sizes
	Needles of different sizes
	Syringes and extension tubings
	Suture material
	Adhesive tape, scissors
	Gloves, gauze, swabs (alcohol and dry)
	Stethoscope, thermometer
	Nasogastric tube of different sizes
	Pulse oximeter
	Cardiac monitor (preferably with ECG leads), if indicated
	Portable Ventilator, if indicated
Infant Status	
	Airway is secured and patent (do a post-intubation chest X-ray before departure to make sure ET tube is at correct position.)
	Venous access is adequate and patent (at least 2 IV lines) and fluid is flowing well.
	Infant is safely secured in transport incubator or trolley.
	Vital signs are charted.
	Tubes - all drains (if present) are functioning and secured.

Pre-Departure Checklist (*continued*)	
Medications	
	Intravenous fluids 0.9% Normal Saline Hartmann's solution 5% Albumin in Normal Saline 0.18% Saline with 10% Dextrose 0.45% Saline with10% Dextrose 10% Dextrose water
	Inotropes Dopamine Dobutamine Noradrenaline Adrenaline
	Sedative/ Analgesia Morphine Midazolam
	Blood product if indicated
	Others Atropine Sodium bicarbonate Sterile water for injection Normal saline for injection Antibiotics if indicated
Documentation	
	Infant notes, referral letter
	X-rays
	Consent form
	Vital signs chart
	Input, Output charts
	Maternal blood (for infant less than 6 months)

Chapter 14:
General Pointers of Care for Infants in NICU

Definition:

1. **Age:** ≤72 hours state in exact hours of age, >72 hours state in complete days

2. **Gestational age classification:**
   - Early Term: 37 weeks 0 days - 38 weeks 6 days
   - Full Term: 39 weeks 0 days - 40 weeks 6 days
   - Late Term: 41 weeks 0 days - 41 weeks 6 days
   - Post Term: 42 weeks 0 days and beyond

   - Preterm: < 37 completed weeks
   - Late Preterm: 34 weeks 0 days – 36 weeks 6 days
   - Moderately Preterm: 32 weeks 0 days – 33 weeks 6 days
   - Very Preterm: 28 weeks 0 days – 31 weeks 6 days
   - Extremely Preterm: ≤ 27weeks 6 days

3. **Birth Weight classification:**
   - Low Birth Weight (LBW): < 2500 g
   - Very Low Birth Weight (VLBW): < 1500 g
   - Extremely Low Birth Weight (ELBW): < 1000 g
   - Small for Gestational Age: < 10th centile of birth weight for age
   - Appropriate for Gestational age: birth weight between the 10th and 90th centile for age
   - Large for Gestational Age (LGA): > 90th centile of birth weight for age

   Birth weight:
   - Plot the birth weight, length and head circumference on the appropriate growth chart
   - Classify birth weight into either AGA, SGA or LGA.
   - If the infant's weight is <2.5kg - classify into LBW, VLBW or ELBW infant.

   Current weight:
   - Note if there is weight loss (%) or weight gain (gm/kg/day).
   - A weight loss of up to 10% in the first 3–5 days for term and up to 15% in the first week for preterm infant is to be expected.
   - Less weight loss is expected with the use of humidified incubators.

3. **General condition:** note if the infant appears active, responsive to handling, having a good tone or whether the infant appears ill, lethargic and desaturates on handling.

4. **Vital signs:** temperature, heart rate, blood pressure, respiratory rate, oxygen saturation and blood glucose level.
   - Temperature regulation
     - Ensure a neutral thermal environment for all infants (i.e. to maintain a core body temperature at rest between 36.5^{o}C and 37.5^{o}C).
   - Heart rate
     - Tachycardia - rule out infection, pain, anemia, drugs or tachyarrhythmias.
     - Bradycardia - primary cause is hypoxia. Other causes include hypothermia, electrolytes imbalance and bradyarrythmias.
   - Blood pressure *(*the estimated mean blood pressure for an infant is that of the gestational age at birth)*

Table 1: Temperature outside of normothermic range

Infants with axillary temperature of < 36.5°C	Infants with axillary temperature of > 37.5°C
• Consider sepsis • Place infant under a prewarm radiant warmer or incubator *(if infant is already in an incubator - check the incubator temperature and skin temperature probe)* • Increase temperature by up to 0.5 degrees per hour until normothermia achieved • Consider skin to skin • Recheck temperature every 30 minutes until two consecutive readings are normothermic	• Consider sepsis • Assess environment • Consider remove layers of clothing or blankets if overwrapping • If infant is in an incubator or under radiant warmer, decrease the set temperature by 0.5°C every 30 minutes until normothermia achieved • Recheck temperature every 30 minutes until two consecutive readings are ≤37.5°C. ***Consider if this is an indication that the infant is ready to be wean off incubator.*

a. Hypotension
   - o It is often indicating inadequate systemic blood flow
   - o Causes include hypovolemia, abnormal peripheral vasoregulation (eg. sepsis) and myocardial dysfunction.
   - o The first line of treatment is volume administration. If the infant is hypotensive and there has been a history of volume loss at birth or risk of sepsis, administer normal saline bolus (limited to 10-20 ml/kg). *Do not treat hypotension in preterm infants if the infant is otherwise stable, responsive and having a good tone. It is wise to observe first and repeat the measurement after 1 hour. Signs of hypoperfusion (poor peripheral pulses, rapid pulse, poor capillary refilling and cold peripheries) are not very reliable and specific to hypotension in preterm infants. Similar signs may also be a manifestation of hypothermia.

   - If hypotension persists despite volume correction, inotropic agents such as dopamine, dobutamine and adrenaline may be needed. In refractory hypotension, corticosteroids maybe considered.

b. Hypertension
   - o May occur in up to 3% of NICU admission.
   - o It is commonly due to renal or cardiovascular abnormalities such as renal artery stenosis, coarctation of aorta, polycystic kidney disease or thromboembolic renal artery or vein complications secondary to umbilical catheterization.
   - Respiratory rate and oxygen saturation.
     - o Look for sign of respiratory distress (cyanosis, apnoea, tachypnoea, nasal flaring, chest recession or grunting) which may indicate the need for respiratory support.
     - o Tachypnoea while on ventilator may suggest inadequate ventilation.
     - o Oxygen desaturation with minimal or no sign of respiratory distress may be a manifestation of congenital heart disease.
   - Blood glucose level
     a. Hypoglycaemia *(*Refer chapter on Neonatal Hypoglycaemia)*.
     b. Hyperglycaemia.
        - o Hyperglycaemia is less commonly encounter than hypoglycaemia among infants. It is more common in preterm compared to term infants.
        - o Among the causes of hyperglycaemia in infants include physiological stress causing an increase in stress hormones e.g. pain, hypoxia, respiratory distress or sepsis. Others include high glucose infusion rate or medication such as corticosteroids, caffein etc.

5. Ventilation

Table 2: Endotracheal tube size and position

Infant weight	ETT size	ETT position (orotracheal intubation)
< 750g	2.5	5.5 - 6 cm
750 - 1000g	2.5	6 – 6.5 cm
1000g - 2000g	3.0	7 – 7.5 cm
2000g - 3000g	3.5	8 – 8.5 cm
> 3000g	3.5-4.0	9 cm

Note:
- *Ensure ETT position by listening for equal air entry and checking with CXR.*
- *Ensure the tip of the ETT is at T2*
- *The length of ETT beyond the lips should be checked as to be just sufficient for comfortable anchoring and not excessively long to reduce dead space*

Table 3: Initial Conventional Ventilator Settings

Initial setting (in most situations)	
Total Flow	8 - 10 L/min
Peak Inspiratory Pressure (PIP)	20-25 cmH_2O **NB - lower in ELBW infants and those ventilated for non-pulmonary cause i.e. normal lungs)*
Positive End Expiratory Pressure (PEEP)	4 - 5 cmH_20
Inspiratory time	0.3 - 0.35sec **NB - the I:E ratio should not be inverted (i.e., > 1) unless requested specifically by a specialist*
Ventilator rate	40 - 60/min
FiO_2	Based on initial oxygen requirement on manual positive pressure ventilation.
When Volume Guarantee is used (VG)	4 - 6ml/kg **NB - *Minute volume = tidal volume (volume per breath) x rate per minute. Minute volume should be about 0.1 – 0.3L/kg/min*
Note: Management must be individualized	

- Suction of ETT
  - Performed only when needed, as it may be associated with desaturation and bradycardia.
  - During suctioning, the FiO_2 may need to be increased as guided by the SPO_2 monitor during suctioning.
  - Remember to reduce to the level needed to maintain SaO_2 90 - 94%.
- Adjustment of ventilator setting is made according to:
  - Infant's clinical picture
  - Pulse oximetry reading
  - Arterial or capillary blood gaseous
  - Tailor the ventilator settings to the infant's blood gas result.

Table 4: Adjusting the ventilator settings

Adjusting the ventilator setting	
• To ↑ PaO_2	• Increase FiO_2 • Increase PEEP • Increase PIP • Rarely, increase I/E ratio (prolong inspiration)
• To ↓ PaO_2	• Decrease FiO_2 • Decrease PEEP • Decrease PIP • Rarely, increase I/E ratio (prolong inspiration)
• To ↓ $PaCO_2$	• Increase rate • Increase PIP • Increase PEEP in worsening lung disease • Decrease PEEP in recovery phase • Increase set tidal volume in volume targeted ventilation
• To ↑ $PaCO_2$	• Decrease rate • Decrease PIP • Decrease set tidal volume in volume targeted ventilation

- High frequency oscillatory ventilation (HFOV) is often used as a rescue mode of ventilation when conventional ventilation fails, or very high pressures are needed. Rescue use should occur early enough to avoid serious complications of conventional ventilation

Table 5: Arterial blood gases level within the acceptable range

Blood gases	Range
pH	7.25 – 7.40
PaO_2	50 - 70 mmHg (for premature infants) 60 - 80 mmHg (for term infants)
$PaCO_2$	40 - 60 mmHg **NB. the trend is not to 'chase' the $PaCO_2$ by increasing ventilator settings unless there is respiratory acidosis
SaO_2	90 - 94% for preterm infants Above 95% for term infants
Note: Overventilation should be avoided as it may worsen the infant's condition.	

- Sedation and paralysis
  - Current evidence does not support routine use of sedation and paralyzing agents in preterm infants
  - Paralysis has been shown to result in poorer lung function, more dependent oedema and longer duration of ventilation.
  - Use morphine, midazolam or fentanyl infusion as an analgesia and sedation if clinically indicated
- If infant deteriorates on ventilator, consider the following:
  - Worsening of primary condition, e.g., RDS or congenital pneumonia
  - Mechanical problem
    - ETT dislodge or obstructed
    - ETT displaced or too deep
    - Pneumothorax
    - Ventilator tube disconnected
    - Ventilator malfunction
  - Overventilation of the lung
  - Pneumonia such as nosocomial pneumonia
  - PDA or heart failure
  - Persistent pulmonary hypertension
  - Pleural effusion

6. **Skin care:** A vital component of care especially for preterm infants.
   - Avoid direct plastering onto skin and excessive punctures for blood taking and setting of infusion lines.
   - Meticulous attention must be given to avoid extravasation of infusion fluid and medication which can lead to phlebitis, ulceration and septicemia.
   - Group the blood taking together to minimize skin breaks/ breakage of indwelling arterial lines.
   - Observe limbs and buttocks prior to insertion of umbilical lines and at regular intervals afterwards to look for areas of pallor or poor perfusion due to vascular spasm.

7. **Newborn Physical Examination**
   - Dysmorphism
   - Cardiovascular system.
     - Assess for peripheral pulses, more importantly femoral pulses.
     - Look for active precordium
     - Listen for the presence of cardiac murmur.
   - Abdominal examination
     - Review if there is any vomiting or feeding intolerance.
     - Examine for abdominal distension, presence of bowel sound or organomegaly.
     - Examine the genitalia and ensure anal patency.
     - Monitor bowel movement, urine output and for any high gastric aspirates.
   - Central nervous system
     - Examine the anterior fontanelle for the size and tension as well as feel the sutures to look for overriding or separated sutures.
     - Measure head circumference closely (every 1/2 - 1hourly) if indicated e.g. In infants with subaponeurotic haemorrhage.
     - Assess the sensorium, tone, movement, response to procedures (e.g. oral suctioning).
     - Look at the back/ spine for spina bifida.
     - The presence or absence of seizures should also be noted.

- Evidence of infection
  - Is there a possibility of infection? Is the infant on antibiotics?
  - Fungal infection should be considered if the infant is a preterm infant who has been on several courses of broad-spectrum antibiotics and on total parenteral nutrition.
  - Consider discontinuing antibiotics if the blood culture is negative and the infant improved "too quickly" after starting antibiotics, probably responding to other measures such as dehydration or inadequate ventilatory support.

8. Nutrition, Fluid and Electrolytes

- Intravenous fluid
  - Generally, Dextrose 10% on the first day and sodium and potassium (QSD10% + 1/2gm KCL) is added on the second/third day of life.
  - Total fluid requirement and rate of increment

a. Empiric fluid therapy for **term** infants:
0-24 hours: 60 ml/kg/day
24-48 hours: 90ml/kg/day
48-72 hours: 120ml/kg/day
> 72 hours : 150 ml/kg/day

b. Empiric fluid therapy for **preterm** infants:
0-24 hours : 60 ml/kg/day
24-48 hours : 80ml/kg/day
48-72 hours : 100ml/kg/day
Day 4 : 120 ml/kg/day
Day 5 : 140ml/kg/day
*More increment may be needed if there is evidence of dehydration i.e., excessive weight loss and/or hypernatremia >145mmol/L

- Total Parenteral Nutrition (TPN). Refer to chapter on Parenteral Nutrition for the Newborns
- Enteral feeding. Refer to chapter on Enteral Feeding in Preterm and High-risk Infants

9. Monitoring

- Weight (at least 2-3 times a week)
- Input and output balance (ensure urine output is >1ml/kg/hr after the first day of life)
- Glucose level (Blood glucose)
- BUSE - correct imbalances after considering the underlying cause.

**Fluid and electrolyte therapy will be influenced by the infant's underlying illness and complications and adjustments will have to be done based on this condition.*

Chapter 15:
The Preterm Infant

Early and Late Complications
Hypothermia
Respiratory distress syndrome (RDS), Apnoea
Hypotension, Patent ductus arteriosus (PDA)
Intraventricular haemorrhage, Periventricular leukomalacia (PVL)
Gastrointestinal: Paralytic ileus, Necrotizing enterocolitis (NEC)
Hypoglycaemia, Hyperglycaemia
Neonatal Jaundice
Hypoprothrombinaemia
Fluid and Electrolyte disorders: Hyponatraemia, hyperkalemia, metabolic acidosis
Septicaemia
Anaemia
Osteopaenia of prematurity
Retinopathy of prematurity (ROP)
Chronic lung disease
Neuro-developmental disability
Psychosocial problems

Management

Prenatal Care

- Before delivery, the resuscitation team should have a pre-delivery briefing including antenatal history and intrapartum history including maternal GBS status and intrapartum antibiotics, antenatal steroid and antenatal magnesium sulphate
- Antenatal counselling can be done for selected cases such as those at borderline viability or those with anticipated guarded outcome.
- The resuscitaire should be pre-warmed and ideally the temperature in the delivery room should be 26^{o}C

Delivery Room Stabilisation

1. Adequate Resuscitation
   - Resuscitation of the preterm is in accordance with the most recent Malaysian Neonatal Resuscitation Program (MyNRP).

2. Thermoregulation
   - Hypothermia can cause hypoxia, hypoglycaemia, respiratory and metabolic acidosis, cardiovascular instability and neurologic compromise.
   - For infants < 32 weeks' gestation, polyethylene plastic wrap or bag should be used to prevent hypothermia (without drying the infant)
   - Target admission temperature 36.5-37.5°C

3. Delayed cord clamping (DCC)
   - Unless contraindicated, DCC for at least 30-60 s should be encouraged

4. Respiratory
   - In spontaneously breathing preterm infants, use early continuous positive airway pressure (CPAP)
   - If the infant is apneic, inadequate respiration or heart rate < 100bpm, start PPV

Transfer from Delivery Room to Neonatal Unit (NNU)

- Once infant is stabilized, use a pre-warmed transport incubator (if available).
- Continue CPAP or PPV during transfer, if needed, with adequate monitoring.

Admission to NNU

- Ensure thermoneutral temperature for infant. An incubator or radiant warmer is necessary for more premature and ill infants.

Table 1: Criteria of infants who require provision of thermoregulation assistance

Criteria of infants	Recommended device of thermoregulation assistance
• Infants < 30 weeks of gestation regardless of weight.	Incubator with ambient humidity **To start as soon as possible to prevent transepidermal water loss*
• Infants >30 to ≤32 weeks of gestation • Infant with birth weight of < 1800gm	Incubator
• Term infants who require cardiopulmonary support • Term infant with temperature instability • Infants who require surgical intervention	Open care radiant warmer

Incubator Humidity
All infants < 30 weeks' gestation should be nursed in an incubator with humidity

Table 2: Suggested Guideline for Incubator Humidity for Preterm Infants

	Infants ≤ 27 weeks' gestation	28- < 30weeks' gestation
Admission	Commence humidity of at least 80%.	Commence humidity at 70-80%
Week One	Wean gradually to 70-80%	If temperature and fluid balance stable after 72 hours, begin weaning by 5% each day
Week Two	If temperature and fluid balance stable on day 8, begin weaning by 5% each day	Discontinue when 40% is achieved
Week Three -Four	Discontinue incubator humidity when 40% is achieved	
Note: the duration and percentage of humidity may vary and depends on the infant's gestational age, serum sodium levels, fluid balance and skin condition. Weaning humidity should only continue when clinically indicated as appropriate		
After successful staged reductions, the infant's skin should have keratinised fully at the end of this period		

- Maintain SpO_2 target between 90-95% in the VLBWs
- Weight, head circumference (OFC), length measurements should be done on admission. Assess the gestational age with New Ballard score when stable
- Monitor vital signs

Immediate Care for Symptomatic infants

- Obtain Venous access (via UVC/PICC or peripheral vein) and Arterial access (via UAC or peripheral arterial line)
- Investigations are necessary as indicated and include:
  - Blood gases.
  - Blood glucose
  - Full blood count with differential WBC and IT ratio (if available)
  - Blood culture.
  - Chest X-ray (if respiratory signs and symptoms are present)
- Start on 10% dextrose drip or Parenteral Nutrition as soon as possible (refer to PN chapter)

Guidelines for the Use of Surfactant

Infant selection and thresholds for treatment should be individualized and tailored to local unit practices.

A. Clinical indications

Surfactant replacement therapy should be considered in the following:

- Preterm infants with clinical and radiographic evidence of RDS or on respiratory support with oxygen requirement > 0.3-0.4 to maintain SpO_2 target.

B. Timing of therapy

- Prophylactic surfactant is no longer recommended
- For infants with worsening RDS, early rescue surfactant (within the first 2 hours of age) should be provided.
- Intubated preterm infants with RDS who are to be transported to a different neonatal unit should be given a dose a surfactant prior to transfer

C. Repeat Doses

- A repeat dose can be given 6 hours after the first dose if there is evidence of ongoing moderate to severe RDS and persistent oxygen requirements, FiO_2 > 0.3-0.4

D. Methods of administration

- Endotracheal administration after intubation
- Intubation, surfactant administration and Extubation (INSURE)
- Surfactant administration via a thin catheter
  - Less invasive surfactant administration (LISA) method – a small catheter (usually a feeding tube) is placed in the trachea with a Magill forceps under direct laryngoscopy.
  - Minimally Invasive Surfactant Technique (MIST) method – a more rigid adult vascular catheter (e.g., angiocath 16G, length 13cm) is placed in the trachea (hence avoiding the use of Magill forceps

E. Potential complications and management

- During administration, transient bradycardia, oxygen desaturation and ETT blockage can occur – temporarily stop surfactant administration, provide ventilation or oxygen as necessary, and resume administration after patient is stable.
- ETT obstruction – if suspected, observe saturations and chest wall movement. Re-intubate if obstruction is not alleviated and ventilation is impaired.
- Pneumothorax – can occur due to sudden changes in pulmonary compliance if ventilation settings are not appropriately changed.
- Pulmonary hemorrhage – ensure adequate PEEP

F. Special considerations

- Storage and handling: Surfactant is stored in a refrigerator at +2 to +8^{0}C. Surfactant should be slowly warmed to room temperature before administration. Gently turn vial upside-down to obtain a uniform suspension. DO NOT SHAKE.
- Unopened, unused vials of surfactant that have been warmed to room temperature can be returned to the refrigerator within 24 hours for future use

Assess the need to start antibiotics (refer to Neonatal Sepsis chapter for preterm infants ≥35 weeks)

o For those infants< 35 weeks' gestation consider clinical condition of the infant and risk benefit balance

Apnoea of prematurity

o Common in infants born < 34 weeks' gestation.
o Consider starting caffeine or aminophylline in those less than 32 weeks or with apnoea of prematurity

Immunisation:

- Hep B vaccine: Refer to Management of Perinatal Hepatitis B Virus (HBV) transmission chapter
- BCG vaccine is given on discharge.
- Routine immunisation should generally follow the schedule according to chronological age regardless of birth weight and gestational age (except for Hepatitis B vaccine) rather than corrected age
- Defer immunisation in the presence of acute illnesses.

Supplements:

- At birth: intramuscular (IM) Vitamin K (0.5 mg for BW<1.5 kg; 1 mg for BW ≥ 1.5 kg) to prevent haemorrhagic disease of newborn.
- Refer to Enteral Feeding in the Neonates Chapter for other supplements.

Developmental Care

- Developmental care and Kangaroo care should be encouraged as evidence have shown better growth and neurodevelopmental outcome as well as to increase bonding with the parents.
- This can be done when the infant is stable

Screening

- Cranial Ultrasound. Suggested recommendation for screening for preterm infants ≤ 32 weeks:
  - First screening: Within first week of life
  - Second screening: 10-14 days of life
  - Third screening: 28 -30 days of life
  - Subsequent screening: Around 36 weeks or at discharge or monthly or more often if clinically indicated
- Screening for Retinopathy of Prematurity (ROP)
  *Refer to the latest Malaysian CPG guidelines for ROP screening.
- Thyroid function test
  Refer Consensus *Guidelines on Screening, Diagnosis and Management of Congenital Hypothyroidism in Malaysia*
- Hearing assessment.
  Refer to the *Guidelines for Neonatal Hearing Screening (MOH) 2022* to be done before discharge

Discharge Criteria

The infants are discharged once they are well, showing good weight gain, established oral feeding and gestational age of at least 35 weeks.

Discharge planning

1. To primary health care for follow up and immunization should be as per the Malaysian immunization schedule.
2. Palivizumab (RSV immunoglobulin) is advised for high-risk infant to prevent severe RSV disease whenever possible.
3. Monitor for metabolic bone disease of prematurity and to treat accordingly.
4. Late preterm infants with no associated complications can be followed up in the health clinics
5. High -risk preterm infants need to be followed up for growth and neurodevelopmental outcome
6. Parental education including basic life support. (BLS)

Chapter 16:
Enteral Feeding in Preterm and High-risk Infants

Introduction

- The goal of enteral nutrition is to meet nutrient needs and to achieve as near to normal weight gain and growth as possible.
- Enteral feeding should be introduced as soon as possible. This means starting in the labour room itself for the well infant.
- Mother's own milk (MOM) is the milk of choice for all newborn infants.
- Normal caloric requirements in:
  - Term infants: 110 kcal/kg/day
  - Preterm infants: 115 – 140 kcal/kg/day

(Preterm infants who have had a more eventful course need up to 160 kcal/kg/day to have adequate weight gain)

Types of milk for Newborn feeding

- Mother's Own Milk (MOM)
- Donor Human Milk (DHM)
- Term infant formula
- Term/ Preterm infant formula

Mother's Own Milk (MOM)

MOM is the first choice as studies have shown that breast fed infants have lower risk for necrotizing enterocolitis (NEC), lower rates of late onset sepsis and had better neurodevelopment outcomes.
However, MOM alone does not meet the nutritional requirements of the very preterm infant as it has:

- Insufficient calories and protein for optimal early growth.
- Insufficient sodium to compensate for high renal sodium losses.
- Insufficient calcium and phosphate - predisposes to osteopenia of prematurity.
- Low in vitamins and iron relative to the needs of a preterm infant.

Human Milk Fortifier (HMF)

- It is recommended to add HMF to MOM in infants <32 weeks or <1500 grams.
- HMF should be added to MOM when enteral feeding is at 50 - 100 ml/kg/day.
  *Check the dilution as it may vary between different brands.

Donor Human Milk

When MOM is not available, DHM is preferred over infant formula.
DHM is associated with reduced NEC rates compared with infant formula.
DHM should be pasteurized.
As with MOM, DHM should be fortified with HMF to meet the nutritional requirements and achieve better growth.

Infant Formula

Infant formula should only be used when MOM and DHM are not available.
There are 2 types of infant formula: Preterm formula and term formula.
Preterm formula maybe considered for very preterm (< 32 weeks' gestation) or < 1500 grams infants

When to initiate feeding?

- As soon as possible for the well term infants and hemodynamically stable preterm infants

Minimal enteral nutrition (MEN)

MEN or trophic feeding is recommended in preterm and high-risk infants.
The principle is to commence very low volume enteral feeds (< 25 ml/kg/day) on day 1 - 3 of life.

- MOM or DHM is the preferred type of milk.
- For extremely low birth weight (ELBW), or growth-restricted infants, if by 24–48 h, MOM or DHM is not available, to consider formula milk.

Rate of advancement?

- Generally, the rate of advancement is ~20 to 30 ml/kg/day.
- Implementation of standardized feeding protocol in each NICU has been shown to enhance nutrient intakes, improve growth and prevent preterm morbidities.
- Routine measurement of gastric residual volume is not recommended in the absence of other signs of feeding intolerance.
- IUGR babies with reversed end-diastolic flow on antenatal Doppler should advance slowly and preferentially start with MOM or DHM.
- Target feeding volume :
  Aim to reach full enteral feeding (150–180mL/kg/day)
  a. ~ 2 weeks in babies weighing <1000 g at birth and
  b. ~ 1 week in babies weighing 1000–1500 g
- Target weight gain rates should be around 15-25g/kg/day.

Strategies of administering enteral feeding

Nasogastric vs Orogastric Route

- Both methods can be used as there is no preference between these two methods

Continuous vs. intermittent bolus feeding.

- There is inadequate evidence to determine whether bolus or continuous feeding is superior in clinically stable preterm infants.
- Intermittent bolus feeding is the preferred method.
- Nutrients (fat and calcium) could be lost when feeding by continuous feeding.
- Continuous feeding may be useful in infants with underlying gastrointestinal disease.

2 hourly versus 3 hourly feeding

- There are no clinically important differences

Cup feeding

- If the infant can suckle and mother is not with the infant, cup feeding is preferable to bottle feeding to prevent nipple confusion.

When to initiate oral feeding

- Coordination of sucking and swallowing usually develops around 32 -34 weeks postmenstrual age
- Oral feeding should be initiated when the infant show signs of readiness which typically occurs between 32 – 34 weeks postmenstrual age.
- In preterm infants feeding difficulties can be due to:
  a. ineffective suck and swallow mechanism
  b. poor airway-digestive transit along the upper gastrointestinal tract (GIT)
- Anticipate feeding difficulties in preterm infants with risks of suppressed respiration and delayed nipple feeding.

When to stop HMF or Preterm Formula?

- Stop adding HMF to MOM or DHM when infants are breastfeeding on demand and have achieved good growth
- Consider stopping preterm formula when infants are 35-37 weeks postmenstrual age and have achieved good growth

Vitamin and mineral supplementation

- *Vitamins:* a premature infant's daily breast milk/ breast milk substitute intake will not adequately supply the daily Vitamin D requirement.
- Multivitamin drops providing Vitamin D 400 IU per day can be given after day 14 of life when reaching full feeding.
- The supplement is continued for 3-4 months post discharge.
- *Iron:* Premature infants have reduced intra-uterine iron stores and can become rapidly depleted of iron when active erythropoiesis resumes.
- Therefore, infants of birth weight < 2000g should receive iron supplements.
- Iron intake is given at a dose of 2-3 mg/kg elemental iron per day.
- Start on day 14, to continue until 3-4 months post discharge or until review.
  * Infants who have received multiple blood transfusions may not require as much iron supplementation

COMPOSITION OF VARIOUS MILK

Component		Cow's milk	Standard formula	Mature breastmilk	Preterm formula	Preterm breastmilk
Carbohydrate	g/100ml	4.6	7.5	7.4	8.6	6.4
Fat	g/100ml	3.9	3.6	4.2	4.4	3.1
Protein	g/100ml	3.4	1.5	1.1	2.0	2.7
Casein : Lactalbumin ratio		4:1	2:3	2:3	2:3	2.3
Calories	KCal/100ml	67	67	70	80	74
Sodium	mmol/l	23	6.4	6.4	14	17
Potassium	mmol/l	40	14	15	19	17
Calcium	mg%	124	46	35	77	29
Phosphate	mg%	98	33	15	41	13
Iron	mg%	0.05	0.8	0.08	0.67	

Chapter 17:
Parenteral Nutrition for Newborns

Parenteral nutrition should be considered as a short-term bridge to provide nutritional support until full enteral nutrition can be provided.

Indications for starting neonatal parenteral nutrition

1. Preterm infants born before 31+0 weeks
2. Preterm infants born at or after 31+0 weeks if sufficient progress is not made with enteral feeding in the first 72 hours after birth.
3. Preterm and term infants who are unlikely to establish sufficient enteral feeding, e.g., in infants with:
   - a congenital gut disorder
   - a critical illness such as sepsis including NEC.

CONSTITUENTS OF NEONATAL PARENTERAL NUTRITION

Overview of energy and macronutrient requirements based on major recommendations

		Day of life (DOL) 1	Advancing PN	Goal PN
Energy (kcal/kg/d)				
ESPGHAN	Term	45-50	-	75-85
	Preterm	45-55	-	90-120
NICE	Term and Preterm	40-60	Increase over 4 days	75-120
		Non nitrogen energy provided by 60-75% carbohydrate, 25-40% fat 20-20kcal non nitrogen energy per gram of amino acid		
Carbohydrate (mg/kg/min)				
ESPGHAN	Term	2.5-5	Advance over 2-3 days	5-10 (max 10)
	Preterm	4-8		8-10 (max 12)
NICE	Term	4- 6.25	Increase over 4 days	6.25-11.1
	Preterm			
Protein (g/kg/d)				
ESPGHAN	Term	1.5	-	1.5-3
	Preterm	1.5	-	2.5-3.5
NICE	Term	1-2	Increase over 4 days	1.5-3
	Preterm	1.5-2		3-4
Fat (g/kg/d)				
ESPGHAN	Term	Start no later than D2 OL > 2 is not recommended on D1 OL	-	
	Preterm		-	4 (max)
NICE	Term	1-2	Increments of 0.5-1	3-4
	Preterm			
		Infants with parenteral nutrition associated liver disease, consider giving a composite lipid emulsion rather than pure soy lipid emulsion		

Adapted from Groh-Wargo, Barr SM. Parenteral Nutrition. Clin Perinatol. 2022 Jun;49(2):355-379

Calcium and Phosphate

	Preterm and Term	Calcium (mmol/kg/day)	Phosphate (mmol/kg/day)
NICE	First 48 hours after birth	0.8-1.0	1.0-2.0
	After 48 hours after birth	1.5-2.0	2.0
	Ratio of calcium to phosphate Preterm : 0.75:1 Term : 1:1		

Vitamins

- Add daily intravenous fat-soluble and water-soluble vitamins as soon as possible after starting parenteral nutrition, to maintain standard daily requirements.
- Add fat-soluble and water-soluble vitamins in the intravenous lipid emulsion to improve their stability.

Trace elements

- Give daily intravenous trace elements as soon as possible after starting parenteral nutrition.
- Standard formulations of TPN contain zinc, copper, selenium, manganese, fluoride and iodide.

Administration of neonatal parenteral nutrition

A. Venous access

- Use a central venous catheter to give neonatal parenteral nutrition.
- Only consider using peripheral venous access to give neonatal parenteral nutrition if:
  - special formulation for peripheral PN is available and it would avoid a delay in starting parenteral nutrition
  - short-term use of peripheral venous access is anticipated, for example, less than 3 days.
  - it would avoid interruptions in giving parenteral nutrition
  - central venous access is impractical

B. Shielding PN from light

- Light protection is recommended for both PN bags and administration sets

Complications of Parenteral Nutrition

1. Hyperglycemia
2. Hypertriglyceridemia
3. Metabolic bone disease
4. Liver toxicity: Parenteral Nutrition Associated Liver Disease (PNALD)and Intestinal Failure Associated Liver Disease (IFALD)
5. Aluminium toxicity
6. Related to composition of PN solution (calcium/phosphate precipitation)
7. Catheter - related complications i.e. sepsis, extravasation

Suggested Monitoring for Infants on Parenteral Nutrition

Monitoring

Test	First 3-7 days	Thereafter
Electrolytes, BUN, HCO_3, Creatinine	Daily or as needed	Once or twice a week
Ca, PO_4, Mg, bilirubin, albumin	As needed	Once a week
Triglyceride	24 hours after each increase	Once a week or when sick
Blood glucose	4-6 hourly	Once or twice a day
Liver function test including alkaline phosphatase	As needed	Once weekly or fortnightly

Australasian Neonatal Parenteral Nutrition Consensus Group 2017

Stopping Neonatal Parenteral Nutrition

For preterm infants, consider stopping PN once tolerating enteral feeds 100 -120ml/kg/day

Chapter 18:
Neonatal Hypoglycemia

Introduction

- There is no single plasma glucose concentration or duration of hypoglycemia that can predict permanent neurologic injury in high-risk infants.
- Neonatal blood glucose concentrations are usually lower in the first 48 hours of life during normal neonatal transition from intrauterine to extrauterine life.

Measurement of blood glucose

- Heel stick blood glucose (whole blood) – measured with glucometer (at point of care)
- Plasma blood glucose – performed in the laboratory (RBS).

Plasma glucose values tend to be 10%-18% higher than whole blood values because of the higher water content of plasma.

Note: Blood glucose levels (BGL) can be measured using either method.

Target Blood Glucose Level (BGL)

Clinical hypoglycemia is defined as a plasma glucose concentration low enough to cause symptoms and/or signs of impaired brain function.

- Target BGL for infants remains controversial but is commonly accepted as BGL ≥ 2.6 mmol/L in a term or preterm infant < 48 hours old
- In term infants < 4 hours old, BGL > 1.5 mmol/L is acceptable if the infant is well, asymptomatic and tolerating feeds and repeat glucose is ≥ 2.6 mmol/L.
- BGL < 1.5 mmol/L is considered severe, regardless of age
- For infants > 48 hours old, it is recommended to keep BGL ≥ 3.3 mmol/L to be above the threshold for neuroglycopenic symptoms
- For infants with a persistent hypoglycemia or suspected of a congenital hypoglycemia disorder, to keep BGL ≥ 3.9 mmol/L.

Screening

BGL should only be measured in infants with clinical signs of hypoglycemia, or who are known to be at risk of hypoglycemia.

Infants who are at increased risk of hypoglycemia and need glucose screening are:

- Large for gestational age (weight >90th percentile)
- Small for gestational age (weight <10th percentile) or intrauterine growth restriction (IUGR)
- Preterm infants < 37 weeks gestation
- Post-mature infants > 42 weeks' gestation
- Infant of diabetic mother
- Perinatal stress: Birth asphyxia, maternal pre-eclampsia/ eclampsia, meconium aspiration syndrome, erythroblastosis fetalis, hypothermia, polycythemia
- Maternal use of beta-blocker
- Family history of a genetic form of hypoglycemia
- Congenital syndromes (e.g., Beckwith-Wiedemann), abnormal physical features (e.g. midline facial malformations, microphallus)

Clinical Signs of Hypoglycemia

- Jitteriness
- Cyanosis
- Seizures
- Apnoeic episodes
- Tachypnoea
- Weak or high-pitched cry
- Floppiness or lethargy
- Poor feeding
- Irritability

Note: Hypoglycemia may be asymptomatic therefore monitoring is important for all high-risk cases

MANAGEMENT

Management Of Infants at Risk for Hypoglycaemia

- Well infants who are at risk:
  - Immediate skin to skin with mother after birth and breastfeeding must be initiated within 1 hour of birth. If necessary, supplement feeding until breastfeeding is established.
  - Initial BGL should be done 30 minutes after completion of the first feed.
  - Subsequent glucose monitoring must be done pre-feeds 3-6 hourly.

- Sick infants or unable to feed:
  - Check BGL on admission and set up IV Dextrose 10% drip according to normal fluid requirement.

Rapid Stepwise Approach to Hypoglycemia

1. **BGL < 1.5 mmol/L or < 2.6 mmol/L with symptoms:**
   - Assess and document any symptoms.
   - Need urgent treatment.
   - Establish vascular access and confirm BGL in blood gas machine or laboratory (RBS).
   - Give IV Dextrose 10% 2-3 ml/kg bolus.
   - Followed by IV Dextrose 10% drip at 60-90 ml/kg/day (for day 1 of life)
   - If the infant is already on IV Dextrose 10% drip, consider increasing the rate or the glucose infusion rate (GIR) (to achieve 6-8 mg/kg/min of glucose delivery)
   - Repeat BGL 30 minutes after dextrose bolus.

2. **BGL 1.5 - 2.5 mmol/L (within the first 4 hours of life) and asymptomatic**
   - Supplement feed with expressed breast milk (EBM) or formula milk according to daily fluid requirement
   - Repeat BGL 30 minutes after completed feeding:
     - If BGL < 1.5 mmol/L: Refer to (1)
     - If BGL 1.5 - 2.5 mmol/L: Consider another supplement feed and repeat BGL after 30 minutes.
     - If BGL is below target level, to re-check BGL every 30 minutes.
     - If BGL not improving after 2 feeds, to consider starting IV Dextrose 10% infusion
     - Once BGL is above target level for 2 subsequent feeding, to monitor 3-6 hourly pre-feed
     - Stop monitoring once BGL stable for at least 24 hours
     - Consider using neonatal oral 40% Dextrose gel (if available) followed by oral feeding

3. Management of persistent hypoglycemia

- If hypoglycemia persists despite IV Dextrose 10% infusion, to check that IV infusion of dextrose is adequate and running well.
- Increase volume by 20-30 ml/kg/day and/ or increase dextrose concentration to 12.5% or 15%.
- IV Dextrose concentrations of more than 12.5% must be infused through a central line.
- If hypoglycemia still persists despite GIR > 8-10 mg/kg/min, consider Glucagon 0.5-1 mg stat (IV, IM or subcutaneous) then 5-10 mcg/kg/hour as maintenance
  - Glucagon is only useful where there are sufficient glycogen stores such as in infant of diabetic mother.
  - In high doses (>20mcg/kg/hour), glucagon can cause paradoxical insulin secretion and rebound hypoglycemia and should be avoided.
- If hypoglycemia occurs in neonates with poor glycogen stores as in IUGR and SGA infants, or in adrenal insufficiency, increase the GIR to 12mg/kg/min. If hypoglycaemia persists despite a glucose infusion rate (GIR) of > 12mg/kg/min, a short course (1-2 days) of IV hydrocortisone 1-2 mg/kg / dose bd or tds may be considered.
  - Prolonged hydrocortisone is only beneficial in those with adrenal insufficiency.

- A subset of IUGR/ SGA infants may have hyperinsulinaemic hypoglycemia (HH) with sufficient glycogen stores.
  To determine glucagon responsiveness, a glucagon challenge test should be done – IM/IV/ Subcutaneous 0.5mg or 1mg can be given, and if there is a rise of 1.7mmol/L after 10-15 mins, this implies there are sufficient glycogen stores and glucagon infusion can be continued.

- Hypoglycaemia persisting > 48 hours of life require further **investigations***:
  - Obtain "critical" sampling when BGL < 2.6 mmol/L after 48 hours of life
  - Plasma glucose (RBS)
  - Blood Gas
  - Serum Lactate
  - Serum Ammonia
  - Serum Ketones (beta-hydroxybutyrate)
  - Free fatty acid levels
  - Insulin +/- C-peptide
  - Cortisol
  - Growth hormone
  - Plasma amino acids, acylcarnitine and urine for organic acids

*Take blood investigations before an increase in rate of dextrose infusion when hypoglycemia persists despite dextrose infusion.

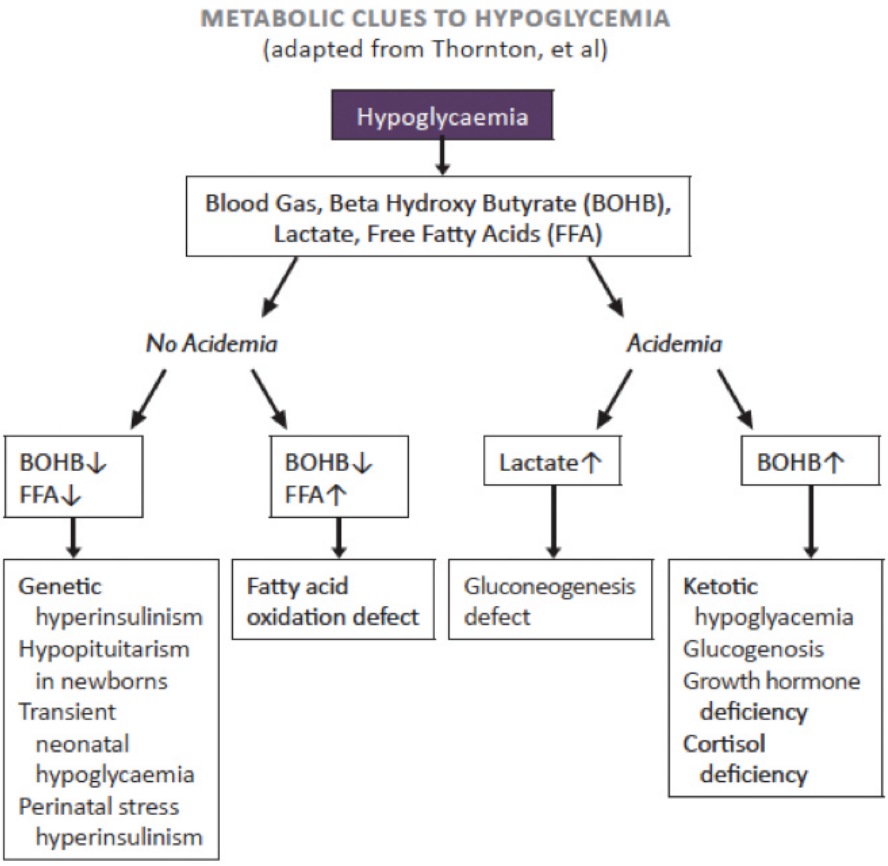
4. Management of recurrent or resistant hypoglycemia

- Consider this if failure to maintain normal blood sugar levels despite a GIR of 15 mg/kg/min,

OR

- When stabilization is not achieved by 7 days of life.
- High levels of glucose infusion may be needed in the infant to achieve euglycemia.
- Consult paediatric endocrinologist.
- Differential diagnoses:
  - Hyperinsulinaemic states: Infant of diabetic mother, perinatal stress, intra-uterine growth restriction, congenital syndromes affecting growth (e.g. Beckwith-Wiedemann syndrome, Sotos syndrome) and Primary genetic hyperinsulinism.
  - Metabolic disorders: Galactosaemia, Glycogen storage disease, Gluconeogenesis defect, Fatty acid oxidation defect and Mitochondrial disorders
  - Endocrine disorders: Hypopituitarism, Adrenal insufficiency (e.g. Congenital Adrenal Hyperplasia, ACTH deficiency) and Growth hormone deficiency

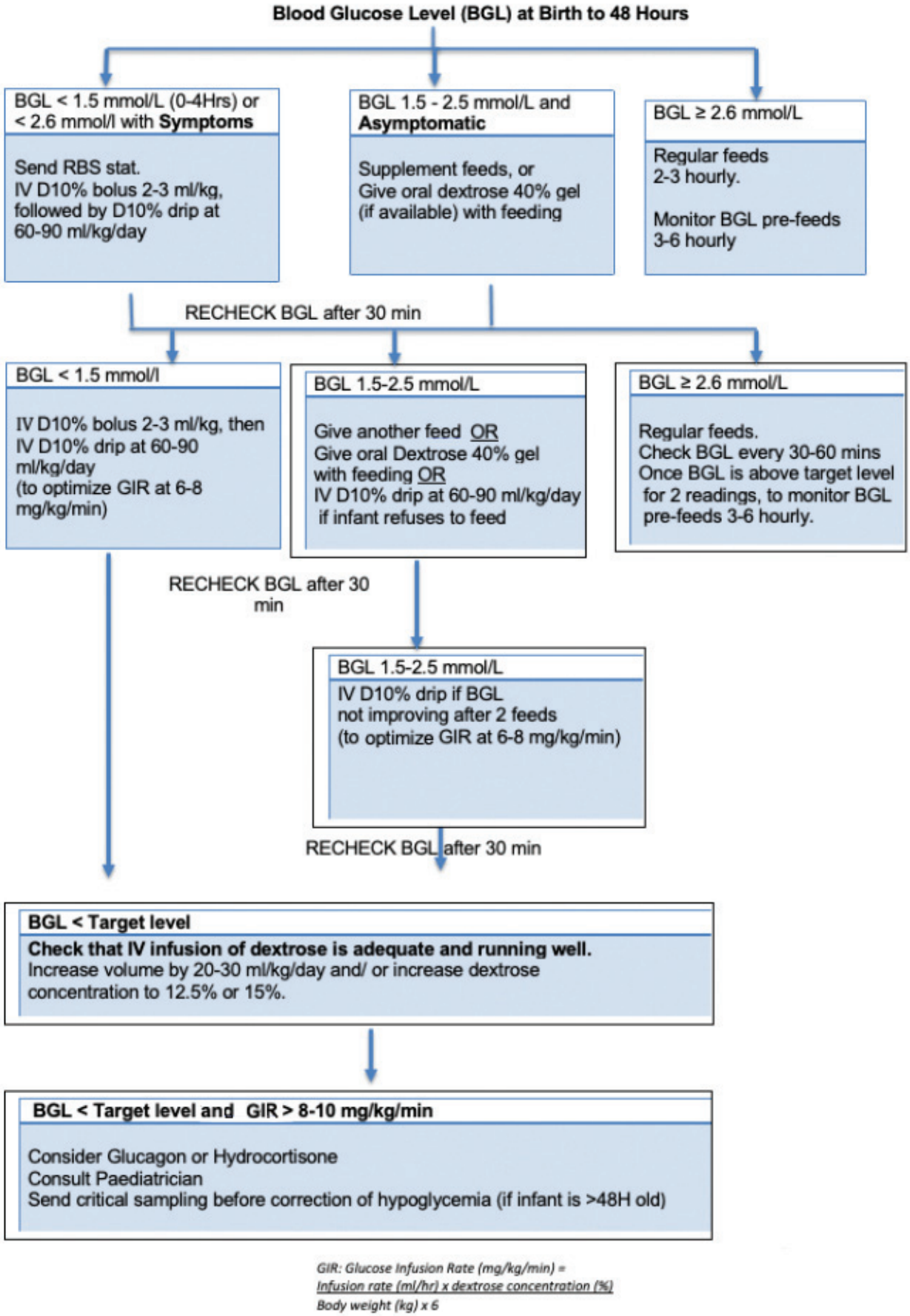
- **Medical treatment**
  - PO Diazoxide 5-20 mg/kg/day in three divided doses. It reduces insulin secretion, therefore useful in hyperinsulinemia. Can be used in SGA infants with hyperinsulinaemic hypoglycemia
  - PO Chlorothiazide 5-10 mg/kg/day divided into two doses, or Hydrochlorothiazide 1-2 mg/kg/dose bd. Use in conjunction with Diazoxide to reduce the side effects of fluid retention.
  - SC Octreotide (synthetic somatostatin) 5-35 mcg/kg/day bd/tds or as infusion.



Pearls and Pitfalls in Management

- Depending on severity of hypoglycemia, maintain some oral feeds as milk has more calories than 10% dextrose.
- Breastfeeding should be encouraged as it is more ketogenic.
- Feed infant with as much milk as tolerated and infuse glucose at a sufficient rate to prevent hypoglycemia. The dextrose infusion is then reduced slowly while milk feeds is maintained or increased.
- Avoid giving multiple boluses of glucose as they can cause a rapid rise in blood glucose concentration in which may be harmful to neurological function and may be followed by rebound hypoglycaemia.
- Any bolus given must be followed by a continuous infusion of glucose. There is no place for treatment with intermittent glucose boluses alone.
- Ensure volume of IV fluid is appropriate for infants, taking into consideration concomitant problems like cardiac failure, cerebral oedema and renal failure. If unable to increase volume further, increase dextrose concentration.

MANAGEMENT ALGORITHM FOR NEONATAL HYPOGLYCEMIA



GIR: Glucose Infusion Rate (mg/kg/min) =
Infusion rate (ml/hr) x dextrose concentration (%)
Body weight (kg) x 6

Chapter 19:
Neonatal Sepsis

Definition

Neonatal sepsis is a clinical syndrome with systemic manifestations resulting from the presence of pathogenic microorganisms in the first month of life.

Main Classifications

	Early Onset	Late Onset
Classification	• Presents within the first 72hours of life • Generally acquired through vertical transmission	• Presents after 72hours of life • Usually nosocomial or community-acquired
Risk Factors	• Prematurity • Low birth weight • Maternal pyrexia >38˚C • Prolonged rupture of membranes >18hours • Maternal colonization with group B Streptococcus (GBS)	• Prematurity • Low birth weight • Mechanical ventilation • Central line access • Parenteral nutrition • Prolonged use of antibiotic therapy • Overcrowded nursery • Sick contact
Major Microbial Causes	• GBS • *Escherichia coli* • *Streptococcus viridans* • *Enterococcus spp* • *Staphylococcus aureus* • *Haemophilus spp* • *Group A Streptococcus*	• Coagulase-negative staphylococci • *Staphylococcus aureus* • *Enterococcus* spp • GBS • Enterobacter spp • *Escherichia coli* • *Pseudomonas* spp

Clinical Features of Sepsis

	Clinical Features
General	Temperature instability, “infant just doesn’t look right or well”, rashes, mottled skin
Neurology	Irritability, lethargy, seizures, abnormal Moro reflex, bulging fontanelle, high-pitched cry, hypo-/hypertonia, apnea
Respiratory	Apnea, tachypnea, cyanosis, respiratory distress
Cardiovascular	Tachy-/bradycardia, hypotension, delayed capillary refill, diminished pulses, cold and clammy skin
Gastrointestinal	Poor feeding, vomiting, diarrhea, abdominal distension, hepatomegaly
Renal	Oliguria
Metabolic	Hypo-/ hyperglycaemia, metabolic acidosis
Hematological	Jaundice, splenomegaly, pallor, petechiae, purpura, bleeding

Investigations

- Full blood count (FBC): Hemoglobin (Hb), total white blood cell with differential, platelets
- Blood culture (≥1ml of blood)
- Where available :
  - Serial c-reactive protein (CRP) taken after 6hours of life and subsequently 24hours apart.
- Where indicated:
  - Lumbar puncture, CXR, AXR
  - Urine culture in late onset sepsis

Management

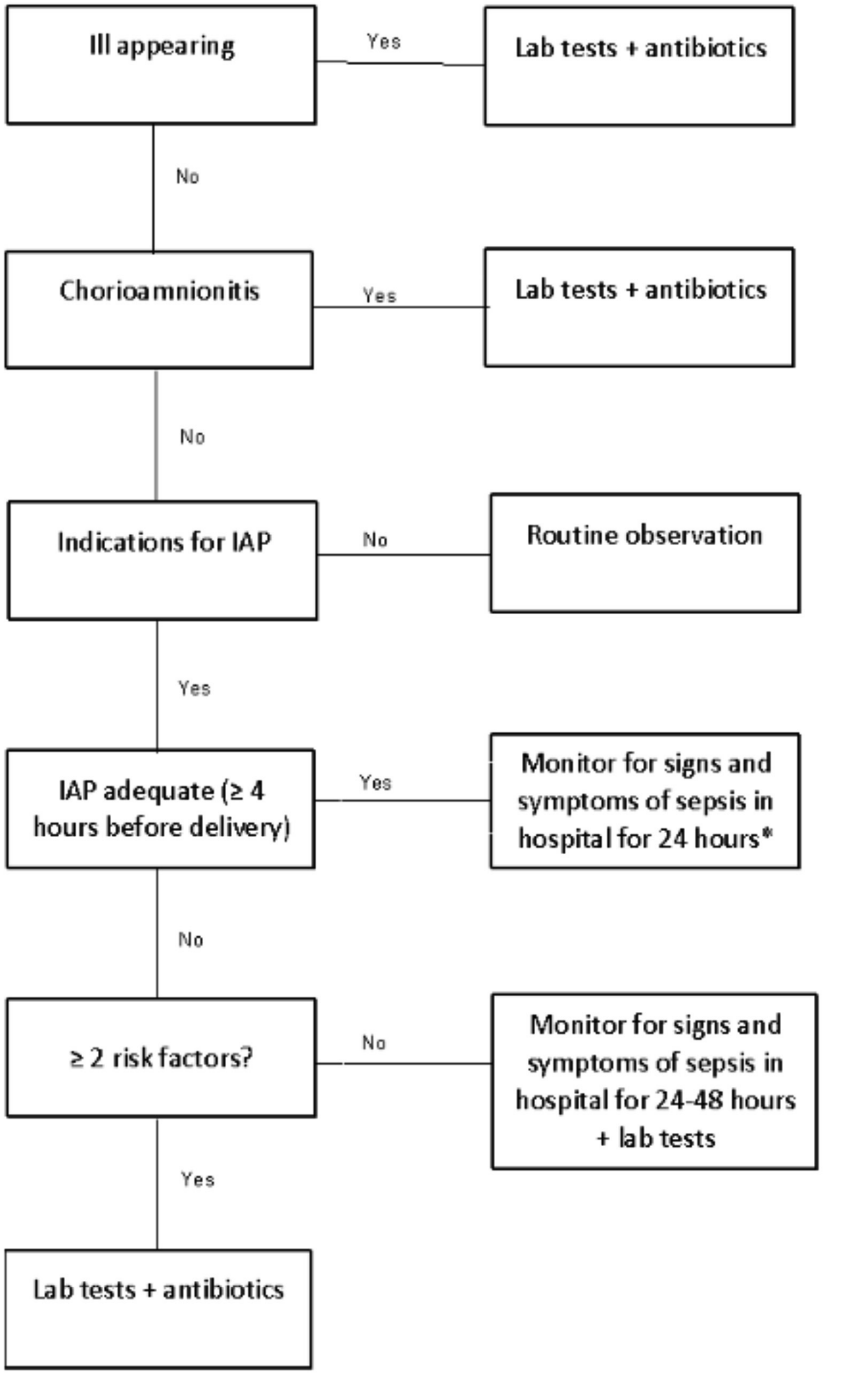
- Empirical antibiotics
- Start immediately when diagnosis is suspected. Do not wait for culture results.
- Perform necessary investigations prior to antibiotic administration if possible. *(Do not delay in administering antibiotics if prompt investigations are not possible.)*
- Trace culture results after 36-48 hours. Adjust antibiotics accordingly. Stop antibiotics if cultures are sterile and infection is clinically unlikely.

<table>
<tr><th colspan="3">Recommended Antibiotics</th></tr>
<tr><td colspan="2">Early Onset</td><td>• IV C-Penicillin/Ampicilin and Gentamicin
• Specific choice when specific organisms suspected</td></tr>
<tr><td rowspan="2">Late Onset</td><td>Community acquired</td><td>• IV C-Penicillin/Cloxacillin and Gentamicin for non-CNS infection
• IV C-Penicillin and IV Cefotaxime for CNS infection</td></tr>
<tr><td>Nosocomial infection
(Choice depends on prevalent organisms in the nursery and its sensitivity)</td><td>• MRCoNS/MRSA : IV Vancomycin
• Non-ESBL gram negative rods: IV Cephalosporin
• ESBLs: IV Carbapenams
• Pseudomonas: IV Ceftazidime
• MSSA: IV Cloxacillin</td></tr>
<tr><td colspan="2">Anaerobic infection
(e.g. Intraabdominal sepsis)</td><td>• IV Metronidazole</td></tr>
<tr><td colspan="2">Fungal sepsis
(may consider if infant not responding to antibiotics especially in preterm/VLBW or with indwelling long lines)</td><td>• IV Fluconazole
• IV Amphotericin B</td></tr>
</table>

- Duration of Antibiotics
  - Staphylococcus aureus bacteremia:
    - 2 weeks for uncomplicated bacteremia
    - 4-6 weeks for treatment of endocarditis or bacteremia complicated by slower resolution or presence of metastatic infection
    - At least 6-8 weeks of therapy for osteomyelitis
  - Group B Streptococcus (Streptococcus agalactiae) infection:
    - 14 days for bacteremia without a defined focus OR an isolated urinary tract infection without bacteremia
    - For uncomplicated meningitis, repeat lumbar puncture 48-72hours. If repeat CSF culture negative, IV Gentamicin can be stopped, and continue IV Benzyl Penicillin or Ampicillin for a total of 21 days. Longer courses of antibiotics may be needed in cases of complicated meningitis.
    - 4-6 weeks for endocarditis and osteomyelitis
  - Gram negative bacteremia:
    - 10-14 days for bacteremia without meningitis
    - At least 3 weeks for bacteremia with meningitis, may be up to 6 weeks in cases of complicated meningitis

- Consider removing central lines
- Supportive care is essential, which may include intravenous fluids and nutrition, pressor medications, respiratory support.
- Correct hematological and metabolic abnormalities.
- Therapy with IV immune globulin has no effect on the outcomes of suspected or proven neonatal sepsis.

Management of Neonates born at ≥ 35 weeks with Risk of Early-Onset Sepsis



Risk factors for EOS

- GBS carrier, bacteriuria
- GBS sepsis in previous neonate
- Confirmed or suspected chorioamnionitis
- Spontaneous onset of preterm labour
- Rupture of membrane > 18 hours

Suspected chorioamnionitis

- Intrapartum temperature ≥ 38°C plus ≥ one of the following:
  - Maternal leucocytosis
  - Purulent cervical drainage
  - Fetal tachycardia

**Early discharge after 24hours can be considered if infant remains well, easy access to healthcare facilities and parents understand signs and symptoms of sepsis as well as action to be taken*

Indications of Intrapartum Antibiotics (IAP)

- Preterm labour
- GBS colonisation, bacteriuria or infection during current pregnancy
- GBS colonisation, bacteriuria or infection in previous pregnancy and have not had a negative test for GBS collected between 35-37 weeks gestation in current pregnancy
- Previous infant with an invasive GBS infection
- Chorioamnionitis
- Intrapartum temperature ≥ 38°C
- Amniotic membrane rupture ≥ 18 hours

Chapter 20:
Neonatal Encephalopathy and Hypothermia Therapy

Introduction

Neonatal Encephalopathy (NE) is a clinical defined syndrome of disturbed neurological function, manifested by a subnormal level of consciousness, difficulty in initiating and maintaining respiration, depression of muscle tone and reflexes and often seizures; in the earliest days of life of an infant born ≥ 35 weeks of gestation.

Moderate or severe NE occurs in 2/1000 live births; usually affects full term infants.

The terminology NE is preferred to Hypoxic Ischemic Encephalopathy (HIE) unless it is possible to document a significant hypoxic-ischemic insult in the peripartum or intrapartum period.

Causes of Neonatal Encephalopathy

1. Hypoxic-ischaemic event
2. Central nervous system (CNS) malformations
3. Intracranial haemorrhage
4. Intracranial infection
5. Cerebral infarction/stroke
6. Metabolic disorders
7. Drug toxicity
8. Drug withdrawal
9. Electrolyte imbalances
10. Seizure disorders

Table 1 : Criteria suggestive of HIE in the newborn

1. Early onset of moderate or severe encephalopathy in newborn ≥ 35 weeks gestational age. (If aEEG available – amplitude range- lower below 5, higher below 10, i.e. low amplitude aEEG, suggest more severe encephalopathy)
2. Neonatal signs consistent with an intrapartum or peripartum event:
   - Arterial cord pH < 7.0, base deficit ≥ 12 mmol/L.
   - Apgar score of ≤ 5 at 5 and 10 minutes of life
   - Evidence of multiorgan system dysfunction within 72 hours of birth
   - Neuroimaging evidence of acute brain injury seen on brain MRI consistent with hypoxia–ischemia

   Type and timing of contributing factors that are consistent with intrapartum timing
   - A sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery
   - Fetal heart rate pattern that becomes abnormal during labour or after a sentinel event
3. The absence of an infectious cause, a congenital malformation of the brain, an inborn error of metabolism or other condition, which could explain the encephalopathy.

In a large Western Australian study, risk factors for neonatal encephalopathy were mainly seen in the antenatal period (69%) as compared to the intrapartum period (25%) and only 4% were due to intrapartum hypoxia. There is no definitive test or set of markers that accurately identifies, with high sensitivity and specificity, an infant in whom neonatal encephalopathy is attributable to an acute intrapartum event.

In neonates confirmed to have neonatal encephalopathy, assessment following the criteria listed in Table 1, will determine the likelihood of an acute peripartum/intrapartum event as a contributing factor, especially when more of the elements from each of the item categories in the table are met.

ASSESSMENT OF NEONATE WITH NEONATAL ENCEPHALOPATHY

Consider the possibility of other causes of neonatal encephalopathy

TABLE 2: Monitoring of Staging of Neonatal Encephalopathy

Categories		Moderate	Severe	Date / Time						
1	**Level of conciousness**	Lethargy	Stupor/Coma							
2	**Activity**	Decreased	Absent							
3	**Posture**	Strong distal flexion	Decerebrate							
4	**Tone**	Hypotonia	Flaccid							
5	**Primitive reflexes**									
	Suck	Weak	Absent							
	Moro	Incomplete	Absent							
6	**Autonomic function**									
	Pupils	Miosis	Dilated/non-reactive							
	Heart rate	Bradycardia	Variable							
	Respiration	Periodic breathing	Apnoea							
	Seizures									

- *Tick (√) if signs are present.*
- *Presence of seizures qualifies for moderate/severe neonatal encephalopathy.*
- *Presence of at least 1 sign in 3 or more categories (1 to 6) qualifies for moderate/severe neonatal encephalopathy.*

Staging of encephalopathy

1. *Modified Sarnat Classification*
   - This is mainly used in term infants or infants > 35 weeks gestation. It is not useful in premature infants.
   - Presence of seizures OR signs in at least 3 of the 6 categories in Table 2, in keeping with moderate/severe encephalopathy, is used as a criteria for starting hypothermia therapy.
   - If decision to start hypothermia therapy is yet to be determined, to monitor on an hourly basis, for 6 hours, until decision to start is made.

2. *Thompson Encephalopathy Score*
   - An alternative assessment using scoring system to monitor severity of encephalopathy
   - To commence hypothermia therapy as soon as the Thompson score is ≥ 7 from birth to 6 hours, and the infant fulfils other criteria for hypothermia therapy.

HYPOTHERMIA THERAPY

All the following four criteria must be fulfilled, in order to start hypothermia therapy:

1. Neonates born at ≥ 35 weeks gestation
2. < 6 hours of life
3. Evidence of asphyxia, as defined by the presence of at least 2 of the following 4 criteria:
   a. Any acute perinatal event that may result in HIE (such as but not limited to placental abruption, cord prolapse, severe Foetal Heart Rate (FHR) abnormality etc.)
   b. Apgar scores ≤ 5 at 10 min or continued need for resuscitation with positive pressure ventilation +/- chest compressions
   c. Cord pH < 7.0 or base deficit of -12mmol/L or more
   d. If cord pH is not available, arterial pH <7.0 or BE > -12mmoL/L within 60 min of birth
4. Evidence of moderate-severe encephalopathy, as evidenced by presence of seizures, OR fulfilling criteria in Modified Sarnat staging (Table 2).

Neonates with the following criteria should not receive hypothermia therapy:

- Oxygen requirement > 80%, that is not responsive to treatment
- Severe coagulopathy (including thrombocytopenia) not responsive to treatment, OR severe intracranial bleeding
- Severe intrauterine growth retardation (IUGR), eg. birth weight ≤ 1.8 kg.
- Major lethal congenital abnormalities
- Infant unlikely to survive.

Before starting hypothermia therapy

- Ensure adequate resuscitation and support for the neonate.
- Neonates should be kept at normothermia until decision to start hypothermia therapy is made. Avoid hyperthermia > 37°C as this can increase the risk of adverse outcome.
- Medications with sedative effects should be avoided before decision to start hypothermia therapy is made, as it may affect the assessment of neurological status.

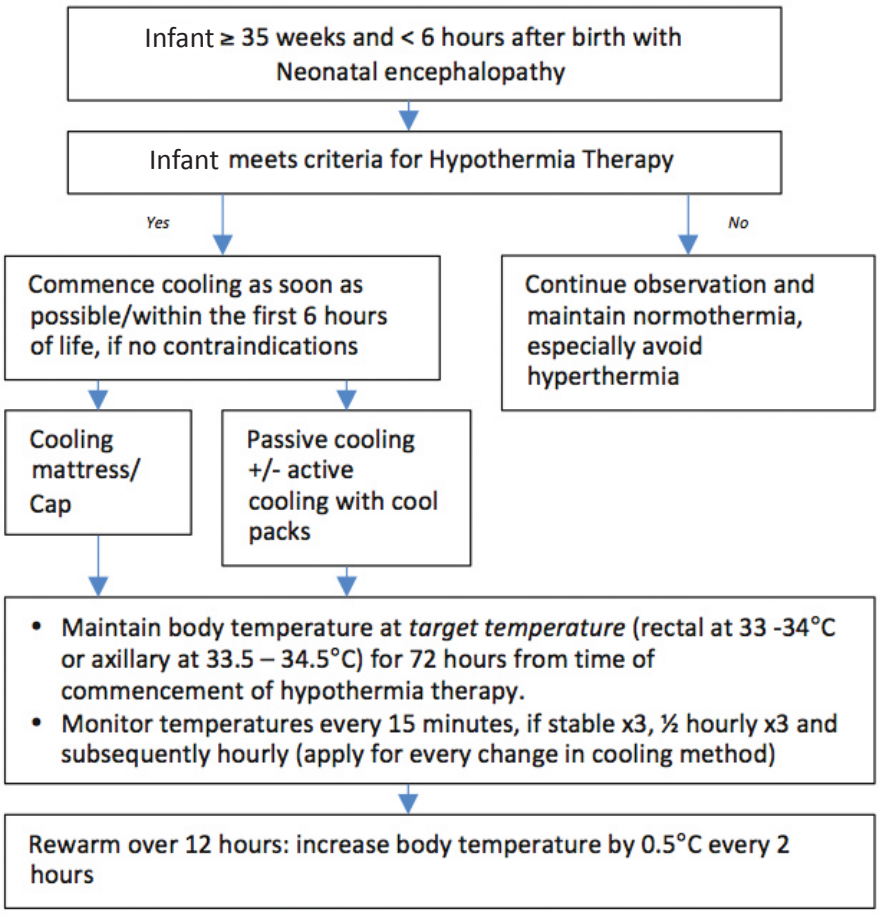
When to start hypothermia therapy

- Hypothermia therapy should be started as soon as possible, after the infant has been adequately resuscitated and supported.
- To start within 6 hours after infant is born.

Methods of hypothermia therapy

A. Total body cooling (with hypothermia therapy device)
B. Selective head cooling
C. Passive cooling +/- active cooling (with cool packs)(*refer Table 4*)

THERAPEUTIC HYPOTHERMIA FLOW CHART



Application of Rectal Temperature Probe

- Insert Rectal Temperature Probe at least 5 cm into anus, to accurately measure the infant's core temperature.
- Secure the probe at 10 cm measurement, with tape, to the upper inner thigh.
- Connect rectal probe to cable, temperature module and monitor; (or to servo-controlled hypothermia therapy device).
- Set temperature alarm limits at 33°C (low) and 34°C (high) during the cooling period.
- Record time of initiating Hypothermia therapy.

Duration of hypothermia therapy

- Therapy should be continued for 72 hours from the commencement of cooling.
- Consider stopping hypothermia therapy early (to rewarm over 12 hours), in the presence of:
  - Persistent hypoxemia, despite treatment
  - Life-threatening coagulopathy/bleeding, despite treatment
  - An arrhythmia (not sinus bradycardia) requiring medical treatment
  - If palliative care considered and after mutual agreement between parents and clinicians.

Rewarming

- Aim is to rewarm slowly over 12 hours and to avoid hyperthermia.
- If using hypothermia therapy device, to complete rewarming using device before turning on radiant warmer.
- If using passive cooling method, apply skin probe and turn the radiant warmer on with the servo set at 34.5°C, and increase the set temperature by 0.5°C every 2 hours until 36.5°C and rectal temperature is 37°C. (Rewarming can occur too rapidly, so infants need close monitoring. If infant is rewarming too rapidly increase set temperature by 0.5°C every 4 hours instead and avoid hyperthermia)
- Monitor infant's temperature carefully for 24 hours after normothermia has been achieved to prevent rebound hyperthermia.
- Monitor closely for seizures, as this can happen during the rewarming phase, especially if done too rapidly.

Side effects during hypothermia therapy and rewarming

- Sinus bradycardia
- Decreased blood pressure
- Increased oxygen requirement
- Mild thrombocytopenia
- Increased bleeding tendency
- Prolonged drug half-life
- Too rapid rewarming causing peripheral vasodilatation and hypotension

Table 5: Active cooling with cool packs

Rectal Temperature (Axillary temperature in brackets)	Number of cool packs	Areas to apply
>35.0°C (>35.5°C)	2*	under shoulders, along sides
34.0 – 35.0°C (34.5 -35.5°C)	1	along sides
<34.0°C (<34.5°C)	0	Nil
**Having > 2 packs prevents radiant heat loss and makes it more difficult to achieve target temperature.*		

Table 4: PASSIVE COOLING +/- ACTIVE COOLING WITH COOL PACKS

Passive cooling is a method of hypothermia therapy using environmental temperature to cool infant to target temperature.

Aims

- To achieve body temperature 33.5°C - 34.5°C (axillary) or 33°C - 34°C (rectal) (*target temperature*) within 60 minutes of commencing cooling.
- To achieve hypothermia initially with **passive cooling**.
- If body temperature remains > 35.5°C (axillary) or > 35°C (rectal) within 60 minutes of starting, then **active cooling** should be started.
- To keep infant in target temperature for 72 hours then rewarm slowly over 12 hours.

Procedure of passive cooling

- Infant must be nursed on open warmer (NOT closed incubator) with warmer switched off.
- Nurse infant naked and unfasten diapers.
- Record time of commencement of passive cooling and rectal or axillary temperature every 15 minutes (*refer flow chart*).
- If axillary temperature drops below 34°C (rectal temperature < 33.5°C), set radiant warmer on servo-controlled mode at the lowest temperature to achieve target temperature.

Procedure of active cooling with cool packs

- Store cool packs in 4°C fridge (NOT freezer), when not in use.
- Cool packs must be wrapped in cotton bags when applied. They should never be applied directly to the skin.
- Place cool packs under the shoulders/upper back (under the head) and/or across the chest. Cool packs should not be placed at the axilla as it interferes with axillary temperature monitoring.
- Number of cool packs to be used depends on measured body temperature (refer Table 5).
- Aim to achieve target temperature within the first hour of cooling.
- Record the time of commencement of active cooling and monitor temperatures every 15 minutes (*refer flow chart*).
- If rectal temp drops to <34°C (axillary temp <34.5°C), remove all cool packs and repeat temperature in 15 minutes. Then continue with passive cooling.

MONITORING OF NEONATE WITH NEONATAL ENCEPHALOPATHY

- Continuous cardiorespiratory monitoring; blood pressure (invasive blood pressure monitoring, if available), heart rate and rectal or axillary temperature monitoring.
- Amplitude – integrated EEG (aEEG) monitoring, if available. aEEG can be helpful in predicting outcome and identifying seizure activity.
- Blood investigations (*refer table 6*)

Table 6: Blood investigations monitoring

Blood investigation	Frequency	Comment
Blood gas	4 hourly initially, then as required by clinical state	- Includes glucose, ionized calcium and lactate (if available) - Arterial access is usually obtained
Full blood count	12 hourly initially, then at least daily until day 3 - 5	
Electrolytes	8 – 12 hourly initially, then at least daily until day 3 - 5	
INR and APTT clotting studies	On day 1 and then, if abnormal, daily until day 5 or stable	
Liver function test	On day 2 and 5	

SUPPORTIVE MANAGEMENT OF NEONATE WITH NEONATAL ENCEPHALOPATHY

1. **Respiratory support:** Aim for normal oxygen saturations and normocarbia (using lowest ventilatory support as needed by neonate, especially if minimal or no concurrent respiratory disease).
2. **Hypotension:** If infant has impaired tissue perfusion with low blood pressure, consider treatment with volume replacement and/or inotropes. Choice of therapy should be guided by possible aetiology and clinical assessment. In a hypovolemic state with history of blood loss (e.g. bleeding placenta previa, etc.), a fluid bolus of 10 ml/kg of normal saline may be given. Avoid multiple fluid boluses (unless volume loss) in view of possible impaired cardiac contractility, and renal impairment. Initiation and choice of inotropes/vasopressors should be guided by clinical assessment (e.g. dobutamine in the presence of reduced cardiac contractility).
3. **Renal Impairment:** Total fluid management can be started at 60 ml/kg/day, but if evidence of renal impairment is present (with poor urine output and low sodium), total fluid may be reduced down to 40 ml/kg/day, plus any measured losses. Careful monitoring for diuresis (following period of oliguria) is important, to guide fluid therapy and avoid hypovolemia. Medications with nephrotoxic side effects should be avoided or used with therapeutic drug monitoring.
4. **Nutrition:** Trophic enteral feeding (10 – 20ml/kg/day) can be cautiously introduced once the initial biochemical and metabolic disturbance are corrected, usually after about 24 hours. Consider giving parenteral nutrition during the initial period. Normoglycemia should be maintained.
5. **Sedative Therapy:** Signs of distress include tachycardia (heart rate consistently above 110 bpm in a neonate undergoing hypothermia therapy), facial grimacing and irritability. Ventilated infants may be given low dose morphine infusion (≤10mcg/kg/hour) and may be discontinued after 24-48 hours to reduce the risk of accumulation and toxicity.

6. **Seizures:** Clinical and electrographic seizures should be treated with antiepileptic medications (Refer to Chapter on ***Neonatal seizures***). Prophylactic antiepileptic medications should not be started.
7. **IV access:** Neonates undergoing hypothermia therapy will usually have difficult IV insertions and blood taking, and therefore, requires umbilical arterial and venous catheters insertion.
8. **Family support:** Parents should be engaged as soon as possible, and supported with clinical progress of the infant and explanation about medical therapies, including hypothermia therapy. If the infant exhibits impaired neurological function prior to discharge, parents should be involved in the rehabilitative therapies, including feeding and physiotherapy.

Chapter 21:
Neonatal Jaundice

Introduction

Jaundice can be detected clinically when the level of bilirubin in the serum rises above 85µmol/l (5mg/dl).

Causes of neonatal jaundice (NNJ)

- Haemolysis due to ABO or Rh-isoimmunization, G6PD deficiency, microspherocytosis, drugs.
- Physiological jaundice.
- Cephalohematoma, subaponeurotic haemorrhage.
- Polycythaemia.
- Sepsis, meningitis, urinary tract infection, intra-uterine infection.
- Breastfeeding and breastmilk jaundice.
- Gastrointestinal tract obstruction: increase in enterohepatic circulation.

Risk factors for Significant Neonatal Jaundice
Prematurity
Down Syndrome
Jaundice in the first 24 hours of life
Mother with Blood group "O" or Rhesus negative
G6PD deficiency
Rapid rise of total serum bilirubin
Sepsis
Lactation failure in exclusive breastfeeding
High predischarge bilirubin level
Cephalohematoma or bruises
Infant of diabetic mother
Family history of severe NNJ in siblings

Approach to an infant with jaundice

History

- Age of onset.
- Previous siblings with NNJ, kernicterus, neonatal death, G6PD deficiency.
- Mother's blood group (from antenatal history).
- Gestation: the incidence of hyperbilirubinaemia increases with prematurity.
- Presence of abnormal symptoms such as apnoea, difficulty in feeding, feed intolerance and temperature instability.

Physical examination

- General condition, gestation and weight, signs of sepsis, hydration status.
- Signs of acute bilirubin encephalopathy (ABE) should be assessed for all babies with severe NNJ (see BIND score)
- Pallor, plethora, cephalohaematoma, subaponeurotic haemorrhage.
- Signs of intrauterine infection e.g., petechiae, hepatosplenomegaly.
- Cephalo-caudal progression of severity of jaundice.

The adequacy of breastfeeding, weight and hydration status of all infants should be assessed during the first week of life. Infants with weight loss > 7% should be referred for further evaluation and closely monitored for jaundice.

Bilirubin Induced Neurological Dysfunction (BIND score)			
Clinical Signs	**Score**	**Date**	**Time**
Mental Status			
Normal	0		
Sleepy but arousable; decreased feeding	1		
Lethargy, poor suck and/or irritable/jittery with strong suck	2		
Semi-coma, apnoea, unable to feed, seizures, coma	3		
Muscle Tone			
Normal	0		
Persistent mild to moderate hypotonia	1		
Mild to moderate hypertonia alternating with hypotonia, beginning arching of neck and trunk on stimulation	2		
Persistent retrocollis and opisthotonus - bicycling or twitching of hands and feet	3		
Cry Pattern			
Normal	0		
High pitched when aroused	1		
Shrill, difficult to console	2		
Inconsolable crying or cry weak or absent	3		
TOTAL BIND SCORE			

- Advanced ABE (score 7 - 9): urgent bilirubin reduction intervention is needed to prevent further brain damage and reduce the severity of sequelae
- Moderate ABE (score 4 - 6): urgent bilirubin reduction intervention is likely to reverse this acute damage
- Mild ABE (score 1 - 3): subtle signs of ABE

Note: An abnormal or 'referred' Auditory Brainstem Response (ABR) is indicative of moderate ABE. Serial ABR may be used to monitor progression and reversal of acute auditory damage and could be indicative of the effectiveness of bilirubin reduction strategy.

Methods of Detecting Jaundice:

- Visual Assessment (Kramer's rule)
- Transcutaneous Bilirubinometer (TcB) –
  - → TSB should be measured if TcB exceeds or is within 50µmol/l (3mg/dL) of the phototherapy threshold or if the TcB is ≥ 256µmol/l (15mg/dL).
  - → TcB is not to be used for infants on phototherapy and not recommended for infants less than 24hours of life.
  - → TcB can be used for monitoring if it has been 24 hours since cessation of phototherapy.
- Total Serum Bilirubin (TSB)

All newborn infants should be visually assessed for jaundice at every opportunity.

Visual Assessment of Neonatal Jaundice (Kramer's rule)

Area of the Body	Level	Range of Serum Bilirubin	
		µmol/L	mg/dL
Head and neck	1	68 - 133	4 - 8
Upper trunk (above umbilicus)	2	85 - 204	5 - 12
Lower trunk and thighs (below umbilicus)	3	136 - 272	8 - 16
Arms and lower legs	4	187 - 306	11 - 18
Palms and soles	5	≥ 306	≥ 18

Management

Indications for referral to hospital:

- Jaundice within 24 hours of life.
- Jaundice below umbilicus (corresponds to serum bilirubin 200-250 µmol/L).
- Jaundice extending to soles of feet: **Urgent referral as it is a sign of severe NNJ**.
- Family history of significant haemolytic disease or kernicterus.
- Any unwell infant with jaundice.
  - Infants with conjugated hyperbilirubinaemia should be referred to a hospital as soon as possible.
  - Infants with prolonged unconjugated hyperbilirubinaemia can be investigated and referred only if the jaundice does not resolve or a definitive cause found.

(Refer **Prolonged Jaundice chapter**).

Investigations

- In infants with severe hyperbilirubinaemia, early-onset neonatal jaundice (<24 hours) or rapid rise of TSB (>8.5µmol/L/h or >0.5mg/dL/h), further evaluation may be required to ascertain underlying cause and extent of haemolysis. This may include:
  - G6PD testing (if not screened)
  - mother's and infant's blood groups
  - direct antiglobulin test (DAT)
  - full blood count (FBC) ± peripheral blood picture
  - reticulocyte count
  - septic workup (if infection is suspected)

All infants should be screened for Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. The result should be reviewed within 24 hours.

G6PD enzyme assays may be considered in infants suspected to have G6PD deficiency but with normal/ indeterminate Fluorescent Spot Test.

Treatment

Use of sunlight exposure to reduce jaundice should be avoided due to risk of dehydration and sunburn.

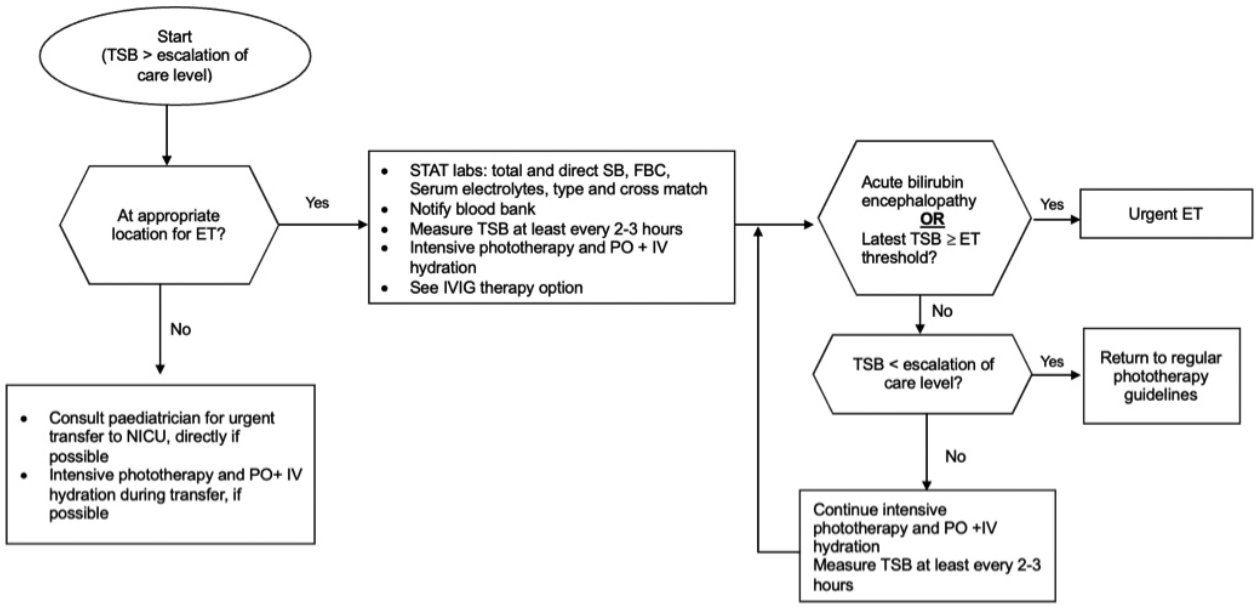
Phototherapy

- Phototherapy is the mainstay of treatment in NNJ. Various devices are available to provide phototherapy such as fluorescent tubes, Light Emitting Diode (LED), fibreoptic and halogen bulbs.
- Effective phototherapy is achieved with optimal irradiance and adequately exposed body surface area rather than the number of phototherapy units.
- Effective phototherapy consist of:
  - blue light range (around 475nm)
  - irradiance of minimum of 15µW/cm²/nm for conventional phototherapy
  - irradiance of minimum of 30µW/cm²/nm for intensive phototherapy
  - distance of the light source not exceeding 30 - 50 cm from the baby
- Irradiance of phototherapy units should be regularly checked.
- Phototherapy should be commenced when total serum bilirubin (TSB) reaches phototherapy threshold for neonatal jaundice.
- Overhead phototherapy is preferred to underneath phototherapy.
- LED phototherapy is preferred in preterm infants.
- Once the infant is on phototherapy, visual observation as a means of monitoring is unreliable. TSB levels must be obtained to guide the management.
- Escalation of care with preparation for possible exchange transfusion (ET) is required when the TSB is 34µmol/l (2mg/dL) below the ET threshold.

Escalation of Care

- The current ET threshold (AAP 2022 guidelines) is higher as compared to previous guidelines
- Escalation of care refers to the intensive care that some infants with high TSB require to prevent the need for an ET and possibly prevent kernicterus.
- Care should be escalated when an infant's TSB reaches or exceeds the escalation-of-care threshold, defined as 2 mg/dL (34umol/L) below the ET threshold, as detailed in Figure 1
- Initiating escalation of care is a medical emergency and whenever possible, the infant should be admitted directly to the NICU rather than through the emergency department to avoid delaying care
- While preparing for possible ET, infants should receive intravenous hydration and intensive phototherapy.
- TSB should be measured every 2-3 hours until it is below the escalation of-care threshold.

Figure 1: Approach to escalation of care. The escalation of care threshold is 2mg/dL (34umol/L) below the ET threshold



Adapted from Kemper AR, Newman TB, Slaughter JL, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics. 2022;150(3): e2022058859

Care of infants during phototherapy

- Vital signs should be regularly monitored including temperature and hydration status.
- Should be placed in supine position with adequate exposure.
- Eyes must be covered to prevent retinal damage.
- Breastfeeding should be continued.
- Turn off phototherapy and remove eye pads during feeding and blood taking.

Prevention of severe neonatal jaundice

- All infants discharged before 48 hours of life should be seen by a healthcare provider in an ambulatory setting or at home within 24 hours of discharge.
- For infants with severe jaundice admitted for treatment, early follow-up is needed to detect rebound jaundice after discharge.
- Predischarge screening should be used to prevent severe neonatal jaundice (NNJ) in late preterm and term infants.
- Clinical risk factor assessment or/and predischarge bilirubin levels [TcB or TSB] can be used as predischarge screening.
- Universal predischarge bilirubin screening may be considered for all infants if resources are available.
- All G6PD deficient infants should be admitted and monitored for NNJ during the first five days of life. A TSB should be done if there is clinical jaundice.
- Term G6PD deficient infants with birth weights >2500g may be discharged earlier on day four of life if the TSB is <160µmol/L (9mg/dL) and followed-up closely.

Additional notes

- Mothers who received Rho(D) immune globulin (RhIG) can have positive antibody screen for anti-Rh(D). RhIG can cause a positive DAT in infant but generally no hemolysis. Hence, if an infant's DAT is positive only to anti-Rh(D) because the mother received RhIG antenatally and mother is not known to have Rh(D) antibodies prior to RhIG, the infant can be treated as DAT negative.

Intravenous immunoglobulin (IVIG)

- IVIG has been used to reduce the rate of haemolysis in infants with immune haemolytic disease. However, studies on its efficacy have been inconclusive.
- IVIG 0.5 to 1g/kg over 2 hours may be given to infants with isoimmune hemolytic disease (i.e., DAT positive) whose TSB reaches or exceeds escalation of care threshold OR when TSB rise more than 8.5µmol/L/hr.
- Dose can be repeated in 12hours if indicated.

Follow up

- Infants with ABE should have long-term follow-up to monitor for neurodevelopmental sequelae.
- Term and late preterm infants with TSB >20mg/dL (342µmol/L) or exchange transfusions should have Auditory Brainstem Response (ABR) testing done within the first three months of life. If the ABR is abnormal, early referral to the audiologist for early intervention and neurodevelopmental follow-up should be continued.
- Healthy term and late preterm infants with non-haemolytic hyperbilirubinaemia and TSB <25mg/dL (428µmol/L) may be followed-up at the primary care level.

CONVENTIONAL PHOTOTHERAPY (PT) AND EXCHANGE TRANSFUSION (ET) THRESHOLDS IN INFANTS ≥35 WEEKS GESTATION WITH NO NEUROTOXICITY RISK FACTORS*

Adapted from AAP Guidelines

Age	≥38 weeks		37 weeks		36 weeks		35 weeks	
Hours of life	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)
6	5.9(101)	18.8(321)	5.5(94)	17.8(304)	4.9(84)	16.7(285)	3.4(58)	15.6(266)
12	7.1(121)	19.7(337)	6.6(113)	18.7(320)	6.0(103)	17.5(299)	5.5(94)	16.4(280)
24	9.3(159)	21.4(366)	8.7(149)	20.3(347)	8.2(140)	19.1(327)	7.6(130)	17.9(306)
48	13(222)	24.0(410)	12.4(212)	23.1(395)	11.8(202)	21.9(374)	11.2(191)	20.7(354)
72	15.8(270)	25.9(443)	15.1(258)	25.2(431)	14.5(248)	24.1(412)	13.8(236)	22.9(391)
96	17.7(303)	27.0(462)	17.0(291)	26.6(455)	16.3(279)	25.5(436)	15.6(267)	24.5(419)
>120	17.9(306)	27.0(462)	17.2(294)	26.7(456)	16.4(280)	25.7(439)	15.7(268)	24.7(422)

- *Start intensive phototherapy at TSB of 3 mg/dL (51 µmol/L) above the level for conventional phototherapy or when TSB increasing at >0.5 mg/dL (8.5 µmol/L) per hour.*

The AAP exchange transfusion guidelines for infants ≥35 weeks' gestation recommend:

- *ET if infant shows signs of moderate or advanced ABE or*
- *ET if TSB is above the ET threshold (ET threshold is higher as compared to previous Paediatric protocol 4th ed)*
- *Refer to "escalation of care "Figure 1*

CONVENTIONAL PHOTOTHERAPY (PT) AND EXCHANGE TRANSFUSION (ET) THRESHOLDS IN INFANTS ≥35 WEEKS GESTATION WITH ANY NEUROTOXICITY RISK FACTOR*

Adapted from AAP Guidelines

Age	≥38 weeks		37 weeks		36 weeks		35 weeks	
Hours of life	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)
*6	4.3(74)	15.5(265)	3.9(67)	15.0(256)	3.3(56)	14.4(246)	2.8(48)	13.8(236)
*12	5.5(94)	16.3(279)	5.0(85)	15.7(268)	4.4(75)	15.2(260)	3.9(67)	14.6(250)
24	7.5(128)	17.7(303)	7.0(120)	17.2(294)	6.4(109)	16.6(284)	5.9(101)	16.1(275)
48	11.0(188)	20.1(344)	10.5(180)	19.7(337)	9.8(167)	19.1(327)	9.2(157)	18.5(316)
72	13.6(232)	22.1(378)	13.1(224)	21.7(371)	12.4(212)	20.9(357)	11.6(198)	20.1(344)
96	15.2(260)	23.5(402)	14.9(255)	23.1(395)	14.0(239)	22.1(378)	13.1(224)	21.1(361)
>120	15.2(260)	23.5(402)	15.0(256)	23.2(397)	14.1(241)	22.3(381)	13.3(227)	21.3(364)

***Neurotoxicity Risk Factors:**

- Isoimmune haemolytic disease, G6PD deficiency or other haemolytic conditions
- Sepsis
- Any significant clinical instability in previous 24 hours
- Albumin < 30g/L (if measured)

- *Start intensive phototherapy at TSB of 3 mg/dL (51 µmol/L) above the level for conventional phototherapy or when TSB increasing at >0.5 mg/dL/hr (8.5 µmol/L/hr).*

The AAP exchange transfusion guidelines for infants ≥35 weeks' gestation recommend:

- *ET if infant shows signs of moderate or advanced ABE or*
- *ET if TSB is above the ET threshold (ET threshold is higher as compared to previous Paediatric protocol 4th ed)*
- *Refer to "escalation of care "Figure 1*

PHOTOTHERAPY (PT) AND EXCHANGE TRANSFUSION (ET) THRESHOLDS FOR PRETERM INFANTS ≤34 WEEKS GESTATION

Adapted from NICE Guidelines

Age	23 weeks		24 weeks		25 weeks	
Hours of life	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)
6	2.5(45)	5(90)	2.5(45)	5(90)	3(50)	6(100)
12	3 (55)	6(105)	3.5(60)	6.5(110)	3.5(60)	6.5(110)
24	4.1 (70)	7.6(130)	4.1 (70)	7.9 (135)	4.7 (80)	8.2 (140)
48	5.9 (100)	10.5(180)	6.5 (110)	10.9 (185)	6.5 (110)	11.1 (190)
72	7.6 (130)	13.5 (230)	8.2(140)	14.0(240)	8.8 (150)	14.6 (250)
96	7.6 (130)	13.5 (230)	8.2(140)	14.0 (240)	8.8(150)	14.6 (250)

Age	26 weeks		27 weeks		28 weeks	
Hours of life	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)
6	3(50)	6(100)	3(50)	6(100)	3(50)	6(100)
12	3.5(60)	6.5(110)	3.5(60)	6.5(110)	3.5(60)	6.5(110)
24	4.7(80)	8.2(140)	4.7(80)	8.2(140)	5.3 (90)	8.8(150)
48	7.0(120)	11.7 (200)	7.6(130)	12.0(205)	7.6(130)	12.3(210)
72	9.4 (160)	15.2 (260)	10.0(170)	15.8 (270)	10.5(180)	16.4(280)
96	9.4 (160)	15.2 (260)	10.0(170)	15.8(270)	10.5 (180)	16.4 (280)

Age	29 weeks		30 weeks		31 weeks	
Hours of life	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)
6	3(50)	6(100)	3(50)	6(100)	3(50)	6(100)
12	3.8(65)	6.7(115)	3.8(65)	6.7(115)	4(70)	7 (120)
24	5.3 (90)	8.8(150)	5.6(95)	8.8(150)	5.9 (100)	9.1(155)
48	8.2(140)	12.9 (220)	8.5(145)	12.9(220)	9.1(155)	13.5(230)
72	11.1 (190)	17.0 (290)	11.7(200)	17.5 (300)	12.3(210)	18.1(310)
96	11.1(190)	17.0 (290)	11.7(200)	17.5(300)	12.3 (210)	18.1 (310)

Age	32 weeks		33 weeks		34 weeks	
Hours of life	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)	PT Threshold TSB mg/dL (µmol/L)	ET Threshold TSB mg/dL (µmol/L)
6	3(50)	6(100)	3(50)	6(100)	3(50)	6(100)
12	4(70)	7 (120)	4(70)	7 (120)	4(70)	7 (120)
24	5.9 (100)	9.4(160)	5.9(100)	9.4(160)	6.5(110)	10.0(170)
48	9.4(160)	14.0 (240)	10.0(170)	14.3(245)	10.0(170)	14.6(250)
72	12.9(220)	18.7(320)	13.5(230)	19.3 (330)	14.6(240)	20.0(340)
96	12.9(220)	18.7(320)	13.5(230)	19.3(330)	14.6 (240)	20.0 (340)

Chapter 22:
Exchange Transfusion

Introduction

- Exchange transfusion (ET) is indicated for severe hyperbilirubinaemia.
- Kernicterus has 10% mortality and 70% long term morbidity.
- Mortality within 6 hours of ET ranged from zero death to 3 – 4 per 1000 exchanged term infants.
- Causes of death include kernicterus itself, necrotizing enterocolitis, infection and procedure related events.

Indications

Double volume exchange

- Blood exchange transfusion to lower serum bilirubin level and reduce the risk of brain damage associated with kernicterus.
- Hyperammonemia
- To remove bacterial toxins in septicaemia.
- To correct life-threatening electrolyte and fluid disorders in acute renal failure.

Partial exchange transfusion

- To correct polycythemia with hyperviscosity.
- To correct severe anemia without hypovolaemia.

Preparation of infant

- Signed Informed Consent from parent.
- Ensure resuscitation equipment is ready and available.
- Stabilize and maintain temperature, pulse and respiration.
- Obtain peripheral venous access for maintenance IV fluids.
- Proper gentle restraint.
- Continue feeding the infant; omit only the LAST feed before ET.
- If < 4 hours from last feed, empty gastric contents by nasogastric (NG) aspiration before ET.

Type of Blood to be used.

- Fresh Whole Blood (preferably irradiated), less than 5 days old OR if whole blood is unavailable, reconstitute Packed Red Blood Cells and FFP in a ratio of 3:1.
- Rh isoimmunisation: ABO compatible, Rh-negative blood.
- Other conditions: Crossmatch with infant and mother's blood.
- In Emergencies if Blood type unknown (rarely): 'O' Rh-negative blood.

Procedure (Exchange Transfusion)

- Volume for double exchange is 2x circulating blood volume (Term infant: 2x 80ml/kg = 160ml/kg)
- Connect infant to a cardiac monitor.
- Take baseline observations (either via monitor or manually) and record down on the Neonatal Exchange Blood Transfusion Sheet.
- The following observations are recorded every 15 minutes: heart rate, respiration, oxygen saturation
- Doctor performs the ET under aseptic technique using a gown and mask.
- Cannulate the umbilical vein to a depth of NOT > 5-7cm in a term infant for catheter tip to be proximal to the portal sinus (for push-pull technique ET through UVC). Refer to section on procedure for umbilical vein cannulation.
- Aliquot for removal and replacement – 5-6mls/kg (Not more than 5-8% of blood volume).
  - Maximum volume per cycle – 20mls for term infants, not to exceed 5 ml/kg for ill or preterm infants.
  - To monitor vital signs closely – whether infant able to tolerate the aliquot per cycle.
- At the same time, the nurse keeps a record of the amount of blood given or withdrawn.

Isovolumetric or continuous technique

- Indication: where UVC cannulation is not possible e.g., umbilical sepsis, failed cannulation.
- Blood is replaced as a continuous infusion into a large peripheral vein while simultaneously removing small amount of blood from an arterial catheter at regular intervals, matching the rate of the infusion closely
  - E.g.: In a 1.5kg infant, total volume to be exchanged is 240mls.
  - Delivering 120mls an hour allowing 10 ml of blood to be removed every 5mins for 2 hours.
- Care and observation for good perfusion of the limb distal to the arterial catheter should be performed as per arterial line care

Points to note

- Warm blood with blood warmer OR Pre-warm blood to body temperature using a water bath.
- Avoid other methods, e.g., placing under radiant warmer, massaging between hands or placing under running hot water, to minimize preprocedural hemolysis of donor blood.
- Shake blood bag gently every 5-10 cycles to prevent settling of red blood cells.
- Rate of exchange: 3 -4 minutes per cycle (1 minute 'out', 1 minute 'in', 1-2 minute 'pause' excluding time to discard blood and draw from blood bag).
- Syringe should be held vertical during infusion 'in' to prevent air embolism.
- Total exchange transfusion duration should be 90-120 minutes utilizing 30-35 cycles.
- Begin the exchange transfusion with an initial removal of blood, so that there is always a deficit to avoid cardiac overload.
- Routine administration of calcium gluconate is not recommended.
- Remove the UVC after procedure unless a second exchange transfusion is anticipated and there was difficulty inserting the UVC.
- Continue intensive phototherapy after the procedure.
- Repeat exchange transfusion may be required in 6 hours for infants with high rebound SB.
- Feed after 4 hours if infant is well and a repeat exchange transfusion is not required.
- If infant is anemic (pre-exchange Hb <12 g/dL) give an extra aliquot volume of blood (10mls/kg) at the end of exchange at a rate of 5mls/kg/hr after the exchange transfusion.
- Avoid administering any medication during the procedure

Investigations

- Pre-exchange (1st volume of blood removed)
- Serum Bilirubin (total, direct and indirect)
- FBC
- Blood C&S via peripheral venous blood
- HIV, Hepatitis B (baseline)
- Others as indicated

Post-exchange
(Discard initial blood remaining in UVC before sampling)

- Serum Bilirubin (total, direct and indirect)
- FBC
- Capillary blood sugar
- Serum electrolytes and Calcium
- Others as indicated

Complications of Exchange Transfusion
Catheter related
Infection
Haemorrhage
Necrotizing enterocolitis
Air embolism
Vascular events
Portal, Splenic vein thrombosis (late)
Haemodynamic problems
Overload cardiac failure
Hypovolaemic shock
Arrhythmia (catheter tip near sinus node in right atrium)
Electrolyte/Metabolic disorders
Hyperkalemia
Hypocalcemia
Hypoglycaemia or Hyperglycaemia

Post ET Management

- Maintain intensive phototherapy.
- Monitor vital signs: Hourly for 4 - 6 hours, and 4 hourly subsequently.
- Monitor capillary blood sugar: Hourly for 2 hours following ET.
- Check serum Bilirubin 4 - 6 hours after ET.
- Maintain strict input and output record
- Monitor appearance of abdomen and lower limbs with routine observations for 24 hours
- Commence feeds after 3-4 hours if clinically stable, abdomen soft and not for repeat ET
- Observe for signs of feed intolerance: vomiting and abdominal distension

Follow-up

- Long term follow-up to monitor hearing and neurodevelopmental assessment.

Partial Exchange Transfusion

- To correct hyperviscosity due to polycythemia. Assuming whole blood volume is approximately 80 ml/kg

$$\text{Volume Exchanged (ml)} = \text{Blood Volume} \times \frac{\text{(Initial PCV – Desired PCV)}}{\text{Initial PCV}}$$

- To correct severe anemia without hypovolaemia

$$\text{Packed Cell Vol required (ml)} = 80 \text{ ml} \times \text{Bwt (kg)} \times \frac{\text{(Desired Hb – Initial Hb)}}{\text{22 g/dL - Hbw}}$$

Where Hbw is reflection of the Hb removed during partial exchange transfusion:
Hbw = = [Hb desired + Hb initial]/ 2

Chapter 23:
Vascular Spasm and Thrombosis

Thromboembolism (TE) is being increasingly recognized as a significant complication of intravascular catheters in sick newborn infants. Many factors contribute to neonatal catheter-related thrombosis, including the small caliber of the vessel, endothelial damage, abnormal blood flow, design and site, duration of catheterization and composition of the infusate, in addition to the increased risk of thrombus formation in sick infants. Sepsis, prematurity and central catheters are the most common correlates of thrombosis in the NICU (J Matern Fetal Neonatal Med 2022).

Risk factors for neonatal thrombo-embolism

Maternal Risk Factors
Oligohydramnios
Prothrombotic disorder
Pre-eclampsia
Diabetes
Intrauterine growth restriction
Chorioamnionitis
Prolonged rupture of membranes
Autoimmune disorders

Delivery Risk Factors
Emergency Caesarean Section
Fetal heart rate abnormalities
Instrumentation

Neonatal Risk Factors
Central catheters
Congenital heart disease
Sepsis
Birth asphyxia
Respiratory distress syndrome
Dehydration
Congenital nephritic/nephrotic syndrome
Necrotizing enterocolitis
Polycythemia
Prothrombotic disorders
Surgery
Extracorporeal membrane oxygenation
Prematurity

(J Pediatr 2018)

Definitions

- *Vascular spasm* – transient, reversible arterial constriction, triggered by intravascular catheterization or arterial blood sampling. The clinical effects of vascular spasm usually last < 4 hours from onset, but the condition may be difficult to differentiate from the more serious TE. The diagnosis of vascular spasm may thus only be made retrospectively on documenting the transient nature of the ischemic changes and complete recovery of the circulation.
- *Thrombosis* – complete/partial occlusion of arteries/veins by blood clot(s).

Assessment

Clinical diagnosis

- Peripheral arterial thrombosis/ vasospasm – pallor or cyanosis of the involved extremity with diminished pulses or perfusion.
- Central venous line (CVL) associated venous thrombosis – CVL malfunction, superior vena cava (SVC) syndrome, chylothorax, swelling and livid discolouration of extremity.
- Aortic or renal artery thrombosis – systemic hypertension, haematuria, oliguria.

Diagnostic imaging

- Contrast angiography is the "gold standard", but difficult to perform in critically ill neonates and requires infusion of radiocontrast material that may be hypertonic or cause undesired increase in vascular volume.
- Doppler ultrasonography – portable, non-invasive, useful to monitor progress over time. False positive and false negative results may occur, as compared to contrast angiography.

Additional diagnostic tests

- Obtain detailed family history in all cases of unusual or extensive TE.
- In the absence of predisposing risk factors for TE, consider investigations for thrombophilic disorders in severe and neonatal onset: anticardiolipin, antithrombin III, protein C, protein S deficiency.

Management of vascular spasm

- Immediate measures to be taken:
  - Lay the affected limb in a horizontal position.
  - If only one limb is affected, warm (using towel) the opposite unaffected limb to induce reflex vasodilatation of the affected limb.
  - Maintain neutral thermal environment for the affected extremity, i.e., keep heat lamps away from the area.
- Inform the paediatrician immediately.
- Consider removing the catheter. If mild cyanosis of the fingers or toes is noted after insertion of an arterial catheter, but peripheral pulses are still palpable, a trial of reflex vasodilatation with close observation is reasonable – check continuously to see that the cyanosis is improving within a few minutes. **A white or "blanched" appearing extremity is an indication for IMMEDIATE removal of the catheter**.
- Other risk factors contributing to thrombosis include dehydration, sepsis, and polycythemia. These factors may need to be corrected immediately.
- Maintain good circulatory volume. If there is no immediate improvement with removal of catheter, consider giving volume expansion of 10 ml/kg of normal saline.
- Topical nitroglycerine – using patch or topical 2% ointment at a dose of 4 mm/kg body weight, applied as a thin film over the affected body area; may be repeated after 8 hours. Monitor for hypotension and be prepared to treat immediately.
- If the limb ischaemia persists for > 1 hour without any improvement, refer urgently to the radiologist/ surgeon.
  An urgent doppler ultrasound scan is needed to ascertain whether the limb ischemia is caused by vasospasm or thrombosis.

Management of catheter-related thromboembolism

- Management of vascular TE may involve one or more of the following: supportive care, anticoagulation, fibrinolytic therapy, surgical intervention.
- Treatment for neonates is highly individualized and is determined by the extent of thrombosis and the degree to which diminished perfusion to the affected extremity or organ affects function.
- Consultation with a paediatric haematologist, orthopaedic or vascular surgeon may be required.
- Initial management
  - As for vascular spasm for peripheral arterial ischemia
  - Removal of catheter as soon as blanching is seen.
  - Supportive care – correct volume depletion, electrolyte abnormalities, anemia and thrombocytopenia; treat sepsis.
- Anticoagulant/ thrombolytic therapy
- The risk of serious bleeding associated with antithrombotic therapy in neonates must be balanced against the possibility of organ or limb loss or death without appropriate treatment. Data on the efficacy and safety of specific therapeutic agents in neonatal population are limited. (Chest 2012)

  - Contraindications:
    - Major surgery within the last 10 days.
    - Major bleeding: intracranial, pulmonary, gastrointestinal.
    - Pre-existing cerebral ischemic lesions.
    - Invasive procedures within 3 days
    - Known history of heparin induced thrombocytopenia or allergy to heparin.

  - Relative contraindications –
    - Platelet count < 50 $X10^9$/L; (100 $X10^9$/L for ill neonates)
    - Fibrinogen levels<100mg/dL
    - Severe coagulation factor deficiency
    - INR > 2
    - Hypertension

    Note: anticoagulation/thrombolytic therapy can be given after correcting these abnormalities.

  - Precautions:
    - no arterial punctures
    - no subcutaneous or IM injections
    - no urinary catheterizations
    - avoid aspirin or other antiplatelet drugs
    - monitor serial ultrasound scans for intracranial hemorrhage

- Anticoagulants
  - Standard or unfractionated heparin (UFH)
    - UFH should be limited to clinically significant thromboses with the goal of preventing clot expansion or embolism.
    - Anticoagulant, antithrombotic effect limited by low plasma levels of antithrombin in neonates. For dosage see Table below.
    - Optimal duration is unknown but therapy is usually given for 5-14 days
    - Monitor thrombus closely during and following treatment.
    - Complications: Bleeding (2% major hemorrhage rate), heparin- induced thrombocytopenia. Due to UFH short half-life, cessation of infusion usually resolves any bleeding. If not, correct any coagulation deficiencies

    Antidote: Protamine sulphate if anti-factor Xa > 0.8 u/ml:
    - see Table on next page for dosage. One mg of protamine neutralizes 100U UFH
    - Anti- Factor X activity (if available) aimed at 0.35-0.7 U/mL.
    - Baseline aPTT is prolonged at birth and aPTT prolongation is not linear with heparin anticoagulant effect. Therefore, Anti-factor X activity more effectively monitors UFH use in newborn infants.

Recommended dosing of unfractionated heparin (UFH)

Clinical indication	Traditional dosing	Current recommended dosing
Asymptomatic or symptomatic thrombus but non-limb threatening	*Bolus dose* 75 U/kg IV over 10 mins *Maintenance dose* 28 U/kg/h	**<28 wks GA** *Bolus dose* 25 U/kg IV over 10 mins *Maintenance dose* 15 U/kg/h **28-37 wks GA** *Bolus dose* 50 U/kg IV over 10 mins *Maintenance dose* 15 U/kg/h **> 37 wks GA** *Bolus dose* 100 U/kg IV over 10 mins *Maintenance dose* 15 U/kg/h

Monitoring:
- Maintain anti-factor Xa level of 0.35-0.7 U/ml (Target aPTT range 1.5-2 times upper limit of normal)
- Check anti-factor Xa level 4 h after loading dose and 4 h after each change in infusion rate
- Full blood count, renal profile, platelet count, and coagulation screening
- (including aPTT, PT and fibrinogen) should be performed before starting UFH therapy
- Platelet count and fibrinogen levels should be repeated daily for 2-3 days once therapeutic levels are achieved and at least twice weekly thereafter

Adjustment of UFH according to aPTT after loading and initial maintenance				
aPTT	**Bolus**	**Hold (mins)**	**% rate change**	**Repeat aPTT**
<50	50 U/kg for term	0	+10	4 hours
50-59		0	+10	4 hours
60-85		0	0	next day
85-95		0	-10	4 hours
96-120		30	-10	4 hours
>120		60	-15	4 hours
Once aPTT is in therapeutic range, a full blood count and aPTT can be checked daily or as clinically indicated				

Recommended dosing of protamine for reversal of heparin therapy	
Heparin: Time since last dosing	**Protamine dose**
< 30 min	1 mg/100 u heparin received
30-60 min	0.5 - 0.75 mg/100 u heparin received
60-120 min	0.375 - 0.5 mg/100 u heparin received
>120 min	0.25 - 0.375 mg/100 u heparin received
Maximum dose	50 mg
Infusion rate	10 mg/ml solution; rate < 5 mg/min

- Low molecular weight heparin (LMWH)
  - Advantages: Subcutaneous administration. Heparin induced thrombocytopenia is rarely associated with LMWH.
  - Although adverse effects are rare, major complications such as hematoma at site of injection, intracranial hemorrhage have been described.
  - Antidote: Omit 2 doses if an invasive procedure is required. Protamine is partially effective. If enoxaparin was given within 8 hours, give protamine 1mg per 1mg enoxaparin by intravenous slow push. If > 8 hours since last enoxaparin dose, give protamine 0.5mg per 1mg enoxaparin by slow intravenous push. (UpToDate)

  Note : LMWH have specific activity against factor Xa so therapy is monitored using anti-FXa and not aPTT. However, monitoring of anti-FXa levels may not presently be available in most laboratories.

Recommended dosing of low molecular weight heparin (LMWH)		
Clinical indication	**Traditional dosing**	**Current recommended dosing**
Asymptomatic or symptomatic thrombus but non-limb threatening	Subcutaneous (SC) 1.5 mg/kg q 12h	**Term neonates** SC 1.7 mg/kg q 12h **Preterm neonates** SC 2.0 mg/kg q 12h
Monitoring: • Goal of anti-factor Xa levels of 0.5-1.0 U/mL • Check level 4 hours after second dose and then weekly • If infants with high hemorrhagic profile, use dosing of SC 1mg/kg q 12 h • FBC should be monitored periodically depending on bleeding risks (Platelet should be maintained > 50 x 10^9 /L during treatment • Guidelines for adjusting LMWH therapy are published in other sources		

- Thrombolytic agents
  - Consider thrombolytic agents (r-tPA: recombinant tissue plasminogen activator is the thrombolytic agent of choice as has better clot lysis in vitro and lower risk of hypersensitivity) if there is limb/life threatening thrombus
  - Decision for thrombolytic therapy in newborns ideally be made by multidisciplinary team with input from surgical and hematology specialist because of high risk of major bleeding. Parents or caregivers should be involved in the decision-making process and be fully informed about the therapeutic options and risks.
  - Contraindications – related to increased risk of bleeding:
    - Major surgery or hemorrhage within previous 10 days
      Neurosurgery within 3 weeks
      Severe asphyxia event within 7 days
      Any invasive procedures within 3 days
      Seizures within 48 hours
      Prematurity < 32 weeks gestation
      Septicemia
      Active bleeding
      Inability to maintain platelets > 100 x10^9/L or fibrinogen > 100 mg/dL
  - Supplementation with plasminogen in the form of FFP is recommended to ensure adequate thrombolysis.
  - Thrombi that have been present for several days may be resistant to thrombolysis with failure rates up to 50%
  - Dosing tPA:
    - tPA 0.1-0.2 mg/kg/h (without loading) given over 6 hours. If response inadequate, can be repeated with an increase dose
    - Alternative regime of 24h infusion at initial dose of 0.03mg/kg/h with subsequent dose adjustment according to response (UpToDate)
  - Simultaneous infusion of UFH 10U/kg/h is recommended to inhibit clot propagation.

- Monitoring
  - Monitor fibrinogen levels, thrombin time and plasminogen levels, (if on UFH - coagulation profile) before starting, 4-6 hours after starting and 12-24 hourly thereafter.
  - Imaging studies of thrombus before initiation, 4-6 hours after starting and every 12-24 hours to allow discontinuation of treatment as soon as clot lysis is achieved.
  - Maintain fibrinogen >100-150mg/dL with cryoprecipitate (1U/5kg)
  - Platelet count –before initiation, 4-6 hourly after starting treatment, every 12-24 hourly thereafter – minimum of 100 $x10^9$/L dependent on bleeding risk
  - Cranial imaging before initiation and then daily
  - Complications: bleeding, embolization. Have compresses and localized thrombin available for localized bleeding.
- No IM injections, no arterial punctures, no urinary catheterization, no rectal temperature
- Alternative to thrombolytic therapy is surgical thrombectomy. This is rarely performed as the success of the procedure is limited by the small size of the blood vessel and clinical stability of the newborn with thrombosis.

Chapter 24:
Patent Ductus Arteriosus in the Preterm

Introduction

Gestational age is the most important determinant of the incidence of patent ductus arteriosus (PDA). The other risk factors for PDA are lack of antenatal steroids, respiratory distress syndrome (RDS) and need for ventilation.

Clinical Features

- Wide pulse pressure / bounding pulses
- Systolic or continuous murmur
- Tachycardia
- Hyperactive precordium
- Apnoea
- Increased need for supplemental oxygen
- Increased work of breathing
- Increased in ventilator requirements
- Radiological evidence of cardiomegaly / pulmonary oedema

The clinical signs lag behind the echocardiography diagnosis of haemodynamically significant PDA by nearly 2 days.

Complications

- Congestive cardiac failure
- Intraventricular hemorrhage (IVH) / Periventricular Leukomalacia (PVL)
- Pulmonary hemorrhage
- Renal impairment
- Necrotising enterocolitis
- Retinopathy of prematurity
- Chronic lung disease

Diagnosis

- If echocardiography service is available, confirm and evaluate the significance of PDA
- Supportive PDA should be identified before commencement of pharmacological closure. The following supportive PDA should not be closed :
  - Duct dependent structural heart diseases
  - Persistent pulmonary hypertension of newborn
  - Right ventricular dysfunction
- Table 1 summarizes the echocardiography parameters to determine the haemodynamic significance of PDA (HsPDA).
  - Treatment is considered in moderate to severe haemodynamic significance
- In addition to echocardiographic indices, the HsPDA should be interpreted by considering the gestational and chronological age and by assessing the vulnerability of organs at risk for over circulation (the lungs), or hypoperfusion (e.g., the brain, intestines, and kidneys).

Parameter	Haemodynamic significance		
	Mild	Moderate	Severe
PDA diameter			
2D diameter (mm) PDA : LPA diameter ratio	< 1.5 < 0.5	1.5 – 3 0.5 – 1	≥ 3 ≥ 1
PDA Doppler			
Vmax (m/s) Systolic to Diastolic velocity ratio LV chamber dilatation (Z score)	2.5 <2 <+2.0	1.5 – 2.5 2 – 4 +2.0 - +3.0	< 1.5 > 4 > +3.0
Pulmonary Overcirculation			
LA to Ao ratio Mitral valve E to A ratio IVRT (m/s) LPA Vmax diastole (m/s) LVO 9ml/kg/min) Pulmonary Vein D wave (m/s)	< 1.5 < 1 > 40 < 0.3 < 200 < 0.35	1.5 – 2 < 1 30 – 40 0.3 – 0.5 200 – 300 0.35 – 0.45	> 2 > 1 < 30 > 0.5 > 300 > 0.45
Systemic Hypoperfusion			
Abdominal Ao diastolic flow Celiac artery diastolic flow MCA diastolic flow	Forward Forward Forward	Absent Absent Forward	Reversed Reversed Absent / Reversed

2D, Two-dimensional; Ao, aorta; IVRT, isovolumic relaxation time; LA, left atrium; LPA, left pulmonary artery; LV, left ventricle; LVO, left ventricular output; MCA, middle cerebral artery; PDA, patent ductus arteriosus; Vmax, maximum velocity.

Management

- Supportive therapy
  - Adequate positive end-expiratory pressure (PEEP) to reduce left-to-right ductal flow and improve systemic blood flow
  - Maintenance of hematocrit at 35 to 40 percent
  - Judicious fluid restriction (be careful not to compromise on nutrition/growth and systemic perfusion)
  - Avoidance of loop diuretics during pharmacological closure (eg. Frusemide), but consider thiazide diuretics (eg. Hydrochlorothiazide) or potassium sparing diuretics (e.g. Spironolactone) instead if indicated

- Pharmacologic closure
  - Indicated for preterm infants with haemodynamically significant PDA, still requiring ventilator support
  - Use IV if oral contraindicated in infant with abdominal signs

Drug	Route	Dosage	Frequency	Comments
Indomethacin	IV / Oral	**< 48 hours of life :** Day 1 : 0.2 mg/kg/dose Day 2 & 3 : 0.1 mg/kg/dose **>48 hours of life :** Day 1 - Day 3 : 0.2 mg/kg/dose	Daily for 3 days	**IV** : infusion over 20 – 30 minutes Inspect for particulate matter and discolouration prior to administration **Oral** : ensure that suspension is freshly prepared and well mixed before serving
Ibuprofen	IV / Oral	**Low dose :** Day 1 :10 mg/kg/dose Day 2 & 3 : 5 mg/kg/dose **> 72 hours of life (High dose) :** Day 1 :20 mg/kg/dose Day 2 & 3 : 10 mg/kg/dose	Daily for 3 days	**IV** : infusion over 15 – 30 minutes **Oral** : give via intragastric tube with milk feeds to minimize risk of gastrointestinal irritation. If NBM, give via intragastric tube and flush with 0.5 ml water for injection
Paracetamol	IV / Oral	15 mg/kg/dose	6 hourly for 3 – 7 days	**IV** : Infusion over 15 minutes **Oral** : Can be given with or without feeds. Shake bottle well before measuring dose

- Contraindications for pharmacologic closure :
  - Infant is proven or suspected to have infection that is untreated
  - Bleeding, especially active gastrointestinal or intracranial
  - Platelet count < 60 x 10^9 /L
  - NEC or suspected NEC
  - Impaired renal function : creatinine > 140 µmol/L, blood urea > 14 mmol/L.
  - Duct dependent structural heart disease
  - Persistent pulmonary hypertension of newborn
  - Right ventricular dysfunction

- Monitor:
  - Urine output and renal function. If urine output <0.6 ml/kg/hr after a dose given, withhold next dose until output back to normal.
  - GIT complications e.g. gastric bleeding, perforation.
  - Hyperbilirubinemia (ibuprofen)
  - Liver toxicity (ALT > 50 iU/L for paracetamol usage)
  - Pulmonary hypertension (ibuprofen)

- Surgical ligation / Transcatheter Closure
  - Persistence of a symptomatic PDA and failed 2 courses of pharmacological treatment
  - If medical treatment fails or contraindicated

- In older preterm infant who is asymptomatic, i.e. only cardiac murmur present in an otherwise well infant – no treatment required. Follow-up as necessary. Most PDA in this group will close spontaneously.

Pearls and Pitfalls in Management

- There is a higher success rate in closure of PDA if indomethacin is given in the first two weeks of life.
- For infants who fail to respond to initial pharmacological therapy, a second course results in 40 percent rate of ductal closure
- Consider different pharmacological agents for the second course therapy if feasible
- Oral ibuprofen has similar efficacy compared to IV ibuprofen

Chapter 25:
Persistent Pulmonary Hypertension of the Newborn

Introduction

Persistent pulmonary hypertension (PPHN) of the newborn is a syndrome of failed circulatory adaption at birth. It is characterized by

- Elevated pulmonary vascular resistance (PVR) resulting in decrease pulmonary flow
- Right (R) to left (L) shunting of deoxygenated blood across the PFO and PDA result in differential cyanosis. Oxygen saturation in the lower limb is 5-10% lower than right upper limb.
- Labile hypoxaemia with marked change in oxygen saturation with minimal or no change in settings of ventilator due to changes in the volume of R to L shunt.

Classification

- *Underdevelopment:* hypoplastic vasculature e.g., congenital diaphragmatic hernia, pulmonary hypoplasia in oligohydramnios secondary to renal disease or chronic leakage of amniotic fluid.
- *Maldevelopment:* normal lung with remodeled pulmonary vasculature as in idiopathic PPHN, chronic fetal hypoxia
- *Maladaptation:* parenchymal lung diseases e.g., Meconium Aspiration Syndrome (MAS), Pneumonia/ sepsis, Respiratory Distress Syndrome (RDS), asphyxia
- Intrinsic Obstruction: polycythaemia with intravascular obstruction and increase PVR.

Diagnosis

- PPHN is clinically suspected in near term or term infants who have variable oxygen saturation.
- Physical Examination - some of the infants may have signs of respiratory distress. Single loud second heart sound.
- Differential pre and post ductal oxygen saturation (between 5-10%). Lack of differential does not preclude PPHN.
- ABG – Hypoxaemia disproportional to degree of lung disease.
- 2D Echocardiography with colour flow doppler confirm diagnosis with right to left shunting at PFO and PDA.
- Hyperoxia test if no 2D Echo available: PaO_2>150 mmHg in FiO_2 100% for 5-10 min excludes most CHD. A PaO_2 < 150 mmHg doesn't exclude congenital heart disease or PPHN.
- Chest x-ray – evidence of underlying parenchymal disease e.g. MAS, RDS, pneumonia. Oligaemic lung fields in idiopathic PPHN.
- FBC with differential to evaluate for high hematocrit level (polycythaemia) and risk of underlying infection.

Differential Diagnosis

- Differentiating PPHN from cyanotic heart disease soon after admission is important.
- Preductal and postductal oxygen saturations of more than 5-10% or PaO2 differences of 10-20 mmHg between right upper limb and lower limbs helps to differentiate PPHN from structural heart disease.
- The diagnosis is confirmed with 2D Echocardiography which may not be available in all hospitals.

Management

PPHN management involves restoration of the cardiopulmonary adaptation and to minimize ventilator- and oxygen-induced pulmonary injury.
This includes treatment of the underlying disease, maintenance of normal systemic BP, decrease pulmonary vascular resistance and ensure adequate tissue oxygenation.

- Supportive care
  - Maintain normothermia, correct metabolic and hematologic abnormalities e.g., hypoglycemia, hypocalcaemia, hypomagnesaemia, polycythaemia and acidosis. Antibiotics if clinically indicated.
  - Ensure minimal handling and stimulation
  - Provide sedation and analgesia as required to avoid agitation and asynchrony with ventilator, e.g., morphine infusion 10-20 mcg/kg/hr.
  - In the event of systemic hypotension, a fluid bolus of 10ml/kg of normal saline can be given, followed by dopamine 5-10 mcg/kg/min or noradrenaline of 0.05 – 0.5mcg/kg/min. Higher doses of dopamine infusion can aggravate PVR disproportionately to systemic vascular resistance (SVR). There is some evidence that noradrenaline may selectively reduce PVR and increase SVR.
- Mechanical ventilation
  - Avoid underinflation and overinflation of the lungs as this leads to increase in PVR
  - Adopt “Gentle” ventilation strategies with optimal PEEP and relatively low PIP or tidal volume (TV) for adequate lung expansion. Aim is to limit volutrauma, barotrauma and atelectrauma.
  - Consider HFOV if PIP > 28 and TV > 6ml/kg are required to maintain lung expansion and good gas exchange.
  - Target PaO_2 55-80 mmHg, with permissive hypercapnia and pH 7.30-7.45. Avoid hyperoxaemia.
- Surfactant therapy may be considered in PPHN secondary to parenchymal lung disease - RDS, MAS and pneumonia (benefit is greatest for mild to moderate disease).
- Inhaled Nitric Oxide (iNO)
  - Potent vasodilator which selectively dilates the pulmonary circulation without decreasing systemic BP.
  - Indicated in neonates with PPHN with oxygenation index (OI)> 15-25. Start at 20 ppm. Response should be fairly rapid.
  - Once a sustained response is seen, FiO_2 is gradually weaned to ≤ 60%. iNO can be weaned from here on by 5ppm every 4 hours (or as dictated by blood gas). There should be a sustained rise in PaO_2 of at least ≥ 60mmHg (pre- ductal SaO_2 ≥ 90%) in between weaning. Once iNO is 5 ppm, wean by 1 ppm every 4hours. Gradual weaning prevents rebound pulmonary vasoconstriction.

- Sildenafil
  - Can be considered for the following indications for treatment of PPHN:
    a. An adjuvant to iNO in NO-resistant PPHN or to facilitate weaning of iNO where weaning has been difficult or slow
    b. Primary treatment of PPHN where iNO is not available or is contraindicated
  - Its safety and effectiveness have not been established in large RCTs. Until further evidence is available, the initial dosing strategy would include initiating therapy with oral sildenafil at 0.5 mg/kg/dose 6-hourly and if there is no response, increasing the dose up to a maximum of 2 mg/kg/dose.
  - Response time varies from 20 minutes to 3 hours after oral administration. Duration of treatment is not yet well defined, and one approach is to taper off the medication after a clear response and improvement is seen in the infant.
  - The treatment should also be discontinued after 6-8 doses if there is no improvement. It should be reduced or stopped completely if hypotension develops despite inotropic support.
- Intravenous magnesium sulphate ($MgSO_4$) can cause reduction of pulmonary artery pressures in animal studies. Only observational studies are available showing it can be helpful in infants. It is associated with systemic hypotension. In centers without iNO, $MgSO_4$may be used. A loading dose of 200 mg/kg $MgSO_4$ is given intravenously over 20 minutes followed by continuous infusion at the rate of 20- 50mg/kg/h to obtain a serum magnesium level between 3 - 5.5 mmol/l. Inotropes may be required to keep mean arterial blood pressure between 40-45 mmHg. Some of the studies commenced on dopamine 5-10mcg/kg/min prior to starting magnesium therapy.
- Other agents: e.g., Milrinone, Alprostadil (prostaglandin E1) are not recommended to be used without supervision and in consultation with a Neonatologist or Paediatric Cardiologist. It is advisable to have ECHO facilities readily available for guiding therapeutic decisions in these complex situations.
- ECMO is a supportive measure that allows the neonatal heart and lung to recover from the underlying disease in iNO resistant PPHN. It is not available in this country. Newer therapies – Superoxide dismutase, arginine, bosentan and citrulline are under investigation
- Nutritional support should not be overlooked in the overall management of the infant.
- Developmental outcomes – long term multidisciplinary follow up is necessary as PPHN is associated with neurodevelopmental, cognitive and hearing abnormalities.

Chapter 26:
Ophthalmia Neonatorum

Definition

Conjunctivitis occurring in the first 28 days of life with clinical signs of erythema and oedema of the eyelids and palpebral conjunctiva, purulent eye discharge with one or more polymorphonuclear cell per oil immersion field on a Gram stained conjunctival smear.

Diagnosis

- Essentially a clinical diagnosis
- Laboratory diagnosis to determine aetiology
- Eye swab for Gram stain (fresh specimen to reach laboratory in 30 mins)
- Gram stain of intracellular gram negative diplococci - high sensitivity and specificity for Neisseria gonorrhoea.
- Eye swab for culture and sensitivity.
- Conjunctival scraping for indirect fluorescent antibody identification for Chlamydia
- Nucleic acid amplification tests (NAATs) - gold standard for diagnosing Chlamydia (not available in Malaysia)

Aetiology

Sexually transmitted bacteria (*Neisseria gonorrhoea, Chlamydia trachomatis*), non-sexually transmitted bacteria mainly from gastrointestinal tract and skin, virus (adenovirus, herpes virus and enterovirus) and chemical.

Gonococcal

- Most important bacteria by its potential to damage vision.
- Typically presents with profuse exudate and swelling of the eyelids 2 to 5 days after birth.
- Without treatment, the infection can extend from superficial epithelial layers into the subconjunctival connective tissue and the cornea, leading to ulceration, scarring, and visual impairment.
- The infant should be hospitalized and observed for response to therapy and for disseminated disease (e.g. arthritis, sepsis, meningitis)
- Presumptive treatment should be started after obtaining cultures in high risk group (e.g. mother with no prenatal care, history of sexually transmitted diseases (STD), or substance abuse)
- Treatment:
  - Systemic: Ceftriaxone 25-50mg/kg (max. 250 mg) IV or IM single dose, or Cefotaxime 100 mg/kg IV or IM single dose (preferred if premature or hyperbilirubinaemia present)
  - The eyes should be irrigated frequently with sterile normal saline until the discharge clears. Topical antibiotic therapy alone is inadequate.
  - Disseminated infections : Ceftriaxone 25-50mg/kg/day IV or IM in single daily dose for 7 days, or Cefotaxime 25mg/kg/dose every 12 hours for 7 days and 10-14 days for meningitis.
  - *Note: Ceftriaxone is not recommended for use in preterm infants, neonatal hyperbilirubinaemia and concurrent administration in calcium containing solutions*
- For asymptomatic infants whose mothers have untreated gonococcal infection, treatment with a single dose of one of the following: Ceftriaxone 25-50mg/kg (max. 250 mg) IV or IM single dose, or Cefotaxime 100 mg/kg IV or IM single dose or Ceftazidime 50mg/kg IV or IM single dose.
- Preventive measure is the most effective by diagnosing and treat the infection in pregnant women.

Chlamydia

- Unilateral or bilateral conjunctivitis with peak incidence between 5 to 14 days of life.
- Eye discharge is initially copious then becoming mucopurulent. It is associated with eye swelling and chemosis.
- Untreated infants may have persistent conjunctivitis for months that may result in corneal and conjunctival scarring.
- Treatment:
  - Empirical treatment until the result is available.
  - Oral azithromycin 20mg/kg once daily for 3 days.
  - Erythromycin base 50mg/kg/d in 4 divided doses for 14 days, is an alternative.
    - Note: Caution both azithromycin and erythromycin are associated with increased risk of hypertrophic pyloric stenosis
  - Topical therapy is not effective.

Other bacterial causes

- Includes Staphylococcus aureus, Streptococcus viridans, Haemophilus, E.coli, Klebsiella species and Pseudomonas. Most are hospital acquired conjunctivitis which can be treated with topical antibiotics except for Pseudomonas.
- Ophthalmia neonatorum caused by Pseudomonas is rare but may cause corneal perforation, endophthalmitis and blindness. These infants need assessment by an ophthalmologist and require a combination of systemic and topical aminoglycosides with occasional subconjunctival injection.
- Treatment:
  - Local: Chloramphenicol, gentamicin eye ointment 0.5%, both eyes (Change according to sensitivity, duration according to response), or in non-responsive cases refer to ophthalmologist and consider Fucithalmic, Ceftazidime 5% ointment bd to qid for a week. Eye toilet
  - Local treatment may be unnecessary if systemic treatment is given.

Herpes simplex virus

- Uncommon, accounting less than 1% of ophthalmia cases
- High index of suspicion in infants with unilateral chemosis, serosanguineous discharge that rarely becomes purulent, presence of vesicular lesions surrounding eyelids or oral ulcers and lymphadenopathy
- Early detection and prompt treatment to prevent complications including disseminated disease and meningoencephalitis.
- Systemic treatment
  - IV Acyclovir 30mg/kg/d in 3 divided doses for 14 days
  - Topical 0.15% Ganciclovir or 1% Trifluridine

Important Notes

- Refer infants to an ophthalmologist for assessment.
- Ophthalmia neonatorum due to gonococcal or *Chlamydia trachomatis* infection is a notifiable disease
- Check VDRL of the infant to exclude associated congenital syphilis and screen for *C. trachomatis* and HIV.
- If positive, the parents should be referred to STD clinic for further assessment and management.

Chapter 27:
Perinatally Acquired Varicella and Postnatal exposure to Varicella infection

Introduction

- In maternal infection (onset of rash) within 7 days before and 7 days after delivery 17-30% develops neonatal varicella with lesions appearing 5-10 days of life. Mortality can be as high as 20% since these infants have not acquired maternal protecting antibodies. Cause of death is due to severe pulmonary disease or widespread necrotic lesions of viscera.
- When maternal varicella occurs 7-21 days before delivery, lesions typically appear in the first 4 days of life and prognosis is good with no associated mortality. The mild course is probably due to the production and transplacental passage of maternal antibodies that modify the course of illness in newborns.
- Infants born to mothers who develop varicella between 7 days before delivery or 7 days after delivery should receive as prophylaxis
    - Varicella Zoster immunoglobulin (VZIG) 125 IU IM as soon as possible after delivery or within 96 hours of initial exposure (to reduce the occurrence of complications and fatal outcomes). Attenuation of disease might still be achieved with administration of VariZIG™ up to 10 days after exposure.
    - For infants born to mothers who develop varicella between 5 days before and 2 days post delivery, add IV acyclovir 15 mg/kg/dose over 1 hour every 8hrly (total 45 mg/kg/day) for 5 days.
    - If Zoster immunoglobulin is not available give IV Immunoglobulin 400 mg/kg (this is less effective) AND IV Acyclovir 15 mg/kg/dose over 1 hour every 8hrly (total 45 mg /kg/day) for 5 days.
    - On sending home, warn parents to look out for new vesicles or baby being unwell, for 28 days after exposure. If so, parents to bring the infant to the nearest hospital as soon as possible (62% of healthy such neonates given VZIG after birth)
- If vesicles develop, give Acyclovir 15 mg/kg/dose over 1 hour every 8hrly (total 30-45 mg /kg/day) for 7-10 days.
- Women with varicella at time of delivery should be isolated from their newborns, breast-feeding is contraindicated. The newborn infant can receive expressed breast milk in the meantime and breast-feeding commenced when all the mother's lesions have crusted.
- Neonates with varicella lesions should be isolated from other infants but not from their mothers.
- It has been generally accepted that passive immunization of the neonate can modify the clinical course of neonatal varicella but it does not prevent the disease and, although decreased, the risk of death is not completely eliminated
- Infants whose mothers develop Zoster before or after delivery have maternal antibodies and they will not need VZIG.
- Recommend immunisation of family members who are not immune.

Assessing the significance of varicella exposure

- The index case could be the health care professional, a family member or a patient
- There should be close contact with the index case:
  - Maternal/neonatal contact.
  - Contact between health care professional or family member and patient
  - Contact in the same room, including large open wards, for 15 minutes or more.
  - Face to face contact, as in conversation.

Postnatal exposure to varicella in the hospital

- Give VZIG within 96 hours to those who have been exposed if they fit the following criteria:
  - All infants born at < 28 weeks gestation or who weighed < 1000g at birth irrespective of maternal history of chickenpox. This group has increased risk of severe varicella up to 6 weeks after birth.
  - All preterm infants born at ≥28 weeks gestation whose mothers have not had chickenpox or whose status is unknown.
  - Infants with significant non-maternal exposure to VZV within the first 7 days of their life if mother have never had varicella infection
  - All immunocompromised infants such as those undergoing immunosuppressive therapy, have malignant disease or are immunodeficient, severe underlying skin disorder.
  - Note that infants who are more than 60 days old or has been given blood transfusion may be VZIG negative even though there is a positive history of maternal varicella – to counsel parents to observe for varicella lesions so infants can be treated early
  - Monitor at risk infant up till end of incubation period i.e. 28 days post initial exposure. Non-immunocompromised infant who can be monitored closely at home and have easy access to hospital, can be discharged earlier.
  - Isolate infant who has varicella infection and susceptible infants who have been exposed to the virus. Treatment of symptomatic infants with acyclovir as above.
  - Screen exposed, susceptible hospital staff for skin lesions, fever, headache and systemic symptoms. They are potentially infective 10-21 days after exposure and should be placed on sick leave immediately should any symptoms or skin lesion arise. If possible, they can also be reassigned during the incubation period to areas where the infants are not as susceptible or non-patient care areas.

Other notes

- In hospitals, airborne transmission of VZV has been demonstrated when varicella has occurred in susceptible persons who have had no direct contact with the index case-infant.
- Incubators are not positive pressure air flow & therefore do not provide isolation. Neonates may not be protected given that they are frequently open for nursing purposes.
- All staff should preferably be screened, and susceptible staff vaccinated for varicella before commencing work in neonatal, oncology and ICU wards. If not, they should receive post exposure vaccination as soon as possible unless contraindications exist such as pregnancy. Post-exposure VZIG to be given to non-immune pregnant staff up to 10 days post initial exposure to prevent complications in the mother and may reduce the risk of fetal varicella syndrome.
- The use of VZIG following exposure does not necessarily prevent varicella and may prolong the incubation period by > 1 week and hence signs or symptoms should be observed for 28 days post exposure.
- VZIG is not presently recommended for healthy full-term infants who are exposed postnatally, even if their mothers have no history of varicella infection. To emphasise to parents to bring back early for treatment with acyclovir if any skin lesion appears within the next 3 weeks.

Chapter 28:
Management of Perinatal Hepatitis B Virus (HBV) transmission (Exposed Infants)

Introduction

The risk of a child developing chronic HBV infection is about 90% when infected perinatally. In Malaysia, universal hepatitis B immunization of newborns has been implemented since 1989.

1. Postnatal Management

Table 1: Hepatitis B Newborn Prophylaxis Protocol

Maternal HBsAg status	Recommendation
HBsAg ± HBeAg positive	• Administer HBIG (Hepatitis B Immunoglobulin) • Administer single-antigen hepatitis B vaccine (birth dose) * within 12 hours of birth. • If possible, both should be given at the same time but in **separate thighs** using separate needles and syringes. • Complete the 4-doses Hepatitis B vaccine series. • (3 Hepatitis B-containing combination vaccine at ages 2, 3, and 5 months with a booster at 18 months (according to the Malaysian National Immunization Programme)
Negative	• Administer single-antigen Hepatitis B vaccine* within 24 hours of birth. • Complete the 4-doses Hepatitis B vaccine series
Unknown (with high risk factors #)	• Test mother for HBsAg. • Administer single-antigen hepatitis B vaccine* within 12 hours of birth • Give HBIG if test positive (must be given **within 7 days of birth**) • Complete the 4-doses Hepatitis B vaccine series

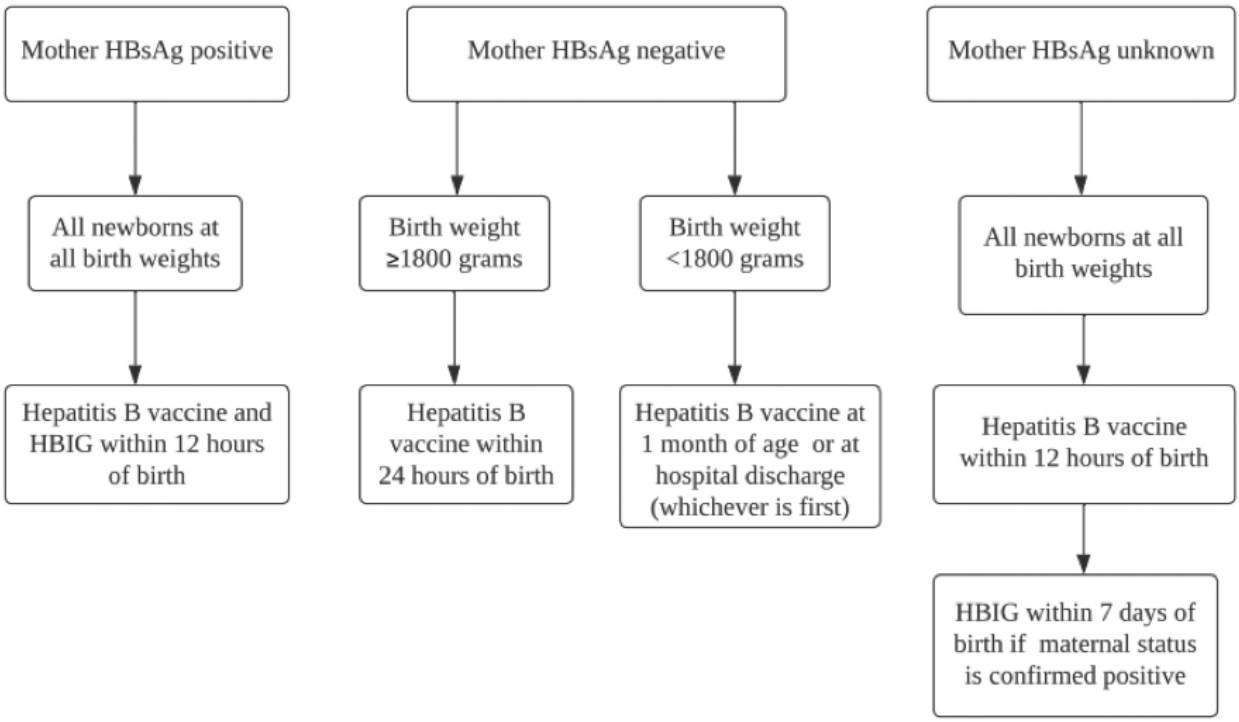
**Do not count the birth dose as part of the vaccine series.*

 # High risk pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g., having more than one sex partner during the previous 6 months, been evaluated, or treated for an STI, recent or current injection-drug use, or having had an HBsAg-positive sex partner)

2. Preterm and/or low birth weight infants

- Low birth weight and preterm newborn infants have decreased immune response to Hepatitis B containing vaccines compared to full-term infants.
- For low-birth-weight infants (<1800 g) and/or those born at <32 weeks' gestation (irrespective of birth weight), it is recommended that the infants complete 4-doses Hepatitis B schedule vaccination (the birth dose is not considered part of the vaccination series)

Figure 1: Administration of Birth Dose of Hepatitis B vaccine by Birth weight and Maternal HBsAg status



Modified from American Academy of Pediatrics, Committee on Infectious Diseases, Committee on Fetus and Newborn. Elimination of perinatal hepatitis B; providing the first vaccine dose within 24 hours of birth. Pediatrics,2017

3. Postvaccination serologic testing (PVST)

- PVST is done to evaluate the effect of hepatitis B immunization and identifying HBV infection in infants. The recommended testing for the infant:
  1) Hepatitis B surface antigen (HBsAg) and level of anti-HBs (antibody to HBsAg)
  2) Timing of measurement:
     a) 9-12 months of age, OR
     b) 1–2 months after the final dose of the vaccine series (if the series is delayed).

4. Interpretation of PVST Results

Table 2: Interpretation of Postvaccination Serologic Testing Results

PVST results	Follow-up Management
1a) Anti-HBs - Positive Antibody Level ≥10 mIU/mL b) HBsAg - Negative	No follow up necessary. Infant is protected.
2a) Anti-HBs – Negative Antibody Level <10mIU/mL b) HBsAg - Negative	No response and infant is susceptible for infection. Needs additional follow up and vaccines Revaccination with an additional dose of monovalent Hepatitis B vaccine and receive PVST 1–2 months later. If repeated PVST still shows no response (anti-HBs remains <10 mIU/mL) the infant should receive two additional doses of monovalent Hepatitis B vaccine to complete the second series, followed by PVST 1–2 months after the final dose.
3a) Anti-HBs -Negative Antibody Level < 10mIU/mL b) HBsAg - positive	Infant is infected with Hepatitis B. Consult with the Paediatric Gastroenterologist for appropriate management and follow-up.

Caution:

1. Do not test the infant before 9 months of age, to avoid detecting anti-HBs from the HBIG given at birth and to maximize the likelihood of detecting late HBV infection.
2. Due to a decrease in antibody to hepatitis B surface antigen (anti-HBs), PVST should not be performed after 12 months of age

5. Breastfeeding

Breastfeeding is not a contraindication for infants born to mothers who are HBsAg positive. Mothers who were not treated with antivirals during pregnancy are encouraged to breastfeed if their newborns have received combined immunoprophylaxis composed of HBIG and hepatitis B vaccine.

6. Counselling

Counsel the mother regarding the necessity and importance of the following:

1. How hepatitis B spreads and how to prevent spreading it.
2. The need for and importance of her infant to complete the primary Hepatitis B vaccination program.
3. Testing her infant between 9 and 12 months of age to make sure the infant is protected and has no infection.
4. The need to get medical follow-up for herself and family members who may be HBV carriers.

Chapter 29:
Bronchopulmonary Dysplasia

Introduction

Bronchopulmonary dysplasia (BPD) is chronic lung disease that occurs in premature infants. Survivors with BPD have serious consequences ranging from chronic cardiopulmonary morbidity to growth failure and developmental delay.

Risk factors for Bronchopulmonary Dysplasia

Bronchopulmonary Dysplasia is a multifactorial disease affecting over 35% of extremely preterm infants Inflammation is one of the key drivers in the pathogenesis of BPD. Interactions of many antenatal, intrapartum and postnatal risk factors induce ongoing inflammation and subsequent aberrant repair process in the preterm lungs.

Prenatal risk factors	Perinatal risk factors	Postnatal risk factors
Intrauterine growth restriction Lack of antenatal corticosteroids Maternal chorioamnionitis Preeclampsia Maternal smoking	Low gestational age Low birth weight Male gender Low Apgar score Perinatal asphyxia	Mechanical ventilation Supplemental oxygen Sepsis Necrotizing enterocolitis Systemic inflammatory response Patent ductus arteriosus

Diagnosis

Preterm <32 weeks gestational age with persistent parenchymal lung disease confirmed by radiography and at 36 weeks post menstrual age requires the following intervention

Diagnosis based on prospective NICHD Jensen 2019 study

GRADES	Invasive ventilation	NIPPV/NCPAP	Nasal cannula flow>2L/min	Nasal cannula flow<2L/min
I MILD	-	-	-	FIO_2>21%
II MODERATE	-	FIO_2>21%	FIO_2>21%	-
III SEVERE	FIO_2>21%	-	-	-

Management

Prevention strategies

a. Avoid intubation and mechanical ventilation. Consider early CPAP use at delivery room for spontaneously breathing preterm infants
b. If invasive ventilation is required, to consider using volume targeted ventilation and early timely extubation to non-invasive respiratory support
c. Minimally invasive surfactant therapy (MIST)/Less Invasive Surfactant Administration (LISA) has been shown to reduce incidence of BPD.

d. Caffeine administration to all infants <30 weeks' gestation reduces the risk of BPD and shortens duration of ventilation and exposure to supplemental oxygen.
e. In preterm infants, target oxygen saturation between 90%-95% ranges
f. Postnatal Corticosteroids use

- Postnatal systemic corticosteroids therapy improves short term lung function and pulmonary outcome of infants with established BPD and reduces risk of BPD in high-risk preterm infants.
- Postnatal steroid therapy is used to prevent and treat BPD. Its use is associated with short and long-term complications.

Short term side effects	Long term side effects
Hyperglycemia Hypertension Intestinal /gastric perforation Late onset sepsis Adrenal suppression	Increased risk of cerebral palsy and neurodevelopmental impairment Hypertrophied cardiomyopathy Severe Retinopathy of prematurity

*Parents should be counselled on the complications of corticosteroid therapy

- To minimize the complications, late systemic use (>8 days) is recommended over early corticosteroids.
- Current recommendations are that postnatal corticosteroids therapy should be reserved for preterm infants who are ventilator-dependent after the first 7-14 days of life and any course should be of low dose and of short duration to facilitate endotracheal extubation
- Suggested low dose dexamethasome regimen (DART) (total cumulative dose 0.89mg/kg)

  - 75mcg/kg/dose 12 hourly for 3 days then
  - 50mcg/kg/dose 12 hourly for 3 days then
  - 25 mcg/kg/dose 12 hourly for 2 days then
  - 10 mcg/kg/dose 12 hourly for 2 day

Long Term Management of Bronchopulmonary Dysplasia

For those with established BPD, the aim of management should be to decrease the risk of early childhood death, prevent cardiovascular disease, optimize growth and ensure appropriate neurodevelopmental outcomes.

General Measures

a. Adequate nutrition for high energy needs in infants with BPD to ensure adequate lung growth and repair.
b. Consider fluid restriction at 150mls/kg/day with caloric-dense feeds to improve lung function and gas exchange. (Low evidence)
c. Immunization – following the national immunization schedule for Malaysia. Passive immunization e.g. Palivizumab or Nirsevimab should be considered for RSV prevention in infants born ≤28 weeks' gestation with an established diagnosis of BPD. Consider annual Infuenza/Flu immunization for the high-risk BPD cohort.
d. Family counselling regarding awareness of environmental irritants, mainly secondary smoke inhalation and minimizing risk of infection. This is to minimize further lung damage.
e. Monitoring with lung imaging for those with severe BPD, severe respiratory symptoms and/or recurrent hospitalizations for respiratory morbidity.

f. Acute episodes of pulmonary decompensation, in the form of exacerbations should be managed based upon the underlying aetiology (infections, severe airway reactivity, pulmonary oedema, tracheobronchomalacia, etc.)
g. Assess for complications of BPD, including monitoring for pulmonary hypertension, systemic hypertension, left ventricular hypertrophy, cardiac dysfunction, growth failure and neurodevelopmental impairment.

Pharmacological intervention

a. Bronchodilators can be considered if there are features of airway hyperreactivity. Routine use is not recommended unless there is clinical evidence of acute bronchoconstriction from acute pulmonary decompensation and needs to be weaned off as soon as no long-term benefit is seen. Be aware of the malacic airway in this group of infants.
b. Inhaled corticosteroids can be considered in subgroups with severe BPD, severe respiratory symptoms, recurrent hospitalization due to respiratory morbidity and symptoms not controlled with regular use of bronchodilators. Clinical effects should be closely monitored during a trial period and discontinued when no positive impact or benefit is seen.

Oxygen supplementation

a. All infants with BPD and extreme preterm infants (<28 weeks' gestation) should ideally have an overnight pulse oximetry monitoring prior to discharge, with or without oxygen
b. For infants with BPD, supplemental oxygen therapy is recommended to maintain a minimum mean SpO_2 of 93%
c. All aspects of care need to be optimized prior to initiation of long-term oxygen therapy (consider airway problems, assess for pulmonary hypertension, manage reflux disease and nutritional requirements, as well as complete repair of inguinal hernia by 36 weeks).
d. Home oxygen therapy will require a multi-disciplinary team approach, with a referral to the Paediatric Respiratory team. Four aspects to be considered are:
    - The infant needs to be fit for discharge
    - A dedicated caretaker for the infant
    - Suitable and safe home
    - Availability of equipment.
e. Follow-up should be arranged in an ambulatory setting to facilitate patient care.

The clinical course in infants with BPD is complex, with multiple morbidities, frequent hospitalizations and often poor continuity of care. The formation of multi-disciplinary care has the potential to improve outcomes and survival in these infants.

Chapter 30:
Non- invasive Ventilation in Preterm Infants

Continuous positive airway pressure (CPAP)

- CPAP is an established mode of non-invasive ventilation (NIV) for infants.
- **Clinical benefits:** improves oxygenation, maintains functional residual capacity (FRC), decreases apnea, reduces work of breathing and splints the upper airways.
- **Limitations and risk:** nasal trauma, air leak syndromes, gastric distension ("CPAP belly")
- **Clinical indications:**
  a. Primary mode of respiratory support - as first line respiratory support for preterm infants. It can be used shortly after birth in spontaneous breathing preterm infants as prophylactic or early CPAP to prevent intubation and mechanical ventilation (MV).
  b. Post-extubation respiratory support
  c. Treatment of apnea of prematurity
- **Clinical management:**
  a. Optimum CPAP pressure is not known and depends on the underlying pathophysiology and severity of illness.
  b. CPAP pressures are generally set between 5-8 cm H_2O. Higher CPAP pressures can be associated with air leaks.
  c. Starting at a pressure 5-6 cm H_2O and increasing by 1 cm H_2O increments, adjusting based on O2 requirements and clinical assessment of work of breathing (WOB)
  d. Short binasal prongs and nasal mask are recommended over single or nasopharyngeal prongs.
  e. Various types of devices may be used to deliver CPAP -no definitive evidence to suggest which CPAP device is superior.
  f. It is more important for the clinical team to be familiar with the devices available and their management.
  g. The evidence regarding the optimum method of weaning is unclear. Gradual weaning of pressure has higher chance of success compared to sudden stopping of CPAP (sudden wean).

Biphasic CPAP, Bilevel CPAP, Duo PAP

- Flow drivers are used to deliver alternating cycles of low pressure and high-pressure at pre-specified intervals
- The high pressures (PIP) used vary between devices and generally range between 9 - 11cm H_2O. The high and low pressures difference is ≤ 4 cm H_2O
- The inspiratory time (IT) is longer (0.5–1 s) and respiratory rates are lower at 20-40/min.

Nasal intermittent positive pressure ventilation (NIPPV)

- NIPPV provides two levels of pressure:
  a. A constant positive end-expiratory pressure (PEEP) and
  b. A higher positive inspiratory pressure (PIP) without an endotracheal tube.
- Set PIP typically in the range of 15 - 22cm H_2O.
- The rate and IT for the PIP is set, making this a time-cycled pressure limited mode of NIV, mimicking invasive mechanical ventilation.
- NIPPV can be synchronized (S-NIPPV) or non-synchronized (NS-NIPPV). Synchronized NIPPV is preferred to non-synchronized NIPPV.
- Most of the conventional mechanical ventilator can deliver NS-NIPPV
- S-NIPPV can be delivered by some ventilators with specific triggering devices.
- **Clinical indications of Biphasic CPAP, Bilevel CPAP, Duo PAP and NIPPV:**
  a. Primary mode of respiratory support in situations where higher mean airway pressure than CPAP may be required.
  b. Post extubation respiratory support
  c. Treatment of apnea of prematurity

Heated Humidified High Flow Nasal Cannula (HHHFNC)

- HHHFNC uses smaller binasal prongs (cannula) than CPAP, with a simpler interface, and delivers heated, humidified gas at flows of more than 1 L/min.
- Typical flows between 2-8L/min is used.
- The pharyngeal distending pressure is not monitored and dependent on multiple factors: flow rate, size of nasal cannula, leak, airway anatomy, and weight of the infants.
- Do not occlude the nostrils and the preferred cannula to nares ratio ~ 0.5.
- Limited data on its use in extremely preterm infants < 28 weeks' gestational age or term infants
- Clinical benefits: less nasal trauma, reduced pneumothorax, more comfortable for the neonate and parent and nursing staff preference
- **Clinical indications:**
  a. Primary mode of respiratory support is associated with a higher rate of treatment failure compared with CPAP and is not recommended.
  For clinicians and units who wish to use as primary respiratory support, it is recommended that its use is limited to infants ≥ 30 weeks' gestation and FiO_2 30% on admission.*
  b. Post-extubation respiratory support in infants ≥ 28 weeks' gestation.*
  *CPAP should be available as a 'rescue therapy' to avoid intubation and MV in the event of failure.
  c. Apnea of prematurity - There is insufficient evidence to recommend its use
  d. 'Weaning' from CPAP. There is insufficient evidence to recommend its use. However, given its benefits, it may be an alternative in those infants with nasal trauma from CPAP.
- **Clinical management**
  a. Start at gas flow 4-6L /min. Choice of starting gas flow should consider the gestational age, disease pathophysiology and current clinical status (O_2 requirement and work of breathing)
  b. Consider escalating to CPAP if FiO_2 consistently > 0.4, continues to have increased work of breathing, increase rates of apnea or bradycardia.
  c. There is no consensus on how to wean HHHFNC. Consider weaning FiO_2 to < 0.3 before weaning flow.

Section 7

RESPIRATORY

Chapter 31:
Asthma

The National Health Mortality and Morbidity Survey 2023 reported that almost half a million children aged 6 to 17 years old in Malaysia have asthma. Prevalence of probable asthma was 7.1% and prevalence of doctor-diagnosed asthma was 5.3%. Asthma still gives rise to considerable morbidity as well as mortality.

Definition

- Asthma is a heterogenous disease with many phenotypes
- It is characterized by chronic airway inflammation, leading to variable/recurrent respiratory symptoms (such as wheeze, shortness of breath, chest tightness and cough) AND variable expiratory airflow limitation.
- Evidence of variable expiratory airflow limitation is demonstrated by:
  - Low FEV1/FVC ratio (at least once during diagnostic process)
  - Significant bronchodilator response/reversibility: > 12% improvement in FEV1 in children < 12 years old (> 12% AND > 200 ml improvement in > 12 years old) in response to administration of a bronchodilator PEF improvement
    - PEF improvement ≥15% post bronchodilator can be used if spirometry is not available.
  - Average diurnal variability ≥15% in children
  - > 12% improvement in FEV1 from baseline in children after 4 weeks of anti-inflammatory asthma treatment (>12% AND > 200 ml improvement in > 12 years old).
- Fractional Exhaled Nitric Oxide (FeNO) is an invasive biomarker of airway inflammation; thus, it helps to establish asthma diagnosis and monitor effectiveness of asthma medication (if the test is available).
- Whenever possible, try to document evidence for the diagnosis of asthma before starting controller treatment (it is more difficult to confirm diagnosis afterwards)

Diagnosis of asthma in children younger than 5 years old

A diagnosis of asthma in young children is often challenging as cough and wheeze are common symptoms either due to preschool wheezing disorders (i.e., viral-induced wheeze or multi-triggered wheeze) or acute bronchiolitis.

The diagnosis is mainly based on symptoms patterns combined with a careful clinical history and physical findings.

A structured clinical assessment to assess the probability of asthma should be based on:

A history of recurrent episodes of symptoms (symptoms of wheeze, cough, breathlessness and chest tightness that vary over time, usually precipitated by allergens, exercise, environmental triggers (e.g., tobacco smoke, dust, air pollutants) or respiratory infections. The variation of symptoms may occur spontaneously or with usage of β2 agonist bronchodilator and ideally demonstrated by variable peak flow measurement, if feasible.

- Recorded observation of wheeze heard by a healthcare professional
- Personal/family history of other atopic conditions (atopic eczema, allergic rhinitis) or asthma in first degree relative
- No other features to suggest alternative diagnoses

Important Points to Note in:	
Clinical History	**Physical Examination**
Current symptoms Pattern of symptoms Precipitating factors Present treatment Previous hospital/PICU admission Typical exacerbations Home/school environment Impact on life style History of atopy Response to prior treatment Prolonged URTI symptoms Family history	***Signs of chronic illness*** Harrison's sulci Hyperinflated chest Eczema/dry skin Hypertrophied turbinate ***Signs in acute exacerbation*** Tachypnoea Wheeze, rhonchi Hyperinflated chest Accessory muscles Cyanosis Drowsiness Tachycardia
Note: Absence of Physical Signs Does Not Exclude Asthma!	

A probability-based approach (Table 1), based on the pattern of symptoms during and between viral respiratory infections may be helpful in the diagnosis, allowing individual decisions to be made about whether to give a trial of controller treatment.

Table 1: Probability-based Approach of Asthma

Probability of asthma:	Low	Moderate	High
Duration of symptoms (cough, wheeze, heavy breathing) during URTI	< 10 days	> 10 days	> 10 days
Number of exacerbations	2-3 per year	>3 per year, or severe episodes	>3 per year, or severe episodes
Interval symptoms (between episodes or exacerbations)	No symptoms	occasional cough or wheeze	cough and/or wheeze during play/ laughing/exercise
Atopy	Nil	Nil	Present
Family history of asthma	Nil	Nil	Present

Some Pointers:

1. For high probability of asthma, a therapeutic trial of low to moderate dose ICS for at least 6 weeks may be commenced and clinical improvement with preventer treatment and worsening of symptoms when treatment is stopped is suggestive of asthma.
2. For low probability of asthma, evaluate for other diagnosis.
3. For intermediate probability of asthma, watchful waiting or a diagnostic trial of low dose of ICS for 3 months and assess response.

A positive family history of allergic disease or the presence of atopy/allergic sensitisation in the child with recurrent wheeze may predict the likelihood of evolving into atopic asthma and its risk may be determined by the modified Asthma Predictive Index (mAPI) (Table 2).

Table 2: Modified Asthma Predictive Index (mAPI)
Four or more wheeze episodes per year with at least 1 major OR 2 minor criterias

Major Criteria	Minor Criteria
Parental history of asthma	Eosinophilia (>4%)
Atopic Eczema (doctor diagnosed)	Wheeze unrelated to colds
Aero- allergen sensitisation	Allergic sensitisation to food i.e. milk, egg, peanuts

Red Flags and Pointers of Other Diagnosis:

- Failure to thrive
- Neonatal or very early onset of symptoms
- Vomiting/feeding problems with respiratory symptoms
- Chronic wet cough (> 4 weeks)
- Fixed monophonic wheeze/stridor
- Failure to respond to controller medications
- No associations of symptoms with typical triggers (eg. URTI)
- Focal / asymmetrical lung findings
- Cardiovascular signs
- Finger clubbing
- Hypoxaemia outside context of acute illness

MANAGEMENT OF CHRONIC ASTHMA

The long-term goals of asthma management for in all age groups are to achieve good symptoms control and risk reduction of asthma exacerbations, asthma-related death, and persistent airflow limitation and medications side-effects.

Good asthma control can be achieved through careful assessment, adjustment of medications and review of treatment response.

Treatment is individualised, taking into account patient's own goals and preference.

Partnership and effective communication skills are important part of management of any chronic diseases.

Inhaled Corticosteroids (ICS) are the recommended preventer drug for asthma treatment.

Newly diagnosed patients should be properly evaluated as to their degree of asthma severity or underlying background asthma (Table 3) and treatment should be started at the most appropriate step to the initial severity (Table 4 & 5)

The new paradigm in the latest GINA 2022 is to use ICS whenever SABA is taken (preferred) even in Step 1 for children < 12 years old. For adolescents (≥ 12 years), it's recommended to use as needed ICS-formoterol (preferred) or alternatively use ICS whenever SABA is taken or use regular low dose ICS, with as needed SABA (Table 4, 5 and 6). SABA alone is not recommended in this age group, as it increases the risk of severe asthma exacerbations.

The choice of preventer/controller is very much depending on cost, availability, expertise, preference of the physician and parental acceptance to ensure compliance.

Table 3: Evaluation of the background of newly diagnosed asthma

Category	Clinical Parameters
Step 1 (Intermittent)	• Daytime symptoms < once a week • Nocturnal waking with asthma < twice a month • No exercise induced symptoms • Brief exacerbations not affecting sleep and activity • Normal lung function
Persistent (Threshold for preventive treatment)	
Step 2 (Mild Persistent)	Daytime symptoms > once a week, < 4-5 days/week Nocturnal waking with asthma > twice a month Exacerbation affecting sleep and activity > once a month PEFR or FEV1 >80% Exercise or activity induced symptoms
Step 3 (Moderate Persistent)	Daytime symptoms daily Nocturnal waking with asthma > once a week Exacerbation affecting sleep and activity > twice a month PEFR or FEV1 60%-80% Exercise or activity induced symptoms
Step 4 (Severe Persistent)	Daily daytime symptoms Daily nocturnal symptoms Daily exercise induced symptoms Exacerbations > 2x/month affecting sleep, activity PEFR or FEV1 < 60%
• This division is arbitrary and the groupings may merge. An individual patient's classification may change from time to time. • There are patients with infrequent but severe or life- threatening attacks with completely normal lung function and no symptoms between episodes. • PEFR = Peak Expiratory Flow Rate; FEV1 = Forced Expiratory Volume in 1 Second.	

Step up treatment is indicated when control cannot be achieved at the current treatment level despite good compliance/adherence, correct inhaler technique, minimising exposure to precipitating factors, and treatment of co-morbidities and psychosocial factors, provided the asthma diagnosis is correct.

Step down treatment shall be considered when asthma control is achieved for at least 3 months with gradual reduction of ICS to the minimum dose required to maintain asthma control.

Table 4: Initial Treatment in Children 5 years and younger

	STEP 1	STEP 2	STEP 3	STEP 4
Preferred Controller Choice	N/A	Daily Low dose ICS (Diagnostic trial of 4-8 weeks)	Medium dose ICS	Continue controller and refer respiratory specialist for assessment
Other Controller options	Consider intermittent short course of ICS at onset of viral illness	*Daily Leukotriene receptor antagonist (LTRA) or Intermittent short courses of ICS at onset of respiratory illness*	*Low dose ICS + LTRA (consider paediatrician or family medicine specialist referral)*	*LTRA or Increase ICS frequency or Add intermittent ICS*
Reliever	*As-needed short-acting beta2-agonist (SABA)*			
Consider this step for children with:	Intermittent asthma (Infrequent viral wheezing and no or few interval symptoms/ unlikely asthma)	Persistent asthma symptoms or severe wheezing episodes	Asthma symptoms not well controlled on low dose ICS	Asthma symptoms not well controlled on medium dose ICS or combination therapy (LTRA)
			Evaluate 5 C (Correct diagnosis, **Compliance** evaluation, **Correct** inhaler technique, **Continuous** exposure to triggers, **Comorbidities** assessment)	

Table 5: Treatment in Children 6 years to 11 years

Asthma management based on levels of control is a step-up and step-down approach as shown in the table below:

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Preferred Controller Choice	Low dose ICS whenever SABA taken	Daily Low dose ICS (see table for ICS doses)	Low dose ICSLABA OR Medium dose ICS OR very low dose ICSFormoterol maintenance and reliever (MART)	Medium dose ICSLABA OR low dose ICSFormoterol maintenance and reliever (MART) Refer to paediatrician	Refer paediatric respiratory physician Asthma phenotypic assessment ± Higher dose ICS-LABA OR Add-on therapy eg LAMA (*Tiotropium*) anti-Ig E , Anti-IL4R, anti-IL 5
Other Controller options	Low dose ICS whenever SABA taken	*Daily LTRA OR low dose ICS whenever SABA is taken*	*Low dose ICS + LTRA*	*Add LAMA (Tiotropium) OR add LTRA*	Only as last resort, consider add-on low dose OCS but consider side effects
Reliever	As-needed short-acting beta2-agonist OR ICS-Formoterol reliever as MART in Step 3 and 4				
Footnote: ICS = Inhaled corticosteroids, LTRA= Leukotriene receptor antagonist, LABA = long acting beta2-agonist, LAMA= Long Acting Muscarinic Antagonist, MART= maintenance and reliever therapy, OCS = oral corticosteroids					

Table 6: Treatment in Adolescents ≥ 12 years

Asthma management based on levels of control is a step-up and step-down approach as shown in the table below:

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Preferred Controller Choice (Track 1)	AIR-only. Low dose ICS-Formoterol as needed		MART with low dose ICS-Formoterol maintenance	MART with medium dose ICS-Formoterol maintenance *Refer paediatric ian	Refer paediatric respiratory physician Asthma phenotypic assessment Add-on LAMA (*Tiotropium*) Consider trial of high dose ICS-Formoterol Consider biologics e.g., anti-Ig E, Anti-IL5/5R, Anti-IL4/4R, Anti-TSLP
Reliever	As-needed low dose ICS-Formoterol reliever as MART				
Other Controller options (Track 2)	Low dose ICS whenever SABA taken	Daily Low dose ICS	Low dose ICS-LABA LTRA	Medium dose maintenance ICS-LABA	Refer paediatric respiratory physician Asthma phenotypic assessment Add-on LAMA (*Tiotropium*) Consider high dose maintenance ICS-LABA Consider biologics e.g., anti-Ig E, Anti-IL5/5R, Anti-IL4/4R, Anti-TSLP
Other Controller options for either track		Low dose ICS whenever SABA taken, Or daily LTRA, Or add *HDM SLIT*	Medium dose ICS whenever SABA taken, Or daily LTRA, Or add *HDM SLIT*	Add LAMA Or LTRA, Or add *HDM SLIT* or switch to high dose ICS	*Add on Azithromycin (adult)* OR Add LTRA Or *low dose OCS but consider side effects*
Reliever	As-needed short-acting beta2-agonist				

Footnote: AIR = Anti-Inflammatory Therapy, ICS = Inhaled corticosteroids, LTRA= Leukotriene receptor antagonist, LABA = long acting beta2-agonist, LAMA= Long-Acting Muscarinic Antagonist, MART= maintenance and reliever therapy, OCS = oral corticosteroids, IL=Interleukin, TSLP= Thymic Stromal Lymphoprotein

Drug Therapy and Delivery Devices

In young children, an MDI and spacer is the preferred method of delivery of β2 agonists and inhaled corticosteroids.

Drug Therapy: Delivery systems available & recommendation for different ages.				
Age (years)	**Oral**	**MDI + Spacer with Mask**	**MDI + Spacer with Mouthpiece**	**Dry Powder Inhaler**
< 5	√	√	x	x
5 – 8	x	√	x	x
> 8	x	√	√	√
Note: MDI = Meter dose inhaler *Mask used should be applied firmly to the face of the child*				

Monitoring of Asthma Control (Review Response and Adjust Treatment) and Risk Factors for Poor Outcomes

Patient should be reviewed 1-3 months after starting treatment, then 3-6 monthly thereafter. Asthma assessment after initiation of treatment is based on levels of Asthma Symptoms Control (Table 7: symptoms control over 4 weeks) as well as risk factors for poor outcomes (Table 8), i.e., risks for future asthma exacerbation and persistent airflow limitation, and medication side effects.

Table 7: Asthma Symptoms Control

	Level Of Asthma Symptoms Control			
In the past 4 weeks, has the patient had:		Well controlled	Partly controlled	Uncontrolled
• Daytime asthma symptoms more than 2x/week? • Any night waking due to asthma? • Reliever needed for symptoms more than 2x/week? (Excluding pre-exercise use) • Any activity limitation due to asthma?	Yes☐No☐ Yes☐No☐ Yes☐No☐ Yes☐No☐	None of these	1-2 of these	3-4 of these

During each follow up visit, these issues need to be assessed. They are:

- Assessment of asthma control based on (Table 9):
- Interval symptoms (daytime symptoms, nocturnal symptoms causing night awakening, frequency of usage of rescue medication and exercise limitation).
- ACT or cACT (childhood Asthma Control Test) or ACQ (Asthma Control Questionnaire) can be used to assess symptoms control.
- Frequency and severity of acute exacerbation.
- Morbidity secondary to asthma.
- Quality of life.
- Lung function - spirometry (FEV1) or Peak Expiratory Flow (PEF) is a useful indicator of future risk. Ideally it is measured at diagnosis, 3-6 monthly after starting treatment and monitored periodically 1-2 yearly thereafter (more frequent in severe or uncontrolled asthma).

Table 8: Risk Factors for Poor Asthma Outcomes

• Uncontrolled asthma symptoms • Medications: High SABA use, inadequate ICS, poor adherence, incorrect inhaler technique • Comorbidities: Obesity, chronic rhinosinusitis, OSAS, stress, reflux and confirmed food allergy • Exposures: Smoking, allergen exposure if sensitized, air pollution • Context: Major psychological or socio-economic problems • Lung function: Low FEV1, especially <60%predicted, high bronchodilator reversibility • Other test: blood eosinophils, elevated FeNO Other major independent risk factors for exacerbations • Ever intubated or in intensive care unit for asthma • ≥1 severe exacerbation in last 12 months
Risk factors for developing persistent airflow limitation • History: preterm birth, low birth weight and greater infant weight gain • Medications: lack of ICS treatment • Exposures: tobacco smoke, noxious chemical Investigations: low initial FEV1, blood eosinophilia
Risk factors for medication side effects • Systemic: frequent OCS, long term and high dose ICS • Local: High dose or potent ICS, poor inhaler technique

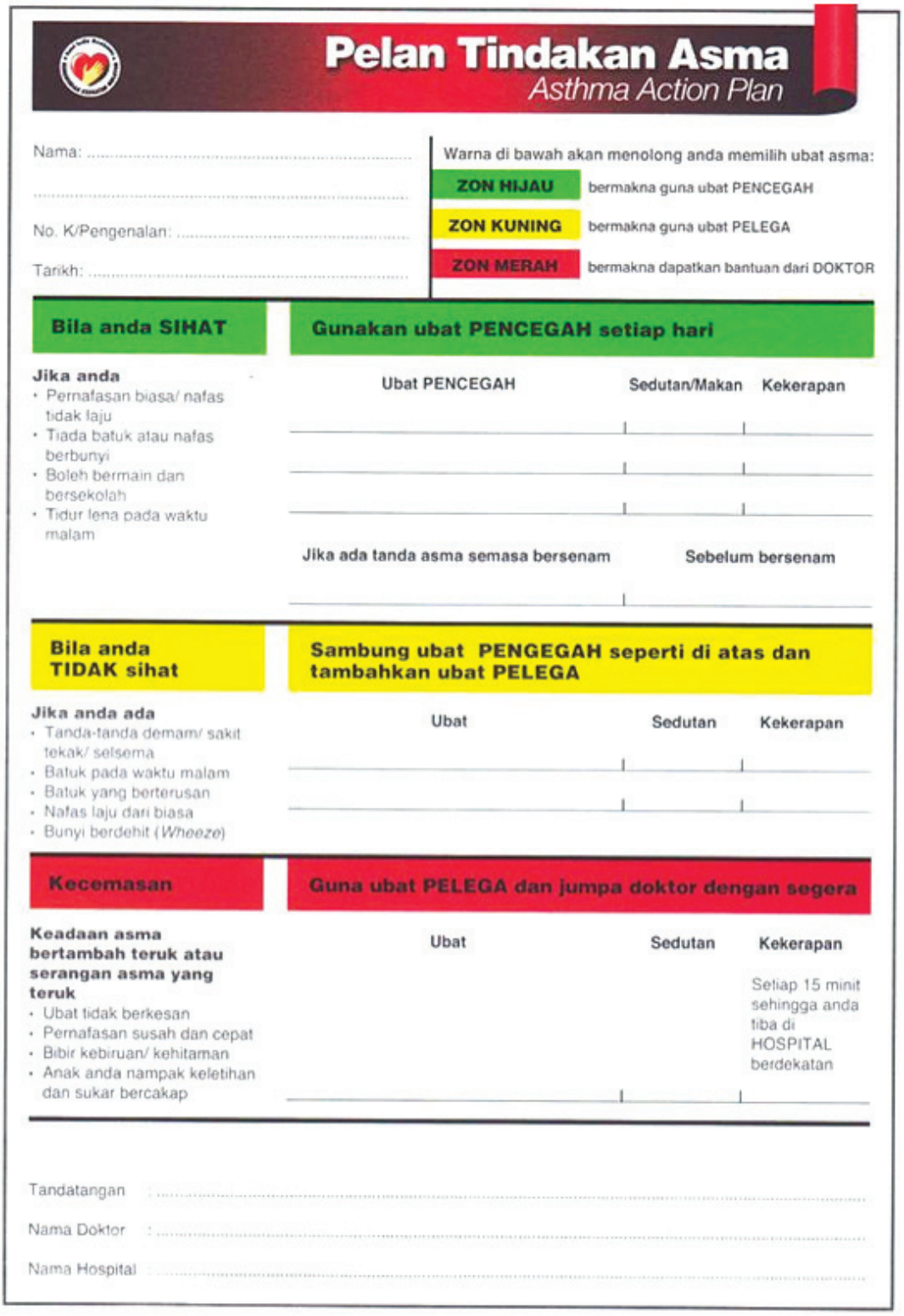
- Compliance to asthma therapy:
  - Frequency.
  - Technique.
  - Medication side-effects
  - Address co-morbidities
  - rhinosinusitis, gastro-oesophageal reflux disease (GERD), obesity, obstructive sleep apnoea syndrome (OSAS), depression and anxiety
- Asthma education:
  - Understanding asthma in childhood.
  - Reemphasize compliance to therapy.
  - Written asthma action plan (Table 10)
  - Identification and avoidance of asthma triggers

- Environmental allergens:
  - House dust mites, animal dander, insects like cockroach, mold and pollen.
  - Useful measures: damp dusting, frequent laundering of bedding with hot water, encase pillow/mattresses with plastic/vinyl covers, remove carpets from bedrooms, frequent vacuuming, remove pets from the household.
  - Cigarette smoke
  - Respiratory tract infections - commonest trigger in children.
  - Food allergy - uncommon trigger, occurring in 1-2% of children
  - Exercise- Although exercise is a recognised trigger, activity should not be limited. Taking a β_2-agonist prior to strenuous exercise, and optimizing treatment, are usually helpful
- Patients with High-Risk Asthma are at risk of developing near fatal asthma (NFA) or fatal asthma (FA) and they should be managed by paediatric respiratory physician, with frequent review and objective assessment of asthma control.

Table 9: Monitoring tools

	≥4 years, < 6 years	6 years
Clinical		
• Clinical symptoms control	√	√
• Childhood asthma control test (c-ACT)	√	√
• Asthma Control Questionnaire (ACQ)	x	√
• Asthma exacerbations	√	√
• Asthma Quality of life Questionnaire (QoLQ)	x	√
Lung function tests		
• Peak expiratory flow (PEF)	√ /x	√
• Spirometry, broncho-dilator response	√ /x	√
• Force oscillation technique (FOT)		√
Bronchial hyper-responsiveness		
• Methacholine/ histamine	√ /x	√
• Exercise	√ /x	√
Inflammatory markers		
• Fraction exhaled NO (FeNO)	√	√

Table 10: Asthma Action Plan



Pelan Tindakan Asma
Asthma Action Plan

Nama: .....

.....

No. K/Pengenalan: .....

Tarikh: .....

Warna di bawah akan menolong anda memilih ubat asma:

ZON HIJAU bermakna guna ubat PENCEGAH

ZON KUNING bermakna guna ubat PELEGA

ZON MERAH bermakna dapatkan bantuan dari DOKTOR

Bila anda SIHAT

Gunakan ubat PENCEGAH setiap hari

Jika anda
- Pernafasan biasa/ nafas tidak laju
- Tiada batuk atau nafas berbunyi
- Boleh bermain dan bersekolah
- Tidur lena pada waktu malam

Ubat PENCEGAH	Sedutan/Makan	Kekerapan

Jika ada tanda asma semasa bersenam	Sebelum bersenam

Bila anda TIDAK sihat

Sambung ubat PENGEGAH seperti di atas dan tambahkan ubat PELEGA

Jika anda ada
- Tanda-tanda demam/ sakit tekak/ selsema
- Batuk pada waktu malam
- Batuk yang berterusan
- Nafas laju dari biasa
- Bunyi berdehit (*Wheeze*)

Ubat	Sedutan	Kekerapan

Kecemasan

Guna ubat PELEGA dan jumpa doktor dengan segera

Keadaan asma bertambah teruk atau serangan asma yang teruk
- Ubat tidak berkesan
- Pernafasan susah dan cepat
- Bibir kebiruan/ kehitaman
- Anak anda nampak keletihan dan sukar bercakap

Ubat	Sedutan	Kekerapan
		Setiap 15 minit sehingga anda tiba di HOSPITAL berdekatan

Tandatangan : .....

Nama Doktor : .....

Nama Hospital : .....

Table 11: Inhaled Drug Dosages for Medications used in Chronic Asthma

Preventive Drugs		Age 6-11 years	Age ≥ 12 years
Corticosteroids			
Beclomethasone Diproprionate (extra-fine particle)	Pressurized Metered Dose Inhaler (pMDI)	Low: 50-100 mcg/day Medium: >100-200 mcg/day High: >200 mcg/day	Low: 100-200 mcg/day Medium: >200-400 mcg/day High: >400 mcg/day
Beclomethasone Diproprionate (standard particle)	Pressurized Metered Dose Inhaler (pMDI)	Low: 100-200 mcg/day Medium: >200-400 mcg/day High: >400 mcg/day	Low: 200-500 mcg/day Medium: >500-1000 mcg/day High: >1000 mcg/day
Budesonide	Dry powder inhaler (DPI), pMDI	Low: 100-200 mcg/day Medium: >200-400 mcg/day High: >400 mcg/day	Low: 200-400 mcg/day Medium: >400-800 mcg/day High: >800 mcg/day
Fluticasone Propionate	Metered dose inhaler Dry powder inhaler	Low: 50-100 mcg/day Medium: >100-200 mcg/day High: >200 mcg/day	Low: 100-250 mcg/day Medium: >250-500 mcg/day High: >500 mcg/day
Ciclesonide (extra-fine particle)	Metered dose inhaler	Low: 80 mcg/day Medium: >80-160 mcg/day High: >160 mcg/day	Low: 80-160 mcg/day Medium: >160-320 mcg/day High: >320 mcg/day
Combination agents			
Fluticasone/ Salmeterol	Metered dose inhaler Dry powder inhaler/Accuhaler	Medium: 50/25 mcg 2 puffs BD High: 125/25 mcg 2 puffs BD High: 250/50 mcg 1 puff BD	Medium:125/25 mcg 2 puffs BD High: 250/50 mcg 1 puff BD
Budesonide / Formoterol	Dry powder inhaler pMDI	Medium: 100/6 mcg 1 puff BD High: 100/6 mcg 2 puffs BD or 200/6 mcg 1 puff BD	Low: 100/6 mcg 1 puff BD Medium:100/6 mcg 2 puffs BD or 200/6 mcg 1 puff BD High: > 200/6 mcg 2 puff BD
Antileukotrienes (Leukotriene modifier)			
Montelukast	Oral	4 mg granules* 5mg/tablet ON chewable	5mg/tablet ON chewable 10mg/tablet ON swallow (≥ 14 years old)

Footnote: * Montelukast granules need to be taken orally with milk, food or directly within 15 minutes of opening the sachet. It shouldn't be mixed with water.

MANAGEMENT OF ACUTE ASTHMA EXACERBATION

- Acute exacerbations are episodes characterised by progressive worsening symptoms of shortness of breath, cough, wheezing and chest tightness, or combination of these symptoms and characterised by progressive decrease in lung function.
- Objective measurements of lung function (spirometry or PEF) are more reliable indicators of severity than symptoms (for those who can perform).
- Exacerbations may occur in a patient with pre-existing asthma diagnosis or occasionally, as the first presentation of asthma.
- Asthma exacerbations require prompt treatment.
- Severe exacerbations can be life threatening and can occur in patients even with mild or controlled asthma.
- Patients at high risk of asthma-related death require special attention, which include intensive education, monitoring, and care advised to seek medical care early during an exacerbation.
- Mild attacks can be usually treated at home if the patient is prepared and has a personal asthma action plan.
- Moderate and severe attacks require clinic or hospital attendance.
- A patient who has brittle asthma, previous ICU admissions for asthma or with parents who are either uncomfortable or judged unable to care for the child with an acute exacerbation should be admitted to hospital.

Goals of treatment of acute asthma exacerbations include:

- To relieve airway obstruction and hypoxaemia or hypercapnea as quickly as possible
- To prevent complications and death
- To prevent further relapses

General principles in the treatment of acute asthma:

- Assessing severity (*mild, moderate, severe or life-threatening*) while starting bronchodilator treatment immediately
  - Based on parameters: *respiratory rate, colour, SpO_2, respiratory effort, degree of dyspnoea, auscultatory lung findings and conscious level*
- Severe acute exacerbation is characterized by hypoxia (SpO_2 in air < 92%), too breathless to talk or speak in one word, tachynoea (RR > 30/min in >5 years, RR > 40/min in 1-5 years old), tachycardia (HR >125/min in > 5 year, > 140/min in 1-5 years old) and PEF 33-50% best or predicted.
- Life-threatening exacerbation features include hypoxia (SpO_2 air < 92%), silent chest, cyanosis, poor respiratory effort, hypotension, exhaustion, confusion and PEF <30% best or predicted.
- The Paediatric Asthma Score (PAS) is one of the methods used to assess severity of acute asthma exacerbation without performing lung function test (Table 12).
- Administering oxygen therapy if pulse oximetry (SpO_2) is < 94% in children.
- Treatment and re-assessments within the indicated time frame according to the Acute Paediatric Asthma Exacerbation Management Pathway (Table 13).
- Administering systemic corticosteroids within the first hour of treatment
- Repeated reassessment of response to treatment and treatment decision (either continuing treatment or adding on treatments) until acute asthma has resolved.

First line treatment or standard therapy:

1. Bronchodilators:

- Inhaled short acting β_2-agonists (SABA): the first line of treatment
- pMDI plus spacer is more efficient than nebulizer. It is a preferred method in mild to moderate acute asthma.
- The nebulised oxygen-driven SABA + SAMA (short acting muscarinic agonists) is recommended in severe and life-threatening acute asthma (beware of high risk of transmitting viral infections during a respiratory pandemic as aerosolized droplets can spread for several meters and remain airborne for more than 30 minutes)
- Frequent doses of ipratropium bromide (SAMA) (every 20–30 minutes) used in addition to β2 agonists for the first hour may be continued for a maximum of two hours for a severe asthma attack. It is safe and efficacious especially in the most severe patients. The ipratropium dose should be tapered to four to six hourly or discontinued.
- Parenteral SABA should be considered in children with severe or life-threatening exacerbations

2. Oxygen:

- The inhaled bronchodilators and oxygen are crucial in relieving hypoxia.
- Oxygen therapy should be titrated using pulse oximetry to maintain SpO2 94-98%. Titrated/ controlled oxygen therapy is associated with lower mortality and better outcomes.
- In acutely distressed patients, give oxygen driven nebulised bronchodilators
- In less severe exacerbations, oxygen can be delivered via nasal prong (especially if using MDI SABAs) or face-mask oxygen.
- Close SpO^2 monitoring is important as SpO^2 may drop during sleep

3. Steroid:

- It can be administered via the oral or IV route (similar efficacy).
- The oral route is preferred as it is quicker to serve, less expensive and less invasive.
- The IV route is indicated in children who are vomiting, unable to tolerate orally and children with severe or life-threatening exacerbations
- Oral and parenteral corticosteroid need at least 4 hours to produce a clinical improvement
- They are usually given for 3-5 days for children and 5-7 days for adolescents 12 years and above and weaning is unnecessary unless the course of steroid exceeds 14 days
- Consider nebulised corticosteroid (Budesonide) combined with SABA and SAMA every 20 minutes during the first hour of treatment in patients with severe /life-threatening asthma
- Nebulised corticosteroids have rapid onset of action than systemic corticosteroids [few seconds to minutes versus 4 hours] via non-genomic effect of inhaled-corticosteroid (ICS). They also have vasoconstrictor effect on the airway mucosa which leads to decrease airway blood flow and reduce clearance of bronchodilators from the airway. ICS potentiates the effect of bronchodilators.

Second line / adjunct therapies: Systemic Bronchodilators:
Should be initiated when there is no response to the first line treatment, Paediatric Asthma Score (PAS) either remains the same or there is further deterioration (suggesting that the inhaled therapy may not reach the airway), or patient is having severe or acute life-threatening exacerbation.

- Consider IV Magnesium Sulphate ($MgSO_4$) as first line option for adjunct/second line intravenous treatment of severe or life-threatening exacerbations. It is safe and beneficial.
- Another alternative or as add on treatment is IV Salbutamol β_2 agonist or Terbutaline. Subcutaneous terbutaline can be used in children with no IV access.

Footnotes on Management of Acute Exacerbation of Asthma:

1. Monitor vital signs such as pulse rate, respiratory rate, blood pressure (BP), SpO_2, colour at least 4 hourly.
2. Hydration – normal maintenance unless intubated then to restrict to 2/3rd maintenance.
3. IV Magnesium Sulphate: Consider adjunct treatment early in severe /life-threatening exacerbations unresponsive to the initial treatment.
4. Ventilatory support: Early use of High Flow Nasal Cannula (HFNC), Non-invasive ventilation (NIV) in patients with moderate to severe respiratory distress may prevent intubation. Intubation and mechanical ventilation should be considered in patients with established acute respiratory failure or showed no improvement with HFNC or NIV despite optimal medical therapies.
5. Role of Aminophylline is debated due to its potential toxicity. To be used with caution, in a controlled environment like ICU.
6. Antibiotics indicated only if bacterial infection or pneumonia is suspected.
7. Chest x-ray is not routinely recommended and must not compromise emergency treatment. It is indicated if suspected complications e.g. pneumothorax, pneumomediastinum, lung collapse or concomitant pneumonia.
8. ABG: should be considered in severe and life-threatening asthma. Normal or raised $PaCO_2$ levels are indicative of worsening asthma.
9. For school aged children, monitor PEF twice /day (am, pm) and pre & post bronchodilator.
10. Avoid sedatives and mucolytics.
11. Antihistamines and IM Adrenaline – therapy of anaphylaxis and angioedema associated with asthma exacerbations.
12. Avoid chest physiotherapy as it may increase patient discomfort
13. Efficacy of prednisolone in the first year of life is poor.
14. Discharge criteria:
    - Stable on 4 hourly inhaled bronchodilators (can by continued at home)
    - Clinically stable, able to eat and sleep well, and PAS ≤7
    - SpO_2 >94% in room air.
    - Post bronchodilator PEF and/or FEV1 should be > 70% of best or predicted
    - Follow up by primary care services within two weeks or earlier.
    - Follow up in a paediatric asthma clinic within one to two months
15. On discharge, patients must be provided with an Asthma Action Plan to assist parents or patients to prevent/terminate asthma attacks.
    The plan must include:
    a. How to recognize worsening asthma
    b. How to treat worsening asthma
    c. How and when to seek medical attention
16. Salbutamol MDI vs nebulized therapy
    < 6 year old: 6 x 100 mcg puff = 2.5 mg Salbutamol nebules.
    > 6 year old: 12 x 100 mcg puff = 5.0 mg Salbutamol nebules.

Criteria for hospital admission

- Failure to respond to standard home treatment.
- Failure of those with mild or moderate acute asthma to respond to nebulised β_2-agonists.
- Relapse within 4 hours of nebulised β_2- agonists.
- Severe or life-threatening acute asthma.

Table 12: Paediatric Asthma Score (PAS) – for children 2-18 years of age

VARIABLE	1 POINT	2 POINTS	3 POINTS
RR			
2-3 year	≤ 34	35-39	>40
4-5 year	≤ 30	31-35	>36
6-12 year	≤ 26	27-30	>31
>12 year	≤ 23	24-27	>28
OXYGEN REQUIREMENTS	>95% on room air	90-95% on room air	<90% on room air or any supplemental oxygen
RETRACTIONS	None or intercostal	Intercostal, and subcostal	Intercostal, subcostal and suprasternal/ supraclavicular
DYSPNOEA	Speaks in sentences	Speaks partial sentences	Speaks in single words or short phrases or grunt
AUSCULTATION	Normal breath sounds to end-expiratory rhonchi only	Expiratory rhonchi	Inspiratory and expiratory rhonchi to diminished breath sounds

Interpretation

Paediatric Asthma Score (PAS)	Severity Of Exacerbation	% Of Peak Flow (Personal Best or Predicted
5 - 7	Mild	>70%
8 - 11	Moderate	50 – 70%
12 - 15	Severe	<50%

Table 13: Acute Paediatric Asthma Exacerbation Management Pathway

MILD (PAS 5-7)	MODERATE (PAS 8-11)	SEVERE (PAS 12-15)	LIFE-THREATENING RESPIRATORY FAILURE
MDI Salbutamol now and every 60min PRN (via MDI and spacer) OR Nebulised Salbutamol Give systemic corticosteroid (oral)	MDI Salbutamol now and every 20min (via spacer) X 3 OR Oxygen driven Nebulised Salbutamol Administer oxygen to maintain SpO2 94-98% Give oral corticosteroid AS SOON AS POSSIBLE after 1st salbutamol dose (within 60 min of triage)	Administer oxygen to maintain SpO2 94 - 98% Oxygen driven Nebulised Salbutamol + Ipratropium Bromide + Steroid now and every 20min X 3 Give oral/IV corticosteroid AS SOON AS POSSIBLE after 1st salbutamol/Ipratropium/steroid dose (within 20 min of triage) Consider IV access or ABG	Lethargy, cyanosis, decreasing respiratory effort and/or rising pCO2 → to assess STAT Administer 100% oxygen Support ventilation (DO NOT OVER VENTILATE) Continuous cardiopulmonary monitoring Oxygen driven Nebulised Salbutamol + Ipratropium Bromide + steroid now and every 20min X 3 back to back/continuous Give systemic corticosteroid AS SOON AS POSSIBLE after 1st salbutamol/Ipratropium/steroid neb (within 20 min of triage) IV $MgSO_4$ (caution: can cause low BP) or SC Terbutaline Obtain IV access & ABG
Complete all of the above within 60min of triage	Complete all of the above within 60min of triage	Complete all of the above within 60min of triage	VITAL SIGNS & PAS q 20 If no improvement Add IV Salbutamol (slow bolus +/- infusion, need continuous ECG monitor for infusion) IV fluid CXR PICU/PHDU admission
VITAL SIGNS & PAS q 60min	VITAL SIGNS & PAS q 30-60 min	VITAL SIGNS & PAS q 20-30 min	
If PAS increase (8-11) to move to "moderate pathway"	If PAS increase (12-15) to move to "severe pathway"	If PAS increase to move to "life-threatening respiratory failure pathway"	
If PAS remained the same or less (PAS 5-7) to consider discharge Provide discharge plan Short course prednisolone	If PAS remained the same (PAS 8-11) to consider admission to move to "severe pathway"	If PAS remained the same repeat with oxygen driven nebulised Salbutamol + Ipratropium every 20min X 3 IV $MgSO_4$ / SC Terbutaline	
	If PAS reduced (5-7) to consider discharge Provide discharge plan Short course prednisolone	If PAS improving (8-11) to move to "moderate pathway"	

Drug Dosages for Medications used in Acute Asthma		
Drug	**Formulation**	**Dosage**
SABA: Short Acting β_2-agonists		
Salbutamol	MDI + spacer	≤ 6 years: 4-6 puffs > 6 years: 8 -10 puffs [1] may administer every 20min x 3
	Nebuliser solution 5mg/ml	0.15 mg/kg ≤ 5 years: 2.5 mg [1,3] > 5 years : 5 mg Consider neat nebulised salbutamol in life threatening asthma
	Intravenous	Single bolus 5-15 mcg/kg over 10 min then 1-5 mcg/kg/min thereafter[3]
Terbutaline	Nebuliser solution 10 mg/ml, 2.5 mg/ml or 5mg/ml respule	0.2-0.3 mg/kg/dose or < 20 kg: 2.5 mg/dose ≥ 20 kg: 5.0 mg/dose
	subcutaneous	5-10 mcg/kg/dose (max 0.5 mg)
SAMA: short acting muscarinic antagonist (anti-cholinergic)		
Ipratopium bromide (used in combination with SABA)	Nebuliser solution 250mcg/ml	< 6 years: 125-250 mcg 6 hourly ≥6 years: 250-500 mcg 6 hourly May administer every 20 min (q20 min) x3 in the first hour of nebulised ipratropium. Can repeat during 2nd hour then 6 hourly
	MDI + spacer (inhaler)	<6 years: 2 puffs q20 min x 3 ≥6 -12 years: 4-8 puffs q20min x 3 ≥12 years: 8 actuations q20 doses x3 in the first hour (1 puff= 20 mcg/puff)
Magnesium sulphate (MgSO4)	Intravenous	Magnesium sulphate 50%, 0.1 mL/kg (50 mg/kg) IV over 20 mins
Corticosteroids		
Prednisolone	Oral	1-2 mg/kg/day (for 3-7 days) Maximum daily dose: • 10 mg prednisolone for children under 2 years of age • 20 mg for children aged 2–5 years • 30–40 mg for children 6-11years • 40-50 mg for 12 years and older for 5-7 days
Hydrocortisone	Intravenous	4-5 mg/kg/dose 6 hourly (max 100mg)
Methylprednisolone	Intravenous	1 mg/kg 6 hourly day 1, then 12 hourly day 2, then 24 hourly
Budesonide	Nebulised	0.5 mg /dose x 3 doses within first 1 hour (max daily dose is 2 mg). It can be mixed with SABA and SAMA solutions
Dexamethasone	PO intramuscular	0.6 mg/kg/dose (max 16 mg) OD for 1-2/7. 0.3-0.6 mg/kg/dose (max 15 mg) stat dose.

Chapter 32:
Acute Bronchiolitis

Aetiology and Epidemiology

- A common respiratory illness in children under 2 years of age and most commonly in the first year of life, peaking between 3 and 6 months old.
- Respiratory Syncytial Virus (RSV) remains the commonest cause of acute bronchiolitis in Malaysia and worldwide.
- Although it is endemic throughout the year, cyclical periodicity with annual peaks occurs, in the months of October, November, December and January

Clinical Features

- Acute bronchiolitis is a clinical diagnosis which typically presents with mild coryza, low grade fever and cough followed by tachypnoea, chest recession, wheeze and respiratory distress.
- The chest may be hyperinflated and auscultation findings include crackles/crepitations, rhonchi, or both.
- Young infants (in particular those under 6 weeks of age) may present with apnoea without other clinical signs.
- The majority of children with viral bronchiolitis have a mild illness and only about 1% of these children require hospital admission

Guidelines for hospital admission in Viral Bronchiolitis		
	Home Management	Hospital Management
Age < than 3 months	No	Yes
Toxic-looking	No	Yes
Chest recession	Mild	Moderate/ Severe
Grunting	No	Yes
Central cyanosis	No	Yes
Wheeze	Yes	Yes
Crepitations on auscultation	Yes	Yes
Feeding	Well	Inadequate
Apnoea	No	Yes
Oxygen saturation	≥95%	<95%
High risk group*	No	Yes

High Risk Group for Severe Bronchiolitis

- Age < 12 weeks
- Premature birth
- Underlying cardiopulmonary disease
- Underlying immunodeficiency
- Underlying neuromuscular disorders

Differential Diagnosis

Consider a diagnosis of pneumonia if the infant or child has:
- high fever (over 39°C) and/or
- persistent focal crackles/crepitations
- severe respiratory distress

Consider a diagnosis of viral-induced wheeze or early-onset asthma rather than bronchiolitis in older infants and young children if they have:
- persistent wheeze without crackles/crepitations or
- recurrent episodic wheeze or
- a personal or family history of atopy

Investigations

- Blood tests
  - Routine full blood count and bacteriological testing is not recommended in infants or children with typical acute bronchiolitis.
  - Consider capillary blood gas in infants or children with severe worsening respiratory distress or impending respiratory failure.
- Chest X-Ray
  - A wide range of radiological changes are seen in viral bronchiolitis:
    - Hyperinflation (most common)
    - Segmental collapse/consolidation
    - Lobar collapse/consolidation
  - A chest x-ray is not routinely recommended, but can be considered for infants or children with:
    - Severe respiratory distress
    - Unusual clinical features
    - An underlying cardiac or chronic respiratory disorder
    - Admission to the intensive care

Management

General measures

- Careful assessment of the respiratory status and oxygenation is critical.
- Oxygen saturation by pulse oximetry (SpO_2) should be performed at presentation and maintained between 94-98% by supplementary oxygen if required.
- Monitor for signs of impending respiratory failure:
  - Signs of exhaustion (eg listlessness or decreased respiratory effort)
  - Recurrent apnoea
  - Failure to maintain adequate oxygen saturation despite oxygen supplementation
- Very young infants who are at risk of apnoea require greater vigilance.

Supportive therapy

- Nasal suctioning
  - Do not routinely perform upper airway suctioning in all infants or children with bronchiolitis.
  - Consider gentle superficial nasal suctioning especially in younger infants who have respiratory distress or feeding difficulties because of upper airway secretions. As young infants are obligate nasal breathers, therefore clearing the nares may improve the work of breathing and feeding.
- Chest physiotherapy
  - No evidence of benefit of any type of chest physiotherapy among children with acute bronchiolitis in regards to length of hospital stays, oxygen saturation or respiratory parameters

Nutrition and Fluid Therapy

- Small and frequent feeding as tolerated can be allowed in children with mild and moderate respiratory distress.
- In children with poor feeding, nasogastric or orogastric feeding can be commenced.
- Consider intravenous fluids in infants or children who:
  - Do not tolerate nasogastric or orogastric fluids or
  - Have impending respiratory failure.

Pharmacotherapy

1. Hypertonic saline
   - Not routinely recommended.
   - There is not enough evidence to routinely recommend nebulised hypertonic 3% saline solution for acute bronchiolitis, as more recent trials and systematic reviews have shown unclear benefits of nebulised hypertonic solution in the management of acute bronchiolitis.

2. Inhaled Bronchodilators
   - Not routinely recommended.
   - Administration of inhaled bronchodilators (such as salbutamol/terbutaline/ipratropium bromide) to infants with a diagnosis of bronchiolitis do not improve oxygen saturation, duration of symptoms or length of hospital stay.
   - However, it might sometimes be difficult to distinguish between wheeze of bronchiolitis and that of early asthma or viral induced wheeze in older infants. Therefore, in infants with persistent wheeze without crackles/crepitations, the possibility of bronchodilator responsive wheeze (particularly if there is a personal or family history of atopy) can be considered.

3. Corticosteroids
   - Not routinely recommended.
   - Corticosteroids, both systemic (such as dexamethasone or prednisolone) and inhaled, are not associated with a clinically significant improvement in disease, as measured by reduction in clinical scores, rates of hospitalization and length of hospital stay.

4. Antibiotics
   - Not routinely recommended as acute bronchiolitis has a viral aetiology and the rate of secondary bacterial infection is extremely low.
   - A detailed review of randomised clinical trials found that the routine use of antibiotics did not improve the duration of symptoms, length of hospital stays, the need for oxygen therapy, or hospital admission.
   - Antibiotics can be considered for infants with:
     - Recurrent apnoea and circulatory impairment
     - Possibility of septicaemia
     - Acute clinical deterioration
     - High white cell count
     - Progressive interstitial changes on chest radiograph

Respiratory support

- High Flow Nasal Cannula (HFNC) and continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BIPAP) are increasingly used as modalities of non-invasive respiratory support for infants with acute, moderate-to-severe bronchiolitis.
- Close monitoring of patients on HFNC and CPAP are needed to prevent deterioration and for early detection of progressive respiratory failure, which may require mechanical ventilation.

Prevention

- General prevention of RSV bronchiolitis includes hand hygiene, avoiding exposure to sick contacts and cigarette smoke exposure, and preferably maternal RSV vaccination at 32-36 weeks gestation.
- The availability of long-acting RSV monoclonal antibody (eg. Nirsevimab) that cover one RSV season offers a better alternative than a short-acting one.
- The indications of RSV monoclonal antibody include chronic lung disease of prematurity (CLDP)/ Bronchopulmonary Dysplasia (BPD) requiring oxygen or medications, haemodynamically significant congenital heart diseases, severe immunodeficiency and extreme prematurity (for Palivizumab).

Chapter 33:
Viral Croup

Aetiology and Epidemiology

- A clinical syndrome characterised by barking cough, inspiratory stridor, hoarse voice and respiratory distress of varying severity.
- A result of viral inflammation of the larynx, trachea and bronchi, hence the term *laryngotracheobronchitis*.
- The most common pathogen is parainfluenza virus (74%), (types 1, 2 and 3). The others are Respiratory Syncytial Virus, Influenza virus types A and B, Adenovirus, Enterovirus, Measles, Mumps and Rhinoviruses and rarely *Mycoplasma pneumoniae* and *Corynebacterium Diptheriae*. Also seen in SARS-CoV-2 especially the Omicron variant

Clinical Features

- Low grade fever, cough and coryza for 12-72 hours, followed by:
- Increasingly bark-like cough and hoarseness.
- Stridor that may occur when excited, at rest or both.
- Respiratory distress of varying degree.

Diagnosis

- Croup is a clinical diagnosis. However, need to consider other life-threatening differential diagnoses such as acute epiglottitis, retropharyngeal / parapharyngeal abscess, peritonsillar abscess, foreign body aspiration, diphtheria and congenital upper airway abnormalities (laryngomalacia, laryngeal web, vocal cord palsy, subglottic stenosis).
- Studies show that it is safe to visualise the pharynx to exclude acute epiglottitis, retropharyngeal abscess etc.
- In severe croup, it is advisable to examine the pharynx under controlled conditions such as in the ICU or Operation Theatre.
- A neck radiograph is not necessary, unless the diagnosis is in doubt, such as in the exclusion of a foreign body.

Assessment of severity

Clinical Assessment of Croup

- *Severity (Westley Croup Severity Score)*

Clinical features	Assigned Score
Level of consciousness	*Normal, including sleep = 0* *Disoriented = 5*
Cyanosis	*None = 0* *With agitation = 4* *At rest = 5*
Stridor	*None = 0* *With agitation = 1* *At rest = 2*
Air Entry	*Normal = 0* *Decreased = 1* *Markedly decreased = 2*
Retractions	*None = 0* *Mild = 1* *Moderate = 2* *Severe = 3*

Total Score	Croup Severity
≤ 2	*Mild*
3 to 7	*Moderate*
8 to 11	*Severe*
>12	*Impending Respiratory Failure*

- Pulse oximetry is helpful but not essential
- Arterial blood gas is not helpful because the blood parameters may remain normal to the late stage. The process of blood taking may distress the child.

Management

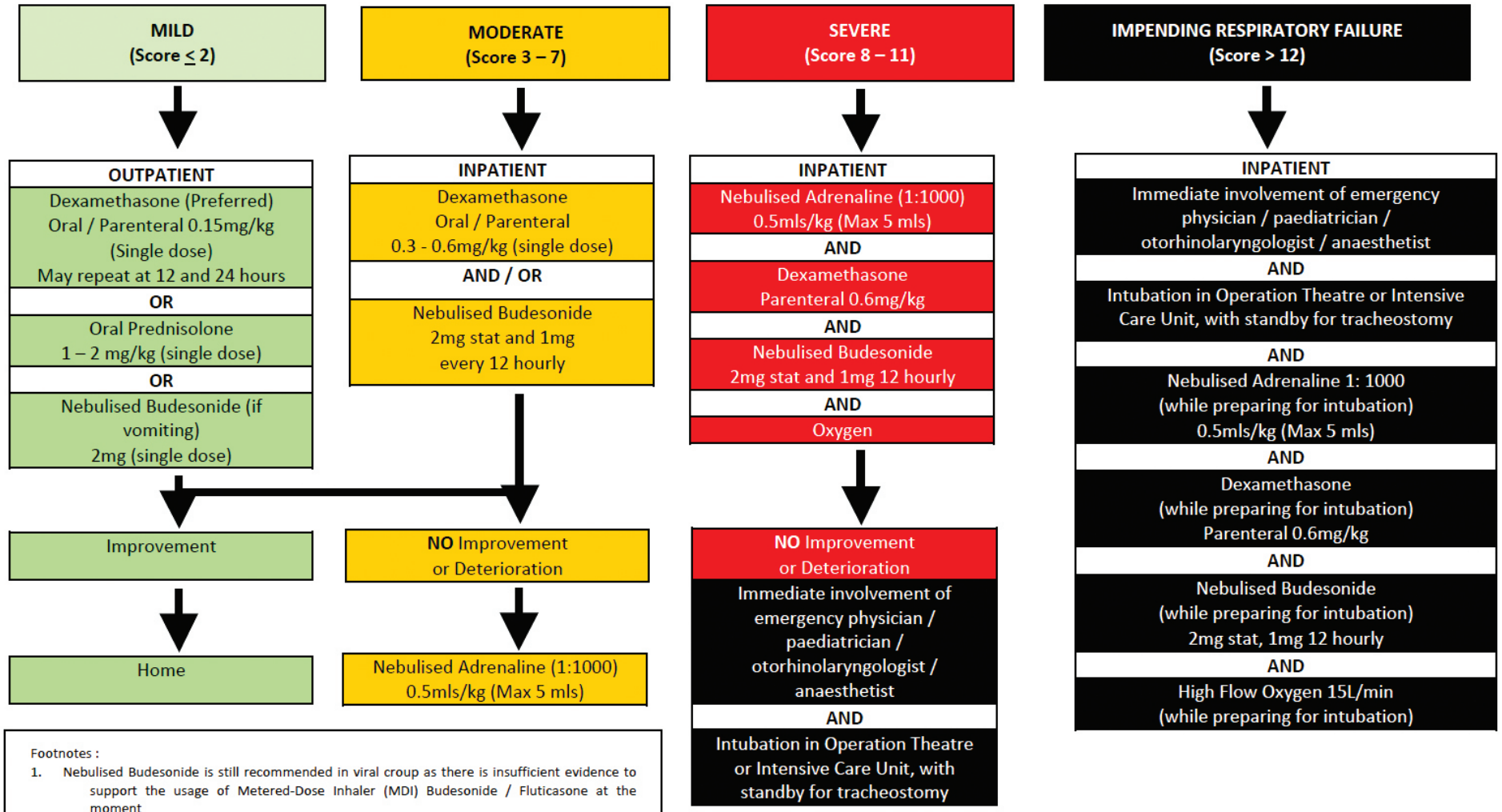
Indications for Hospital admission

- Moderate and severe viral croup.
- Age less than 6 months.
- Poor oral intake.
- Toxic, sick appearance.
- Family lives a long distance from hospital; lacks reliable transport.

Treatment (*refer to Management Algorithm of Viral croup*)

- The sustained action of steroids combined with the quick action of adrenaline may reduce the rate of intubation from 3% to nil.
- Antibiotics are not recommended unless superimposed bacterial infection is strongly suspected or the patient is very ill.
- Intravenous fluids are not usually necessary except for those unable to drink.
- With the Covid-19 pandemic, it is important to minimise distress to the child, as this can worsen upper airway obstruction. Hence, COVID-19 testing should not routinely be performed until deemed safe to do.

MANAGEMENT ALGORITHM OF VIRAL CROUP



Footnotes :

1. Nebulised Budesonide is still recommended in viral croup as there is insufficient evidence to support the usage of Metered-Dose Inhaler (MDI) Budesonide / Fluticasone at the moment
2. There is limited evidence regarding the usage of lower doses of oral / parenteral Dexamethasone (0.15 – 0.3mg/kg) in moderate to severe croup. However, higher dose Dexametasone (0.6mg/kg) is still advocated until more studies comparing smaller doses

Chapter 34:
Pneumonia

Definition

There are two clinical definitions of pneumonia:

- *Bronchopneumonia:* a febrile illness with cough, respiratory distress with evidence of localised or generalised patchy infiltrates.
- *Lobar pneumonia:* similar to bronchopneumonia, except that the physical findings and radiographs indicate lobar consolidation.

Aetiology

- It is often difficult to distinguish viral from bacterial disease.
- Overall, viruses were found to account for around 60% of pneumonia cases, and bacteria for 30% pneumonia cases.
- The common viral aetiological fraction was attributable to Respiratory Syncytial Virus, Influenza A or B, Adenovirus, Parainfluenza Virus, SARS-CoV 2
- A helpful indicator in predicting aetiological agents is the age group. The predominant bacterial pathogens are shown in the table below:

Pathogens for Pneumonia	
Age	**Bacterial Pathogens**
Newborns	*Group B streptococcus, Escherichia coli, Klebsiella species, Enterobacteriaceae*
Infants 1- 3 months	*Chlamydia trachomatis*
Preschool age	*Streptococcus pneumoniae, Haemophilus influenzae type b, Staphylococcal aureus Less common: Group A Streptococcus, Moraxella catarrhalis, Pseudomonas aeruginosa*
School age	*Mycoplasma pneumoniae, Chlamydia pneumoniae and similar to the preschool age group pathogens*

Assessment of severity of pneumonia

The predictive value of respiratory rate for the diagnosis of pneumonia may be improved by making it age specific. Tachypnoea is defined as follows:

< 2 months age : > 60 /min
2- 12 months age : > 50 /min
12 months – 5 years age : > 40 /min

Severe pneumonia should be considered if there are clinical features of pneumonia and one or more of these criteria:

Tachypnoea as defined above or markedly reduced respiratory rate as child tires out with moderate to severe respiratory distress	Significant tachycardia or bradycardia +/- poor perfusion Unable to take orally
Altered mental state, increasing irritability and/or lethargy	Marked increase in usage of accessory muscle
Cyanosis or severe hypoxemia	Empyema

Investigations and assessment

Children with bacterial pneumonia cannot be reliably distinguished from those with viral disease on the basis of any single parameter. Following are helpful investigations:

- *Chest radiograph*
  - Indicated when clinical criteria suggest pneumonia, but not always necessary if facilities are not available or pneumonia is mild.
  - Does not differentiate aetiological agents, but a lobar consolidation pattern suggests bacterial infection and an interstitial pattern suggests viral or atypical agent infection.
- *White blood cell count*
  - Increased counts with predominance of polymorphonuclear cells suggest bacterial cause.
  - Leucopenia suggests either a viral cause or severe overwhelming infection.
- *Blood culture*
  - Sensitivity is low: Positive blood cultures only in 10%-30% of patients.
  - Do cultures in severe pneumonia or if poor response to first line antibiotics.
- *Serological tests*
  - Serology is performed in patients with suspected atypical pneumonia,
  - i.e., *Mycoplasma pneumoniae, Chlamydia, Legionella, Moraxella catarrhalis*
  - Acute phase serum titre for *Mycoplasma pneumoniae* infection, > 1:160 or paired samples taken 2-4 weeks apart with a 4-fold rise is a good indicator of infection. This test should be considered for children aged five years or older.
- *Acute phase reactants (particularly CRP)*
  - Should not be used routinely in all cases of pneumonia
  - If the test is available, combining elevated CRP (>72mg/L) with the presence of clinical signs/ symptoms can help differentiate definite bacterial from presumed viral pneumonia
- *Nasal pharyngeal aspirate or nasal swab for viruses (depending on which panel is offered at your setting)*
  - A less invasive diagnostic respiratory specimen, not routinely needed
  - Consider discontinuing antibiotics if proven positive
  - If positive for Influenza – to consider treating with Oseltamivir
- *Sputum culture and sensitivity*
  - Sputum culture is not routinely performed in children, as it is difficult to get children to expectorate a specimen and the clinical interpretation cannot be standardised
  - Should be considered in severely ill patients, to guide treatment
- *Pleural fluid analysis*
  - If there is significant pleural effusion, drainage and pleural fluid analysis will be helpful in management.

Assessment of oxygenation

- Objective measurement of hypoxia by pulse oximetry avoids the need for arterial blood gases. It is a good indicator of the severity of pneumonia.

Criteria for hospitalisation

- Mild community acquired pneumonia can be treated at home
- Identify indicators of severity in children who need admission, as pneumonia can be fatal. The following indicators can be used as a guide for admission:
  - Children aged 3 months and below, whatever the severity of pneumonia.
  - Fever (more than 38.5 ^{o}C), refusal to feed and vomiting
  - Fast breathing with or without cyanosis
  - Associated systemic manifestation
  - Failure of previous antibiotic therapy
  - Recurrent pneumonia
  - Persistent pneumonia
  - Severe underlying disorder, e.g., Immunodeficiency

Management

- Consideration of antibiotics :
  When treating pneumonia, consider clinical, laboratory, radiographic findings, as well as age of the child, and the local epidemiology of respiratory pathogens and resistance/sensitivity patterns to microbial agents.
- Severity of the pneumonia and drug costs also impact on selection of therapy.

Bacterial pathogens and Recommended antimicrobial agents.

Pathogen	Antimicrobial agent
Beta-lactam susceptible	
Streptococcus pneumonia	Penicillin, cephalosporins
Haemophilus influenzae type b	Ampicillin, cephalosporins
Staphylococcus aureus	Cloxacillin
Group *A Streptococcus*	Penicillin, cephalosporin
Other organisms	
Mycoplasma pneumoniae, Chlamydia pneumoniae and Bordetella pertussis	Macrolides, e.g., erythromycin, azithromycin

- Anti-viral therapy
  - For Influenza virus, consider starting Oral Oseltamivir for 5 days
    <9 months old : 3mg/kg/dose PO q12h
    9-11 months old : 3.5mg/kg/dose PO q12h
    1-12 years old : ≤15 kg : 30mg PO q12h
    15-23 kg : 45mg PO q12h
    23-40 kg : 60mg PO q12h
    >40 kg : 75mg PO q12h

INPATIENT MANAGEMENT

For children with severe pneumonia, the following antibiotics are recommended:

Suggested antimicrobial agents for inpatient treatment of pneumonia	
First line	Beta-lactams: Benzylpenicillin, Amoxycillin, ampicillin, Amoxycillin-clavulanate
Second line	*Cephalosporins:* Cefotaxime, Cefuroxime, Ceftazidime
Third line	*Carbapenem:* Imipenem
Other agents	*Aminoglycosides:* Gentamicin, Amikacin

- Second line antibiotics need to be considered when:
  - There are no signs of recovery
  - Patients remain toxic and ill with spiking temperature for 48 - 72 hours
- A macrolide antibiotic is used in pneumonia from *Mycoplasma or Chlamydia*.
- A child admitted with severe community acquired pneumonia must receive parenteral antibiotics. In severe cases of pneumonia, give combination therapy with a second or third generation cephalosporins and macrolide.
- Staphylococcal infections and infections caused by Gram negative organisms such as *Klebsiella* have been frequently reported in malnourished children.
- Recommended intravenous antibiotics dosage and duration as adapted from the National Antimicrobial Guideline 2019 (MOH) :

Intravenous Antibiotics	Recommended preferred dosage	Duration
Benzylpenicillin	200, 000 units/kg/day in 4 – 6 divided doses	Total duration of antibiotics 5 - 7 days
Amoxicillin / Clavulanate	30mg/kg/dose q8h (max 1.2gm/dose)	
Cefuroxime	100-150mg/kg/day in 3 divided doses (max 6gm/day)	
Ceftriaxone	75-100mg/kg/day in 2 divided doses	
Cefotaxime	150 – 200mg/kg/day in 3 divided doses	
Azithromycin	10mg/kg/dose (max 500mg) on Day 1; then 5mg/kg/dose (max 250mg) on Day 2-5	5 days

Supportive treatment

- *Fluids*
  - Withhold oral intake when a child is in severe respiratory distress.
  - In severe pneumonia, secretion of anti-diuretic hormone is increased and as such dehydration is uncommon. Avoid overhydrating the child.
- *Oxygen*
  - Oxygen reduces mortality associated with severe pneumonia.
  - It should be given especially to children who are restless, and tachypneic with severe chest indrawing, cyanosis, or is not tolerating feeds.
  - Maintain the SpO_2 between 94-98%.

- *Cough medication*
  - Not recommended as it causes suppression of cough and may interfere with airway clearance. Adverse effects and overdosage have been reported.
- *Temperature control*
  - Reduces discomfort from symptoms, as paracetamol will not abolish fever.
- *Chest physiotherapy*
  - This assists in the removal of tracheobronchial secretions: removes airway obstruction, increase gas exchange and reduce the work of breathing.
  - No evidence that chest physiotherapy should be routinely done.
- *Non-invasive/invasive ventilation*
  - Must be considered in patient with severe pneumonia or those in impending respiratory failure.

OUTPATIENT MANAGEMENT

- In children with mild pneumonia, their breathing is fast but there is no chest indrawing.
- Educate parents/caregivers about management of fever, preventing dehydration and identifying signs of deterioration.
- The child should return in two days for reassessment, or earlier if the condition is getting worse.
- Oral antibiotics can be prescribed.
- Recommended oral antibiotics dosage and duration as adapted from the National Antimicrobial Guideline 2019 (MOH) :

Oral Antibiotics/ Anti-viral	Recommended preferred dosage	Duration
Amoxicillin	80-90mg/kg/day in 2 divided doses	5 – 7 days
Amoxicillin / Clavulanate	45mg/kg/day in 2 divided doses	5 – 7 days
Cefuroxime	30mg/kg/day PO in 2 divided doses	5 – 7 days
Erythromycin Ethyl succinate	30-50mg/kg/day PO in 2 divided doses	5 – 7 days
Azithromycin	10mg/kg/dose PO on Day 1 (max. 500mg/day), followed by 5mg/kg/dose PO q24h on Day 2-Day 5 (max.250mg/day) 10mg/kg/dose PO q24h	5 days 3 days

COMPLICATED PNEUMONIA

- Must be suspected in cases of persistent fever for more than 48 hours after starting intravenous antibiotic with the presence of localizing signs i.e., stony dullness on percussion with reduce/absent breath sound over affected lobe.
- Parapneumonic effusion, empyema thoracis, necrotizing pneumonia, lung abscess and bronchopleural fistula need to be considered.
- Repeat chest x-ray, and consider ultrasound thorax if the above complications are suspected
- Early consult with a paediatric respiratory specialist is advised
- Occasionally a CT thorax is warranted in cases where necrotizing pneumonia, lung abscess or bronchopleural fistula is suspected

Staphylococcal infection

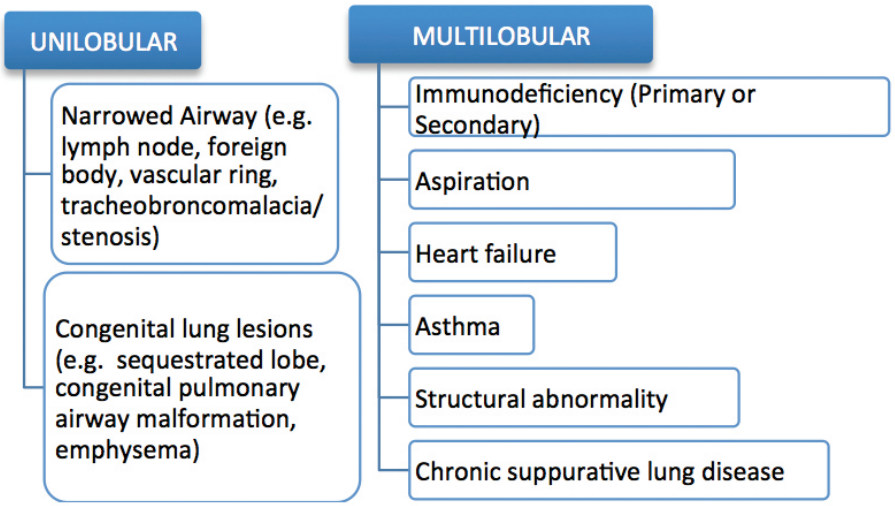
- *Staphylococcus aureus* is responsible for a small proportion of cases.
- A high index of suspicion is required because of the potential for rapid deterioration. It chiefly occurs in infants with a significant risk of mortality.
- Radiological features include multilobar consolidation, cavitation, pneumatoceles, spontaneous pneumothorax, empyema, pleural effusion.
- Treat with high dose Cloxacillin (200 mg/kg/day) for a longer duration
- Drainage of empyema often results in a good outcome.

Necrotising pneumonia and pneumatoceles

- It is a result of localized bronchiolar and alveolar necrosis.
- Aetiological agents are bacteria, e.g., *Staphylococcal aureus, S. Pneumonia, H. Influenza, Klebsiella pneumonia* and *E. coli*.
- Give IV antibiotics until child shows signs of improvement.
- Total antibiotics course duration of at least 3 to 4 weeks.
- Most pneumatoceles disappear, with radiological evidence resolving within the first two months but may take as long as 6 months.

RECURRENT PNEUMONIA

- Recurrent Pneumonia is defined as two or more episodes of pneumonia in 12 months or three episodes altogether with radiographic clearance in between.
- Persistent pneumonia however, is defined as persistence of symptoms and radiological changes for 6 weeks or more, despite treatment
- Identifying the underlying cause is the main factor,
  1. Host factor (e.g., Immunodeficiencies, airway abnormality)
  2. Aetiological factor (e.g., atypical organism)
  3. Environmental factor (e.g., overcrowding, exposure to secondary smoke)
- Approach to unilobular and multilobular causes of recurrent pneumonia



- Thorough investigation must be carried out to identify the cause of recurrent pneumonia for appropriate management to be commenced.

Chapter 35:
Empyema Thoracis in Children

Introduction

Empyema thoracis is a complication from respiratory infection with pus formation in the pleural cavity. Common pathogens are Streptococcus pneumoniae, Staphylococcus aureus, Streptococcus pyogenes, Hemophilus influenza and occasionally gram-negative bacilli like Salmonella spp. Tuberculosis should be considered in cases with unresolved empyema thoracis and contact risk.

Pathophysiology of Para-Pneumonic Effusion

Para-Pneumonic effusion (PPE) can be divided into 3 stages depending on onset of the disease and disease progression[1]. (Figure 1)

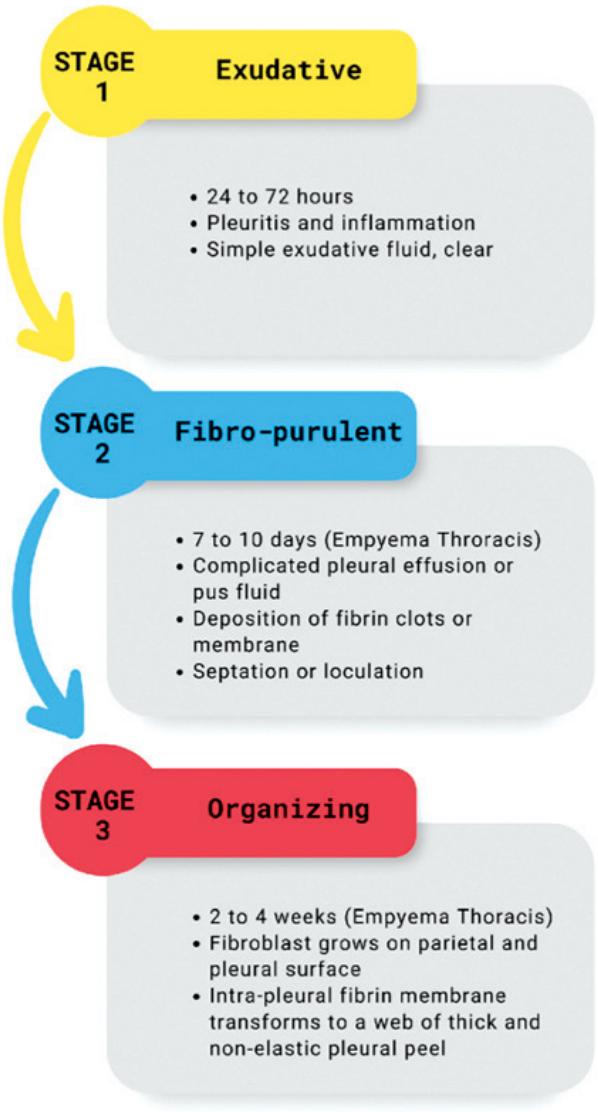


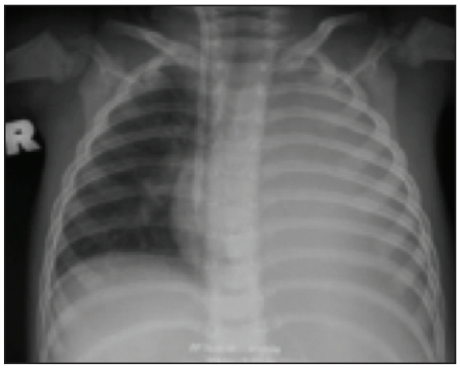
Figure 1: Stages of Para-Pneumonic Effusion (PPE)

Clinical presentation of Para-pneumonia effusion (PPE)

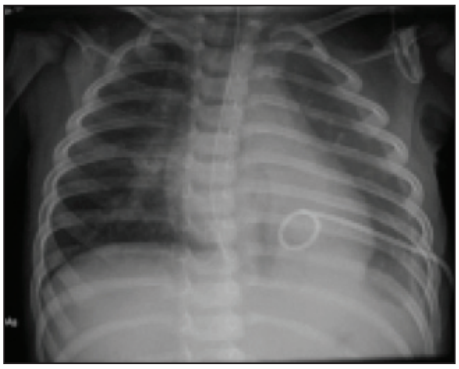
Initial presentation of PPE is similar with other lower respiratory tract infections e.g. fever and cough. Complications of pneumonia should be suspected with worsening or persistent symptoms and signs after 48 hours of antibiotic treatment. Further assessment with repeat Chest radiograph and ultrasound Thorax are required for confirmation of PPE diagnosis and staging of its severity.

Radiological Imaging in Para-pneumonic effusion (PPE)

There are three imaging modalities required in managing PPE. Chest radiograph is essential in detecting fluid in the pleural cavity. (Figure 2)



2a: Before drainage



2b: After drainage

Figure 2: Chest radiograph of Left Para-pneumonic effusion (PPE)

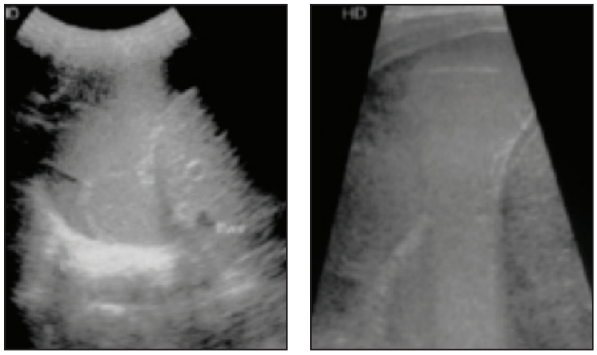
An ultrasound of the Thorax is the most important radiological investigation in determining the stage of the PPE to guide appropriate treatment. Daily Chest Radiograph or Ultrasound Thorax is not necessary. Computed Tomography Thorax (CT Thorax) is not indicated in most cases.

Management of Empyema Thoracis

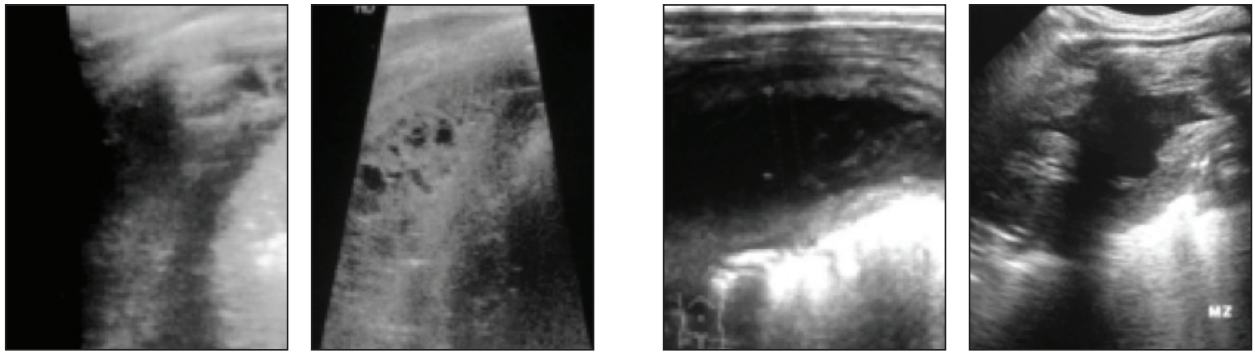
The principle of management include good and adequate anti-microbial therapy, pleural fluid drainage and supportive care which include oxygen therapy, fluid and nutritional management.

i. Anti-microbial therapy

The anti-microbial of choice is Penicillin or Cephalosporins e.g. Cefuroxime and Ceftriaxone. In young children, Cloxacillin may be considered for staphylococcus infection. Carbapenem may be considered in cases not responding to Penicillin or Cephalosporins. Parenteral administration of anti-microbial is important during initial phase. However, the total duration of therapy including oral therapy varies from three to six weeks; determined by the severity of disease.



3a: PPE Stage 1



3b: PPE Stage 2

3c: PPE Stage 3

Figure 3: Stage of Para-pneumonic Effusion (PPE) by ultrasound Thorax

ii. Pleural drainage

Pleural fluid must be drained as soon as possible for both diagnostic evaluation and therapeutic purposes. Indications for continuous pleural drainage include respiratory distress, moderate to large amount of pleural fluid and septicaemia. Evaluation of pleural fluid is important to identify the causal pathogens.

a. Pleural Drainage with Intra-Pleural Fibrinolytic agent therapy

In the late Stage 1 or early Stage 2, additional intra-pleural fibrinolytic agent like Urokinase or Streptokinase will facilitate the drainage of pleural fluid, reduce hospital stay and may avoid surgical intervention. The intra-pleural fibrinolytic agent in Stage 3 is not indicated.

Intra-pleural fibrinolytic agent is generally safe when used cautiously. Contraindications of intra-pleural fibrinolytic therapy are haemothorax, pneumothorax and hypersensitive to intra-pleural fibrinolytic agents. Complications of intra-pleural fibrinolytic therapy are uncommon such as fever, intra-pleural haemorrhage, pain and allergic reaction. Intra-pleural fibrinolytic therapy technique is described in Figure 4.

CONFIRM DIAGNOSIS AND STAGE OF PPE

- Presence of intra-pleural-fluid collection by chest radiograph and Ultrasound of the thorax

TREATMENT STEP 1: PPE Stage 2

- Insert chest drainage under sedation (General anaesthesia if required) on the site of PPE.
- The type of pleural drain may be either conventional chest tube or the pigtail catheter (under USG guidance) determined by the availability and expertise.
- Connect to the drainage bottle

TREATMENT STEP 2: PPE Stage 2

- Infuse Fibrinolytic agent in the intra-pleural space of affected site via the chest drain if no contra-indications
- Choice of agent depends on availability and patient allergy status (Streptokinase, Urokinase, Alteplase). Calculate the dose (Table 1)
- Clamp the chest drain for 4 hours
- During clamping period, encourage patient to ambulate or repositioning regularly
- After 4 hours, release the clamp and drain the fluid
- Monitor side effects during the infusion and clamping period.

TREATMENT STEP 3: PPE Stage 2

- Repeat the procedure (Step 2) according to the type of intra-pleural fibrinolytic agent used and patient's condition
- Repeat Chest radiograph after the last drainage
- Daily Chest Radiograph and Ultrasound Thorax are not recommended unless there is specific indication.

TREATMENT STEP 4: PPE Stage 2

Remove chest drain when the drainage is less than 2ml/kg/day

Figure 4: Intra-pleural fibrinolytic agent therapy

Intra-pleural Fibrinolytic agent	Dose Weight < 10 kg	Dose Weight >10 kg	Duration of therapy (up to)
Urokinase	10,000 iu in 10-40 ml Normal Saline Given twice a day	40,000 iu in 40 ml Normal Saline Given twice a day	3 days
Streptokinase	25,000 u/ kg in 50-100 ml Normal Saline Given daily (Not exceed 250,000 u per dose)	250,000 u in 50-100 ml Normal Saline Given daily	3-5 days
Alteplase (Tissue plasminogen activator)	0.1 mg/kg in 10 ml Normal saline Given daily Dwell time is 1 hour	0.1 mg/kg (max 6 mg) in 1 ml/kg (max 50 ml) Given daily Dwell time is 1 hour	3 days

Table 1: Recommended dose for intra-pleural fibrinolytic therapy

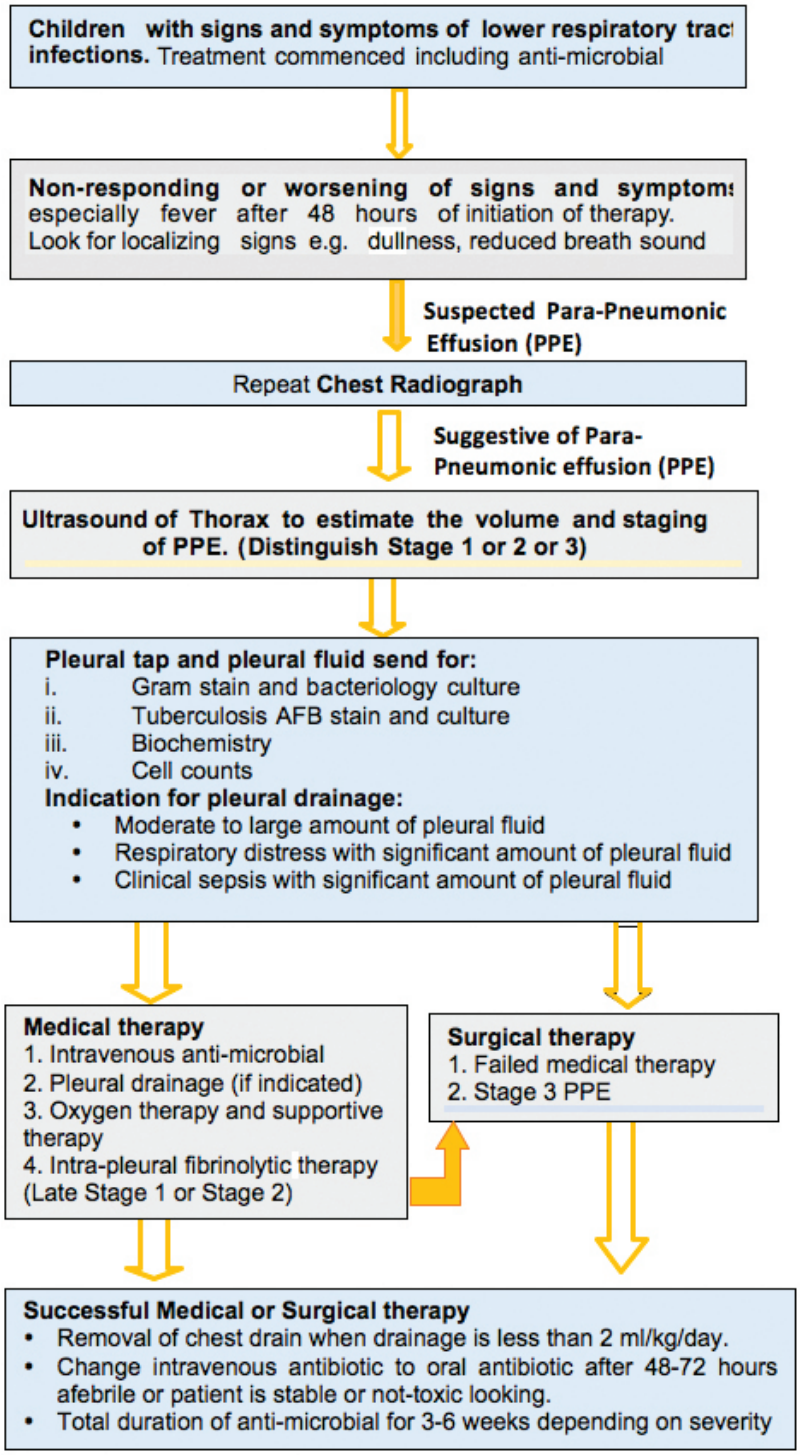


Figure 5: Approach to Para-pneumonic Effusion

iii. Surgical intervention in Empyema Thoracis

There are two surgical procedures available for empyema thoracic in Malaysia i.e. Video-assisted Thoracoscopic Surgery (VATS) and thoracotomy with debridement and decortication.

SUMMARY

Approach for Para-Pneumonic Effusion in children is dependent on its severity. Staging of PPE via ultrasound Thorax is crucial to determine type of therapy. Additional therapy with Intra-pleural Fibrinolytic agent is useful in Late Stage 1 and Stage 2 but not Stage 3. Summary of the approach and management is outlined in Figure 5.

Chapter 36:
Sleep Disordered Breathing

Introduction

- Sleep-disordered breathing (SDB) refers to a collection of ventilatory disorders characterized by recurrent partial or complete cessation of breathing resulting in multitude of night and day time symptoms
- Upper airway dysfunction during sleep characterised by snoring and/or increased respiratory effort that result from increased upper airway resistance and pharyngeal collapsibility.
- Sleep disordered breathing is a spectrum of breathing disorders ranging from benign snoring to obstructive sleep apnea (OSA) depending on the varying degree of airway obstruction.

Definitions

- Primary snoring:
  Habitual snoring (>3 nights per week) without apnoeas, hypopnoeas, frequent arousals from sleep or gas exchange abnormalities
- Upper airway resistance syndrome:
  Snoring, increased work of breathing, frequent arousals, but no recognisable obstructive events or gas exchange abnormalities
- Obstructive hypoventilation:
  Snoring and abnormally elevated end-expiratory carbon dioxide partial pressure in the absence of recognisable obstructive events
- Obstructive sleep apnoea (OSA):
  Recurrent events of partial or complete upper airway obstruction (hypopnoeas, obstructive or mixed apnoeas) with disruption of normal oxygenation, ventilation and sleep pattern

Epidemiology

- Snoring occurs in 7% of children
- Obstructive sleep apnoea (OSA) occurs in 1 – 5 % of children
- Most prominent between 2 – 6 years old

Risk Factors

- Adenotonsillar hypertrophy
- Obesity
- Allergic rhinitis
- Craniofacial anomalies (Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, unrepaired or repaired cleft palate, Pierre Robin sequence, Treacher Collins syndrome)
- Neuromuscular disorders (cerebral palsy, Duchenne muscular dystrophy, myotonic muscular dystrophy)
- Syndromes (Down syndrome, Prader–Willi syndrome)
- Complex abnormalities (achondroplasia, Chiari malformation, mucopolysaccharidoses)
- Prematurity
- Family history of OSA

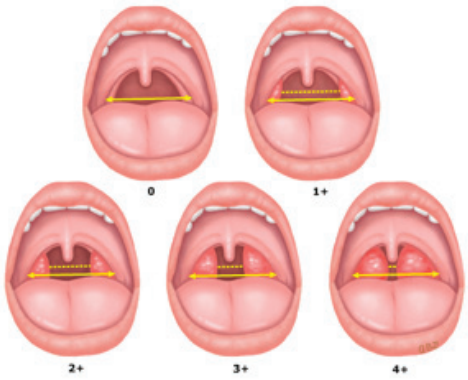
Clinical Features

- Nocturnal Symptoms:
  Habitual snoring (≥ 3 nights per week), apnoea, mouth breathing, choking / gasping in sleep, restless sleep, enuresis
- Daytime Symptoms:
  Daytime somnolence, inattention/hyperactivity, cognitive deficits / academic difficulties, behavioural / mood problems
- Others:
  Failure to thrive, obesity, systemic hypertension, pulmonary hypertension with cor pulmonale

Physical Examination

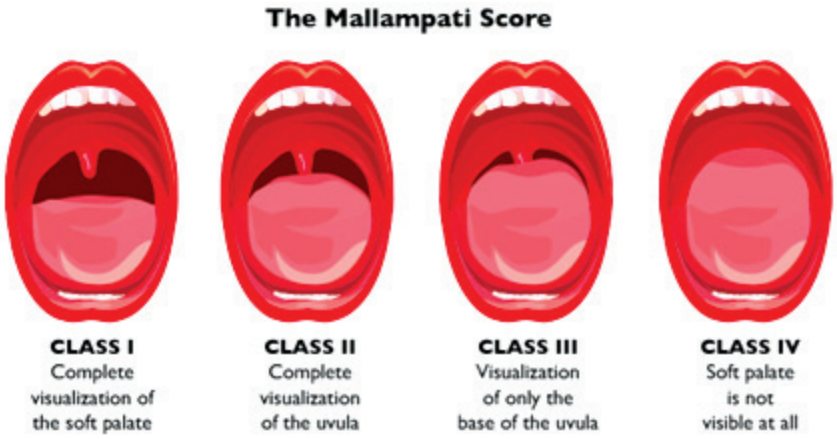
- Growth (failure to thrive, obesity)
- Oropharynx (tonsillar hypertrophy, high and narrow hard palate, adenoid facies)
- Dysmorphism
- Craniofacial features (midface hypoplasia, retrognathia, micrognathia)
- Neuromuscular features
- Cardiopulmonary (blood pressure, loud P_2)

Brodsky Tonsillar Score



Grade	Finding
0	Tonsils in fossa or removed
1+	<25% oropharynx occupied
2+	25%–50% oropharynx occupied
3+	50%–75% oropharynx occupied
4+	>75% oropharynx occupied

Mallampati Score



Indication for Referral to Paediatrician / Paediatric Respiratory Physician / Otorhinolaryngologist (ORL) Surgeon

- Paediatric Sleep Questionnaire (PSQ) ≥ 8 (Refer Appendix 1 and 2)

Investigations

1. To confirm/support the diagnosis
   Polysomnography
   - Level 1: Attended Polysomnography – the gold standard, highly recommended for patients with sleep disordered breathing symptoms and co-morbidities
   - Level 2: Unattended Polysomnography
   - Level 3: Partial Polysomnography/ Home sleep testing
   - Level 4: Nocturnal oximetry trending – Recommended for anaesthesia risk stratification for adeno-tonsillectomy patients without co-morbidities

2. To evaluate the cause/co-morbidities
   - Flexible nasopharyngolaryngoscopy - often used to identify potential sites of airway obstruction in children (e.g. enlarged nasal turbinates, septal deviation, adenoid hypertrophy, lingual tonsil hypertrophy, tongue base prolapses and laryngomalacia). However, it is limited by lack of children cooperation and it may not capture the dynamic of upper airway collapse that may occur exclusively during sleep
   - Drug induced sleep endoscopy - is commonly performed for children who have undergone previous or prior to adenotonsillectomy. It is done in children who are at high-risk for persistent obstructive sleep apnoea (OSA) including those with obesity, severe OSA, Down syndrome, craniofacial anomalies, hypotonia and neurologic impairment
   - Electrocardiogram (ECG), echocardiogram - to evaluate the consequences of sleep disordered breathing on cardiovascular system
   - Airway radiograph (lateral neck X-ray, CT / MRI head and neck) can be considered in cases with suspected airway anomalies / craniofacial anomalies AFTER discussion with respiratory paediatrician / otorhinolaryngology surgeon / plastic surgeon / oral and maxillofacial surgeon etc.

Diagnosis

- Based on BOTH clinical and polysomnographic criteria
  a. Clinical Criteria (As above in Clinical Features)
  b. Polysomnographic Criteria (based on obstructive apnoea hypopnoea index (OAHI) from polysomnography)
     i. Normal:
        OAHI < 1 events / hour
     ii. Mild OSA:
        OAHI 1 – 4.9 events / hour
     iii. Moderate OSA:
        OAHI 5 – 9.9 events / hour
     iv. Severe OSA:
        OAHI ≥ 10 events / hour
- Nocturnal oximetry trending – The McGill Oximetry Scoring System can be used to stratify the severity of obstructive sleep apnoea (OSA) in children and thus to prioritize their treatment

Oximetry Score	OSA Classification	Number of Events of SpO_2 < 90%	Number of Events of SpO_2 < 85%	Number of Events of SpO_2 < 80%
1	Normal / Inconclusive for OSA	< 3	None	None
2	Mild	≥3	≤3	None
3	Moderate	≥3	>3	≤3
4	Severe	≥3	>3	>3

Indication for Treatment

- OAHI ≥ 5 events / hour irrespective of the presence of morbidity
- Treatment may be beneficial if OAHI 1 – 4.9 events / hour especially in the presence of risk factors
- Treatment is considered when positive oximetry or presence of risk factors (in the absence of polysomnography or polygraphy study)

Treatment Consideration (Refer Appendix 3)

- Adenotonsillectomy is the **TREATMENT OF CHOICE** for patients with adenotonsillar hypertrophy and OAHI ≥ 5 events / hour
- Concurrent weight loss if the child is overweight or obese
- Concurrent nasal corticosteroids / montelukast if the child has persistent allergic rhinitis symptoms or obstructive sleep apnoea secondary to adenotonsillar hypertrophy
- Consideration for Continuous Positive Airway Pressure (CPAP) (pre or post adenotonsillectomy for severe OSA) or Bilevel Positive Airway Pressure (BPAP) (for obstructive hypoventilation) (to refer to Paediatric Respiratory Physician for evaluation and initiation)
- Craniofacial surgery for patients with selected craniofacial anomalies
- Rapid maxillary expansion or orthodontic appliances for selected craniofacial and dental anomalies
- Tracheostomy may be considered for patients with obstructed and crowded upper airway that is not responding or suitable for medical / surgical options or non-invasive ventilation

Follow-Up Management

- 6 weeks - 12 months post-intervention: To monitor symptoms of resolution or residual obstructive sleep apnoea (OSA)
- Consider repeating polysomnography / nocturnal oximetry 6 weeks after adenotonsillectomy in children with severe OSA, persistent sleep disordered breathing symptoms or craniofacial / neuromuscular / syndromic diseases
- Consider Continuous Positive Airway Pressure (CPAP) (residual moderate to severe OSA) or Bilevel Positive Airway Pressure (BPAP) (residual obstructive hypoventilation) (to refer to Paediatric Respiratory Physician for evaluation and initiation, if not done previously)

Risk factors for Residual Obstructive Sleep Apnoea (OSA)

- Down Syndrome
- Hypotonic child
- Craniofacial anomalies
- Severe obstructive sleep apnoea (OAHI ≥10)
- Obesity

Appendix 1

PEDIATRIC SLEEP QUESTIONNAIRE

22 items in PSQ	Score	
	No=0	Yes=1
While sleeping, does your child…		
• Snore more than half the time?		
• Always snore		
• Snore loudly?		
• Have "heavy" or "loud breathing"?		
• Have trouble breathing or struggle to breath?		
Have you ever…		
• Seen your child stop breathing during the night?		
Does your child…		
• Tend to breathe through the mouth during the day?		
• Have a dry mouth on waking up in the morning?		
• Occasionally wet the bed?		
Does your child…		
• Wake up feeling unrefreshed in the morning?		
• Have a problem with sleepiness during the day?		
• Has a teacher or other supervisor commented that your child appears sleepy during the day?		
• Is it hard to wake your child up in the morning?		
• Does your child wake up with headache in the morning?		
• Did your child stop growing at a normal rate at any time since birth?		
• Is your child overweight?		
The child often…		
• Does not seem to listen when spoken to directly		
• Has difficulty organizing task and activities		
• Is easily distracted by extraneous stimuli		
• Fidgets with hands or feet or squirms in seat		
• Is "on the go" or often acts as if "driven by a motor"		
• Interrupts or intrudes on others (e.g. butts into conversations or games)		
Total numbers of "Yes" score		
Indicate sleep related breathing disorder (Score>8)		

Responses are "no" = 0, "yes" = 1, and "don't know" = missing

Reference: Chervin RD, Hedger K, Dillon JE, et al. Pediatric sleep questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep Med. 2000:1;1(1):21-32.

Appendix 2

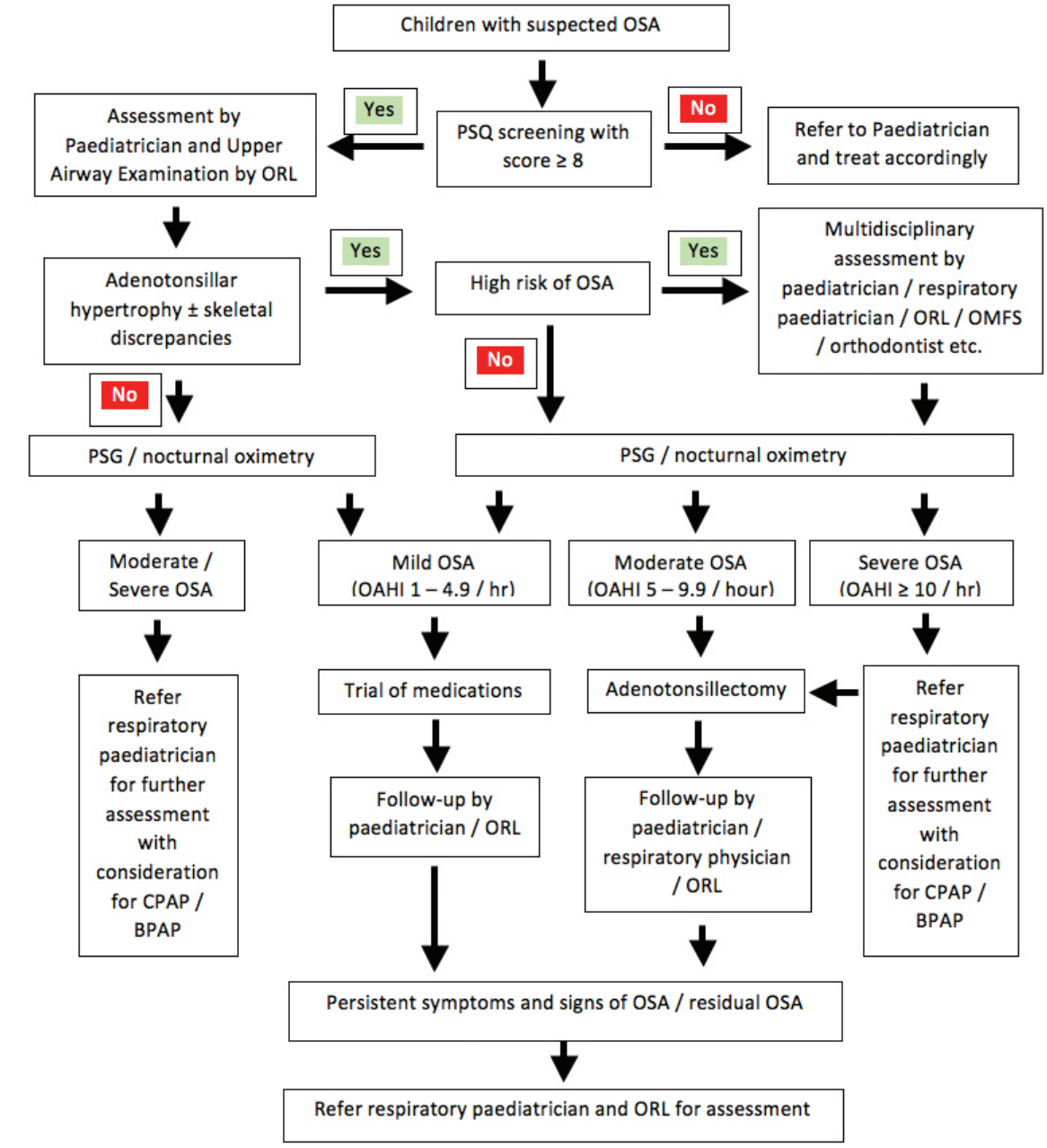
PEDIATRIC SLEEP QUESTIONNAIRE (MALAY VERSION)

22 item PSQ (BM)	Skor	
	No=0	Yes=1
Ketika tidur, adakah anak anda…		
• Berdengkur lebih daripada separuh masa tidurnya?		
• Sentiasa berdengkur?		
• Berdengkur dengan kuat?		
• Bernafas dengan “panjang”dan “dalam”?		
• Mengalami masalah pernafasan atau sukar hendak bernafas?		
Pernahkah anda…		
• Melihat anak anda berhenti bernafas seketika pada waktu tidur?		
Adakah anak anda…		
• Lebih cenderung bernafas melalui mulut pada siang hari?		
• Mengalami mulut kering ketika bangun pagi?		
• Sekali-sekala terkencing di atas katil ketika tidur?		
Adakah anak anda…		
• Berasa kurang segar ketika bangun pagi?		
• Menghadapi masalah mengantuk pada siang hari?		
• Pernah diberitahu oleh guru atau penyelia bahawa anak anda kelihatan mengantuk pada waktu siang?		
• Sukar dibangunkan dari tidur pada waktu pagi?		
• Mengadu sakit atau pening kepala ketika bangun tidur?		
• Mengalami masalah terbantut tumbesaran atau pembesaran?		
• Mengalami berat badan berlebihan?		
Kanak-kanak…		
• Selalunya seperti tidak mendengar apabila bercakap secara berdepan dengannya		
• Selalu mengalami kesukaran mengatur tugas dan aktiviti		
• Selalu terganggu dengan rangsangan luar		
• Kelihatan resah dan sentiasa menggerakkan jari tangan atau kakinya atau gelisah ketika duduk		
• Terlampau aktif atau tidak boleh duduk diam		
• • Selalu menyampuk cakap orang atau mengganggu orang (contohnya, mencelah perbualan orang lain atau mengganggu permainanan)		
Jumlah skor “Ya”		
Mencadangkan masalah pernafasan berkaitan tidur (Sleep disordered breathing) Skor ≥ 8		

Respon “Tidak” = 0, “Ya” = 1, dan “tidak tahu” = missing

Reference: Hasniah AL, Jamalludin AR, Norrashidah AW, et al. Cross-cultural adaptation and reliability of pediatric sleep questionnaire in assessment of sleep-disordered breathing in the Malay speaking population. World J Pediatr. 2012;8(1):38-42.

Appendix 3

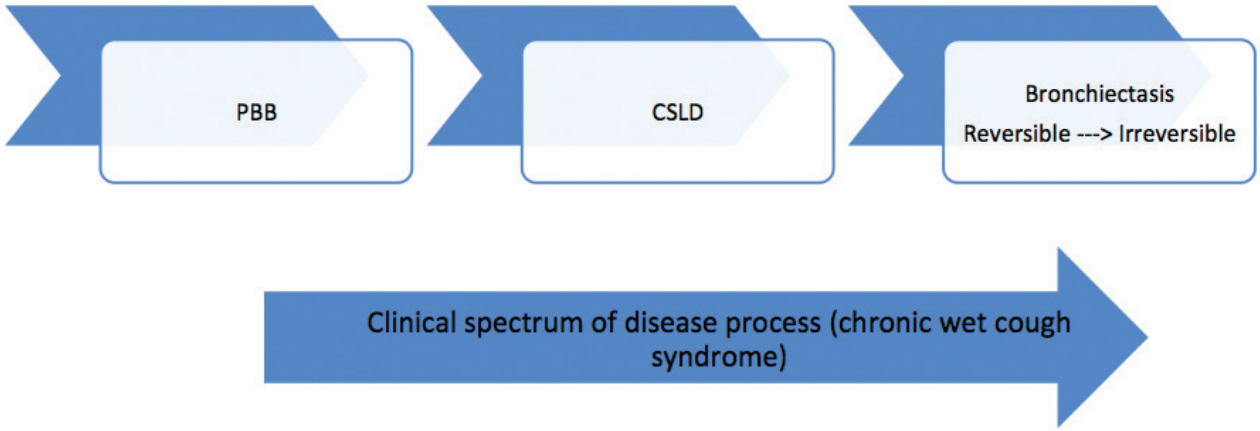


CPAP : Continuous positive airway pressure, BPAP : Bilevel positive airway pressure, OMFS : Oral and maxillofacial surgeon, ORL : Otorhinolaryngologist, OSA : Obstructive sleep apnoea, PSQ : Paediatric Sleep Questionnaire, PSG : polysomnography

Chapter 37:
Chronic Wet Cough and Bronchiectasis

- Chronic cough is a common symptom in children and it is defined as chronic if the duration of cough is more than **4 weeks** in children. Any chronic cough, especially if wet or productive, warrants further evaluation.
- **Protracted bacterial bronchitis (PBB)** is one of the most common aetiology in children with chronic wet cough, however, it has remained largely unrecognised.
  - Protracted bacterial bronchitis (PBB) is a clinical diagnosis of chronic wet or productive cough (>4 weeks), in an ***otherwise well child*** *(often normal physical examination and chest radiograph)*, that responds to a 2 weeks course of an appropriate antibiotic.
  - Confirmed PBB is when there is a positive bacterial culture of sputum or BAL (usual organisms are *Streptococcus pneumoniae, Haemophilus influenza, Moraxella catarrhalis*).
  - Extended PBB - Patients with chronic wet cough who requires a longer duration of antibiotic of 4 weeks for symptoms resolution.
  - Patients with recurrent episodes of PBB in a year (especially if extended PBB) are at higher risk of developing bronchiectasis.
- **Bronchiectasis**- It is originally defined as permanent/irreversible dilatation of the bronchus. Currently, it is defined as a clinical syndrome of chronic or recurrent wet / productive cough with radiological confirmation of bronchial wall dilatation (paediatric Broncho-Arterial ratio (BAR) > 0.8 by High Resolution CT Scan (HRCT) of the thorax in paediatrics). The radiographic bronchial wall dilatation is potentially reversible in early stage of bronchiectasis. The syndrome is characterised by dilated and thickened wall causing mucous retention, bacterial colonisation and destruction of the surrounding tissue due to excessive chronic airway inflammation.
- **Chronic suppurative lung disease (CSLD)** is a term coined for clinical wet cough syndrome WITHOUT chest HRCT findings of bronchiectasis.

Figure 1: Clinical spectrum of disease process (chronic wet cough syndrome)



Clinical Presentation

- The clinical presentation of bronchiectasis in children and adolescents are summarised in table 1.

Table 1: Key Presentation of Bronchiectasis

Key Symptoms	Other signs and symptoms
Chronic wet or productive cough • *failure to respond to 4 weeks of oral antibiotics (OR 20.9, 95% CI 5.4–81.8) of CT bronchiectasis*	Clubbing
Abnormal chest x-ray	Persistent crepitations/crackles
Recurrent pneumonia	Wheeze
Recurrent PBB (>3 episodes per year) • *OR 11.5, (95% CI 2.3-56.0) of CT Bronchiectasis*	Haemoptysis
Feeding difficulties (children with structural/functional aerodigestive problems)	Chest pain
"Asthma" unresponsive to treatment	Reduced Effort tolerance
	Chest deformity
	Failure to thrive

Aetiology

- Bronchiectasis is the 'end-consequence' of many conditions related to recurrent and/or persistent respiratory infections. It is important to identify the underlying aetiologies of bronchiectasis as early treatment may prevent irreversible bronchial structure and further progression of bronchiectasis. Cystic Fibrosis (CF) Bronchiectasis is highly prevalent in Caucasian ethnicity. This chapter mainly focuses on Non-CF Bronchiectasis.
- The aetiologies vary between high income and low to medium income countries, where post-infectious and idiopathic causes are prevalent in the latter countries.
- Thorough history taking, physical examination and targeted investigations are essential.

Table 2: Aetiology of bronchiectasis

Aetiology of Non-CF Bronchiectasis	Other Causes or Associated Co-morbidities
Post-Infectious	Asthma
Immune deficiency : • **Primary:** *Agammaglobulinaemia, Common variable immunodeficiency, IgA deficiency, Selective antibody deficiency, Severe combined immunodeficiency, Ataxia telangiectasia, Hyper-IgE syndrome, Cartilage-hair hypoplasia, Chronic granulomatous disease* • **Acquired:** *HIV, immunosuppressive drugs, cancer*	Chronic Lung Disease of Prematurity
Primary Ciliary Dyskinesia (PCD)	Bronchiolitis Obliterans
Congenital anomalies: *Congenital Tracheobronchomegaly (Mounier-Kuhn Syndrome)* *Tracheobronchomalacia*	Connective tissue diseases (e.g., SLE)
Aspiration syndromes- e.g. GERD, swallowing incoordination	Inflammatory Bowel Disease
Post Tuberculosis (post-TB)	Yellow nail syndromes
Idiopathic	Marfan Syndrome
Others- *post foreign body inhalation, Oesophageal atresia with tracheo-oesophageal fistula (TOF), cardiac disease*	Allergic Bronchopulmonary Aspergillosis (ABPA)
	Polycystic Kidney Disease or other renal disease

Investigations

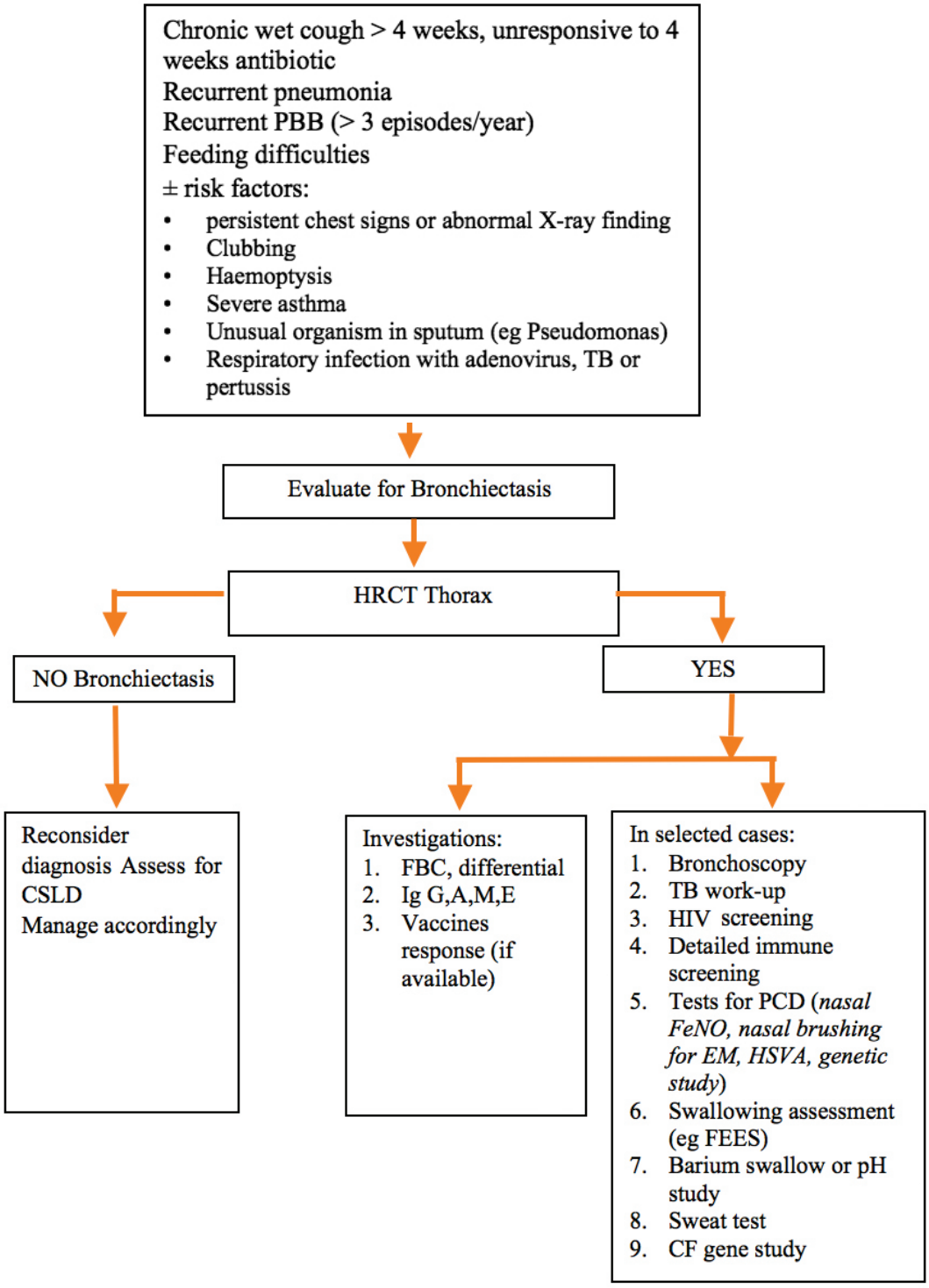
- Investigations are directed towards confirmation of bronchiectasis, identifying underlying aetiology if possible and to assess baseline severity of bronchiectasis and lung impairment.
  1. Imaging techniques of diagnosis confirmation:
     - HRCT Thorax: is the gold standard imaging technique to confirm the diagnosis.
     - The emerging technique is MRI of the chest.
     - Chest radiograph: there is poor agreement between CXR and HRCT findings. Abnormal chest radiograph should alert the possibility of bronchiectasis in a typical clinical context, however a normal CXR does not exclude bronchiectasis.

Table 3: HRCT features of bronchiectasis

HRCT features of BE
Increase BAR for age (> 0.8), signet ring appearance
Bronchial wall thickening
Lack of bronchial tapering, tramline appearance
Presence of bronchial wall in the lung periphery
Structural changes of Bronchial wall– fusiform/cylindrical saccular or cystic changes
Mucous retention/ plugging in the bronchus
Tree-in bud appearance
Mosaic perfusion (reflecting air-trapping)

  2. Investigations to ascertain the underlying diagnosis are listed in the flow diagram (figure 2).
  3. Spirometry does not provide diagnostic information but may serve as a marker of disease severity and progression of lung function. It may show obstructive, restrictive or even mixed obstructive and restrictive lung disease.

Figure 2. Approach to the Diagnosis of Bronchiectasis



Footnote: FBC=full blood count, FeNO= fraction exhale nitric oxide, EM=electron microscopy, HSVA= high speed video analysis, FEES= flexible endoscopic evaluation of swallowing, CF=cystic fibrosis

Management

Management of bronchiectasis can be divided into management during stable state and during a respiratory exacerbation.

Stable State

- Baseline respiratory symptoms, chest signs and respiratory support (if present) should be documented for each child or adolescent with bronchiectasis during their stable state.
  - Baseline respiratory symptoms
    - Presence of cough (dry/wet), sputum (volume, viscosity, colour), exertional symptoms
  - Baseline chest signs
    - Presence of crackles/crepitations, rhonchi, quality of breath sounds, chest deformity
  - Respiratory support
    - Type of respiratory support (oxygen, continuous positive airway pressure, bilevel positive airway pressure)

Management during stable state

1. Airway clearance therapy (ACT)
   - ACT remains the key intervention in children and adolescents with chronic suppurative lung disease.
   - Individualised ACT that is development- and age-appropriate (table 4) is best taught by a paediatric-trained chest physiotherapist.
   - The ACT type and frequency should be reviewed at least biannually by physiotherapists as children or adolescents mature.

Table 4: Types of ACT in different age groups

<table>
<tr><th></th><th>Infant</th><th>Toddler</th><th>Child</th><th>Adolescent</th></tr>
<tr><td rowspan="2">Positioning</td><td colspan="4">Modified gravity-assisted drainage (GAD)</td></tr>
<tr><td colspan="4">Chest Percussion +/- Expiratory Vibration</td></tr>
<tr><td rowspan="3">Expiratory flow modification</td><td rowspan="3">Assisted Autogenic Drainage (AAD)</td><td colspan="2">Blowing games</td><td></td></tr>
<tr><td colspan="3">Forced expirations, Huffing,
Active cycle of breathing technique (ACBT)</td></tr>
<tr><td colspan="3">Autogenic Drainage (AD)</td></tr>
<tr><td rowspan="3">Device</td><td rowspan="3"></td><td colspan="3">Oscillating PEP devices with/without nebuliser</td></tr>
<tr><td colspan="3">High Frequency Chest Wall Oscillation (HFCWO, “vest” therapy)</td></tr>
<tr><td></td><td colspan="2">Oscillating PEP with Forced Expiration Technique (FET)</td></tr>
<tr><td rowspan="3">Exercise</td><td rowspan="3">Severe</td><td colspan="2">Bouncing on a fitball
(supported/unsupported)</td><td></td></tr>
<tr><td colspan="3">Vigorous activity (including active video games),
Physical exercise</td></tr>
<tr><td colspan="3">Vertical acceleration activities eg. trampoline</td></tr>
<tr><td>Others</td><td></td><td colspan="3">Musical wind instruments</td></tr>
</table>

2. Antibiotics to reduce exacerbations

- Long-term macrolide antibiotics is recommended in children or adolescents with bronchiectasis who have had:
  - >1 hospitalised exacerbation or
  - ≥3 non-hospitalised exacerbations in the past 12 months.
- Each course should last for at least 6 months with regular reassessment to determine whether the antibiotic continues to provide a clinical benefit.
- Children or adolescents receiving longer treatment courses (>24-months) should continue to be evaluated for risk versus benefit.
- It is recommended to obtain a lower airway specimen (when possible) to exclude their presence before commencing long-term macrolide antibiotics.

3. Mucoactive Agents

- Recombinant-human DNAse and bromhexine should not be used routinely.
- Inhaled mannitol or hypertonic saline (HS) may be considered in selected patients with:
  - High daily symptoms
  - Frequent exacerbations
  - Difficulty in expectoration
  - Poor quality of life (QoL)
- If well tolerated, the use of HS or mannitol could improve the QoL and facilitate expectoration.
- For HS and mannitol, children should be old enough to tolerate these interventions with pre-inhalation of short-acting beta2-agonists (SABA).
- The first dose of HS or mannitol should be administered under medical supervision.

4. Asthma-type Medications

- In children or adolescents with bronchiectasis, inhaled corticosteroids (ICS) with or without long-acting beta2-agonists (LABAs) are not routinely recommended in either the short or long-term, irrespective of stability or exacerbation.
- ICS may be beneficial in those with eosinophilic airway inflammation, or asthma.
- If treatment with ICS or ICS/LABA is contemplated, every effort should be made to document acute bronchodilator sensitivity (acute spirometric response to SABA), atopy (skin prick tests, specific IgE) and airway eosinophilia (peripheral blood eosinophil count, sputum eosinophils, exhaled nitric oxide).

5. Vaccinations

- Children and adolescents with bronchiectasis are recommended to be fully immunised according to their national immunisation programmes, including pneumococcal and annual seasonal influenza vaccines.

6. Personalised bronchiectasis action plan

- Every child or adolescent with bronchiectasis is recommended to have a personalised action plan that is discussed with the child and caregiver, and should be reviewed regularly.

Respiratory Exacerbation

- Definition
  - Increased respiratory symptoms (predominantly increased cough +/- increased sputum quantity +/- purulence) for ≥ 3 days.
  - For those with immunodeficiency, a lower threshold is suggested (as commencing treatment earlier may be required).
  - Clinicians should not rely on changes in chest auscultation findings and chest x-rays to diagnose an exacerbation as, although important, these findings are not always present.
  - Blood markers (e.g. elevated C-reactive protein, neutrophilia and interleukin-6) provide supportive evidence of the presence of an exacerbation.
- Severe exacerbation
  - Presence of dyspnoea (increased work of breathing) +/- hypoxia, irrespective of duration.

Management during exacerbations

1. Airway clearance therapy (ACT)

- A more intensive and frequent ACT during acute exacerbations have been shown to have no adverse events, with improved sputum clearance, lung function and symptoms.
- Adjustment to the type of ACT during exacerbations may be necessary (eg. exercises may not be feasible).

2. Antibiotics for exacerbation

- Antibiotic treatment for acute exacerbations of bronchiectasis are considered standard of care.
- This has been shown to resolve symptoms and reduce the duration of exacerbations.
- Mild exacerbations
  - The empiric antibiotic of choice is oral amoxicillin-clavulanate for 14 days.
  - However, the type of antibiotics should be based on the patient's airway culture (e.g. those with *Pseudomonas aeruginosa* require different treatment regimens to those without) and history of antibiotic hypersensitivity reactions.
- Severe exacerbations or mild exacerbations that fail to respond to a course of oral amoxicillin-clavulanate for 14 days
  - Admit for intravenous antibiotics and intensive ACT.

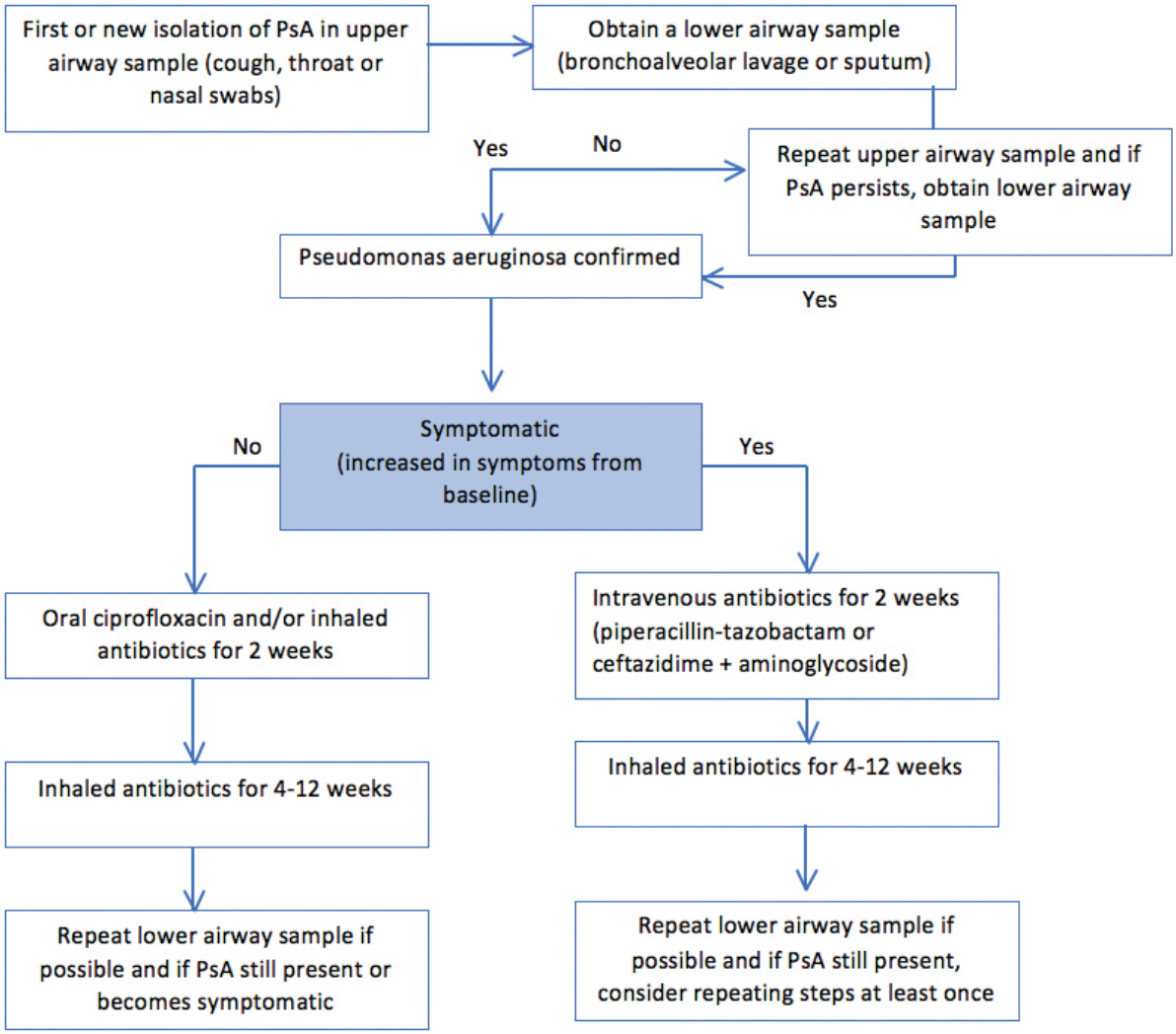
Table 5: Summary of management during stable state and exacerbation

	Stable State	Exacerbation
Airway Clearance Therapy (ACT)	Individualised (age and development-appropriate)	More frequent ACT
Antibiotics	Long-term antibiotics (macrolides) for those with: • >1 hospitalised exacerbation or • ≥3 non-hospitalised exacerbations • in the past 12 months	**Mild exacerbations:** Oral amoxillin-clavulanate for 14 days (*antibiotic of choice depends on patient's lower airway culture) **Severe exacerbation:** Intravenous antibiotics
Mucoactive Agents	Inhaled mannitol or hypertonic saline (HS) for those with: high daily symptoms, frequent exacerbations, difficulty in expectorating sputum, and/or poor QoL	Inhaled mannitol or HS can be incorporated into ACT
Asthma Medications	Individualised (age and development-appropriate)	

3. Antibiotics for eradication treatment

- Pseudomonas aeruginosa
  - Eradication therapy is recommended following an initial or new detection of *Pseudomonas aeruginosa* (Figure 3).
  - Eradication therapy has been shown to improve QoL and reduce exacerbation rates, antibiotics use and hospitalisation

Figure 3: Suggested algorithm for eradication therapy for new detection of Pseudomonas aeruginosa (PsA)



Conclusion

The aim of managing children and adolescents with bronchiectasis is to optimise lung growth, preserve lung function, improve quality of life, minimise exacerbations, prevent complications and, if possible when diagnosed early, reverse bronchial wall dilatation as a marker of structural lung injury.

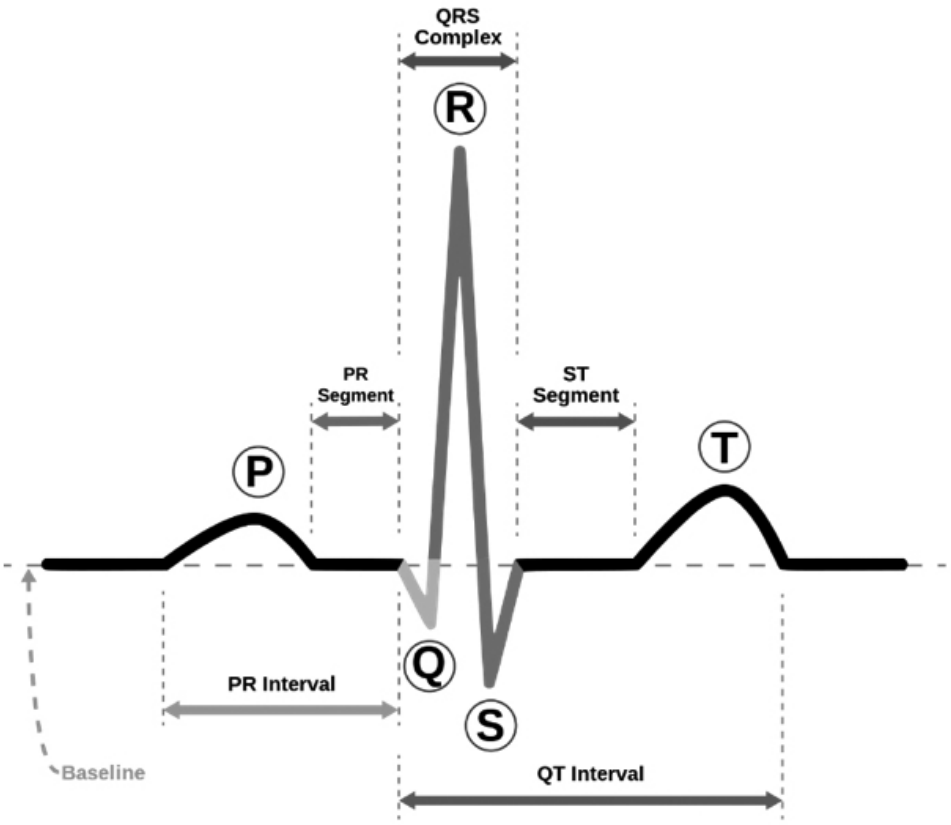
Section 8

CARDIOLOGY

Chapter 38:
Paediatric Electrocardiography (ECG)

Paediatric ECG has a significant role in evaluating children with congenital and acquired cardiovascular pathology. However, it is one of the most often misinterpreted tests in paediatric medicine due to failure to consider age-related developmental changes that occur throughout life from the neonatal period to the adulthood.

The ECG Cycle



P wave	- atrial depolarization
PR segment	- slow conduction through the AV node (AV node delay)
QRS complex	- depolarization of ventricles
T wave	- repolarization of ventricles

Age-Related ECG Changes:

- Most changes relate to the ratio of LV to RV weight
- Birth: RV thicker than LV
- End of the first month: LV heavier than RV (Ratio of LV:RV = 1.5:1)
- By 6 months of age: Ratio of LV/RV = 2:1
- Young adult: Ratio of LV/RV = 2.5:1

Characteristics of Paediatric ECG:

- Rate faster than adults
- All duration and intervals (PR interval, QRS duration, QT interval) are shorter than that of in the adult
- RV dominance of neonate and infant:
- After 12 to 16 years, T wave becomes positive in V1 – V3 (resembling adult ECG)

Systemic Approach to Reading ECG:

1. Rhythm
   Normal sinus rhythm originates from the sino-atrial (SA) node and meets the following requirements:
   - Every QRS is preceded by P wave
   - Uniform PR interval
   - Normal P wave axis (0 to +90°; upright in leads I and aVF)

2. Rate (Atrial and ventricular rates, if different)

$$\text{Rate} = \frac{300}{RR\ interval\ in\ large\ squares}$$

OR

$$\text{Rate} = \frac{1500}{RR\ interval\ in\ small\ squares}$$

3. Axis determination
   QRS axis changes with age: From +125° at birth (range +30° to +180°) to a mean value of +50° by the age of 3 years (adult range -10° to +110°).
   Superior axis deviation (-90° to 180°) is an abnormal finding and can be seen in children with atrioventricular septal defects, tricuspid atresia, inlet ventricular septal defects or after pacemaker implantation.

4. Amplitude and duration (P waves, Q waves, QRS complexes, R/S ratio, QTc)

4. Amplitude and duration (P waves, Q waves, QRS complexes, R/S ratio, QTc)

P waves	• Normally upright in I and aVF • Amplitude < 3 mm, if taller consider right atrial enlargement • Duration < 0.09 sec, if wider consider left atrial enlargement
Q waves	• Normally present in inferior leads (II, III, aVF), anterolateral leads (I, aVL) and almost always present in V5 - V6. Generally, the Q wave should not be larger than 25% of the R wave amplitude in any lead • Deep Q waves in lead aVL may be seen in anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) • Q waves in lead V1 - V3 may be seen in congenitally corrected transposition of great arteries (ccTGA)
QRS complexes	• QRS duration increase with age • • Prolonged QRS duration: • Bundle branch blocks • Wolff-Parkinson-White (WPW) • Ventricular arrhythmia • Decreased amplitude: • Myocarditis • Pericarditis/pericardial effusion
R/S ratio	• In normal infants, the ratio is large in the right precordial leads and small in the left precordial leads • This pattern is reversed in adults
PR interval	• Gradually increase with age • Short PR • Wolff-Parkinson-White (WPW) syndrome • Pompe's disease • Prolonged PR • Rheumatic fever • Myocarditis • Electrolyte imbalance (hyperkalaemia) • Drug-induced (beta blockers, calcium channel blockers, digoxin, amiodarone) • Hypothermia • Athletes
QTc	• Bazett's formula: QTc = QT / √RR interval • Prolonged QTc • Congenital long QT syndrome • Electrolyte imbalance (hypomagnesemia, hypokalemia, hypocalcemia) • Hypothermia • Myocarditis • Raised intracranial pressure • Drug-induced (antihistamines, macrolides, antifungals, prokinetics, antipsychotics)

5. ST segment and T wave abnormalities

ST segment	• ST Elevation/depression of up to 1mm may be normal in limb leads, whereas up to 2mm is normal in left precordial leads (attributed to early repolarization of the heart)
T waves	• V1 - V3 upright at birth up till 1 week of life, then becomes inverted until adolescence age (exact age may vary) • T wave progression to becoming upright in sequence V3, V2, V1

Check calibration of ECG machine!!

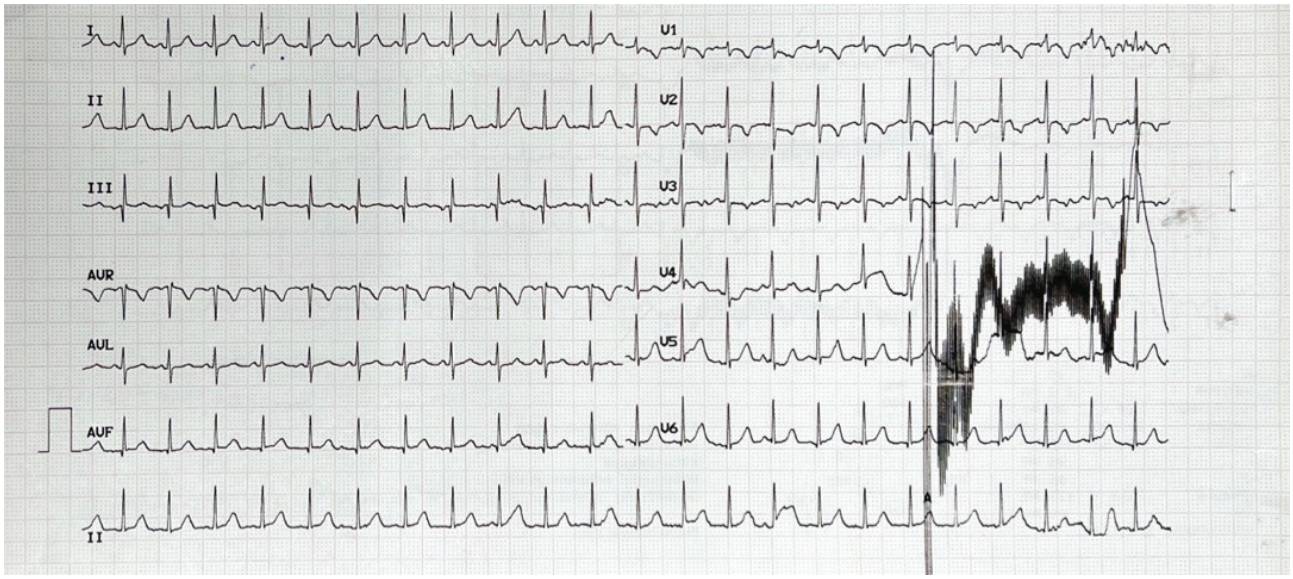
- Vertical 10mm/mV
- Horizontal 25mm/s

Paediatric ECG findings that may be normal:

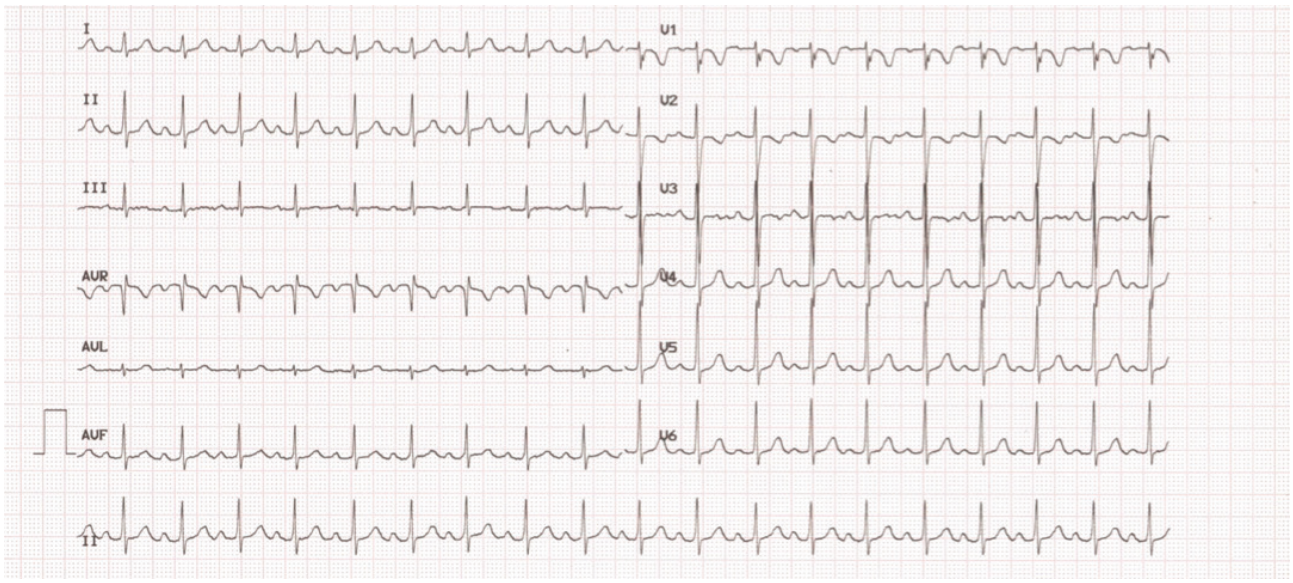
- QRS axis > 90°
- Right precordial T wave inversion
- Dominant right precordial R waves
- Inferior and lateral Q waves
- Elevated J point: normal in some adolescents

Normal ECG Examples in Different Age Groups

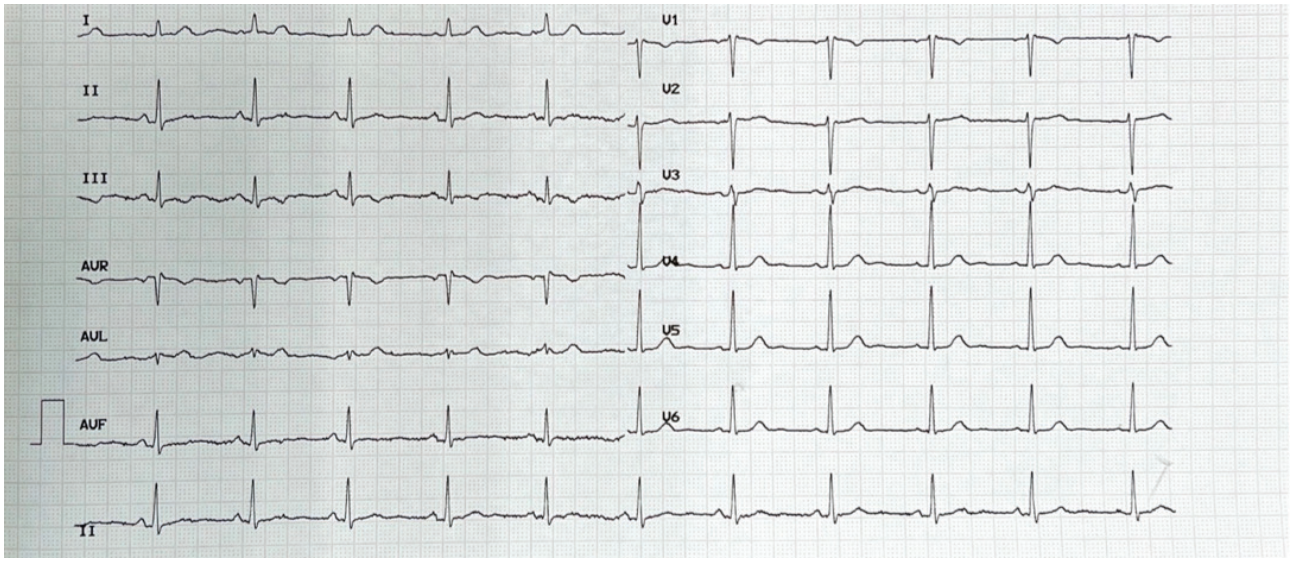
1. 3 months old
    - R wave dominant in V1
    - Negative T waves across right precordial leads



2. 3 years old
   - R wave dominant in V6
   - S wave dominant in V1
   - T waves remain negative in right precordial leads



3. 9 years old
   - QRS axis 0 to +90°
   - Adult pattern QRS progression
   - Upright T waves in precordial leads but may remain inverted in V1 – V3 until late adolescent age



Chapter 39:
Critical Congenital Heart Disease

- Congenital heart diseases (CHD) are the most common birth defects, with an incidence of about 1 per 100 live births
- 25% of CHD are classified as critical congenital heart disease (CCHD)
- CCHD is defined as cardiac lesions which will require cardiac intervention within the first year of life
- Prompt diagnosis is important to identify those that will require early initiation of therapy to prevent severe complications, end organ injury and death

Common CCHD	Hypoxemia	Ductal Arteriosus Dependent
D-transposition of great arteries (TGA)	All	Some
Double outlet right ventricle (DORV)	Some	Some
Truncus arteriosus	All	None
Total anomalous pulmonary venous drainage (TAPVD)	All	None
Ebstein's anomaly	Some	Some
Double inlet left ventricle (DILV)	All	Some
Right obstructive defects		
Tetralogy of Fallot (TOF)	Most	Uncommon
Tetralogy of Fallot with pulmonary atresia (TOF/PA)	All	All
Tricuspid atresia	All	Some
Pulmonary atresia with intact septum (PA/IVS)	All	All
Critical pulmonic valve stenosis (PS)	All	All
Left obstructive defects		
Hypoplastic left heart syndrome (HLHS)	All	All
Coarctation of aorta (CoA)	Some	Some
Interrupted aortic arch (IAA) or aortic arch atresia	Some	All
Critical aortic valve stenosis (AS)	Some	All

CCHD at Risk for Sudden Collapse

- Some CCHD will require early intervention soon after birth to prevent rapid and sudden deterioration, such as severe cyanosis, end-organ damage, cardiovascular collapse, or death

Types of CCHD	Comments	Intervention
Ductal dependent pulmonary circulation	• Critical right outflow tract obstructive lesions causing inadequate pulmonary perfusion, maintained by patent ductus arteriosus (PDA) • PDA closure causes extreme cyanosis and hypoxemia (oxygen saturation <75%), which may lead to hemodynamic instability • Example: Critical pulmonary stenosis or atresia	• Stabilize with IV infusion of Prostaglandin E (IVI PGE) • Early surgical or catheter interventions, e.g. Blalock Taussig shunt, PDA stenting, pulmonary balloon valvuloplasty
Ductal dependent systemic circulation	• Critical left outflow tract obstructive lesions leading to compromised systemic perfusion, maintained by PDA • PDA closure causes impaired systemic perfusion, end-organ damage, and shock • Example: Critical CoA, IAA, critical AS, HLHS	• Stabilize with IVI PGE • Early surgical or catheter interventions, e.g. surgical repair of aortic arch, balloon angioplasty or valvuloplasty
TGA with poor mixing	• TGA with restrictive and inadequate intra-cardiac mixing defects (PFO/ASD/VSD) • Causes rapid and progressive severe cyanosis and hemodynamic instability • PDA alone without good intra-cardiac mixing may not be sufficient to achieve adequate oxygenation	• Emergency balloon atrial septostomy (BAS) • IVI PGE while waiting for transfer to cardiac center • Early surgical repair with arterial switch operation
Obstructed TAPVD	• TAPVD with obstruction of vertical vein draining pulmonary venous confluence • Highest incidence in infra-cardiac type, followed by supra-cardiac type • Causes severe pulmonary edema and pulmonary hypertension, resulting in severe hypoxemia and cyanosis, difficulty ventilating and hemodynamic instability • Obstruction can also occur at atrial level if PFO is restrictive	• Emergency TAPVD repair

IV Prostaglandin E infusion

- Standard dilution: 60mcg/kg in 50mL diluent; 1mL/hr = 20ng/kg/min
- Alternative dilution: 30mcg/kg in 50mL diluent; 1mL/hr = 10ng/kg/min
- Starting dose: 10 – 40 ng/kg/min; maintenance: 2 – 10ng/kg/min
- Adverse effects: apnoea (12%, particularly neonates < 2 kg), fever (14%), flushing (10%), hypotension (4%); prolonged use can cause cortical proliferation of long bones
- Monitoring for clinical response
  - → Ductal dependent pulmonary circulation: monitor systemic arterial oxygen saturation, titrate IVI PGE to achieve saturation of 80-90% to avoid over-shunting and heart failure
  - → Ductal dependent systemic circulation: monitor distal perfusion (pulses, capillary refill, blood pressure) and end-organ perfusion (urine output, acidosis); do NOT titrate IVI PGE based on oxygen saturation
- Causes of poor / non-responders
  - → Non-ductal dependent lesions
  - → Poor mixing in TGA
  - → IV access blockade
  - → Tolerance due to prolonged use
  - → Non-cardiac causes of deterioration (pneumonia, PPHN, sepsis, anaemia)

Newborn Pulse Oximetry Screening

- Recommended for all newborn as routine screening for critical congenital heart diseases
- Also able to detect hypoxemia due to other clinically severe conditions, such as pneumonia, persistent pulmonary hypertension of newborn, sepsis

Recommendation for Performing Newborn Pulse Oximetry Screening
To be done at 24 – 48 hours of life, or as late as possible if the baby is discharged before 24 hours of age.
Oxygen saturation be measured with pulse oximetry probe placed on either foot (post-ductal).
A positive result (failed screening): • A single reading of oxygen saturation <90%, or • 3 readings of oxygen saturation of <95%, separated by 1 hour
Patients who fail the screening test should be assessed clinically, referred for a detailed transthoracic echocardiogram and considered for additional testing such as chest radiography or bloodwork

Chapter 40:
Hypercyanotic Spell

Introduction

Severe and often prolonged episodes of intense cyanosis in patients with underlying unrepaired Tetralogy of Fallot (may also occur in other lesions with anatomy which allow abrupt changes in the ratio of pulmonary-to-systemic blood flow). Although the exact aetiology is unclear, it is believed to be mediated by variable combination of acute worsening of subpulmonic obstruction, decreased systemic vascular resistance, hypovolaemia and increased catecholamines resulting in severely diminished pulmonary blood flow and increased right-to-left shunting of deoxygenated blood into the systemic circulation.

Clinical Presentation

- Peak incidence age: 3 to 6 months.
- Frequently occurs in the morning; precipitated by crying, feeding or defaecation.
- Severe cyanosis, hyperpnoea, lethargy.
- In severe cases, it may lead to loss of consciousness, hypoxic seizure and death.
- Reduced intensity of systolic murmur during the spell.

Management

Treat this as a medical emergency.

- Knee-chest/squatting position:
  - Place the baby on the mother's lap with the knees tucked up underneath the chest.
  - This provides a calming effect, reduces systemic venous return and increases systemic vascular resistance.
- Administer 100% oxygen
- Give IV/IM/SC morphine 0.1 – 0.2 mg/kg to reduce distress and hyperpnoea.
  - Can be repeated once after 3 minutes if the hypercyanotic spell is ongoing

If the above measures fail:

- IV Propranolol 0.05 – 0.1 mg/kg slow bolus over 10 mins.
- Alternatively, IV Esmolol 0.5 mg/kg slow bolus over 1 min, followed by 0.05 mg/kg/min for 4 mins.
  - Esmolol is an ultra-short-acting beta blocker
  - Can be given as continuous IV infusion at 0.01 – 0.02 mg/kg/min.
- Volume expander (crystalloid or colloid) 20 ml/kg rapid IV push to increase preload.
- IV sodium bicarbonate 1 - 2 mEq/kg to correct the metabolic acidosis.

In resistant cases, consider:

- Heavy sedation, intubation and mechanical ventilation.
- IV Phenylephrine (0.01 – 0.02 mg/kg slow bolus) or IV Noradrenaline (0.1 – 0.5 mcg/kg/min infusion) to increase systemic vascular resistance and reduce right to left shunt.
- Emergency modified Blalock-Taussig shunt or right ventricular outflow tract (RVOT) stenting.

Other Notes

A single episode of hypercyanotic spell is an indication for early surgical referral (either total repair or modified Blalock-Taussig shunt/RVOT stenting).

Oral propranolol 0.2 – 1 mg/kg/dose 8 to 12 hourly should be started soon after stabilization while waiting for surgical intervention.

Chapter 41:
Heart Failure

Definition

Failure of the heart to generate an adequate cardiac output to meet the metabolic demand of the body. It is a clinical syndrome characterized by respiratory distress, growth failure, venous congestion and exercise intolerance accompanied by circulatory and neurohormonal derangement.

Aetiology

- Diverse aetiology
- Congenital heart diseases dominate the causes of heart failure in infants and young children
- Acquired heart diseases such as rheumatic heart disease and cardiomyopathies are usually encountered in older children

Congenital heart disease	Acquired heart disease
Volume Overload	
Left to right shunts • Ventricular septal defect (VSD) • Patent ductus arteriosus (PDA) • Atrioventricular septal defect (AVSD) • Aortopulmonary window • Coronary artery fistula	Valvular regurgitation • Rheumatic heart disease • Infective endocarditis
Valvular regurgitation • Ebstein's anomaly • Common atrioventricular valve regurgitation • Pulmonary regurgitation after Tetralogy of Fallot repair	High output failure • Hepatic haemangioma • Vein of Galen malformation • Severe anaemia • Thyrotoxicosis
Pressure overload	
Left heart obstructive lesions • Coarctation of aorta • Aortic stenosis	Systemic hypertension • Post-infectious glomerulonephritis • Takayasu • Chronic kidney disease
Pulmonary arterial hypertension (PAH) associated with congenital heart disease	Pulmonary hypertension • Idiopathic, familial, obstructive sleep apnoea, chronic lung disease
Complex lesions with multiple mechanisms	
Common mixing with unrestrictive pulmonary flow • Truncus arteriosus • Total anomalous pulmonary venous drainage • Transposition of great arteries with VSD ± aortic coarctation • Hypoplastic left heart syndrome • Univentricular heart • Large aortopulmonary collaterals	

Congenital heart disease	Acquired heart disease
Pump failure	
Myocardial ischaemia • Anomalous origin of the left coronary artery from pulmonary artery (ALCAPA)	Myocardial ischaemia • Post Kawasaki disease with coronary artery thrombosis
Systemic right ventricle • Congenitally corrected transposition of great arteries • Post atrial switch	Myocarditis • Viral • Covid-19 multi-systemic inflammatory syndrome (MIS-C)
	Cardiomyopathy • Primary: familial, genetic • Drug-induced: anthracycline • Post-infectious: viral, Chagas disease • Neuromuscular: muscular dystrophies, Friedreich ataxia • Metabolic: Pompe disease, mitochondrial disease, iron overload • Arrhythmias: heart block, tachyarrhythmias

Clinical Presentation

Neonates and young infants often present with features associated with pulmonary congestion such as tachypnoea, respiratory distress, prolonged and interrupted feeding, poor weight gain, hepatomegaly and recurrent chest infections

Older children present with fatigue, poor effort tolerance and growth failure

Common heart failure signs in adults such as raised jugular venous pressure, pedal oedema and basal lung crackles are not usually found in children

Investigations

- Chest X-ray: cardiomegaly, lung plethora
- ECG: to look for arrhythmias, ventricular axis deviation, atrial/ventricular voltage abnormalities
- Echocardiogram: detailed evaluation of cardiac anatomy, ventricular function and haemodynamics

Investigations

General Measures

- Bed rest to reduce the body's metabolic demand
- Oxygen supplementation for patients with respiratory distress and impaired oxygenation due to congested lungs or chest infections.
  - Avoid excessive oxygen in left to right shunt lesions
- Fluid restriction to ¾ normal maintenance if not dehydrated or in shock. Aim for negative fluid balance if in a fluid-overloaded state
- Prompt treatment of lung infection with appropriate antibiotics
- Optimize caloric intake
  - Total caloric intake as high as 150 kcal/kg/day may be required in infants with severe heart failure to compensate for increased energy expenditure for work of breathing. Small and frequent meals are preferred in older children.
  - Increase caloric density by feed fortification (medium chain triglycerides, glucose polymer)
  - Nasogastric tube feeding may be required in infants with poor suck
- Assisted ventilation (either invasive or non-invasive) may be required for patients with acute respiratory failure either from concurrent chest infections or decompensated heart failure

Heart Failure Medications

Frusemide

- Dose: 1 mg/kg/dose OD to QID; continuous IV infusion at 0.1 to 0.5 mg/kg/hour if severely fluid overload
- Always use together with potassium-sparing agents (such as spironolactone or ACE inhibitors) or potassium supplements (1 to 2 mmol/kg/day) to prevent hypokalaemia

Spironolactone

- Dose: 1 mg/kg/dose BD
- Modest diuretic effect, potassium-sparing agent

Captopril

- Dose: 0.1 mg/kg/dose TDS, gradually step up to 1 mg/kg/dose TDS
- Afterload reduction agent
- Monitor serum potassium and renal function. Do not use during acute decompensated heart failure

Carvedilol

- Dose: 0.1 to 0.8 mg/kg/day
- May be used in older children > 2 years old. It decreases metabolic demand by preventing excessive tachycardia and increasing ventricular filling time

Specific Management

Establishing a definitive aetiology is crucial to guide therapy as the definitive treatment is targeted at the aetiology of heart failure. Examples:

Aetiology	Treatment
Congenital heart disease	Surgery • Open heart (e.g. VSD closure) versus closed heart (e.g. PDA ligation) • Curative (e.g. VSD closure) versus palliative (e.g. pulmonary artery banding) • Single-stage versus multi-stage Catheter-based intervention • Device closure (e.g. PDA closure, coil embolization of fistula) • Balloon valvuloplasty/angioplasty (e.g. coarctation of the aorta, aortic stenosis)
Myocarditis (MIS-C, rheumatic)	Aspirin, steroid
Pulmonary arterial hypertension	PAH-targeted therapy (phosphodiesterase 5 inhibitors, endothelin receptor antagonists, prostacyclin analogues)
Arrhythmias	Pacemaker for bradyarrhythmias Catheter ablation for tachyarrhythmias
Metabolic (Pompe)	Enzyme replacement
End-stage cardiomyopathies	Left ventricle assist device, heart transplantation

Chapter 42:
Rheumatic Heart Disease

Introduction

- Acute rheumatic fever (ARF) is a non-suppurative, delayed autoimmune sequelae of pharyngitis and skin infections from Group A streptococcus (GAS) infection.
- The incidence of initial episodes of ARF is highest among the 5 to 15-year-old age group and the incidence of recurrent episodes of ARF is highest within 5 years of initial presentation.

Diagnosis of ARF

Revised Jones Criteria	
Major manifestations	Carditis (including subclinical evidence of rheumatic valvulitis on echocardiogram) Polyarthritis or aseptic monoarthritis or polyarthralgia Sydenham chorea Subcutaneous nodules Erythema marginatum
Minor manifestations	Fever ≥ 38°C Monoarthralgia ESR ≥ 30 mm/h or CRP ≥ 30 mg/L Prolonged P-R interval on ECG*

*If carditis is present as a major manifestation, a prolonged P-R interval cannot be considered as additional minor manifestation.

Diagnosis criteria for ARF	
Initial ARF	2 major manifestations + evidence of preceding GAS infection, **OR** 1 major + 2 minor manifestations + evidence of preceding GAS infection
Recurrent ARF	2 major manifestations + evidence of preceding GAS infection, **OR** 1 major + 2 minor manifestations + evidence of preceding GAS infection, **OR** 3 minor manifestations + evidence of a preceding GAS infection

Investigations recommended for all cases
White blood cell count ESR (repeat weekly once diagnosis is confirmed) C-reactive protein Blood cultures if febrile ECG (repeat as necessary if conduction abnormality is more than a 1st degree heart block) Chest X-ray if clinical or echocardiographic evidence of carditis Echocardiogram (repeat as necessary in 2 to 4 weeks if equivocal or if serious carditis) Throat swab (preferably before giving antibiotics) to culture for Group A Streptococcus Anti-streptococcal serology: both anti-streptolysin O** and anti-DNase B titres, if available (repeat 10-14 days later if 1st test not confirmatory)

Upper limits of normal for P-R interval

Age Group (Years)	Seconds
3 - 11	0.16
12 - 16	0.18
17+	0.20

Medical Treatment

Aim of treatment:

- Eradicate streptococcal infection
- Suppress inflammatory response to minimize cardiac damage
- Symptomatic relief

Eradication Therapy Options for GAS

- IM Benzathine Penicillin (first line) stat dose
- IV C-penicillin for 10 days
- If IM or IV injection is not possible,
  - Oral Penicillin V or Oral amoxicillin for 10 days
  - Oral Erythromycin Ethylsuccinate or Oral Cephalexin for 10 days (if documented penicillin allergy)

Antibiotics	Regimen	Duration
IM Benzathine penicillin (First line)	< 30 kg: 0.6 Mega unit ≥ 30 kg: 1.2 Mega unit	Single dose
IV C-penicillin	50,000 unit/kg QID	10 days
Oral Penicillin V	15 mg/kg QID *Max 500mg per dose*	10 days
Oral Amoxicillin	25 mg/kg TDS *Max 1000mg per dose*	10 days
Oral Erythromycin ethyl-succinate	10 mg/kg QID *Max 500mg per dose*	10 days

Anti-inflammatory Therapy

- Mild/no carditis: Oral Aspirin 80 - 100 mg/kg/day in 3 to 4 divided doses for 2 to 4 weeks, tapering over 4 weeks.
- Pericarditis, pericardial effusion or moderate to severe carditis:
  - Oral Prednisolone 2 mg/kg/day in 2 divided doses for 2 to 4 weeks, taper with the addition of aspirin as above.
  - IV methylprednisolone 30 mg/kg OD (infusion over 1 hour) for 3 days can be considered in severe cases.

Symptomatic Relief

- Bed rest. Restrict activity until acute phase reactants return to normal.
- Anti-failure medications
  - Diuretics, ACE inhibitors, digoxin (to be used with caution).

Surgical Intervention

Surgery is indicated if the patient develops severe uncontrolled heart failure or when there is severe valvular dysfunction (e.g. flail valve).

Indications for Cardiac Surgery in Children with Mitral Regurgitation (MR)
A. Severe MR with symptomatic heart failure; or B. Asymptomatic MR and one of the following echocardiographic parameters: • Impaired LV function • LV end-systolic diameter ≥ 40mm • Enlarged indexed heart size
Indications for Cardiac Surgery/Balloon Valvuloplasty in Children with Mitral Stenosis (MS)
A. Severe MS with symptoms; or B. Asymptomatic severe MS and one of the following: • Mitral orifice area ≤ 1.5 cm^2 • Pulmonary hypertension > 50 mmHg • High thromboembolic risk (history of systemic embolism, dense spontaneous contrast in the left atrium, left atrial thrombus) • Atrial fibrillation
Indications for Cardiac Surgery in Children with Aortic Regurgitation (AR)
A. Severe AR with symptomatic heart failure; or B. Asymptomatic severe AR and one of the following: • LV end-systolic diameter > 50 mm or indexed LV end-systolic diameter > 25mm/m^2 • Impaired LV function
Indications for Cardiac Surgery/Balloon Valvuloplasty in Children with Aortic Stenosis (AS)
A. Severe AS with symptomatic heart failure; or B. Asymptomatic severe AS and one of the following: • AS Doppler mean pressure gradient ≥ 40 mmHg • AS Doppler peak velocity ≥ 4 m/s • Aortic valve area ≤ 1 cm^2 • Impaired LV function

Secondary Prophylaxis of Rheumatic Fever

- IM Benzathine Penicillin 0.6 mega units (< 30 kg), or 1.2 mega units (> 30 kg) every 3 to 4 weeks.
- Oral Penicillin V 250 mg twice daily.
- Oral Erythromycin 250 mg twice daily if allergic to Penicillin.

Duration of prophylaxis

- Mild carditis: Until age 21 years or 5 years after the last attack of ARF; whichever is longer.
- Moderate to severe carditis: Until age 35 to 40 years or 10 years after the last attack of ARF; whichever is longer.

Oral Health Care and Infective Endocarditis Prophylaxis

- All cases of ARF/RHD should be referred for dental assessment.
- All patients with ARF/RHD with valve involvement need endocarditis prophylaxis.

Chapter 43:
Infective Endocarditis

Introduction

Infective endocarditis (IE) is defined as an infection of the endocardial surface of the heart which frequently involves the heart valves. It is associated with high mortality and severe complications. Early and accurate diagnosis is crucial for appropriate treatment to improve outcomes and reduce mortality.

Diagnosis

A high index of suspicion is warranted in any patients with underlying risk factors who present with unexplained fever (90%), loss of appetite and weight loss. Heart murmurs are found in up to 85% of patients. Some may present with complications such as heart failure (up to 58%) and embolic events (25%). Young infants and immunocompromised patients may not have fever.

Pre-existing risk factors:

- Congenital heart disease; whether unrepaired or repaired
- Prosthetic heart valves and intracardiac devices
- Previous history of infective endocarditis
- Native valvular heart diseases such as rheumatic heart disease
- Presence of chronic intravenous access such as indwelling central venous catheters, chemoports and hemodialysis catheters
- Immunocompromised patients

The diagnosis of IE requires a combination of clinical features, microbiological findings and identification of endocardial involvements and extracardiac complications by imaging tools.

Blood cultures

- Remains the cornerstone of diagnosis of IE
- At least 3 sets (to increase yield and reduce false positive rate by skin contaminants)
- There is no necessity to wait for spikes of fever (due to the continuous nature of bacteremia)
- Should be taken at 30 mins intervals between samples
- Should be obtained from peripheral veins and not from central venous catheter using aseptic technique
- Should be taken before commencement of antibiotics
- Each set should include 1 aerobic and 1 anaerobic bottle with a minimal of 3 ml of blood

Echocardiography

- Transthoracic echocardiogram (TTE) should be performed as soon as possible when IE is suspected.
- Findings suggestive of IE include vegetation, abscess, pseudoaneurysm, new dehiscence of the prosthetic valve, fistula, valve leaflet perforation and aneurysm.
- The sensitivity and specificity of TTE are strongly affected by patient's acoustic window and the operator's experience.
- If clinical suspicion of IE remains high despite an initial negative TTE, a repeat TTE or transoesophageal echocardiogram (TEE) is recommended within a week.
- In children, TEE requires general anaesthesia and risk versus benefit must be carefully considered.
- TEE is advisable in cases with prosthetic valves, prosthetic cardiac material and those with poor TTE acoustic window.
- TTE is recommended at the completion of antibiotic treatment to assess treatment response.

Modified Duke Criteria

These criteria can be used as a guide to diagnose IE with an overall sensitivity of 80%. It is not to replace good clinical judgment to treat each individual patient appropriately.

Definite IE	Pathological Criteria • Microorganisms demonstrated by culture or histology of a vegetation, vegetation that has embolized or intracardiac abscess specimen
	Clinical Criteria • 2 major criteria OR • 1 major criterion and 3 minor criteria OR • 5 minor criteria
Possible IE	• 1 major criterion and 1 minor criteria OR • 3 minor criteria
Rejected IE	• Firm alternate diagnosis OR • Resolution of symptoms within 4 days with antibiotic therapy OR • No pathological evidence of IE at surgery or autopsy, with antibiotic therapy ≤ 4 days

Clinical Criteria

Major Criteria	
Blood culture positive for IE	1. Typical microorganisms consistent with IE from 2 separate blood cultures • Viridans streptococci, Streptococcus gallolyticus/bovis, HACEK group, Staphylococcus aureus OR • Community-acquired enterococci in the absence of a primary focus 2. Microorganisms consistent with IE from persistently positive blood cultures • ≥ 2 positive blood cultures of blood samples drawn > 12h apart OR • All of 3 or majority of ≥ 4 separate cultures of blood (with first and last samples drawn ≥ 1h apart) 3. Single positive blood culture for Coxiella burnetti or phase I IgG antibody titer > 1:800
Imaging positive for IE	1. Echocardiogram positive for IE • Vegetation • Abscess, pseudoaneurysm, intracardiac fistula • Valvular perforation or aneurysm • New partial dehiscence of prosthetic valve
Minor Criteria	
1. Predisposition: predisposing heart condition or IV drug use 2. Fever > 38°C 3. Vascular phenomena (including those detected by imaging only): major arterial emboli, septic pulmonary infarcts, infectious (mycotic) aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions 4. Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor 5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE	

Management

Antimicrobial Therapy

General principles:

- Use bactericidal instead of bacteriostatic agents
- Initial high dose parenteral route to achieve high bactericidal effects
- Adequate duration to ensure complete eradication (4 to 6 weeks)

Antibiotic Regimens for Initial Empirical Treatment

Situations	Antibiotic
Community-acquired native valves	IV Ampicillin 200 – 300 mg/kg/day in 4 – 6 divided doses (max 12 g/day) + IV Gentamicin 1 mg/kg 8 hourly + IV Cloxacillin 200 mg/kg/day in 4 – 6 divided doses (max 12 g/day)
Community-acquired native valves (allergic to penicillin)	IV Vancomycin 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day) + IV Gentamicin 1 mg/kg 8 hourly
Prosthetic valve endocarditis	IV Vancomycin 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day) + IV Gentamicin 1 mg/kg 8 hourly + Oral Rifampicin 20 mg/kg/day divided into 3 doses (max 900 mg/day)
Nosocomial and healthcare associated endocarditis	IV Vancomycin 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day) + IV Gentamicin 1 mg/kg 8 hourly ± IV Cefepime 50 mg/kg 8 hourly (max 6 g/day)

Once the causative microorganism is identified and the sensitivity pattern obtained, the empirical regimen should be switched to a definitive regimen.

Antibiotic Regimens for Definitive Treatment of Infective Endocarditis

Antibiotics	Dosage and route	Duration (weeks)	Comments
Major Criteria			
Penicillin G or Ceftriaxone	IV 200,000 – 300,000 U/kg/day in 4 – 6 divided doses (max 12 – 18 MegaU/day)	4	
	IV 100 mg/kd/day in 1 – 2 divided doses (max 4 g/day)	4	
Vancomycin	IV 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)	4	If allergic to beta-lactam
Relatively resistant to Penicillin viridans streptococci, Streptococcus gallolyticus/bovis (MIC 0.125 – 2 µg/ml)			
Penicillin G or Ceftriaxone combined with Gentamicin	IV 200,000 – 300,000 U/kg/day in 4 – 6 divided doses (max 12 – 18 MegaU/day)	4	
	IV 100 mg/kg/day in 1 – 2 divided doses (max 4 g/day)	4	
	IV 1 mg/kg 8 hourly	2	
Vancomycin combined with Gentamicin	IV 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)	4	If allergic to beta-lactam
	IV 1 mg/kg 8 hourly	2	
Methicillin-susceptible staphylococci (MSSA); native valve			
Cloxacillin	IV 200 – 300 mg/kg/day in 4 – 6 divided doses (max 12 g/day)	4 to 6	
Cefazolin	IV 100 mg/kg/day in 3 divided doses (max 2 g/day)	4 to 6	Allergic but non-anaphylactic reactions to Penicillin
Cefazolin	IV 100 mg/kg/day in 3 divided doses (max 2 g/day)	4 to 6	Anaphylactic reactions to Penicillin
Methicillin-resistant staphylococci (MRSA); native valve			
Vancomycin	IV 40 mg/kg/day in 2 – 3 divided doses (max 2 g/day)	4 to 6	
Daptomycin	IV 10 mg/kg daily	4 to 6	Daptomycin is superior to Vancomycin for MIC > 1 mg/L

Methicillin-susceptible staphylococci (MSSA); prosthetic valve			
Cloxacillin with Rifampicin and Gentamicin	IV 200 – 300 mg/kg/day in 4 – 6 divided doses (max 12 g/day)	≥ 6	• Refer MRSA section if allergic to beta-lactam • Start Rifampicin 3 – 5 days after Cloxacillin
	PO 20 mg/kg/day in 3 divided doses (max 900 mg/day)	≥ 6	
	IV 1 mg/kg 8 hourly	2	
Methicillin-resistant staphylococci (MRSA); prosthetic valve			
Vancomycin with Rifampicin and Gentamicin	IV 60 mg/kg/day in 2 – 3 divided doses (max 2 g/day)	≥ 6	• Use Cefazolin if non-anaphylactic reactions to Penicillin • Use Vancomycin if anaphylactic reactions to Penicillin • Start Rifampicin 3 – 5 days after Vancomycin
	PO 20 mg/kg/day in 3 divided doses (max 900 mg/day)	≥ 6	
	IV 1 mg/kg 8 hourly	2	
Enterococcus spp			
Ampicillin	IV 300 mg/kg/day in 4 – 6 divided doses (max 2 g/day)	4	6 weeks duration is recommended for patients • Symptoms > 3 months • Prosthetic valve
with Gentamicin or Ceftriaxone	IV 1 mg/kg 8 hourly	2 to 6	
	IV 100 mg/kg/day in 1 – 2 divided doses (max 4 g/day)	6	
HACEK			
Ceftriaxone or Ampicillin/ Sulbactam	IV 100 mg/kg/day in 1 – 2 divided doses (max 4 g/day)	4 to 6	
	IV 200 – 300 mg/kg/day ampicillin in 4 – 6 divided doses	4 to 6	
Candida spp			
Amphotericin B with Flucytosine	IV 1 mg/kg daily	At least 6 weeks after surgery	• Valve replacement is mandatory • Step down therapy with oral Fluconazole 6 – 12 mg/kg daily for susceptible organism in stable patient after blood clearance of Candida
	PO 100 – 150 mg/kg in 4 divided doses		

Surgical Interventions

Surgical intervention is indicated in the following cases:

- Heart failure: severe valvular regurgitation, obstruction or fistula causing refractory pulmonary edema, cardiogenic shock or severe heart failure symptoms
- Uncontrolled infection: an infection caused by fungi, local extension of an infection (abscess, pseudoaneurysm, fistula, enlarging vegetation), persistently positive blood cultures despite appropriate antibiotic therapy and prosthetic valve endocarditis caused by staphylococci or non-HACEK gram-negative bacteria
- Prevention of embolism: Left-sided vegetation > 10 mm after 1 or more embolic episodes, very large vegetation > 30 mm

Antimicrobial Prophylaxis for Infective Endocarditis

Antibiotic prophylaxis is indicated for the following cardiac conditions:

- Prosthetic cardiac valves, including transcatheter valves and those with prosthetic material used for cardiac valve repair
- Native valvular heart diseases such as rheumatic heart disease
- A previous episode of infective endocarditis
- Congenital heart diseases
  - Any type of unrepaired cyanotic CHD, including those with palliative shunts and conduits
  - During the first 6 months following surgical or transcatheter treatment of CHD with prosthetic material or devices
  - Repaired CHD with residual shunt or valvular regurgitation adjacent to the site of a prosthetic material or device (which inhibits endothelization)

Although antibiotic prophylaxis is not routinely recommended for patients with other cardiac conditions not listed above, they should be advised of the importance of dental and cutaneous hygiene. General preventive measures include:

- At least once a year dental follow up
- Prompt disinfection of any wounds
- Appropriate antibiotic therapy for any focus of bacterial infection
- Discourage piercing and tattooing
- Limit the use of infusion catheters and invasive procedures whenever possible. Strict adherence tocare bundles for central and peripheral cannulae

Procedures which require IE prophylaxis

Under most circumstances, the pre-procedural antibiotic prophylaxis as per routine surgical practice is adequate as IE prophylaxis. If pre-procedural antibiotic is not routinely given, the following recommendations should be used:

Prophylaxis indicated	Prophylaxis not indicated
Dental procedures	
Any procedures requiring the manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa. Examples • Extractions • Periodontal procedures, subgingival scaling, root planning • Replanting avulsed teeth or implant placement	• Local anesthetic injections in non-infected tissues • Treatment of superficial caries • Dental X-rays • Following the shedding of deciduous teeth • Orthodontic bracket placement and adjustment of fixed appliances • Removal of sutures • Supragingival plaque removal
Respiratory tract procedures	
• Invasive respiratory tract procedures which involve incision or biopsy of respiratory mucosa • Drainage of abscess	• Endotracheal intubation • Flexible bronchoscopy without biopsy
Gastrointestinal and Genitourinary procedures	
• Only for those with established infection	• Transoesophageal echocardiography • Gastroscopy, colonoscopy • Cystoscopy • Vaginal or cesarean delivery • Intrauterine contraception device implantation
Skin and soft tissue procedures	
• Only for those with established infection	

Recommended antibiotic for IE prophylaxis

Situation	Antibiotic
No history of allergic to penicillin/ampicillin	Amoxicillin or Ampicillin 50 mg/kg orally or IV
Allergic to penicillin/ampicillin	Clindamycin 20 mg/kg orally or IV

A single dose of antibiotic recommended above should be given 30 – 60 minutes before the procedure. A second dose is not required after the procedure.

Chapter 44:
Kawasaki Disease

Introduction

A systemic febrile syndrome with generalized vasculitis involving small to medium-sized arteries, usually affecting children below 5 years old.

Coronary artery aneurysm is the most important complication which carries risk of coronary artery thrombosis, acute myocardial infarction and death

The aetiology remains unknown; likely of infectious origin in genetically susceptible individuals

Clinical Features

Divided into 3 clinical phases

Phase	Clinical features	Time
Acute	Fever, mucocutaneous signs	1 to 2 weeks
Subacute	Defervescence, periungual desquamation, thrombocytosis, coronary artery aneurysm	2 to 4 weeks
Convalescent	Resolution of signs & symptoms, normalization of acute inflammatory markers	4 to 8 weeks

Typical Kawasaki Disease

Characterized by fever ≥ 5 days and ≥ 4 clinical criteria

Diagnostic Criteria for Kawasaki Disease (KD)
Fever ≥ 5 days AND At least 4 out of the 5 clinical criteria 1. Bilateral non-purulent conjunctivitis 2. Mucosal changes of the oropharynx (injected pharynx, red lips, dry fissured lips, strawberry tongue) 3. Changes in extremities (oedema and/or erythema of the hands or feet, periungual desquamation) 4. Polymorphous rash (usually diffuse maculopapular, occasional scarlatiniform or erythema multiform-like) 5. Cervical lymphadenopathy (at least one lymph node > 1.5 cm)

If coronary artery abnormality is evidenced on echocardiogram, diagnosis can be made with fewer than 4 clinical criteria

Other helpful clinical features in making the diagnosis:

- Neurological: irritability, encephalopathy, aseptic meningitis
- Cardiovascular: myocarditis, pericarditis, valvular regurgitation, non-coronary medium-sized artery aneurysms
- Gastrointestinal: diarrhoea, vomiting, abdominal pain, hepatitis, hydrops of gallbladder, paralytic ileus
- Genitourinary: sterile pyuria, proteinuria, testicular swelling
- Skin: erythema or induration of BCG scar, perianal erythema or excoriation
- Musculoskeletal: transient arthritis

Incomplete Kawasaki Disease

- Clinical features suggestive of KD but fewer than 4 principal clinical criteria
- Frequently encountered in infants < 12 months
- Delayed in diagnosis frequently leads to late institution of treatment and higher incidence of coronary artery complications
- Diagnosis should be considered in any young infants presenting with unexplained prolonged fever and elevated inflammatory markers
- Low threshold for echocardiography

Atypical Kawasaki Disease

Kawasaki disease with atypical clinical presentations such as acute abdomen, acute pancreatitis, cholestatic jaundice, acute kidney injury and pneumonia.

Coronary Artery Complications

- Incidence: 20 to 25% in untreated cases; reduced to 1 to 2% with IVIG therapy
- Severity ranges from ectasia, small, medium to giant aneurysms (> 8 mm)
- Majority of small to medium-sized aneurysms regress over next few months
- Giant aneurysms do not regress and are at risk of developing serious complications such as thrombosis, acute myocardial infarction, stenosis, rupture and sudden death
- High risk groups of developing coronary artery complications
  - Age < 1 year
  - Severe inflammation during acute phase (anaemia, thrombocytopenia, low albumin)
  - Duration of fever > 2 weeks
  - Recurrence of fever after > 48 hours of defervescence

Investigations

Laboratory Test	Common findings
Full blood count	Anaemia, leukocytosis, thrombocytosis (2nd week onwards), thrombocytopenia (in severe cases)
ESR, C-reactive protein	Elevated
Liver function tests	Elevated transaminases, low albumin (in severe cases)
Urinalysis	Sterile pyuria, proteinuria
ECG	Sinus tachycardia, ST changes and Q waves (in myocardial infarction)
CSF	Mononuclear pleocytosis

Echocardiography

- Transthoracic echocardiogram should be performed in all patients with suspected KD to detect coronary artery aneurysms at the following timings
  - Upon diagnosis
  - At 2 to 3 weeks after disease onset
  - At 6 to 8 weeks after disease onset
- A body surface area-adjusted z-score ≥ 2.5 is considered abnormal and requires follow up measurement (https://www.pediatricheartnetwork.org/z-scores-calculator/)
- Additional findings that may be present: ↓ left ventricular function, mitral regurgitation, pericardial effusion

Treatment

IV Immunoglobulin (IVIG)

- 2 g/kg single infusion over 10 - 12 hours
- Divided lower dose may be considered in sick infant who cannot tolerate large volume
- Started as early as possible, preferably within 10 days of disease onset
- May still be beneficial in patients who present after 10 days of illness if persistent fever, presence of coronary artery abnormalities or ongoing systemic inflammation (elevated ESR or CRP)

Oral Aspirin

- Anti-inflammatory effect
  - 30 to 50 mg/kg/day in divided dose
  - Started simultaneously with IVIG
- Anti-platelet effect
  - 3 to 5 mg/kg/day
  - Started 48 to 72 hours after defervescence
  - Duration: 6 to 8 weeks or normalization of ESR and platelet count (whichever later) in patients without coronary artery abnormality
  - In patients with coronary artery involvement, aspirin should be continued until resolution of lesions or indefinitely

Giant coronary artery aneurysm

Additional anti-platelet or anti-thrombotic treatment should be considered to reduce the risk of acute coronary artery thrombosis. The options are

- Oral Clopidogrel
- Oral Warfarin
- Subcutaneous Enoxaparin
- IV Heparin infusion

IVIG Resistance

- 10 to 20% of cases
- Persistent or recurrent fever after IVIG plus Aspirin therapy
- Increased risk of developing coronary artery complications
- Treatment options include
  - Re-treatment with IVIG 2g/kg
  - IV Methylprednisolone 30 mg/kg/day for 3 days followed by oral Prednisolone 2 mg/kg/day tapers over 2 to 3 weeks
  - IV Infliximab 5 mg/kg single infusion over 2 hours

  Consultation with paediatric cardiologists is advisable

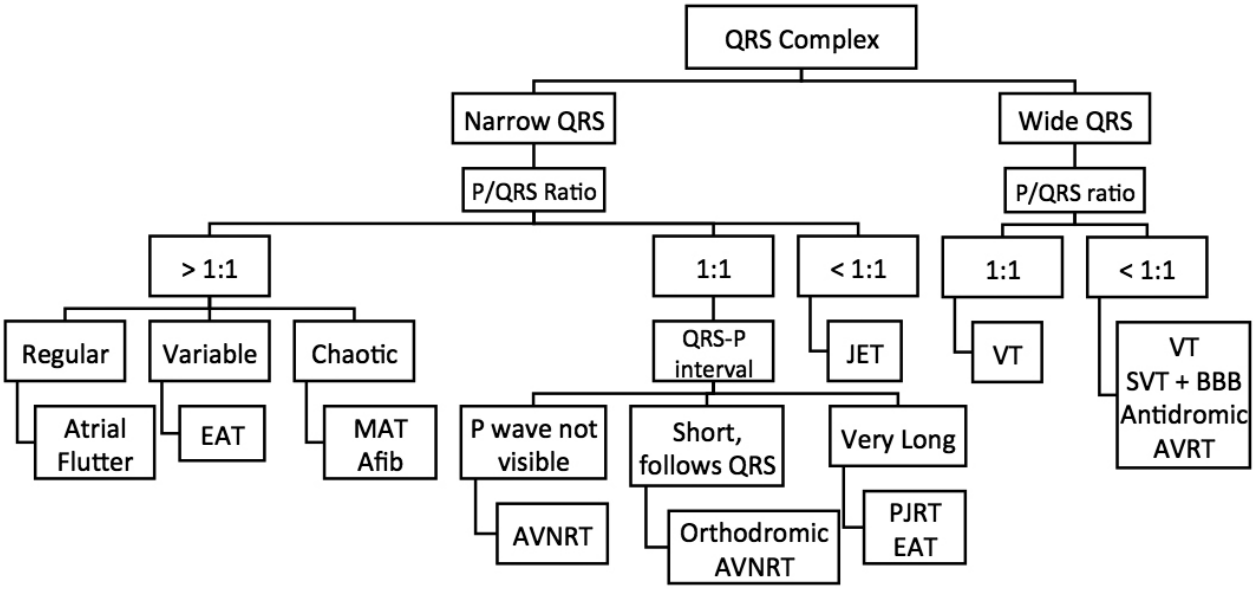
Vaccination

- IVIG impairs the efficacy of live-attenuated viral vaccines
- Delay these vaccinations for at least 11 months

Chapter 45:
Paediatric Arrhythmias

Tachyarrhythmias

Diagnostic Algorithm for Tachyarrhythmias



EAT: Ectopic atrial tachycardia

MAT: Multifocal atrial tachycardia

Afib: Atrial fibrillation

AVNRT: Atrioventricular nodal reentry tachycardia

AVRT: Atrioventricular reentry tachycardia

PJRT: Permanent junctional reciprocal tachycardia

JET: Junctional ectopic tachycardia

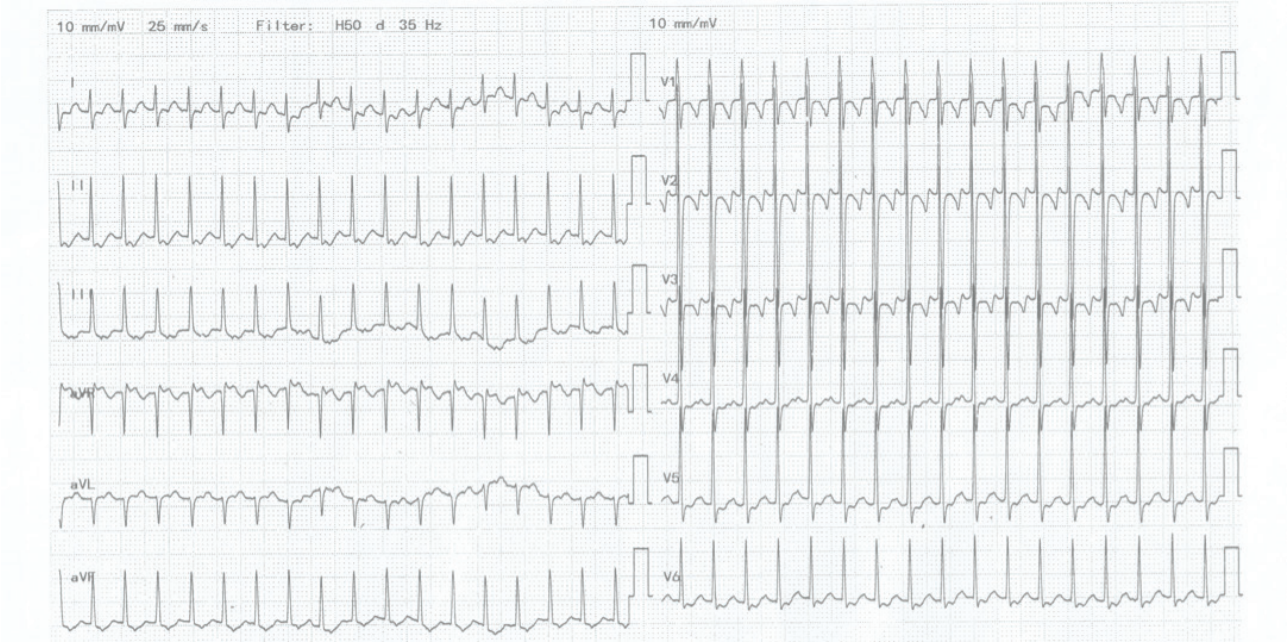
VT: Ventricular tachycardia

SVT + BBB: Supraventricular tachycardia with bundle branch block

Common Childhood Tachyarrhythmias

Atrioventricular Re-entry Tachycardia (AVRT/AVNRT)

- Most common supraventricular tachycardia in paediatrics
- Clinical presentations: palpitation, chest discomfort, pre-syncope, heart failure (especially in young infants as tachycardia may be unrecognized for hours or days). True syncope is uncommon
- ECG
  - Fast rate (250 bpm in infants, 200 bpm in older children)
  - Narrow QRS complex (except in pre-existing bundle branch block, antidromic AVRT)
  - P waves difficult to visualize (either buried within QRS complexes or immediately behind QRS complexes)
  - Constant rate, no beat-to-beat variation



ECG of 8 years old child with AVRT; note the narrow QRS complexes and inverted P waves behind the QRS complexes

- Acute management
  Haemodynamically stable
  - Vagal manoeuvres: apply icepack/ice-cold facecloth over the face for 15 – 30 seconds (infants and toddlers), Valsalva manoeuvre or carotid massage (older children)
  - IV Adenosine: start with 0.2 mg/kg rapid push. Increase by 0.2 mg/kg every 2 mins until tachycardia terminated. Maximum dose 0.6 mg/kg or 12 mg

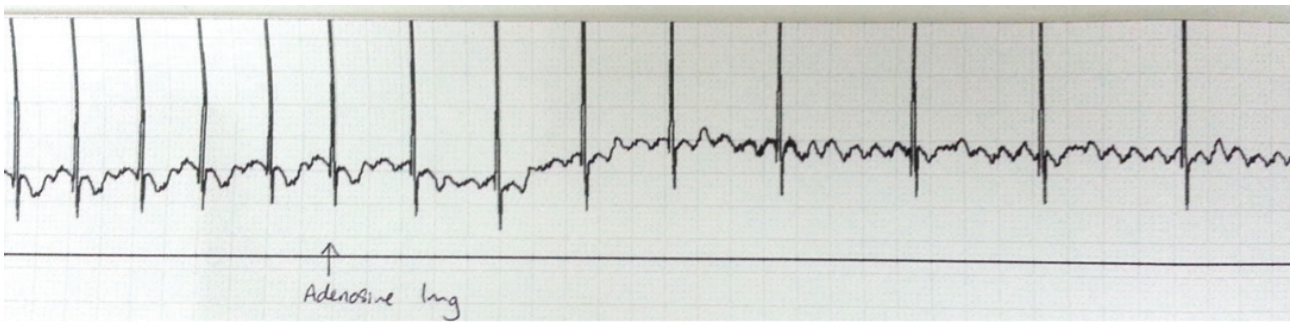
  Haemodynamically stable
  - IV Adenosine as above (if venous access is available)
  - Synchronized DC cardioversion at 0.5 – 1J/kg (if venous access unavailable)
- Causes of IV Adenosine "non-responder"
  - Inadequate IV Adenosine dose
  - Suboptimal administration: poor venous access, slow administration rate
  - Non-responder vs Early recurrence of re-entry tachycardia:

- In non-responders, consider wrong diagnosis: sinus tachycardia (most common reason; IV Adenosine will result in transient slowing down of heart rate followed by acceleration back to previous rate), atrial flutter (appearance of flutter waves during transient slowing down of ventricular rate), ectopic atrial tachycardia/multifocal atrial tachycardia (continuation of tachycardia with AV block), ventricular or junctional tachycardia (no change of heart rate)
- Early recurrence of reentry tachycardia: sudden "jump" of heart rate following initial successful termination of tachycardia. Longer acting anti-arrhythmic drug is indicated (propranolol, digoxin or amiodarone).

- Management of 'difficult' SVT
  Can consider the following:
  - IV Amiodarone
    i. Useful for resistant reentry tachycardia, atrial tachycardias (which will not respond to adenosine) and 'stable' ventricular tachycardia
    ii. Dose: 25 mcg/kg/min for 4 hours then 5 – 15 mcg/kg/min
    iii. More rapid administration of the loading dose can be used but there is a significant risk of hypotension. In children who are unstable, electrical cardioversion is a safer option
  - IV Esmolol
    i. Short acting, cardio selective beta-blocker
    ii. Given as continuous infusion at 25 – 300 mcg/kg/min)
    iii. Rarely given for > 48 hours

Atrial Flutter

- Usually encountered in newborn (idiopathic, may be diagnosed prenatally) or older children with structural heart disease
- ECG
  - Saw-tooth P wave pattern in between QRS complexes (may be difficult to visualize in those with fast ventricular rate but can be unmasked by IV Adenosine)
  - Variable atrioventricular (2:1 or 3:1) conduction
- Acute management
  - Synchronized DC cardioversion at 0.5 – 1 J/kg



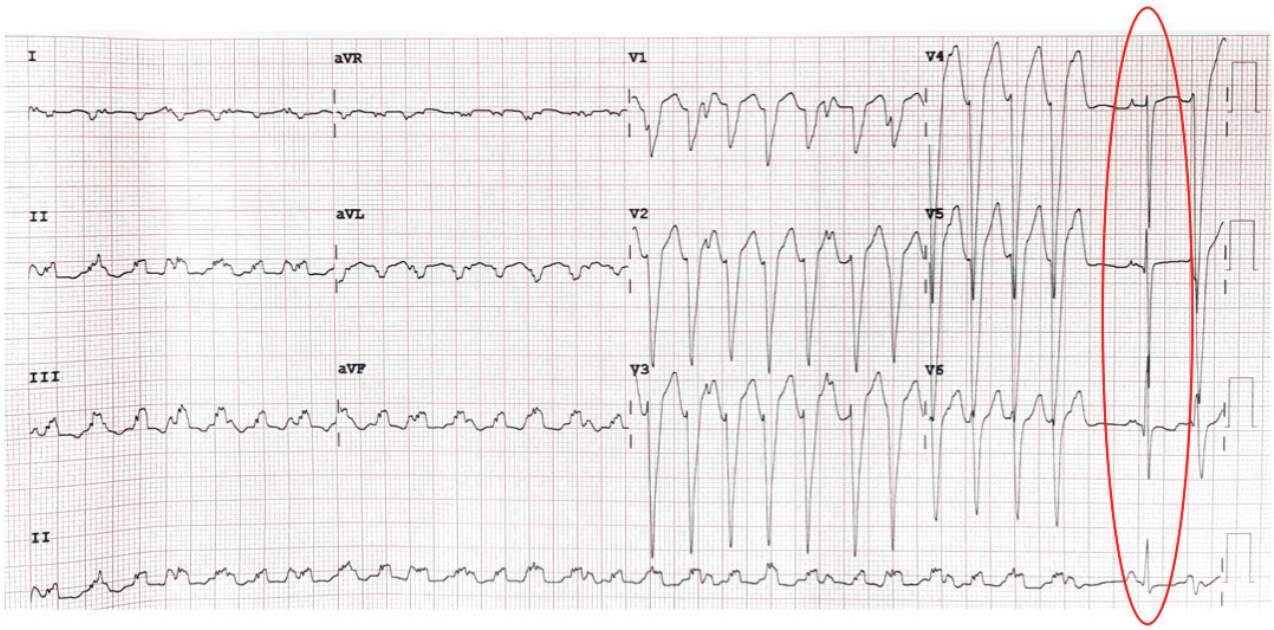
Flutter waves unmasked by IV Adenosine in a newborn

Ventricular Tachycardia

- Serious arrhythmia which potentially may cause haemodynamic compromise and death
- Clinical presentations: palpitation, syncope, sudden death
- Aetiology

Mechanism	Causes
Acute causes	Hypoxia, acidosis Electrolytes imbalance: hyperkalemia, hypokalemia, hypocalcemia Ischaemic: coronary artery occlusion Infective: myocarditis, rheumatic fever Toxic: drug overdose, poisoning Traumatic: cardiac surgery, catheter induced, trauma
Cardiomyopathies	Hypertropic cardiomyopathy Dilated cardiomyopathy Arrhythmogenic right ventricle cardiomyopathy
Structural heart disease	Previous congenital heart surgery Cardiac tumour Coronary artery anomalies
Channelopathies	Congenital long QT syndrome Brugada syndrome Catecholaminergic polymorphic VT
Idiopathic	Idiopathic left ventricular VT (fascicular VT) Idiopathic right ventricular VT

- ECG
  - Wide QRS complexes (may be narrow in neonates and fascicular VT)
  - Atrioventricular dissociation (no relationship between P and QRS complexes)
  - Occasional “capture” and “fusion” beats



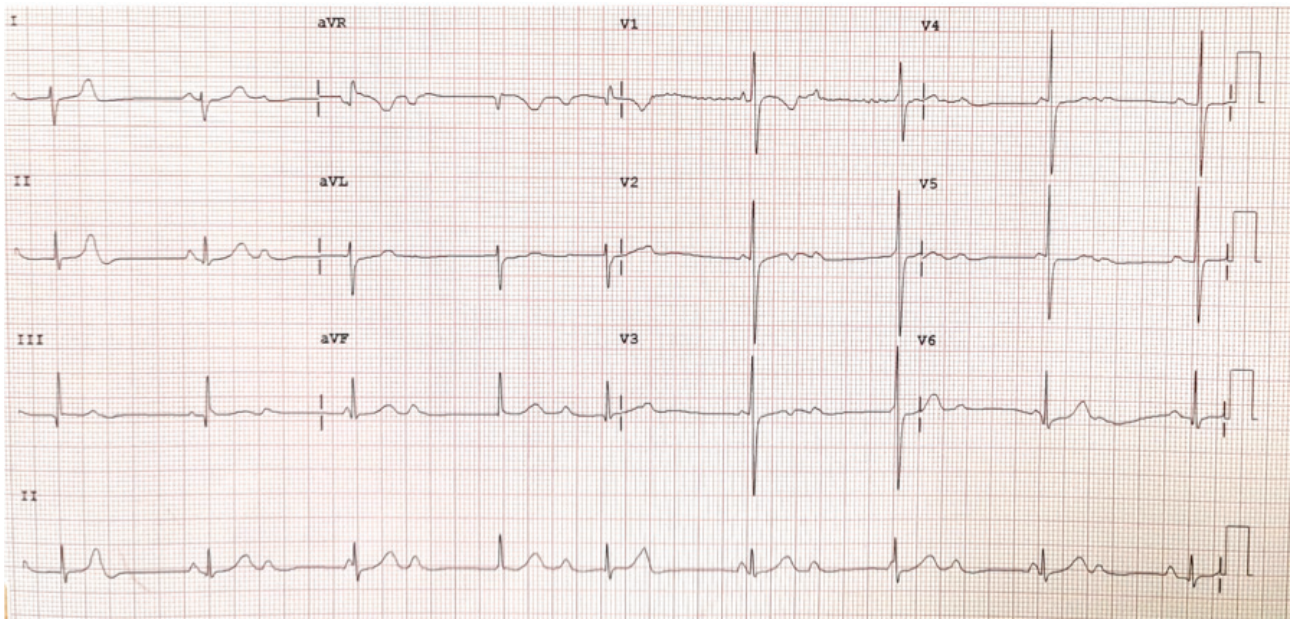
VT in 12 years old child with idiopathic RV tachycardia; note the capture beat (circle)towards the end

- Acute management
  - If haemodynamically unstable, immediate synchronized DC cardioversion at 0.5 – 1 J/kg (or defibrillation at 2 – 4 J/kg if pulseless)
  - If haemodynamically stable, medical cardioversion may be attempted with anti-arrhythmic drugs (IV amiodarone, IV lignocaine)
  - Treat the underlying reversible causes (hypoxia, acidosis, electrolyte imbalance)
  - Certain VT may respond to specific medications
    - Idiopathic left ventricular VT: IV Verapamil
    - Torsade de pointes: IV $MgSO_4$

Bradyarrhythmias

Atrioventricular block

- Classification
  - 1st degree: prolonged PR interval
  - 2nd degree
    - Mobitz type 1 (Wenckebach): progressive PR prolongation before dropped ventricular conduction
    - Mobitz type 2: intermittent drop of ventricular conduction without prior PR prolongation
    - High degree: only every 2nd (2:1) or 3rd (3:1) P waves are conducted
  - 3rd degree (complete heart block): none of the P waves are conducted; atrioventricular dissociation with no relationship between P waves and QRS complexes; escape rhythm may be junctional or ventricular in origin
- 2nd degree (Mobitz type 2 and above) and 3rd degree atrioventricular blocks are always pathological



3rd degree atrioventricular block; note the lack of relationship between P and QRS complexes and slow ventricular rate

- Aetiology

Congenital	Associated with maternal antibody (anti-Ro and anti-La); mother frequently asymptomatic
Congenital heart disease	Congenital corrected transposition of great arteries (L-TGA) Atrioventricular septal defect (AVSD) Left atrial isomerism
Channelopathy	Congenital long QT syndrome
Surgical trauma	Open heart surgery (eg. VSD closure, TOF repair, AVSD repair, Konno procedure) Radiofrequency catheter ablation Transcatheter VSD closure
Myopathy	Muscular dystrophies Kearns-Sayre syndrome
Infection	Diphtheria Rheumatic carditis Infective endocarditis Viral myocarditis

- Acute management of symptomatic bradycardia
  - Identify and treat the reversible causes (hypoxia, acidosis, shock)
  - IV Isoprenaline infusion at 0.05 to 0.5 mcg/kg/min or IV Adrenaline infusion
  - Emergency transcutaneous or transvenous temporary pacing
- Indications for permanent pacing
  - Ventricular rate < 55 bpm (neonates) or < 50 bpm (children); Ventricular rate < 70bpm in a setting of Congenital Heart Disease
  - Pauses > 3 seconds on ambulatory ECG recording
  - Wide QRS escape rhythms
  - Ventricular dysfunction
  - Prolonged QTc or pause-induced torsade de pointes
  - Exercise intolerance
  - Persistent advanced 2nd degree or 3rd degree heart block beyond 7 to 10 days after open heart surgery

Section 9

NEUROLOGY

Chapter 46:
Neonatal Seizures

1. Introduction

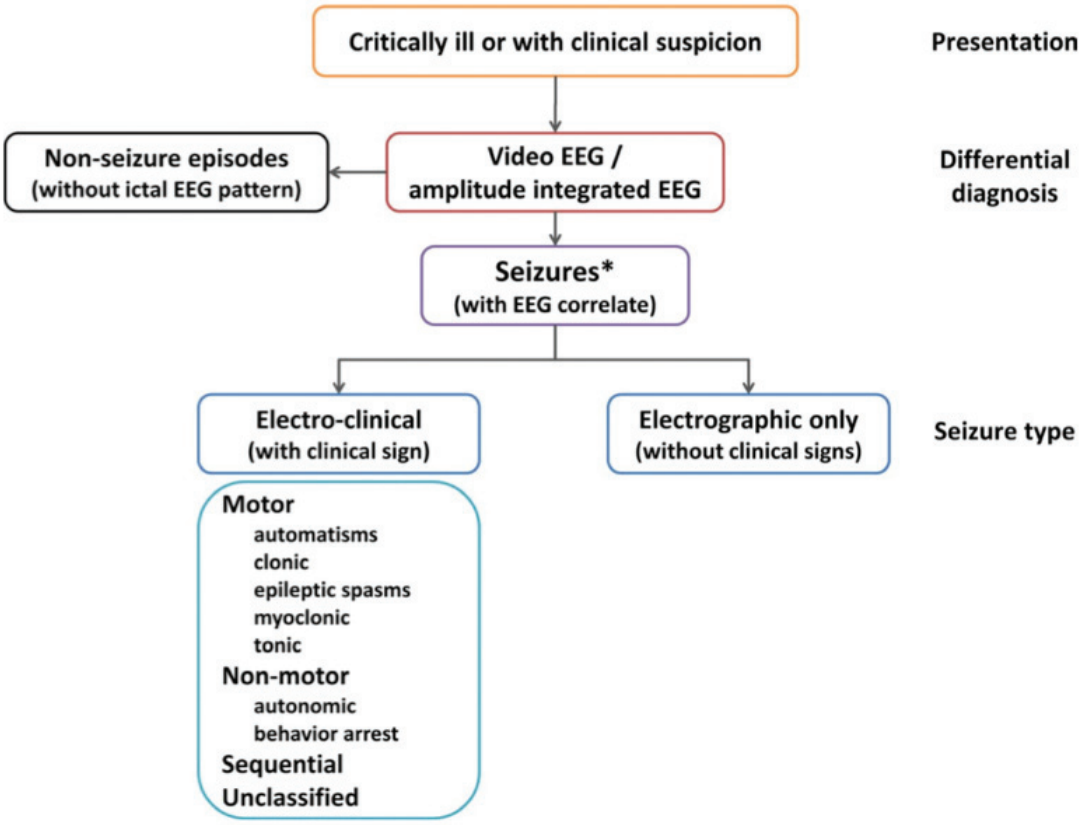
Seizures are the most common manifestation of neurological dysfunction in the newborn and are often acute and provoked by various factors (e.g. hypoxia ischemia, birth trauma). An electroclinical seizure features definite clinical signs simultaneously coupled with an electrographic seizure. The concept of electrographic-only seizures can be seen in specific cohort of patients, especially in neonatal hypoxic ischemic encephalopathy (HIE).

Neonates may also exhibit paroxysmal non-epileptic events than can mimic seizures and it is important to differentiate them from the following:

a. Jitteriness-stimulus sensitive & aborts with gentle limb flexion
b. Benign neonatal sleep myoclonus-only occurs in sleep & aborts with arousal
c. Startle disease (Hyperekplexia)-excessive startle, stimulus sensitive jerks and generalized muscle rigidity

2. Diagnostic framework/classification

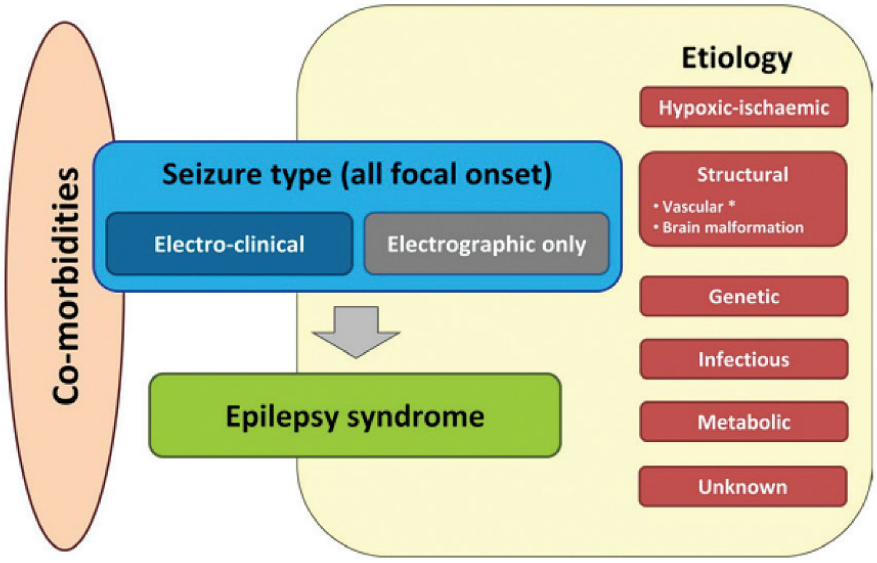
Neonatal seizures may not fit easily into existing classification developed for older children, hence in 2020 the International League Against Epilepsy (ILAE) Neonatal seizure task force established specific guidelines for seizures in the neonatal period. Figure 1 depicts the diagnostic framework for seizures in the neonatal period in which the key role of EEG is emphasized.



Type	Description	Special considerations	Clinical context of seizure type
Automatisms	A more or less coordinated motor activity usually occurring when cognition is impaired Often resembles a voluntary movement and may consist of an inappropriate continuation of preictal motor activity	Typically oral in neonates Behaviour in term and preterm infants may mimic ictal automatisms, thus EEG is mandatory	Seen in HIE and preterm infants Often part of sequential seizure
Clonic	Jerking, either symmetric or asymmetric , that is regularly repetitive and involves the same muscle group	Reliably diagnosed clinically	Seen in neonatal stroke or cerebral haemorrhage Also seen in HIE
Epileptic spasm	A sudden flexion, extension or mixed extension-flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic movement but not as sustained as a tonic seizure	Brief in neonates, difficult to differentiate from myoclonic seizure without EMG channel May occur in clusters	Rare May be seen in IEM or early infantile Developmental and Epileptic Encephalopathy (DEE)
Myoclonic	A sudden, brief (<100msec) involuntary single or multiple contraction(s) of muscle(s) of variable topography (axial, proximal limb, distal)	Clinically difficult to differentiate from non-epileptic myoclonus , requires EEG with EMG	Typical seizure type in IEM and preterm Also seen in early infantile DEE
Tonic	A sustained increase in muscle contraction lasting a few seconds to minutes	Focal, unilateral or bilateral asymmetric	Typical seizure type in early infantile DEE and genetic neonatal epilepsies
Autonomic	A distinct alteration of autonomic nervous system function involving CVS, pupillary, GIT, sudomotor, vasomotor and thermoregulatory functions	May involve respiration (apnoea), EEG mandatory	Rare in isolation Seen in IVH, temporal/occipital lobe lesions. Also described in early infantile DEE
Behavioural arrest	Arrest(pause) of activities, freezing, immobilization, as in behaviour arrest seizure	EEG/aEEG mandatory	Rare in isolation. Commonly part of sequential seizure
Sequential seizure	Events with a sequence of signs, symptoms and EEG changes at different times	Seizure presenting with a variety of clinical signs Several features typically occurring in a sequence, often with changing lateralization within or between seizures	Often seen in genetic epilepsies such as self-limited neonatal epilepsy or KCNQ2 encephalopathy
Electrographic only seizure	Subclinical, epileptic discharges on EEG without clinical manifestation	aEEG/EEG mandatory	Often seen preterm, HIE, critically ill newborns
Unclassified	Due to inadequate information or unusual clinical features with inability to place in other categories	aEEG/EEG mandatory	

3. Aetiology

Seizures in neonates are all focal at onset



4. Management

- Thorough history, physical examination and neurophysiological assessment with amplitude integrated EEG (aEEG)/ continuous video electroencephalography (cEEG) is often required in newborns at risk for seizures.
  Video EEG is the gold standard for diagnosis of neonatal seizures. If access is limited, use aEEG with co-registration of raw channels
- It is very important to delineate whether the abnormal movements/paroxysmal events are seizures. Correlation with aEEG is desirable as this avoids unnecessary and potentially deleterious treatment with antiseizure medications (ASM)
- Controversies regarding extent of treatment (i.e. whether to stop all clinical or electrographic seizures) exist. EEG monitoring to evaluate seizure burden should be initiated. A seizure burden of > 30-60 seconds per hour should be considered an indication to start treatment.
- In acute setting, administer anti-seizure medication (ASM) intravenously to achieve rapid onset of action and predictable blood levels in order to achieve serum levels in the normal therapeutic range.
- Discontinuation of ASM is safe in acute setting and no difference was found in functional neurodevelopment/epilepsy at 24 months among children who was discontinued vs maintained at hospital discharge
- A prolonged duration of ASM maintenance (6-12 weeks) following acute neonatal seizures may be considered in the following circumstances:
  a. Higher probability of seizure recurrence (stroke & hemorrhage)
  b. Abnormal neonatal neurological examination upon discharge
  c. Abnormal EEG background upon discharge
- Routine maintenance ASM is **not recommended** as some ASM (phenobarbitone & phenytoin) have neuro-apoptotic properties.

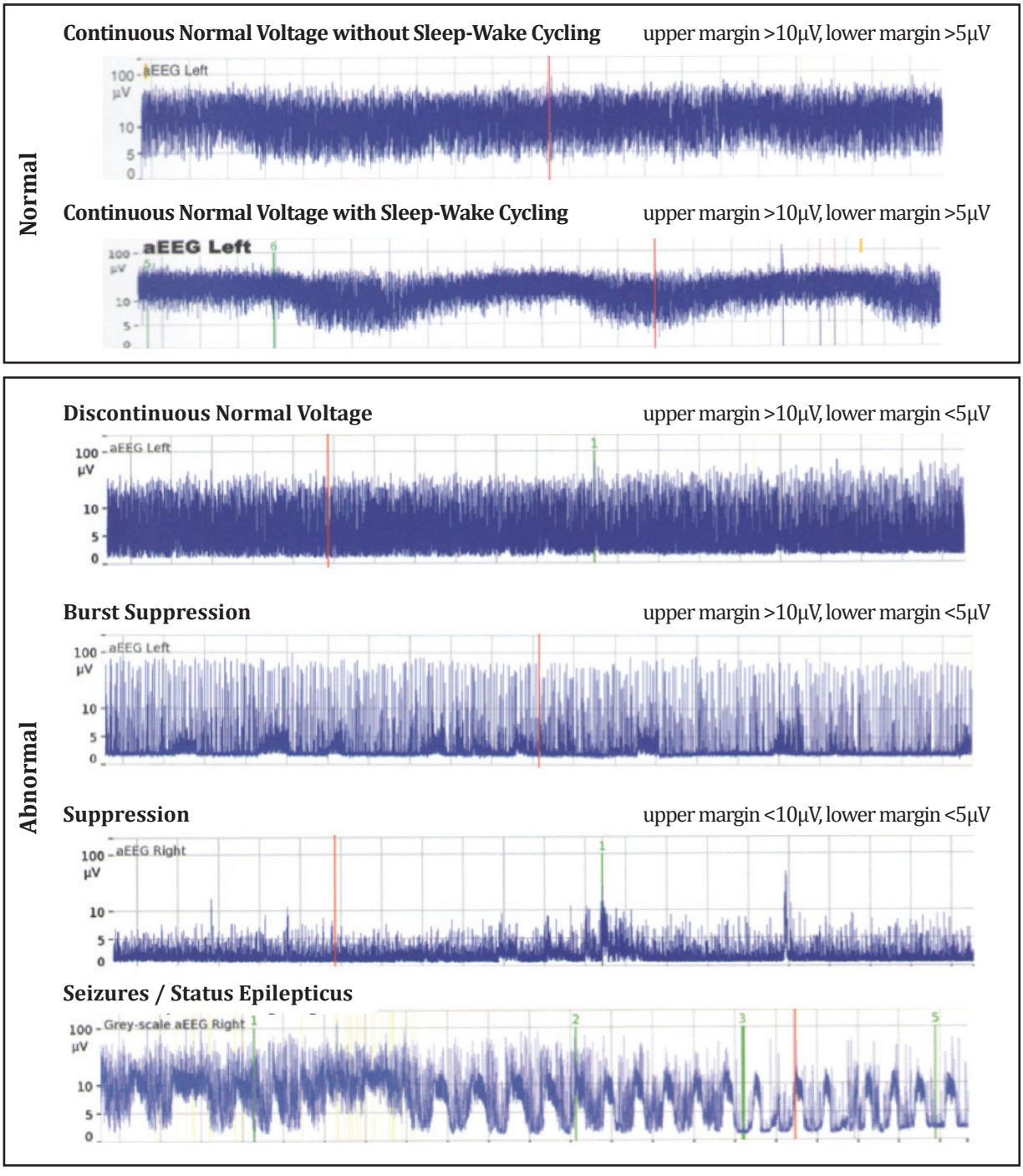
6. Outcomes:

The outcome following neonatal seizures depends primarily on the underlying cause. The presence of both clinical (except focal clonic) and electrographic seizures often indicates brain injury and coupled with abnormal EEG background and abnormal MRI are important determinants for adverse outcome.

Neonatal amplitude-integrated EEG (aEEG)-points to consider

1. Continuity
2. Amplitude of lower margin (Normal>5μV) & upper margin (Normal>10μV)
3. Sleep-wake cycling
4. Seizures

Recognizable patterns of term neonatal aEEG



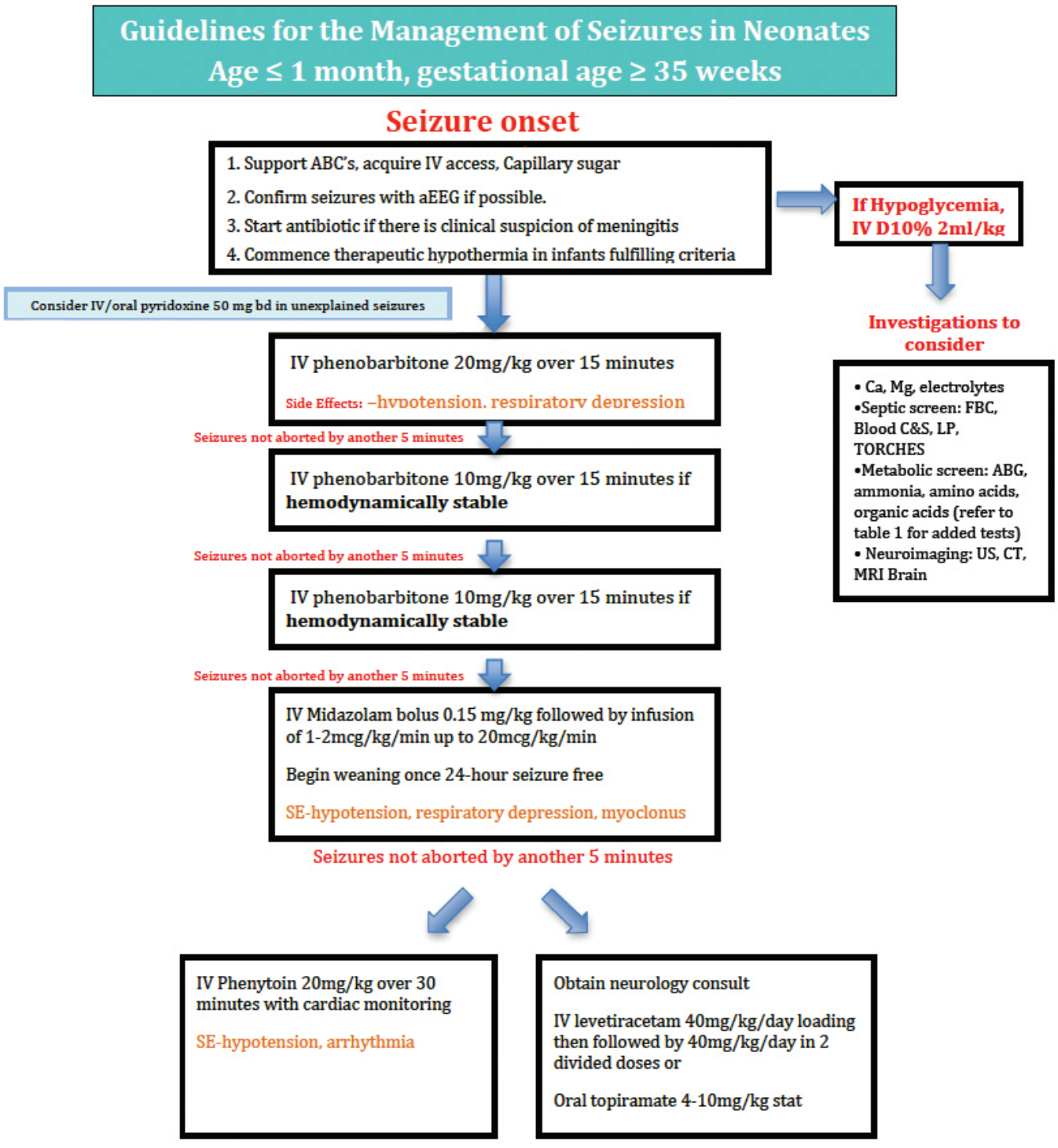
Source: Hellström-Westas, de Vries, Rosen, *Atlas of Amplitude-Integrated EEGs in the Newborn, 2nd edition*

TABLE 1

ADDITIONAL INVESTIGATIONS-WHEN AETIOLOGY OF SEIZURES ARE STILL UNKNOWN

Consider Epilepsy Gene panel or Whole Exome Sequencing (WES) after discussing with neurologist / geneticist

Blood	Urine	Imaging	CSF
VBG, Lactate, Ammonia	Urine Organic Acid	Ultrasound Brain	Biochemistry/gram stain/culture/latex agglutination
Plasma Amino acid	Urine sulphite and sulphocysteine	CT Brain	CSF Lactate
Biotinidase enzyme assay	Urine purine/pyrimidine	MRI Brain +/-MRS# ±MRA/MRV & diffusion studies	Viral studies
Plasma Copper & ceruloplasmin			CSF Amino acid# (Pair with serum)
Serum Transferrin isoform (TIEF)			
Plasma Very long chain fatty acid (VLCFA) & Phytanic acid			
Acylcarnitine profile			


Guidelines for the Management of Seizures in Neonates
Age ≤ 1 month, gestational age ≥ 35 weeks
Seizure onset
1. Support ABC's, acquire IV access, Capillary sugar
2. Confirm seizures with aEEG if possible.
3. Start antibiotic if there is clinical suspicion of meningitis
4. Commence therapeutic hypothermia in infants fulfilling criteria
If Hypoglycemia, IV D10% 2ml/kg
Consider IV/oral pyridoxine 50 mg bd in unexplained seizures
Investigations to consider
• Ca, Mg, electrolytes
•Septic screen: FBC, Blood C&S, LP, TORCHES
•Metabolic screen: ABG, ammonia, amino acids, organic acids (refer to table 1 for added tests)
• Neuroimaging: US, CT, MRI Brain
IV phenobarbitone 20mg/kg over 15 minutes
Side Effects: –hypotension, respiratory depression
Seizures not aborted by another 5 minutes
IV phenobarbitone 10mg/kg over 15 minutes if hemodynamically stable
Seizures not aborted by another 5 minutes
IV phenobarbitone 10mg/kg over 15 minutes if hemodynamically stable
Seizures not aborted by another 5 minutes
IV Midazolam bolus 0.15 mg/kg followed by infusion of 1-2mcg/kg/min up to 20mcg/kg/min
Begin weaning once 24-hour seizure free
SE-hypotension, respiratory depression, myoclonus
Seizures not aborted by another 5 minutes
IV Phenytoin 20mg/kg over 30 minutes with cardiac monitoring
SE-hypotension, arrhythmia
Obtain neurology consult
IV levetiracetam 40mg/kg/day loading then followed by 40mg/kg/day in 2 divided doses or
Oral topiramate 4-10mg/kg stat

Chapter 47:
Epilepsy

Definition

- Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition.
- An epileptic seizure is the transient occurrence of clinical manifestation of abnormal excessive or synchronous neuronal activity in the brain.
- An epileptic syndrome is an epileptic disorder characterized by a cluster of clinical and EEG features, often supported by specific aetiological findings (structural, genetic, metabolic, immune and infectious). It has therapeutic and prognostic implications. Syndromes often have age-dependent presentations and a range of specific co-morbidities.

Operational (Practical) Clinical Definition of Epilepsy

(any of the following conditions):-

- At least two unprovoked (or reflex) seizures occurring >24 h apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years.
- Diagnosis of an epilepsy syndrome.

Imitators of epilepsy: Paroxysmal non-epileptic events

- The first important step in the management of childhood epilepsy is to differentiate epileptic seizures from paroxysmal non-epileptic events.

Table 1: Paroxysmal non-epileptic events (seizure mimics)

Neonates	***Children***
• Apnoea	• Breath-holding spells
• Jitteriness	• Vasovagal / cardiac syncope
• Benign neonatal sleep myoclonus	• Migraine
• Hyperekplexia	• Benign paroxysmal vertigo
Infants	• Tic disorders and stereotypies
• Breath-holding spells	• Rhythmic movement disorder
• Benign myoclonus of infancy	• Parasomnias
• Shuddering attacks	***Adolescents and young adults***
• Sandifer syndrome (Severe gastro oesophageal reflux disease)	• Vasovagal / cardiac syncope
• Benign paroxysmal torticollis of infancy	• Narcolepsy
• Abnormal eye movements (e.g. opsoclonus-myoclonus)	• Hypnic jerks (sleep starts)
• Rhythmic movement disorder (e.g. head banging)	• Periodic limb movements of sleep
	• Paroxysmal dyskinesia
	• Tic disorders
	• Hemifacial spasm
	• Migraine
	• Psychogenic non-epileptic seizures

APPROACH TO A CHILD WITH A FIRST SEIZURE

Definition

One or multiple unprovoked afebrile seizures within 24 hours with recovery of consciousness between seizures.

Notes:

- 25-50% of first unprovoked seizures in children will recur.
- The child who is neurologically normal, with no history of neurologic illness, and no evident acute cause for the seizure has an approximately 25% risk of a recurrent seizure in the next year, and nearly 50% risk of seizure over the next -3 years.
- 70-80% of second seizures will recur.

Clinical factors associated with an increased risk of recurrent seizures are:

- Prior neurologic insult (remote symptomatic seizure)
- Focal seizure
- Significant brain MRI findings
- Abnormal EEG
- Family history of epilepsy

Evaluating The First Afebrile Seizure

- Detailed history to determine if event is a seizure or a paroxysmal non- epileptic event as 30% of patients referred as epilepsy do not have seizures.
- A thorough clinical examination is important to look for any possible underlying aetiology.
- Please exclude acute symptomatic causes such as metabolic, traumatic, vascular or infectious aetiologies.
- Distinguish between acute symptomatic seizures and epilepsy.
- Treating underlying cause of provoked seizures will usually resolve the seizures and long-term anti-seizure medication is not required.

What Investigations Need To Be Done?

Investigations such as FBC, BUSE, Ca, Mg, RBS are indicated if

- Child unwell (vomiting, diarrhoea etc).
- Child not 'alert', lethargic or failure to return to baseline alertness.
- Lumbar puncture indicated if there is suspicion of brain infection.
- Toxicology screening considered if there is suspicion of drug exposure.

Electroencephalograph (EEG):

- EEG should not be **routinely** performed after a first unprovoked generalised seizure in young children who are neurologically normal.
- EEG is recommended after the second or subsequent seizure.
- Rarely required for acute symptomatic seizures.
- EEG in unprovoked seizure may help classify seizure type, epilepsy syndrome and predict recurrence.

Neuroimaging (MRI preferred) indications:

- Persisting postictal focal deficit (Todd's paresis).
- Condition of child not returned to baseline within several hours after the seizure.

Is Treatment Required?

- Treatment with anti-seizure medication is NOT indicated in all patients with a first afebrile seizure as it does not prevent development of epilepsy or influence long term remission.
- However, rescue medication such as rectal diazepam may be prescribed if the unprovoked seizure was prolonged.

APPROACH TO A CHILD WITH EPILEPSY

- The diagnosis of epilepsy is mainly clinical.
- Detailed history of the seizures; i.e. the setting in which the seizure occurs, child's behaviour preceding, during and after the event is critical
- Video (via mobile phone camera) of the actual event is helpful.
- The antenatal, birth, past medical history, developmental milestones and family history should be recorded meticulously.
- Look for dysmorphism, neurocutaneous signs; do thorough CNS and developmental examination.
- Perform general and systemic examinations to look for clues of underlying aetiology.

Stepwise clinical approach:

- Is it a seizure? (refer to table 1)
- Classification of seizure type/types. (refer to table 2, figure 1)
- Identification of epilepsy syndrome.
- Determination of aetiology and assessment of co-morbidity.

Investigations

The following investigations are:

- Full blood count, biochemical investigations such as electrolytes, calcium, magnesium, glucose, liver and renal function tests to exclude metabolic cause and before starting anti-seizure medication.
- Metabolic and genetic studies in clinically indicated cases with associated developmental delay where aetiology has not been identified.
- EEG is important to support the clinical diagnosis of epileptic seizures, classify the seizure type and epileptic syndrome, helps in selection of anti-seizure medication and prognosis.
- EEG performed during sleep increases yield of abnormalities and is important for those patients with seizures predominantly during sleep.
- A 'normal' EEG does not exclude epilepsy as it is a clinical diagnosis and the yield of abnormalities from a single EEG recording is low.

MRI is indicated in:

- Epilepsy occurring in the first year of life, except febrile seizures.
- Focal epilepsy except for the self-limited focal epilepsies list in figure 2.
- Developmental delay or regression.
- Difficult to control / refractory epilepsy.

NB. MRI is not indicated in the typical self-limited epilepsies and the genetic generalized epilepsies e.g. Childhood / Juvenile absence epilepsy, Juvenile myoclonic epilepsy, Epilepsy with GTCS alone.

Table 2: ILAE* Classification of Seizure Types (expanded version)

Focal Onset	Generalised Onset	Unknown Onset
Aware or Impaired Awareness *Motor Onset* automatisms atonic clonic epileptic spasms hyperkinetic myoclonic tonic *Nonmotor Onset* autonomic behaviour arrest cognitive emotional sensory **Focal to bilateral tonic-clonic**	*Motor* tonic-clonic clonic tonic myoclonic myoclonic-tonic-clonic myoclonic-atonic atonic epileptic spasms *Non motor (absence)* typical atypical myoclonic eyelid myoclonia	*Motor* tonic-clonic epileptic spasms Nonmotor behaviour arrest Unclassified

Figure 1: INTERNATIONAL LEAGUE AGAINST EPILEPSY (ILAE) FRAMEWORK FOR CLASSIFICATION OF THE EPILEPSIES

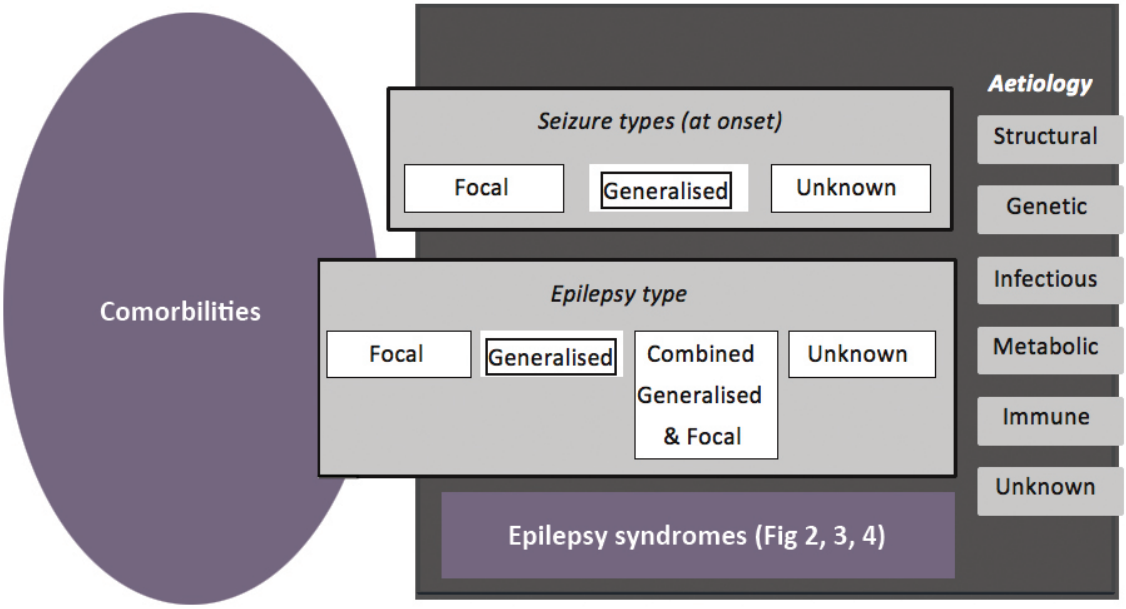


Figure 2

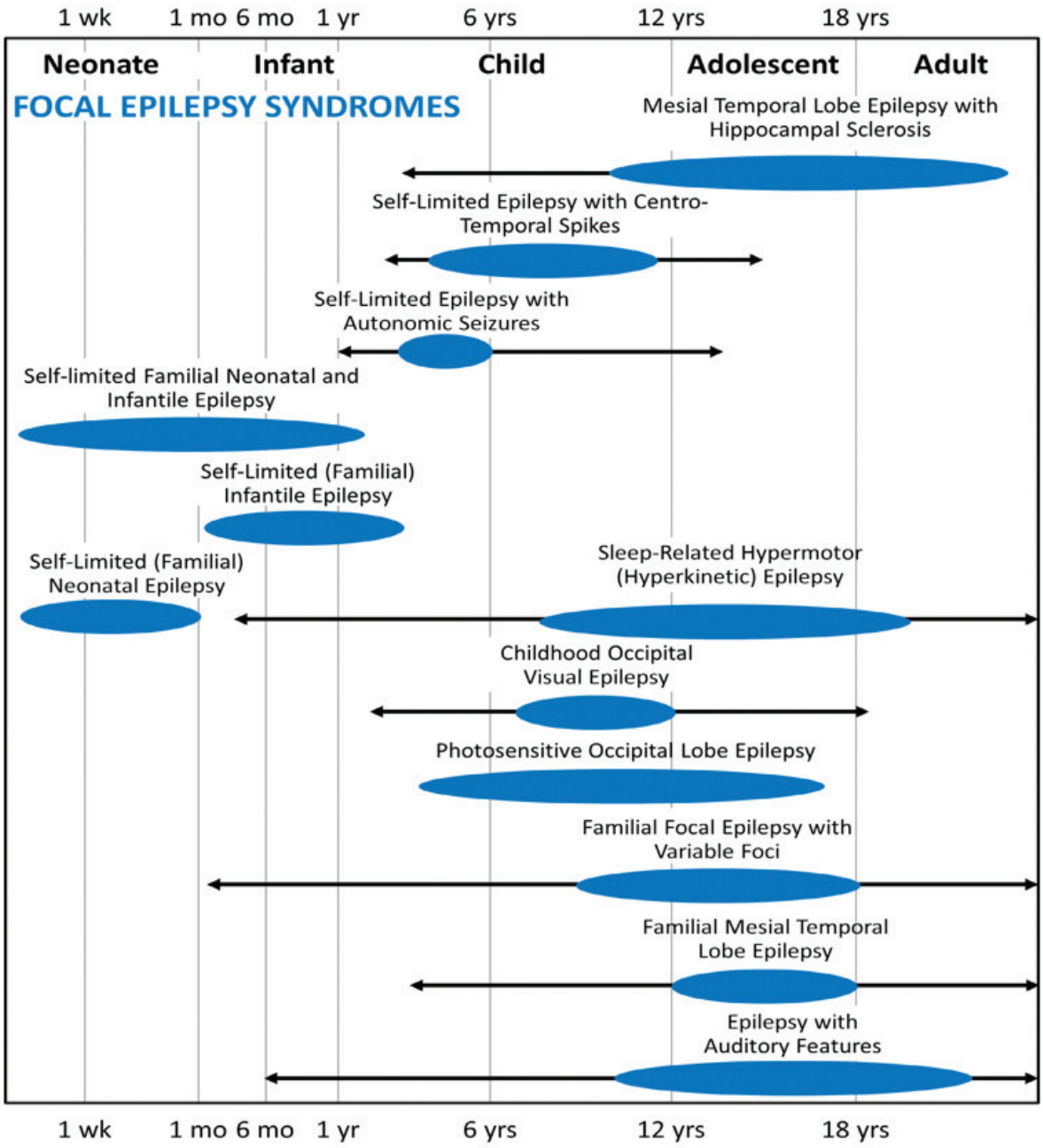

1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs
Neonate
Infant
Child
Adolescent
Adult
FOCAL EPILEPSY SYNDROMES
Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis
Self-Limited Epilepsy with Centro-Temporal Spikes
Self-Limited Epilepsy with Autonomic Seizures
Self-limited Familial Neonatal and Infantile Epilepsy
Self-Limited (Familial) Infantile Epilepsy
Self-Limited (Familial) Neonatal Epilepsy
Sleep-Related Hypermotor (Hyperkinetic) Epilepsy
Childhood Occipital Visual Epilepsy
Photosensitive Occipital Lobe Epilepsy
Familial Focal Epilepsy with Variable Foci
Familial Mesial Temporal Lobe Epilepsy
Epilepsy with Auditory Features

Figure 3

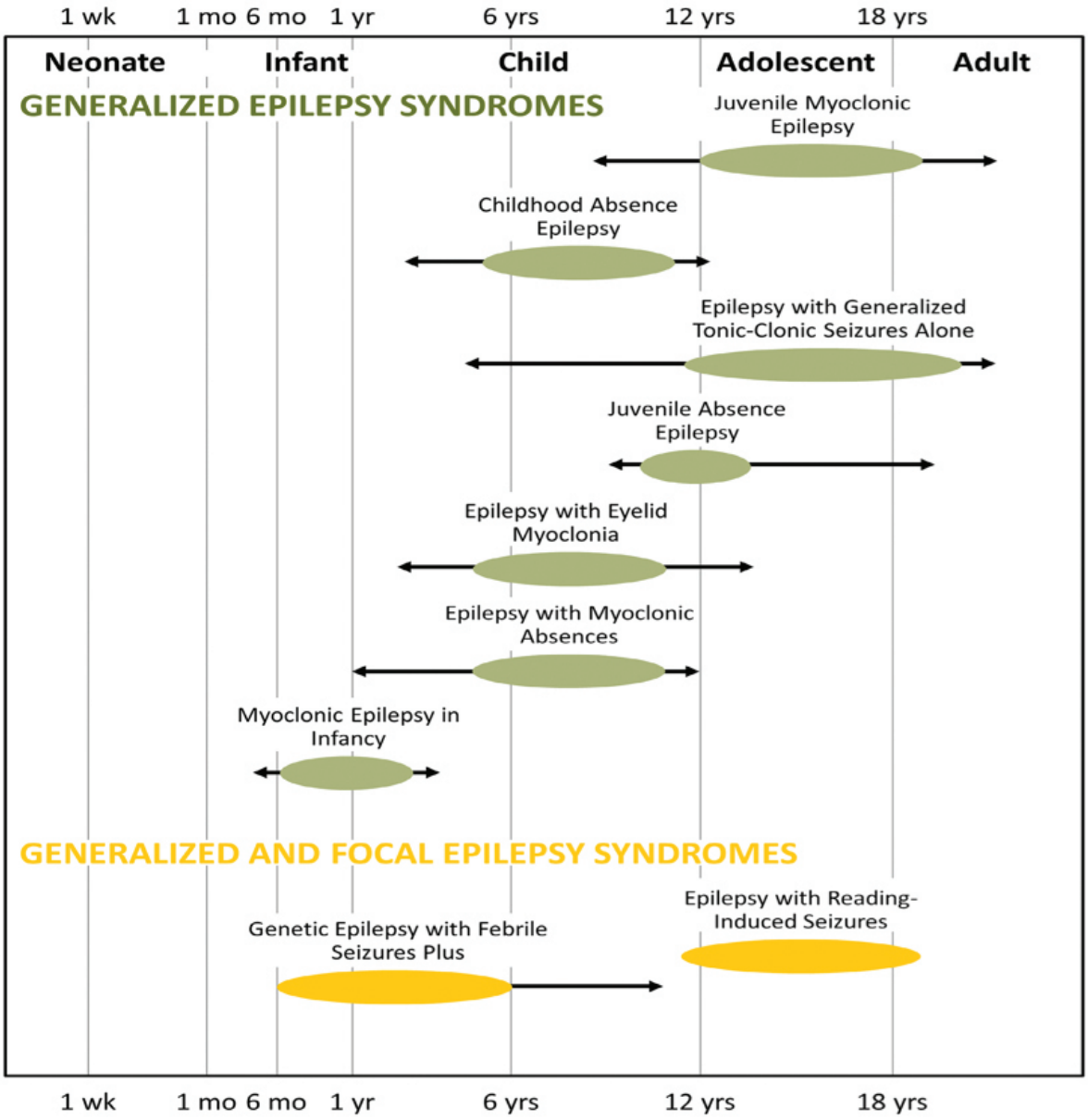
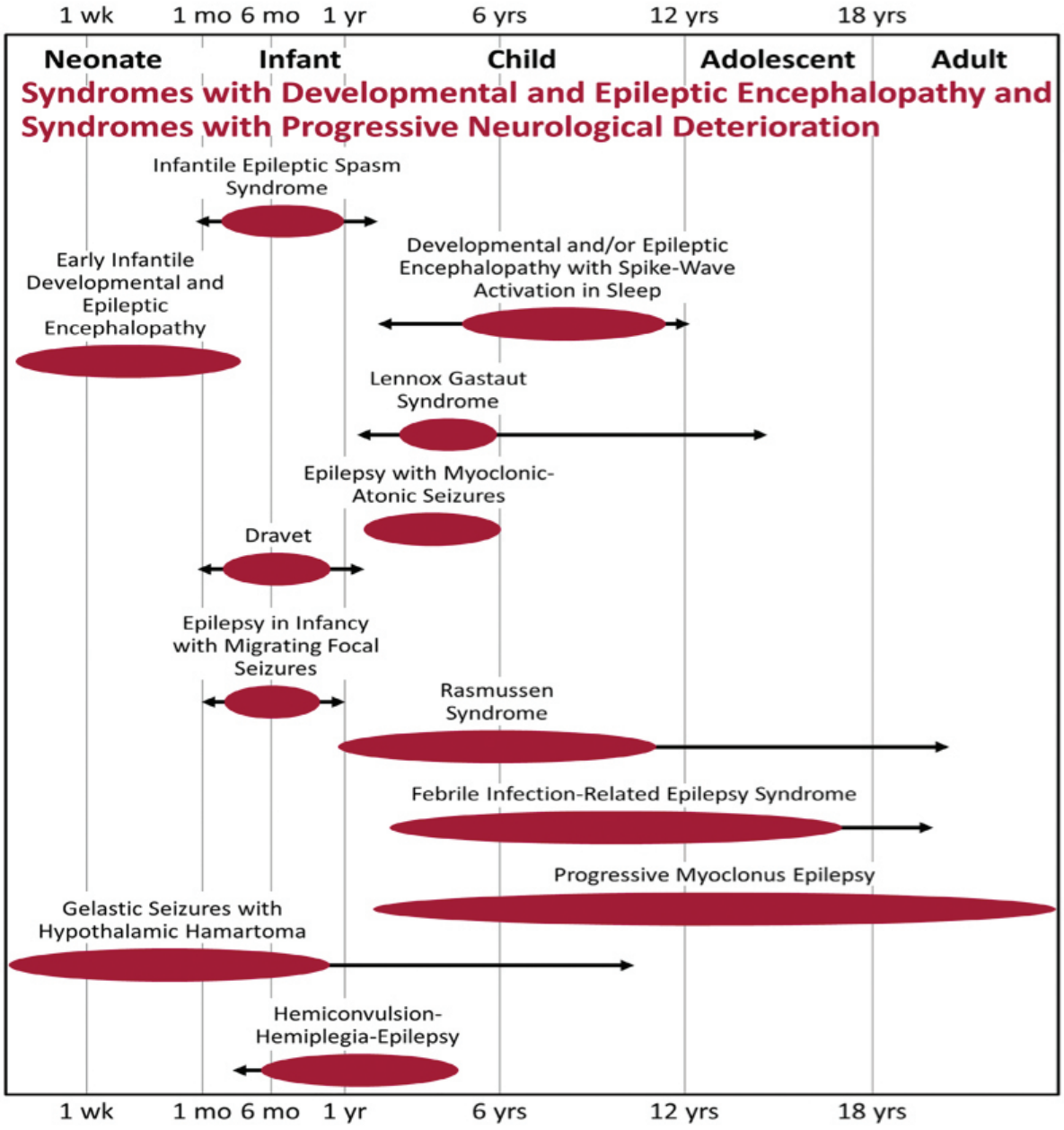

1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs
Neonate
Infant
Child
Adolescent
Adult
GENERALIZED EPILEPSY SYNDROMES
Juvenile Myoclonic Epilepsy
Childhood Absence Epilepsy
Epilepsy with Generalized Tonic-Clonic Seizures Alone
Juvenile Absence Epilepsy
Epilepsy with Eyelid Myoclonia
Epilepsy with Myoclonic Absences
Myoclonic Epilepsy in Infancy
GENERALIZED AND FOCAL EPILEPSY SYNDROMES
Epilepsy with Reading-Induced Seizures
Genetic Epilepsy with Febrile Seizures Plus
1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs

Figure 4


1 wk
1 mo
6 mo
1 yr
6 yrs
12 yrs
18 yrs
Neonate
Infant
Child
Adolescent
Adult
Syndromes with Developmental and Epileptic Encephalopathy and Syndromes with Progressive Neurological Deterioration
Infantile Epileptic Spasm Syndrome
Early Infantile Developmental and Epileptic Encephalopathy
Developmental and/or Epileptic Encephalopathy with Spike-Wave Activation in Sleep
Lennox Gastaut Syndrome
Epilepsy with Myoclonic-Atonic Seizures
Dravet
Epilepsy in Infancy with Migrating Focal Seizures
Rasmussen Syndrome
Febrile Infection-Related Epilepsy Syndrome
Progressive Myoclonus Epilepsy
Gelastic Seizures with Hypothalamic Hamartoma
Hemiconvulsion-Hemiplegia-Epilepsy

Principles on the use of anti-seizure medication (ASM) for Epilepsy

- Attempt to classify the seizure type(s) and epilepsy syndrome.
- Treatment recommended if ≥ 2 episodes (recurrence risk up to 80%).
- Monotherapy as far as possible.
- Choose most appropriate ASM based on epilepsy syndrome, seizure type (if epilepsy syndrome not identified yet) and associated comorbidities.
- Increase dose gradually until seizures controlled or maximum dose reached or side effects occur.
- Add on the second ASM if first medication failed. Optimise second medication, then try to withdraw first medication. (Alternative monotherapy).
- Rational combination therapy (usually 2 or maximum of 3 ASM)
  i.e. combine ASM with different mechanism of action and consider their spectrum of efficacy, interactions and adverse effects.
- Beware of ASM-induced seizure aggravation in certain epilepsy syndromes.
- Trial of vitamins and co-factors such as vitamin B6, pyridoxal phosphate, biotin and folinic acid should be considered in infantile epilepsies not responding to ASM.
- Risk of carbamazepine-induced hypersensitivity reactions, including Steven-Johnson syndrome and toxic epidermal necrolysis, is increased in patients with the HLA-B*1502 allele – ideally testing prior to starting Carbamazepine is recommended.
- Valproate should be avoided if there is clinical suspicion of an underlying neurometabolic disorder or a progressive illness where the underlying aetiology has not been ascertained yet, especially in children < 2years, due to risk of hepatotoxicity.
- Avoid the use of Valproate in postpubertal girls of childbearing potential because of its teratogenic risks.
- Drug level monitoring is **not routinely** done (except phenytoin), unless non-compliance, toxicity or drug interaction is suspected.
- Vitamin D supplementation should be considered for children with risk factors for Vitamin D deficiency, i.e. those on long term ASM, or on more than 1 ASM and poor sunlight exposure.
- When withdrawal of medication is planned (generally after being seizure free for 2 years), consider the underlying epilepsy syndrome, likely prognosis and individual circumstances before attempting slow withdrawal of medication over 3-6 months (duration of weaning maybe longer if using phenobarbitone or benzodiazepine).
- If seizures recur, the last dose reduction is reversed and patient should be re-evaluated.

Selecting anti-seizure medication according to seizure types

FOCAL SEIZURES (with / without evolution to bilateral tonic clonic seizures)
First Line: Carbamazepine**
Second Line: Levetiracetam, Lamotrigine, Zonisamide, Topiramate, Phenytoin, Perampanel#
***(HLA-B1502 should be tested negative prior to using Carbamazepine)*

GENERALIZED SEIZURES
Tonic-clonic / clonic only
First Line: Valproate^
Second Line: Lamotrigine, Levetiracetam, Clobazam, Topiramate, Perampanel#
^(avoid in postpubertal girls of childbearing potential)
Absence
First Line: Valproate, Ethosuximide#
Second Line: Lamotrigine, Levetiracetam
Atonic, tonic
First Line: Valproate, Lamotrigine
Second Line: Clobazam, Topiramate, Rufinamide#(for tonic seizures)
Myoclonic
First Line: Valproate^, Levetiracetam
Second Line Lamotrigine, Clonazepam, Clobazam, Topiramate
^(avoid in postpubertal girls of childbearing potential)

Anti-Seizure medication and other therapies according to Epilepsy Syndromes
Infantile Spasms syndrome*   *First Line:* Steroid (Prednisolone), Vigabatrin#(first line for Tuberous Sclerosis)   *Second Line:* Ketogenic diet, Nitrazepam, Clobazam, Sodium Valproate, Topiramate, Pyridoxine, Zonisamide* (focal-onset spasms)   **(Please consult management with Paediatric Neurologist)*   **Dravet syndrome**   *First Line:* Sodium Valproate, Clobazam   *Second Line:* Topiramate, Levetiracetam, Ketogenic diet, Stiripentol#   **Lennox-Gastaut syndrome**   *First Line:* Sodium Valproate, Lamotrigine   *Second Line:* Topiramate, Clobazam, Rufinamide#   **Epilepsy with Myoclonic-Atonic Seizures (Doose syndrome)**   *First Line:* Sodium Valproate, Lamotrigine, Clobazam   *Second Line:* Ketogenic diet, Levetiracetam   **Childhood absence epilepsy or other absence epilepsy syndrome**   *First Line:* Sodium valproate, Ethosuximide#   *Second Line:* Lamotrigine, Levetiracetam   **Juvenile myoclonic epilepsy**   *First Line:* Sodium valproate, Levetiracetam   *Second Line:* Lamotrigine (may exacerbate myoclonus), Clobazam, Clonazepam, Topiramate   **Self-Limited epilepsy with centrotemporal spikes (SeLECTS)**   *First Line:* Carbamazepine, Levetiracetam   *Second Line:* Valproate, Lamotrigine   *(Rarely, if there is evidence of neuro-regression in patients with SeLECTS, referral to neurologist is suggested).*
 # Currently not in MOH Drug Formulary (can be applied through KPK after consult with neurologist)

Anti-seizure medication that may aggravate selected seizure types	
Phenobarbitone (high doses)	Absence seizures (typical/atypical)
IV Benzodiazepine	Risk of precipitating tonic status in Lennox-Gastaut syndrome
Carbamazepine	Absence, myoclonic, generalised tonic-clonic seizures
Lamotrigine	Dravet syndrome, Myoclonic seizures in Juvenile Myoclonic Epilepsy
Phenytoin	Absence, myoclonic seizures
Vigabatrin	Absence, myoclonic seizures

Adverse Effects of Anti-seizure Medication

Carbamazepine
Common side effects: GI upset, drowsiness, dizziness, ataxia, diplopia, rashes, hyponatremia
Serious side effects: Steven-Johnson syndrome[1] agranulocytosis

Clobazam[2], Clonazepam
Common side effects: Drowsiness, salivary and bronchial hypersecretion, aggression / behavioural changes

Lamotrigine
Common side effects: Rash, dizziness, insomnia, tremor
Serious side effects: Steven-Johnson syndrome

Levetiracetam
Common side effects: Somnolence, asthenia, dizziness, irritability, behavioural changes

Phenobarbitone
Common side effects: Drowsiness, behavioural disturbance, cognitive dysfunction, ataxia, rash
Serious side effects: Steven-Johnson syndrome, agranulocytosis

Phenytoin
Common side effects: Ataxia, diplopia, dizziness, sedation, gingival hyperplasia, rash, hirsutism, megaloblastic anemia
Serious side effects: Steven-Johnson syndrome, agranulocytosis

Sodium valproate
Common side effects: GI upset, tremor, weight gain, hair loss, thrombocytopaenia
Serious side effects: Hepatic toxicity, pancreatitis, encephalopathy

Topiramate
Common side effects: Anorexia, weight loss, somnolence, cognitive dysfunction, word finding difficulty, hypohidrosis, renal calculi, glaucoma

Zonisamide
Common side effects: Somnolence, dizziness, anorexia, weight loss, GI upset, irritability, rashes, hypohidrosis, renal calculi, mood disturbances / psychosis

Vigabatrin
Common side effects: Drowsiness, dizziness, mood changes, weight gain
Serious side effects: Peripheral visual field constriction (tunnel vision)

Perampanel
Common side effects: Dizziness, somnolence, headache, fatigue, irritability, gait disturbances
Serious side effects: Neuropsychiatric effects such as altered mood and aggression

1. Steven-Johnson syndrome occurs more frequently in Chinese and Malay children who carry the HLA-B*1502 allele.
2. Clobazam is less sedative and causes less secretions than Clonazepam

The patients with "Intractable Epilepsy"

Intractable Epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen anti-seizure medication schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

Please re-evaluate for the following possibilities: -

- Is it a seizure or a non-epileptic event?
- Wrong classification of epilepsy syndrome, thus wrong choice of antiseizure medication.
- Anti-seizure medication doses not optimised.
- Poor compliance to anti-seizure medication.
- Anti-seizure medication aggravating seizures.
- Lesional epilepsy, hence a potential epilepsy surgery candidate.
- Progressive epilepsy or neurodegenerative disorder.

When to refer to Paediatric Neurologist?

- Infantile spasms
- Behavioural or developmental regression.
- Poor seizure control despite monotherapy with 2 different anti-seizure medications.
- Difficult to control epilepsies beginning in the first two years of life.
- Structural lesion on neuroimaging.

Advice for Parents

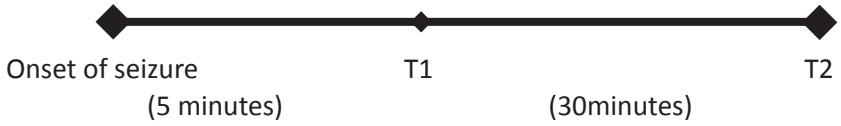
- Educate and counsel on epilepsy.
- Emphasize compliance if on anti-seizure medication.
- Don't stop the medication without doctor's advice as this may precipitate breakthrough seizures.
- Avoid sleep deprivation.
- Use a shower with bathroom door unlocked.
- Avoid cycling in traffic, climbing sports or swimming alone.
- Educate on the emergency treatment of seizures.
- Inform teachers and school about the condition.

First Aid Measures during a Seizure (Advice for Parents / Teachers)
• Do not panic, remain calm. Note time of onset of the seizure. • Loosen the child's clothing especially around the neck. • Place the child in a left lateral position with the head lower than the body. • Wipe any vomitus or secretions from the mouth. • Do not insert any object into the mouth even if the teeth are clenched. • Do not give any fluids or drugs orally (unless using buccal Midazolam to abort seizure). • Stay near the child until the seizure is over and comfort the child as he/she is recovering

Chapter 48:
Status Epilepticus: Management Of Convulsive Status Eilepticus

Definition:

- Definition of convulsive status epilepticus (CSE) is a seizure that continues for greater than 5min.
- After 5min, seizures are unlikely to terminate spontaneously.
- The risk of seizure becoming refractory increases with increasing seizure duration.
- Therefore, treatment should be started once seizure has lasted >5min.
- T1 and T2 are two important operational time points in the conceptional definition of SE.



- T1 is the at time point at which treatment should be started.
- Beyond this point if seizures continue, it is termed continuous seizure activity.
- T2 is the time point at which seizures should have terminated. Beyond which long term complications will ensue.

DOs

- Out of hospital administration of benzodiazepine shows clear benefit due to earlier abolished SE.
- Educating parents/caregiver & EMS on the use of rescue medication, first aid and recovery position is important.
- *Administration of the entire recommended dose of benzodiazepine in the initial treatment is more efficacious than multiple small doses.
- The efficacy of benzodiazepine decreases 20-fold over 30min of SE.
- *Quickly escalate to non-benzodiazepine 2nd line ASM once failed 2 doses of benzodiazepine.
- Three large RCTs have found equal potency for Phenytoin, Levetiracetam and Sodium Valproate.
- Children who have frequent seizures/under the pediatric neurology follow up usually have an individually tailored guideline. “Ask the parent for follow-up book.”
- There is no evidence of ideal 3rd line agent: thiopentone, propofol, ketamine and midazolam.
- However midazolam is the safest in pediatric age group.
- Other investigation at the refractory stage: CT/MRI/Autoimmune screen/metabolic & genetic studies accordingly.
- Do not forget to look hard for underlying etiology and treat accordingly.

DON’Ts

- Avoid valproate if suspected inborn error of metabolism or liver dysfunction.
- Avoid phenytoin in Dravet Syndrome.
- Do not give phenytoin too rapidly as it can cause bradycardia/asystole.

Maintenance/Monitoring

- Often maintenance dose is forgotten.
- In sepsis, monitor calcium and magnesium levels, as they can be low.
- Monitor glucose, aim for 4-8mmol/L.
- Measure serum sodium and treat if < 125mmol/L (3ml kg 3% sodium chloride)
- Consider temperature control if hyperthermic.
- Consider meningitis, encephalitis, raised ICP.
- Consider TBI if signs of trauma.

Status Epilepticus: Management Of Convulsive Status Epilepticus (SE)

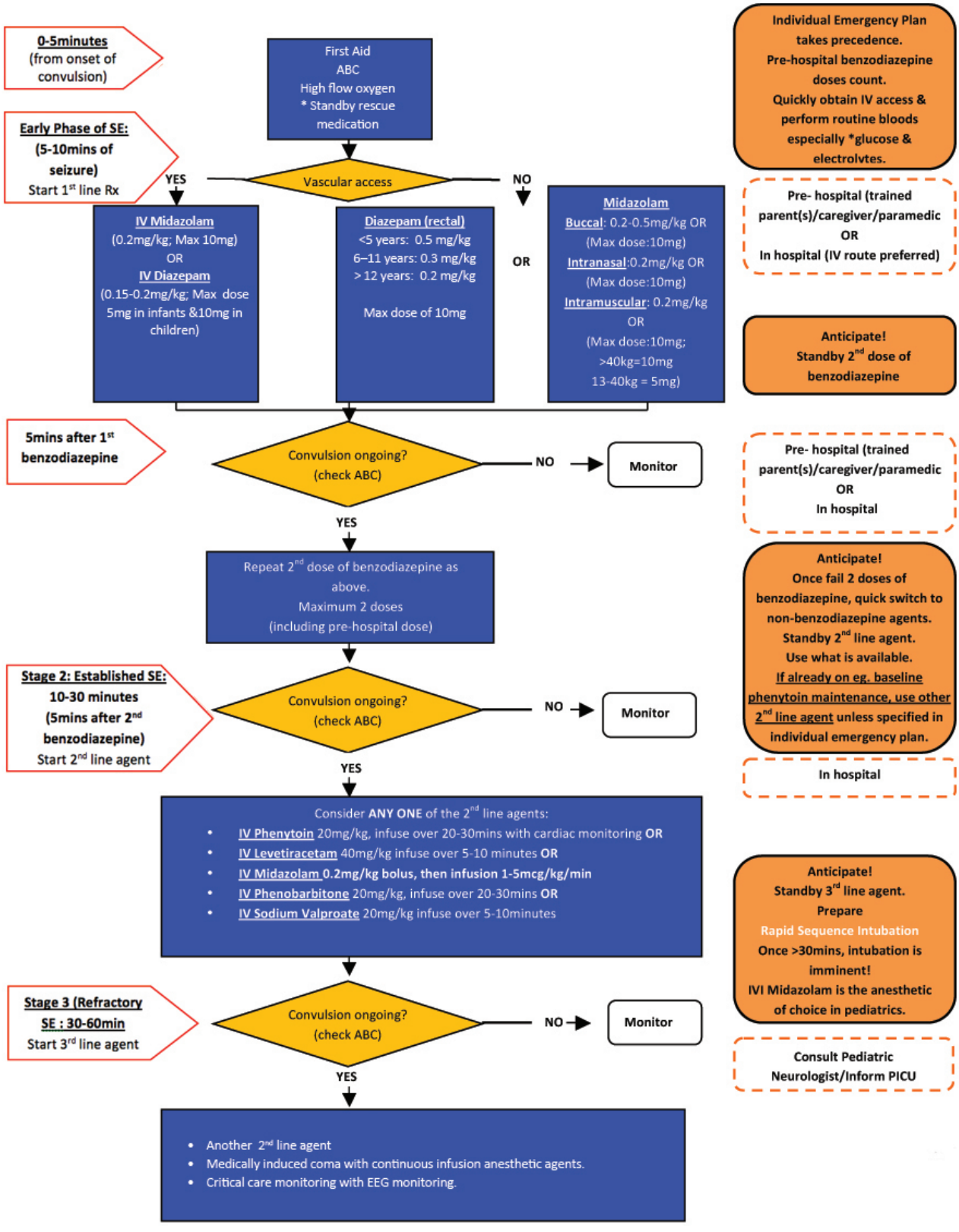


Table 1: with drug doses, maximum doses, dilution and infusion rates.

Drug (IV route)	Doses/ Max dose/ dilution/Max concentration
Diazepam	0.2mg/kg slow bolus (at 2mg/min; max 10mg)
Midazolam	Bolus: 0.2mg/kg bolus (at 2mg/min; Max 10mg) then infusion: 3-5mcg/kg/min up to a max 15mcg/kg/min)
Phenytoin	20mg/kg (Max loading: 1.25gm) Dilute in 0.9% saline Max. concentration at 10mg/ml; Infuse over 20-30 minutes With cardiac monitoring
Phenobarbitone	20mg/kg (Max loading 1gm; infusion at 25-50mg/min)
Levetiracetam	40mg/kg Infused over 10minutes then 20mg/kg 12 hourly
Sodium Valproate	20mg/kg (Max loading: 1.25gm, given over 1-5minutes at 20-50mg/min), then infusion 1-5mg/kg/hour for 6-12hours

Chapter 49:
Febrile Seizures

Definition

- Seizures occurring in association with fever in children between 6 months and 5 years of age, in whom there is no evidence of intracranial pathology or metabolic derangement.
- No comprehensive local epidemiological data. Studies in Western countries quote a figure of 2-5% of children < 5 years experiencing febrile seizures.

Classification of Febrile Seizures	
Simple Febrile Seizures • Duration < 15 minutes • Generalised seizure. • Does not recur during the febrile episode	*Complex Febrile Seizures* • Duration > 15 minutes • Focal features • >1 seizure during the febrile episode • Residual neurological deficit post-ictally, such as Todd's paralysis

Management

- Not all children need hospital admission. The main reasons for admission are: -
  - To exclude intracranial pathology especially infection.
  - Fear of recurrent seizures.
  - To investigate and treat the cause of fever besides meningitis /encephalitis.
  - To allay parental anxiety, especially if they are staying far from hospital.
- Investigations
  - The need for blood counts, blood sugar, lumbar puncture, urinalysis, chest X-ray, blood culture etc, will depend on clinical assessment of the individual case.
  - Lumbar puncture
    Must be done if: (unless contraindicated - see Chapter on Meningitis)
    - Any symptoms or signs suggestive of intracranial infection
    - Persistent lethargy and not fully interactive

    Should be considered if:
    - Age < 12 months old especially if child has not received Hib and pneumococcal immunization
    - Prior antibiotic therapy
  - Serum calcium and electrolytes are rarely necessary.
  - EEG is not indicated even if multiple recurrences or complex febrile seizures.
- Parents should be counselled on the benign nature of the condition.
- Control fever
  - Avoid excessive clothing
  - Use antipyretic e.g. syrup or rectal Paracetamol 15 mg/kg 6 hourly for patient's comfort, though this does not reduce the risk of seizure recurrence.
- Parents should also be advised on **First Aid Measures during a Seizure**.
  Rectal Diazepam
  - Parents of children with high risk of recurrent febrile seizures including those with febrile status epilepticus should be supplied with Rectal Diazepam (dose: 0.5 mg/kg).
  - They should be advised on how to administer it if the seizures last more than 5 minutes.

- Prevention of recurrent febrile seizures.
  Antiseizure medications are not recommended for prevention of recurrent febrile seizures because:
  - The risks and potential side effects of medications outweigh the benefit.
  - No medication has been shown to prevent the future onset of epilepsy.
  - Febrile seizures have an excellent outcome with no neurological deficit nor any effect on intelligence.

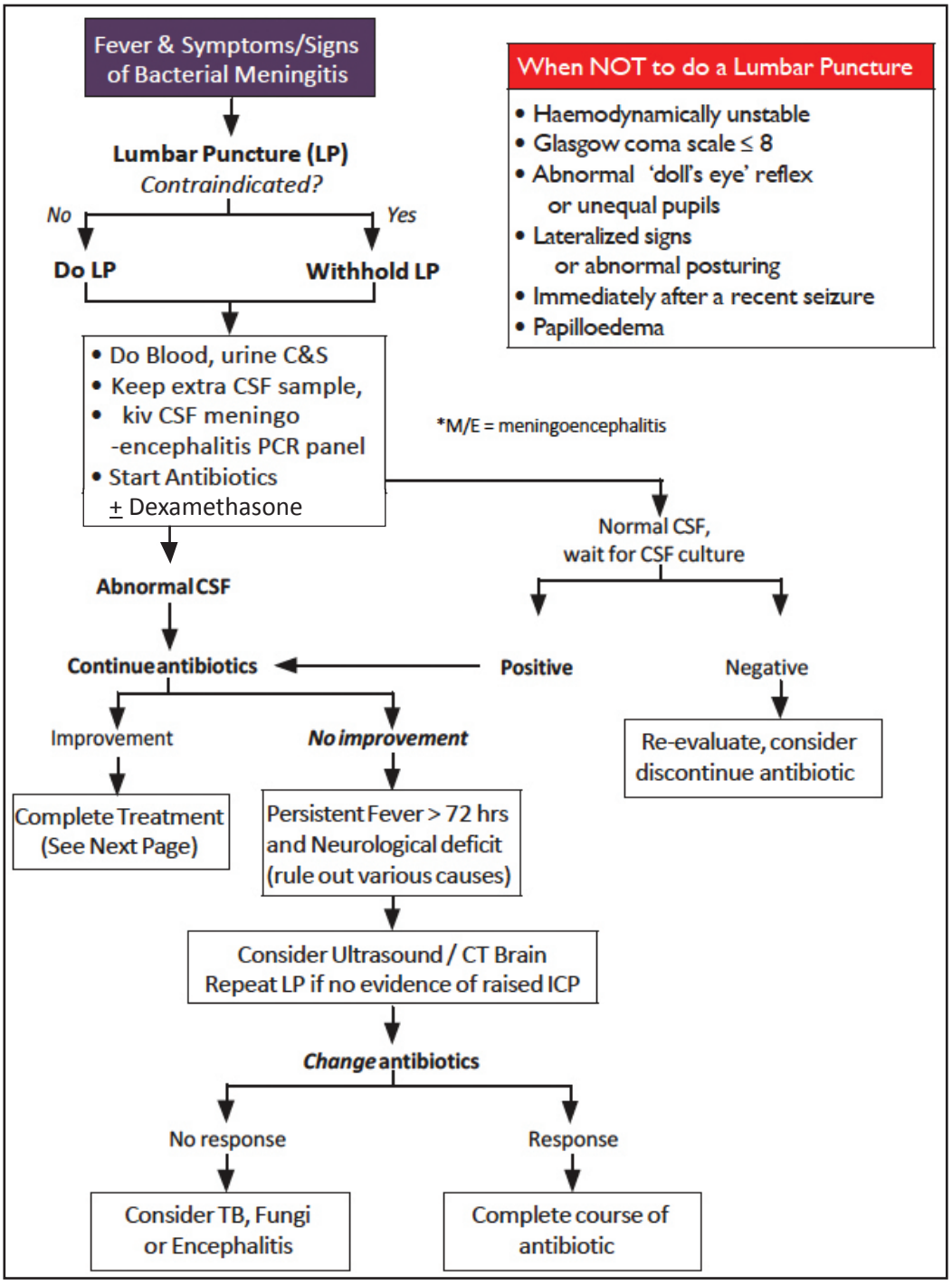
Risk factors for Recurrent Febrile Seizures
• Family history of Febrile seizures • Age < 18 months • Low degree of fever (< 40°C) during first febrile seizure. • Brief duration (< 1 hr) between onset of fever and seizure. ** If No risk factor, then < 15 % risk of recurrence* *If ≥ 2 risk factors, then > 30 % risk of recurrence* *If ≥ 3 risk factors, then > 60 % risk of recurrence*
Risk factors for subsequent Epilepsy
• Neurodevelopmental abnormality • Complex febrile seizures • Family history of epilepsy
Prognosis in Febrile Seizures
Febrile seizures are benign events with excellent prognosis • 2 - 5 % of population have febrile seizures. • 30 % recurrence after 1st attack. • 48 % recurrence after 2nd attack. • 2 - 7 % develop subsequent afebrile seizure or epilepsy. • No evidence of permanent neurological deficits following febrile seizures or even febrile status epilepticus.

Chapter 50:
Meningitis

Introduction

- Meningitis is still an important infection in paediatrics.
- Morbidity is also high. A third of survivors have sequelae of their disease. However, these complications can be reduced if meningitis is treated early.

APPROACH TO A CHILD WITH FEVER AND SIGNS/ SYMPTOMS OF MENINGITIS



Cerebrospinal fluid values in neurological disorders with fever				
Condition	**Leukocytes (mm^3)**	**Protein (g/l)**	**Glucose (mmol/l)**	**Comments**
Acute Bacterial Meningitis	100 - >50,000	Usually 1- 5	<0.5 - 1.5	Gram stain may be positive
Partially-treated Bacterial Meningitis	1 - 10,000 Usually high PMN, but may have lymphocytes	> 1	Low	CSF may be sterile Organism can be identified from CSF meningo-encephalitis PCR panel
Tuberculous Meningitis	10 - 500 Early PMN, later high lymphocytes	1- 5	0 - 2.0	Smear for AFB, GeneXpert MTB test + in CSF; High ESR
Fungal Meningitis	50 – 500 Lymphocytes	0.5 - 2	Normal or low	CSF for Cryptococcal Ag
Encephalitis	10 - 1,000 Lymphocytes	Normal / 0.5-1	Normal	CSF virology and HSV DNA PCR

Recommended antibiotic therapy according to likely pathogen			
Age Group	**Initial Antibiotics**	**Likely Organism**	**Duration (if uncomplicated)**
< 1 month	C Penicillin + Cefotaxime	*Group B Streptococcus* *E. coli*	21 days
1 - 3 months	C Penicillin + Cefotaxime	*Group B Streptococcus* *E. coli* *H. influenzae*	10 – 21 days
> 3 months	C Penicillin + Cefotaxime, OR Ceftriaxone	*H. influenzae*	7 – 10 days 10 – 14 days 7 days

Note:
- Review antibiotic choice when infective organism has been identified
- Ceftriaxone gives more rapid CSF sterilisation as compared to Cefotaxime or Cefuroxime.
- If Streptococcal meningitis, request for MIC values of antibiotics.

	MIC level	***Drug of choice***
. Penicillin-susceptible	≤ 0.06 mcg/ml	C Penicillin
. Penicillin-resistant & Cefotaxime/Ceftriaxone sensitive	≥ 0.12 mcg/ml ≤ 0.5 mcg/ml	Cefotaxime or Ceftriaxone
. Penicillin & Cefotaxime / Ceftriaxone resistant	≥ 2 mcg/ml	High dose Cefotaxime or Ceftriaxone + Vancomycin

- Extend duration of treatment if complications e.g. subdural empyema, brain abscess.

Use of Steroids to decrease the sequelae of bacterial meningitis

- Best effect achieved if given before or with the first antibiotic dose.
- Dose: Dexamethasone 0.15 mg/kg 6 hourly for 4 days.
- Give steroids if CSF is turbid and patient has not received prior antibiotic.

Supportive measures

- Monitor temperature, pulse, BP and respiration 4 hourly and input/output.
- Nil by mouth if unconscious.
- Judicious fluid management with careful monitoring to ensure adequate circulating volume while being aware of the possibility, albeit uncommon of developing SIADH. Patient may need more fluid if dehydrated.
- If fontanell is still open, note the head circumference daily. Consider cranial ultrasound or CT scan if effusion or hydrocephalus is suspected.
- Seizure chart.
- Daily neurological assessment is essential.
- Observe for 24 hours after stopping therapy and if there is no complication patient can be discharged.

Persistent fever in a patient on treatment for meningitis, consider:

- Thrombophlebitis and injection sites e.g. intramuscular abscess.
- Intercurrent infection e.g. pneumonia, UTI or nosocomial infection.
- Resistant organisms. Inappropriate antibiotics or inadequate dosage.
- Subdural effusion, empyema or brain abscess.
- Antibiotic fever.

Indications for CT or MRI brain (with contrast)

Useful to detect complications

- Prolonged depression of consciousness.
- Prolonged focal or late seizures.
- Focal neurological abnormalities.
- Enlarging head circumference.
- Suspected subdural effusion or empyema.

Indications for Subdural drainage

- Rapid increase in head circumference with no hydrocephalus.
- Focal neurological signs.
- Increased intracranial pressure.
- Suspected subdural empyema.

Follow up (Long term follow up is important)

- Monitor head circumference.
- Monitor the child's development and learning.
- Ask for any occurrence of seizure or any behavioural abnormalities.
- Assess vision, hearing and speech.
- Request for early formal hearing assessment in cases of proven meningitis
- Until child shows normal development (usually until 4 years old).

Prognosis depends on

- Age: worse in younger patients.
- Duration of illness prior to effective antibiotics treatment.
- Causative organism: more complication with H. influenzae, S. pneumoniae.
- Presence of focal signs.

Chapter 51:
Autoimmune Encephalitis (AE)

Introduction

- Autoimmune encephalitis (AE) is an increasingly recognized cause of encephalopathy/encephalitis in children.
- Many antibodies against the central nervous system (CNS) are responsible for the clinical manifestations; though some cases do not have any antibodies detected.
- Early diagnosis and treatment is associated with better neurocognitive outcomes.
- Anti-N Methyl D Aspartate receptor (NMDAR) AE is the most common type in children.
- Relapse occurs in 20-25% of cases.

Diagnostic criteria for Possible Autoimmune Encephalitis

All three of the following criteria should be met:

- Subacute onset (rapid progression of < 3 months) of working memory deficits, altered mental status or psychiatric symptoms.
- At least one of the following:
  - New focal CNS findings
  - Seizures (new onset)
  - CSF pleocytosis (> 5 cells/mm^3 in white cell count)
  - MRI features suggestive of encephalitis

  Reasonable exclusion of alternative causes

Diagnostic criteria for Antibody-Negative but Probable Autoimmune Encephalitis

All four of the following criteria should be met:

- Subacute onset (rapid progression of < 3 months) of working memory deficits, altered mental status or psychiatric symptoms.
- Exclusion of other well defined syndromes of encephalitis (E.g. Acute Disseminated EncephaloMyelitis (ADEM), anti Myelin Oligodendrocyte Glycoprotein (MOG) associated encephalitis etc).
- Absence of antibodies in the serum or CSF, and at least two of the following:
  - CSF pleocytosis, oligoclonal bands or elevated CSF IgG index, or both
  - MRI features suggestive of autoimmune encephalitis
- Reasonable exclusion of alternative causes

Definite diagnosis of Autoimmune Encephalitis:

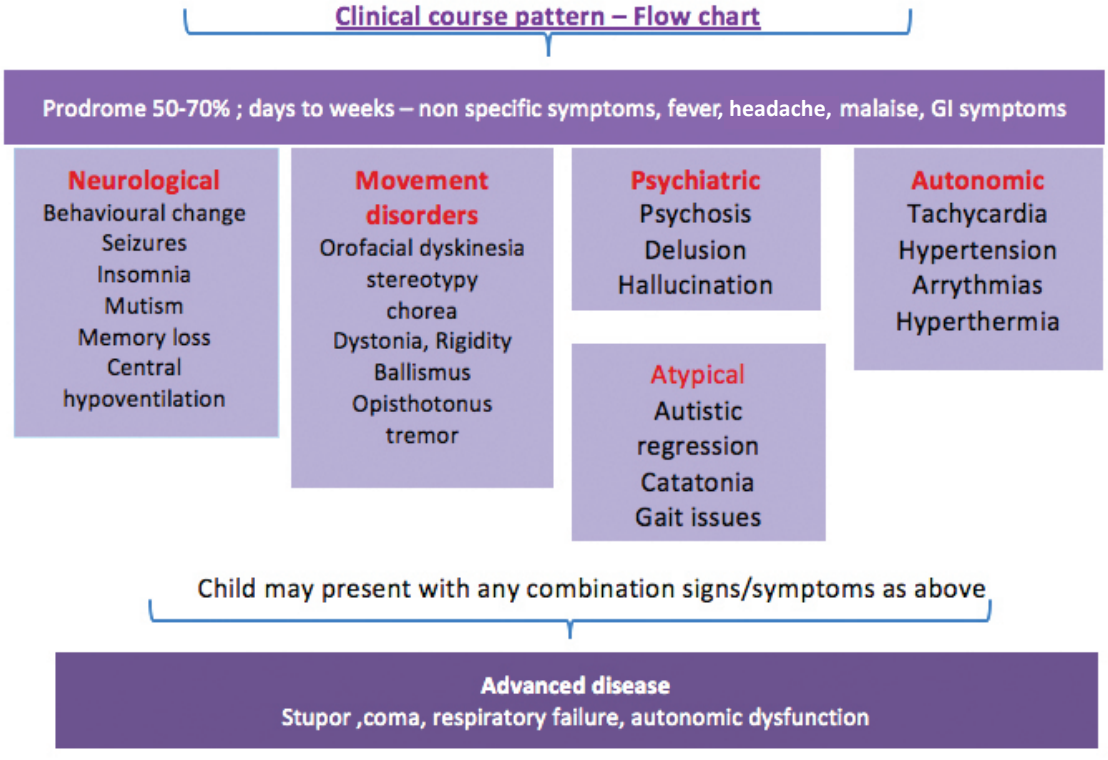
Positive anti-NMDA receptor antibody test (or other autoimmune antibodies positive) after reasonable exclusion of other disorders.

Differential Diagnosis

- CNS infections (bacterial, viral , TB, fungal, SSPE)
- Epileptic disorders
- CNS demyelination (ADEM, multiple sclerosis, neuromyelitis optica)
- CNS vasculitis (primary CNS vasculitis, SLE)
- Hashimoto's encephalopathy
- Neoplastic disorders
- Toxic, metabolic, drug toxicity
- Mitochondrial diseases
- Inborn errors metabolism
- Autistic regression

Suspect AE when a child presents with varied combination of the following:

- Unusual manifestations in a child with acute encephalitis syndrome
- Adolescent girls
- Subacute to chronic course
- Polysymptomatic syndrome
- Encephalopathy
- Seizures: Focal, generalized, status epilepticus, multifocal, and super-refractory status epilepticus
- Movement, gait, and balance disorders
- Psychiatric features
- Autonomic disturbances
- Delirium and catatonia
- Cognitive slowing
- Relapse/recurrence of CNS symptoms after treatment of viral encephalitis
- Involvement of multiple domains, e.g., cognition and extrapyramidal system, etc. ; CSF: Features of inflammation in absence of infection



Differentiation between autoimmune encephalitis (AE) and acute infectious encephalitis.		
Salient features	***Autoimmune encephalitis***	***Infectious encephalitis***
Clinical manifestations	- Seizures, movement disorders, speech abnormalities, sleep problems, and behavioral issues - Fever in 50% - Autonomic dysfunction - Rash is rare	- Fever, seizures, and altered sensorium. Most cases have fever. - Rash may be present in VZV and HSV encephalitis.
CSF	Mild CSF pleocytosis	Marked CSF pleocytosis
MRI brain	- MRI may be normal (50–66%), especially early in the course. - Basal ganglia often involved - Lateral temporal lobes and insula less commonly involved.	- Mesial temporal lobe involvement is characteristic (HSV) - Lateral temporal lobe and insula may be involved - Basal ganglia usually spared (except JE)

Investigations

- Serum and CSF for anti-NMDA receptor antibody (at IMR)
- Serum and CSF for other autoantibodies (only available at private lab)
- CSF for biochemistry, cytology, oligoclonal band, IgG index
- EEG (background slowing , extreme delta brushes ,epileptic activities)
- MRI brain (abnormal signal at medial temporal lobes, cerebral cortex, cerebellum, brainstem, basal ganglia, contrast enhancement. Maybe normal or non-specific)
- Tumour screening (ultrasound scan for ovarian or testicular teratoma)- ***optional***
  (+ other relevant investigations to rule out the alternative diagnoses as necessary)

Treatment *(Consult Pediatric Neurologist)*

Immunotherapy:

1st line:
IV Methylprednisolone 10mg/kg/dose 8 hourly (up to 1 g daily) for 5 days
followed by oral prednisolone (1-2 mg/kg/day) ±
Intravenous immunoglobulin 2 g/kg over 2-5 days ***and /or*** plasmapheresis

2nd line : Cyclophosphamide, Rituximab → **3rd line :** Tocilizumab

Maintenance therapy:
oral steroids/ monthly pulsed steroids/Azathioprine /Mycophenolate Mofetil

Supportive therapy:
Aimed at managing the seizures, movement disorders, behavioural impairment, sleep issues and psychological support for parents.

Chapter 52:
Status Dystonicus(SD)

Introduction

Definition of SD:

Increasingly frequent and severe or extreme episodes of generalized dystonia /dystonic spasms (sustained involuntary muscle contraction leading to abnormal postures and movement) which requires urgent hospital admission.

- Represents the severe end of a spectrum of worsening dystonia.
- Early recognition of deterioration and timely intervention likely to improve outcomes.
- It is a **medical emergency** with high morbidity and mortality but often under-diagnosed.

Early Recognizing signs:

- Fever
- Tachycardia
- Respiratory status change
- Hypertension
- Profuse sweating
- Autonomic instability
- Elevated serum CK

Triggering factors

- Intercurrent illness or infection
- Pain from any source
  - GI (gastro-oesophageal reflux, constipation)
  - Dental (ulcers, caries)
  - Orthopaedic (dislocated hip, fractures)
- Trauma
- Surgical procedures or anaesthetics stressors
- Medications (weaning off or introduction of new medications such as haloperidol, metoclopromide)

Complications of Status Dystonicus

- Severe pain
- Hyperpyrexia
- Exhaustion from sleep deprivation and exertion
- Dehydration with electrolyte disturbance from excess sweating
- Rhabdomyolysis leading to myoglobinaemia and raised creatine kinase
- Acute renal failure
- Bulbar dysfunction with risk of pulmonary aspiration
- Respiratory failure and death

Biochemical derangements:

- Electrolyte imbalance (hypocalcemia, hyperkalemia)
- Acid-base disturbance
- Elevated creatinine phosphokinase (usually > 1000 IU/L)
- Myoglobinaemia/ Myoglobinuria

Differential diagnosis:

- Neuroleptic malignant syndrome
- Serotonin syndrome
- Malignant hyperthermia
- Paroxysmal sympathetic hyperactivity

Management:

Categorize the stage - Risk categorization

Dystonia Severity Action Plan (DSAP): Staging the severity of worsening dystonia		
Grade	**Description**	**Suggested Action**
1	Sits comfortably (1-2 hours), regular sleep (at least 6 hours uninterrupted), stable on medication	No assessment or change in medications required
2	Irritable and cannot settle Posturing interferes with seating activity Cannot tolerate sitting down despite baseline medication	Assessment (within days) Adjust medication or dystonia plan
3	Cannot tolerate lying down Sleep disturbed No signs of metabolic disturbance or airway compromise	Urgent assessment Exclude metabolic decompensation Escalate management +/- hospital admission
4*	**Clinically as in Stage 3, but with metabolic disturbances: fever, dehydration, abnormal electrolytes, creatine kinase > 1000 IU/L, myoglobinuria.**	**Consider PHDW admission Please refer to management guidelines below**
5*	**Severe generalized dystonia. As per stage 4 with full metabolic decompensation or respiratory-cardiovascular compromise requiring organ support.**	**PHDW/PICU admission**

Stage 4 and 5 constitute status dystonicus*

A. Manage triggering factors- e.g: infection, GERD, constipation, etc
B. Supportive care
   - Airway- intubation and ventilation as needed in those with cardiorespiratory compromise
   - Hydration and feeding- additional IV fluids especially in rhabdomyolysis, feeding via nasogastric or nasojejunal tubes (maintain good urine output)
   - Monitoring- urine output, vital signs, sleep wake charting, biochemical investigations (urea, creatinine, electrolytes, CK, myoglobinuria, etc).
   - Avoid unnecessary procedures that may cause pain
   - Adequate analgesia for pain
   - Comfort- appropriate positioning and handling, reduce environmental stimuli, address emotional and psychological contributing factors
   - Ensure adequate sleep (sleep is known to relieve dystonia): melatonin, chloral hydrate, benzodiazepines
   - Others: inotropes, dialysis, temperature control (antipyretics/cooling blankets required)
C. Dystonia specific Management (consider referral to paediatric neurologist)

Sedatives and /or muscle relaxants /anti-dystonic agents may be used alone / combination.

- Regular syrup chloral hydrate (10-50mg/kg/dose, 4-6 hourly)
  Maximum dose: 2g/dose and not exceeding 200mg/kg/day
- Oral, buccal, infusion IV midazolam (low dose 0.1-0.5 mcg/kg/min) and titrated accordingly (or oral / rectal diazepam)
- Oral baclofen (2.5mg bd – 5mg tds starting dose)
  Maximum dose: 40mg/day (<7 years old) or 60mg/day (>8 years old)
- Oral benzhexol (0.5mg daily/bd/tds starting dose) and increase gradually
  Maximum dose: 2mg/kg/day or 40mg/day
- Clonidine enteral (age 2-17yrs old - 0.5–1.5 / 2 microgram/kg) and can be given 3-8 hourly
- Levodopa – considered in cases of dystonia of unknown cause
- IM botulinum toxin injection – considered for **severe focal dystonia only**
- Oral gabapentin* (10 mg/kg daily starting dose and increase)
  Maximum dose: 60mg/kg/day and not exceeding 2.4g /day
  * Gabapentin can be used for SD when associated with **pain/dystonic spasms**

<u>Extreme care</u> should be taken to monitor children when using combinations of drugs with sedating properties.

Indications for paralysis and intubation include:

- Airway compromise / respiratory failure
- Refractory status dystonicus
- Severe metabolic compromise e.g. renal failure requiring haemodialysis

Supportive Management

- Treat any known triggers (eg Infection, GERD, constipation)
- Address any emotional and psychological contributing factors
- Appropriate positioning, minimal handling, & reduce environmental stimuli

Management Flow chart (DSAP stg 4 /5)
Monitor respiratory and renal function fever, pH, CK
myoglobinuria
Treat underlying cause/trigger: Antibiotics,
Immunotherapy , metabolic disturbance\Pain control
Should consider
endotracheal intubation
Regular neurological assessment performed during
Therapeutic window
Oral anti-dystonia medications
Resolution
YES
NO
IV midazolam infusion
Resolution ?
YES
NO
+iv ketamine +optimise (A)
Resolution?
YES
NO
Review and fine tune the above
steps + focus on aetiology +
consider paralysing agents + discuss
with Paediatric Neurologist
A
Baclofen
Trihexyphenidyl
Clonazepam
Clonidine (oral or
IV)
Or combination
Discharge with same oral doses
and review

Chapter 53:
Acquired Demyelinating Syndromes (ADS)

Introduction

These disorders consist of monophasic and polyphasic (recurrent) diseases with acquired immune/antibody mediated injury to the white matter in the central nervous system, optic nerve or spinal cord

Monophasic Acquired Demyelinating Syndromes

Optic neuritis

- Acute visual loss (unilateral/bilateral), central scotoma or reduced visual fields, impaired colour vision often accompanied by painful eye movement.
- Relative afferent pupillary defect (RAPD +ve) and optic disc swelling may be present.
- MRI may show optic nerve swelling +/- optic nerve sheet inflammation.
- Visual evoked potentials (VEP) will reveal evidence of pre-chiasmatic optic pathway abnormalities and optical coherence tomography (OCT) may be abnormal due to axonal nerve damage.

Acute transverse myelitis

- Acute onset of motor and sensory deficits, often bilateral and include a sensory level with bowel and bladder dysfunction.
- Maximal deficits occur between 4 hours - 21 days after symptom onset.
- MRI may demonstrate swelling +/- abnormal signal with contrast enhancement of the spinal cord.

Acute Disseminated Encephalomyelitis (ADEM)

- Acute onset of encephalopathy (behavioural change or altered consciousness) with multifocal neurological deficits/signs
  i.e. limb weakness, numbness, cerebellar ataxia, cranial nerve palsy speech, impairment, visual loss, seizures and spinal cord involvement.
- MRI will show multiple areas of abnormal signal intensities in the white matter.
- No other aetiologies can explain the clinical presentation and neuroimaging findings.

ADEM: Common Differential Diagnoses
• CNS infection – Bacterial, tuberculous meningitis, viral encephalitis • Viral Associated Encephalopathies • Autoimmune Encephalitis • Guillain-Barre syndrome/ Bickerstaff Brainstem Encephalitis • Acute stroke / CNS Vasculitis • Mitochondrial disorders • CNS Haemophagocytic Lymphohistiocytosis (HLH) • Primary CNS Lymphoma / Tumours

Other Investigations (as required based on clinical presentation)

- Cerebrospinal fluid - FEME, cultures, oligoclonal bands, IgG Index, viral encephalitis panel/ Herpes PCR, lactate
- Antibodies – serum aquaporin-4 antibody (AQP4-Ab), serum Myelin Oligodendrocyte Glycoprotein (MOG)-Ab
  (CSF AQP4-Ab maybe considered in seronegative cases if clinically suspect NMO)
- Infection screen – Viral encephalitis serology, mycoplasma, etc.
- Vasculitis screen (ESR, C3, C4, ANA).
- Evoked potentials - visual, auditory and somatosensory.

Treatment

Supportive measures

- Vital signs monitoring, maintain blood pressure
- Assisted ventilation for "cerebral / airway protection"
- Anticonvulsants for seizures
- Antibiotics / Acyclovir for CNS infections if febrile, awaiting cultures, PCR result.

Definitive immunotherapy (First line Therapy)

- IV Methylprednisolone 30mg/kg/day (max 1 gm), given daily or in divided doses, for 3 to 5 days.
- Followed by oral Prednisolone 1-2 mg/kg/day (max 60 mg) daily to complete for 2 weeks. (Total duration of high dose steroids)
- Give longer course of oral prednisolone for ADEM, and transverse myelitis with residual deficit: high dose (1-2 mg/kg/day) for 3-4 weeks, then to taper the dose gradually over another 2-4 weeks).
- If no response consider:
  - IV Immunoglobulins 2 gm/kg over 2 - 5 days and/or referral to a paediatric neurologist.
  - Therapeutic plasma exchange (TPE)
    (referral to paediatric neurologist should be considered in case of poor response to steroids)

Second line therapy (in consultation with a Neurologist)

- Rituximab, Azathioprine, MMF

Relapsing/Multiphasic Acquired Demyelinating Disorders

- These rare disorders present with chronic relapsing and remitting demyelination of the central nervous system.
- The most common of these are Myelin Oligodendrocyte Glycoprotein Antibody Associated Disorders (MOGAD). Neuromyelitis Optica Spectrum Disorder (NMSOD) and Multiple Sclerosis occur less commonly in the paediatric age group.
- An early neurologist consult is recommended for any relapsing ADS as timely and appropriate treatment of these conditions is essential in improving long-term outcome.

Chapter 54:
Acute Flaccid Paralysis

Introduction

Acute Flaccid Paralysis (AFP) occurs when there is rapid evolution of motor weakness (< than 4 days), with a loss of tone in the paralysed limb. This excludes weakness due to trauma and spastic paralysis.

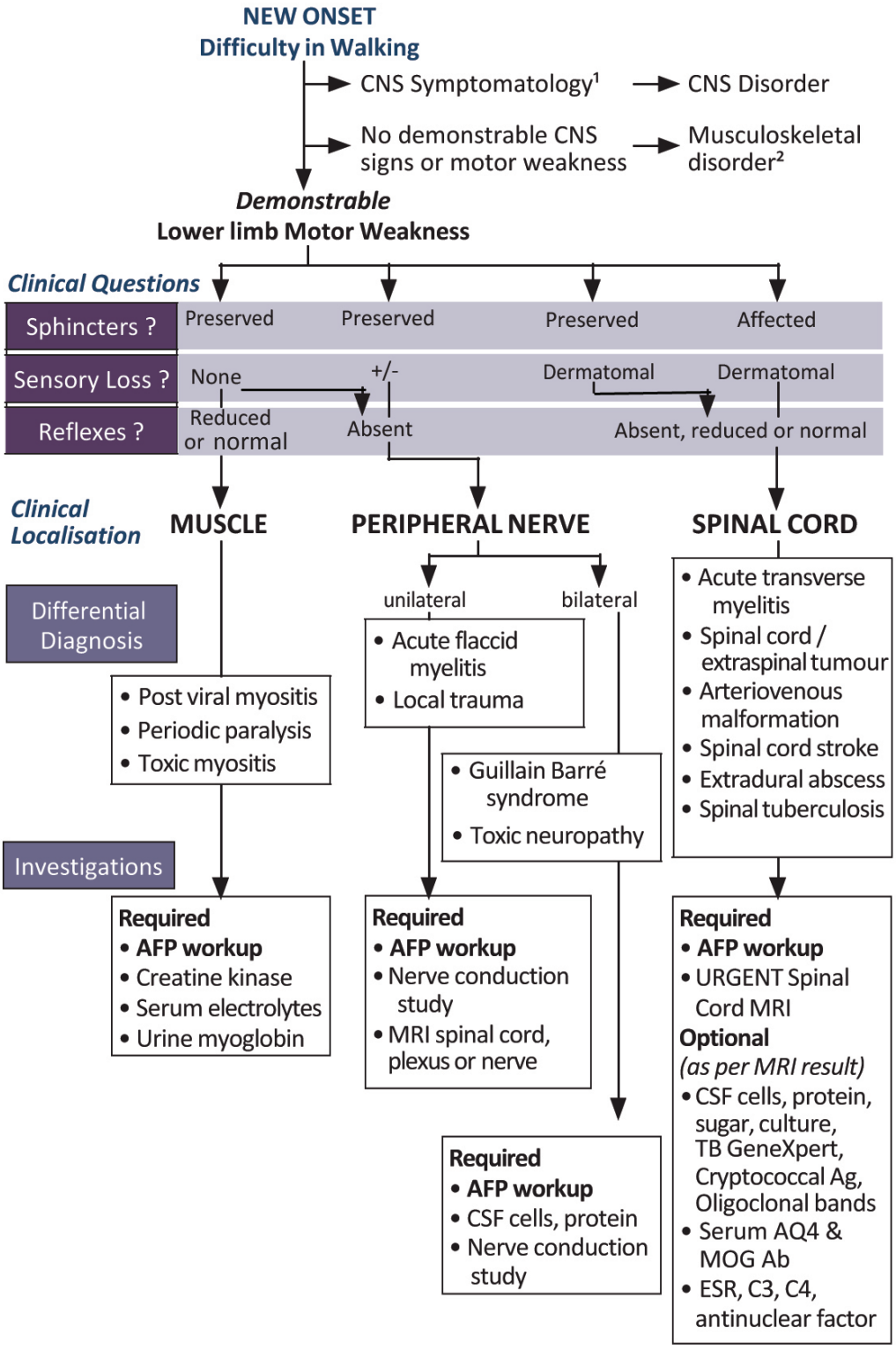
AFP is a ***medical emergency*** as unnecessary delays can result in death and disability. Children with AFP need to be assessed and managed carefully. A simple algorithm is provided on the next page.

AFP surveillance in children

- Collection of stools for enterovirus in children with AFP is an important part of the Global Polio Eradication Initiative (GPEI).
- For Malaysia to remain a polio-free country we need to prove that none of our cases of AFP are caused by poliovirus infection. To do this we have to report all cases of AFP aged < 15 years, send stools for enterovirus isolation using a standardised protocol, and follow up children with AFP to determine the outcome.

Protocol for AFP surveillance in Malaysia		
Step	**Timing**	**Description**
Case Detection	At diagnosis	• Follow case definition for AFP
Case Reporting	Within 24 hours	• Inform and fax the completed AFP case investigation form to regional health officer / health inspector according to local protocol
Timing of stool specimens	Within 2 weeks of onset of paralysis	• 2 stool specimens collected no less than 24 hours apart
Collection of specimens		• Fresh stool. Avoid rectal swabs. (at least 8g – size of an adult thumb). • Place in a sterile glass bottle.
Transport of stools	As soon as able	• Maintain a cold chain of 2 - 8°C. Transport in frozen ice packs or dry ice. • Ensure stool specimens arrive at IMR within 72 hours of stool collection. • Caution: avoid desiccation, leakage; • Ensure adequate documentation and use AFP Case Laboratory Request Form
Follow up of patients	60 days from paralysis	• To determine whether there is residual paralysis on follow up • To send a second case investigation form with follow-up findings and final diagnosis

CLINICAL APPROACH TO A CHIILD WITH ACUTE FLACCID PARALYSIS



Notes: 1. Headache, vomiting, seizures, encephalopathy, cranial nerve deficits, ataxia, brisk tendon reflexes, upgoing plantar response.
2. Soft tissue, joint or bony causes of walking difficulty.

Guillain Barré Syndrome

Introduction

Guillain Barré syndrome (GBS) is a post-infectious inflammatory disorder affecting the peripheral nerves.

Clinical Pearls on GBS in Children

- Rapidly progressive, bilateral and relatively symmetric weakness of the limbs with decrease or absent reflexes. In atypical cases, weakness may begin in the face or upper limbs, or asymmetrical at onset.
- Sensory symptoms, e.g. limb pain and hyperesthesia, are common.
- Bladder and bowel involvement may occasionally be seen, but is never present at onset and never persistent.
  (if so, think of spinal cord disorder)
- CSF protein level and nerve conduction studies may be normal in the first week of illness.
- GBS variants and overlapping syndrome:
  - Miller Fisher syndrome - cranial nerve variant characterised by opthalmoplegia, ataxia and areflexia.
  - Bickerstaff's brainstem encephalitis - acute encephalopathy with cranial and peripheral nerve involvement.

Management

The principle of management is to establish the diagnosis and anticipate / pre-empt major complications.

- *A Clinical* diagnosis can be made by a history of progressive, ascending weakness (< 4 weeks) with areflexia, and an elevated CSF protein level and normal cell count ("protein-cellular dissociation").
- Nerve conduction study is *Confirmatory.*

Initial measures

- Give oxygen, keep NBM if breathless. Monitor PEFR regularly
- Admit for PICU / PHDW care, if having:
  - Respiratory compromise (deteriorating PERF).
  - Rapidly progressive tetraparesis with loss of head control.
  - Bulbar palsy.
  - Autonomic and cardiovascular instability.
- Provide respiratory support early with BiPAP or mechanical ventilation

Hughes Functional Scale for GBS	
0	Normal
1	Minor symptoms, capable of running
2	Able to walk up to 10 meters without assistance but unable to run
3	Able to walk 10 meters with assistance of one person, or a walker
4	Unable to walk
5	Requires assisted ventilation

Specific measures

- IV Immunoglobulins (IVIG) 2 gm /kg total over 2 - 5 days in the first 2 weeks of illness, with Hughes function scale 3 and above or rapidly deterioration
- IVIG is as efficacious as Plasma exchange in both children and adults, and is safer and technically simpler.
- 10 % of children with GBS may suffer a relapse of symptoms in the first weeks after improvement from IVIG. These children, may benefit from a second dose of IVIG.

General measures

- Prophylaxis for deep vein thrombosis should be considered for patients ventilated for GBS, especially if recovery is slow.
- Liberal pain relief, with either paracetamol, NSAIDs, gabapentin or opiates.

Important:

If patient shows disease progression or no improvement after IVIG treatment, to refer to paediatric neurologist for further evaluation

Chapter 55:
Approach To The Child With Altered Consciousness

Introduction

Definition: Altered consciousness is any measure of arousal other than normal. There is a wide range of presentation that includes *lethargy, confusion, somnolence, obtundation, stupor and coma*. This is considered an **acute neurological emergency** characterised by significant brain impairment, necessitating a rapid and methodical approach to evaluation and treatment.

Aetiology

Table 1: Differential Diagnosis of Altered Consciousness in Children	
Traumatic Cause	
Accidental and Non-Accidental Injury	
Non-Traumatic Causes	
Hypoxia-Ischemia: Cardiac/respiratory arrest, ALTE, Severe hypotension. **Infection:** Sepsis, Bacterial meningitis, Viral encephalitis/meningo-encephalitis, Cerebral abscess, Shunt infection, Cerebral malaria **Inflammation/ Demyelination:** Acute disseminated encephalomyelitis (ADEM), Acute necrotizing encephalopathy of childhood (ANE), Para/post-infectious encephalopathy **Seizures:** Subtle motor status epilepticus (SE), Non-convulsive status epilepticus (NCSE), Post-ictal state	**Metabolic:** Diabetic ketoacidosis, IEM crises (hyperammonaemia), Hypoglycaemia, Renal failure (uraemia), Hypo/hypernatremia **Vascular:** Hypertensive encephalopathy, stroke/ central venous thrombosis/infarction, Intracerebral haemorrhage (from aneurysm or AVM) **Toxic:** Acute poisoning, drug ingestion **Hydrocephalus:** CNS infection complication, CNS tumour.

APPROACH

Initial Assessment

Check ABCD – Airway, Breathing, Circulation, check capillary glucose.
Monitor HR, BP, respiratory Rate, SpO_2, urine output.

- Consider intubation if airway compromised.
- Give O_2 if SpO_2<95%.
- IV fluid boluses 10ml/kg if signs of shock.
- Correct hypoglycaemia if capillary glucose <3mmol/L.

Determination of Conscious Level

Use AVPU (A=alert, V=response to verbal, P=response to pain, U= unresponsive) or Glasgow Coma Scale (GCS) modified for children.

- Consider intubation if no response to Pain, or GCS≤8 and not improving.
- If GCS < 12 monitor ¼ hourly till improves.
- If GCS ≥12 monitor hourly.

Table 2: Modified Glasgow Coma Scale (GCS) for Infant and Children			
Area Assessed	**Infant**	**Children**	**Score**
Eye Opening	Open spontaneously	Open spontaneously	4
	Open in response to verbal stimuli	Open in response to verbal stimuli	3
	Open in response to pain only	Open in response to pain only	2
	No response	No response	1
Verbal Response	Coos and babbles	Oriented, appropriate	5
	Irritable cries	Confused	4
	Cries in response to pain	Inappropriate words	3
	Moans in response to pain	Incomprehensible words or nonspecific sounds	2
	No response	No response	1
Motor Response	Moves spontaneously and purposefully	Obeys commands	6
	Withdraws to touch	Localizes painful stimulus	5
	Withdraws in response to pain	Withdraws in response to pain	4
	Responds to pain with decorticate posturing (abnormal flexion)	Responds to pain with decorticate posturing (abnormal flexion)	3
	Responds to pain with decerebrate posturing (abnormal extension)	Responds to pain with decerebrate posturing (abnormal extension)	2
	No response	No response	1

Recognition of Increased Intracranial Pressure (ICP) and Other Indications for Intubation.

Increased ICP is likely if clinically has **papilloedema** (may not be seen in hyperacute increased ICP), or if 2 of the following (**signs of brain herniation**):

1. GCS < 8, or deteriorating GCS
2. Non-reactive, unequal pupils
3. Abnormal doll's eye reflex
4. Decorticate, decerebrate posturing
5. Abnormal breathing - Cheyne-Stokes, hyperventilation or irregular/gasping breathing.

In infants, check for tense fontanelle. Papilloedema is rare in infants.
The presence of increased ICP or signs of brain herniation necessitates intubation.

Other consideration for intubation:

- Airway compromised by obstruction or vomiting.
- Poor respiratory effort.
- SpO_2<92% despite high flow O_2
- Signs of shock persist after 40ml/kg of fluid boluses

Assessment for Underlying Aetiology

Pertinent history: Vomiting, headache, fever, convulsions, alternating periods of consciousness, trauma, ingestion of medications, presence of any medications in the child 's home, any infant deaths in the family, duration of symptoms.

Table 3 : Recommended Investigation

Core Investigation	Other Investigation
Blood gas RBS FBC, BUSE, LFT Plasma lactate Plasma ammonia (toxic if>150 umol/l) Blood culture Urinalysis (dipstick at bedside) 10 ml of urine to be saved for later analysis	*May be needed when initial investigations are unyielding:* Serum calcium and magnesium (if seizures), IEM screening Viral screening e.g. herpes, influenza, coronavirus Vasculitis screen BFMP Toxicology screen EEG if suspected non convulsive seizures.
Neuroimaging	**Lumbar Puncture**
Urgent CT brain if increased ICP, or suspected brain abscess or cause is unknown. MRI is recommended within 48 hours if diagnosis remain uncertain.	Delay until child more stable with no increased ICP, shock or seizures.

Management

Treat the concurrent condition and underlying causes e.g. shock, sepsis, seizures, hypoglycaemia, electrolyte imbalance.

Managing Raised Intracranial Pressure

General measures: Nursing Position head in the midline. Elevate head of bed up to 15-30^{o}. Avoid unnecessary suction and procedures. Avoid hyper or hypothermia. Avoid internal jugular central venous line. Adequate sedation and analgesia. Do not lower high BP unless hypertensive crisis or in acute glomerulonephritis.

Ventilation: Maintain good oxygenation, normocapnia ($PaCO_2$ 35 - 40 mmHg). Avoid excessively high PEEP.

Fluid and electrolyte: Keep patient well hydrated. Avoid hypo-osmolar fluid or plain dextrose solutions. Monitor serum sodium and respond accordingly:

- ↓sodium, ↓urine output: Consider SIADH →fluid restriction.
- ↓sodium, ↑urine output: Consider cerebral salt wasting → replace renal sodium loss.
- ↑sodium, polyuria (> 5ml/kg/h): likely central diabetes insipidus → Fluid replacement and consider desmopressin.

Hyperosmolar therapy Consider IV mannitol or hypertonic saline.

- IV Mannitol 0.25 - 0.5 g/kg. May repeat after 2-6 hour. Avoid prolonged use > 72 hours.
- Hypertonic saline (3% NaCl) 5-10 ml/kg. May repeat 2 ml/kg after 2-6 hours or infusion at 0.1-1.0 ml/kg/hr. Recommended in hypotension but avoid in severe hyponatraemia.

Both agents can be used concurrently but keep serum osmolality < 320 mmol/L.

Surgical decompression: When medical measures fail, surgical decompression may be indicated such as external ventricular drainage or decompressive hemicraniectomy.

Chapter 56:
Childhood Stroke

Introduction

- The overall incidence of stroke in children is estimated 2.5-13 per 100,000 children / year.
- Ischaemic stroke, including arterial ischaemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) is increasingly diagnosed in children.

Arterial Ischaemic Stroke (AIS)

- Incidence: 1 in 3,500 live births; 0.5-2 per 100,000/year for childhood stroke
- Recurrence occurs in 12-20% of childhood AIS

Definition of AIS

1. Acute onset (may be evolving) of focal ± diffuse neurological disturbance and persistent for 24 hours or more, **AND**
2. Neuro-imaging showing focal ischaemic infarct in an arterial territory and of maturity consistent with the clinical features

Clinical features

- Typically sudden, maximal at onset (but may be evolving, waxing & waning)
- Focal deficits: commonest - motor deficits (hemiparesis), sensory deficits, speech / bulbar disturbance, visual disturbance, unsteadiness
- Diffuse neurological disturbance: altered consciousness, headache
- Seizures
- Other non-specific features in neonatal stroke including apnoea, feeding difficulty, abnormal tone

Risk Factors for Paediatric AIS:

Cardiogenic
Congenital & acquired heart diseases, cardiac procedure, arrhythmia

Arteriopathy
- Dissection
- Moyamoya disease or syndrome (Down, NF1 etc)
- Post-varicella arteriopathy / focal cerebral arteriopathy of childhood
- Vasculitis:
  Childhood primary angiitis of CNS
  Secondary vasculitis
  (Infective vasculitis, SLE, Takayasu)

Prothrombotic disorders
- Inherited thrombophilia
- Acquired thrombophilia: Nephrotic syndrome, malignancy, L-Asparaginase, anti-phospholipid syndrome

Acute disorders
- Head and neck disorder: Trauma, infection - meningitis
- Systemic disorders:
  Sepsis, asphyxia, shock

Chronic disorders
- Iron deficiency anaemia
- Haemoglobinopathy (sickle cell)
- Connective tissue diseases (Marfan, Ehlers Danlos)
- Monogenetic disorders:
  DADA2, ACTA2, COL4A1 etc.
- Metabolic disorders: Homocystinuria, dyslipidaemia, *stroke mimickers* such as mitochondrial cytopathy (MELAS, POLG1)

Investigations

- Laboratory workup:
  - Basic tests: FBC / FBP, renal profile, LFT, RBS, lipid profile, iron study
  - Thrombophilia screen: PT/PTT/INR, protein C, protein S, anti-thrombin III, factor V Leiden, lupus anti-coagulant, anti-cardiolipin, serum homocysteine level
    -Further tests may include lipoprotein A, prothrombin gene mutation, ADAMTS13 gene (if suspected thrombotic thrombocytopaenic purpura)
    -If perinatal / neonatal stroke: consider maternal thrombophilia screening (lupus anti-coagulant, anti-cardiolipin)
  - Vasculitis workup (if indicated): C3, C4, CRP, ESR, ANA, p-ANCA, c-ANCA
    -Consider further tests : dsDNA, ENA, autoinflammatory syndromes genetic panel
  - Others: lactate & VBG for MELAS, CSF sampling (if suspected CNS infection or inflammation), infective screening (HSV 1&2, VZV serology & CSF DNA PCR)
- Cardiac assessment : ECG (± Holter) & Echocardiogram (± bubble study)
- Neuro-imaging: (consult radiologist)
  - Goals – to ascertain any infarction, haemorrhages, evidence of clots / vasculopathy and to exclude stroke-mimics
  - Both brain parenchymal and head + neck arterial imaging (ideally from the arch of aorta) should be performed.
  - MRI brain + MRA - the ideal modality; If MRI cannot be readily or safely performed, then to do urgent CT brain ± CTA.

Brain parenchymal imaging	Head + neck arterial imaging
Cranial ultrasound If fontanelle still patent Quick, no radiation but limited information	***Carotid artery ultrasound Doppler*** May be useful in carotid arteriopathy (dissection or stenosis)
CT scan Quick, sensitive for haemorrhages but may miss early, small and posterior fossa infarction	***CT Angiogram*** May be included during the urgent CT brain or considered in certain cases (eg: inconclusive / indeterminate finding in MRA, posterior circulation stroke) but risk of contrast and radiation
MRI scan *(include DWI+ADC, GE / SWI / haemoflash)* Good parenchymal details and sensitive for early infarction	***MR Angiogram (MRA)*** No radiation but susceptible to flow dropout artefact

Digital Subtraction Angiogram: to consider if inconclusive / indeterminate finding in MRA/CTA, suspected vascular malformation or disease of small vessels, as endovascular therapy or presurgical workup for moyamoya but risk of radiation, contrast and stroke

MR vessel wall imaging: useful to further delineate the aetiology of arteriopathy (e.g.: dissection, inflammatory vs non-inflammatory arteriopathy)

Management

- General care
  - Resuscitation: Airway, Breathing , Circulation
  - Admit to ICU if indicated for close vital signs and GCS monitoring (post-infarction cerebral oedema may worsen 2-4 days after acute stroke)
  - Workup for the underlying risk factor(s) and treat accordingly
- Acute neuro-protective care:
  - General measures of ICP control
  - Maintain normothermia, normoglycemia, normovolemia, good BP (50^{th}-95^{th} centile), adequate oxygenation and acceptable CO_2
  - Monitor fluid & acid-base balance and treat seizures aggressively
- Decompressive surgery: to consider in malignant MCA infarction or large cerebellar infarction
- Acute Anti-thrombotic therapy:
  - Consult paediatric neurologist (and haematologist if available) for the necessity, choice and monitoring of anti-thrombotic therapy. If stroke due to cardiac disease/procedure/operation, should also consult cardiologist and/or cardio-thoracic surgeon.
  - If no contraindications (see below), anti-thrombotic is generally advised to prevent recurrence (except neonatal AIS). During the initial stage, to consider aspirin or anti-coagulation therapy (ACT) - either UFH or LMWH ACT is preferred in stroke due to cardiac or thrombophilic causes.
- Recanalization therapy: (thrombolytics and endovascular thrombectomy)
  - Not readily available in the local setting yet, may be helpful in certain paediatric patients who fulfill stringent criteria
- Secondary preventive therapy:
  - Aspirin : initially 3-5mg/kg/day (max 300mg), reduced to 1mg/kg/day (max 75mg) after 14 days of stroke onset or if having side effects

Duration: at least 2 years but may be longer (case by case basis). Caution with long-term aspirin. (See below)

  - Alternatively, LMWH or warfarin may be preferred in the presence of intracardiac clots, major cardiac disease, severe prothrombotic disorders and extra-cranial dissection (controversial)
- Other therapies: revascularization surgery in Moyamoya, immunotherapy in CNS vasculitis etc

Possible contraindications of anti-thrombotic therapy
Infarction associated with significant hemorrhage
Large infarction with the worry of secondary haemorrhagic transformation
Uncontrolled hypertension
Pre-existing bleeding tendency or any risk of significant bleeding
Caution with Aspirin
Reye syndrome has been linked to use of aspirin during febrile illness
Reduce aspirin by 50% during fever > 38°C
Withhold for 3-5 days if suspected/confirmed varicella / influenza infection

Childhood Cerebral Sino-venous Thrombosis (CSVT)

Introduction

- 20-30% of childhood stroke caused by CSVT
- 30-40 % of CSVT leading to venous infarction (parenchymal involvement)
- More than 50% of venous infarction (parenchymal involvement) associated with haemorrhage
- Consider CSVT if the infarction (parenchymal involvement) corresponding to cerebral sino-venous drainage territory or infarction (parenchymal involvement) with haemorrhagic component not following arterial territory and not caused by cerebral vascular malformation

Clinical features *(Typically sub-acute)*

- Diffuse neurological disturbance:
- Headache, seizures, altered sensorium, features of increased intracranial pressure (papilloedema, 6th cranial nerves palsy)
- Focal deficits if venous infarction (parenchymal involvement)

Risk factors

- Prothrombotic conditions (Inherited, L-asparaginase, nephrotic syndrome)
- Acute disorders (Head & neck trauma / infection, dehydration, sepsis)
- Chronic disorders (SLE, thyrotoxicosis, iron deficiency anaemia, malignancy)

Laboratory workup

- Basic tests : FBC / FBP, renal profile, LFT, iron study, thyroid function test
- Thrombophilia screen (as in the AIS guideline)
- Others depending on the possible risk factor(s)

Neuro-imaging

- Brain parenchymal imaging (as in the AIS guideline)
- Cerebral Venogram
  - MR Venogram-TOF (time-of-flight): susceptible to flow dropout artefact
  - CT Venogram: may be better than MRV-TOF, but risk of contrast and radiation

Management

- General care and acute neuro-protective care (as in the AIS guideline)
- Consult Paediatric neurologist for the anti-coagulation therapy (ACT)
- ACT : generally required unless otherwise contraindicated
- Consult neuro-surgery if infarction (parenchymal involvement) associated with haemorrhage

Chapter 57:
Infection-Triggered Encephalopathy Syndromes

Definition:

Acute onset of impaired consciousness ± seizures, usually during the febrile period or after an antecedent infection.
Not due to direct CNS infection, toxic or metabolic disturbance and demyelinating process (ADEM).

Postulated pathophysiology:

1. "Cytokine storm" eg : IL-1β, IL-6 and TNF-α, resulting in neuronal injury
2. Neuronal excitotoxicity and prolonged or repetitive seizures, inducing a cyclical cascade of inflammation
3. Genetic susceptibility & characteristic of the developing brain

Associated pathogens : Influenza virus (most common), HHV6, rotavirus, RSV, HHV7, EBV, CMV, Varicella, Dengue virus, SARS-CoV, measles, mumps, mycoplasma etc.

Clinical, laboratory and radiological features:

FIRES (Febrile Infection-Related Epilepsy Syndrome):
- Focal (especially orofacial) or generalised seizures, leading to refractory status epilepticus, preceded by fever 24 hours to 2 weeks prior to onset of status epilepticus.
- EEG characteristically shows clusters of clinical and electrographic seizures, often with hemispheric shifting patterns.
- Neuroimaging mostly normal, CSF may show pleocytosis only.

HHES (Hemiconvulsion Hemiplegia Epilepsy Syndrome - Figure 1):
- Fever and prolonged focal/hemi-convulsive status epilepticus, complicated by hemiplegia & epilepsy (often drug resistant)
- Neuroimaging: cytotoxic oedema on brain MRI in the acute stage and later hemispheric atrophy.
- May have underlying structural (e.g. subtle dysplasia) or genetic (e.g. HNRNPU mutation) abnormalities

ANE (Acute Necrotising Encephalopathy - Figure 2):
- Acute encephalopathy +/- seizures following viral illness (most commonly influenza A), associated with shock and multiple organ injury, and laboratory abnormalities such as elevated liver enzymes, hypoglycemia, and lactic acidosis, suggestive of a systemic inflammatory response.
- Neuroimaging: CT-scan (bilateral thalamic hypodensity), typical "target-like appearance" / "tricolour pattern" in MRI brain
- Most ANE are sporadic. Rarely familial ANE (ANE1) are due to a genetic abnormality (RANBP2)
- Differentials: Japanese encephalitis, Leigh disease, Deep venous thrombosis, biotin / thiamine responsive basal ganglia disease

AESD (Acute Encephalopathy with Biphasic Seizures and Late Reduced Diffusion - Figure 3):

- Acute febrile status (>30 min) and altered sensorium, followed by transient improvement before clusters of 'secondary' seizures between days 3-9 and worsening encephalopathy (not all may have this biphasic pattern)
- Neuroimaging is characteristic, with normal MRI at onset, then symmetric, white matter restricted diffusion (best seen on DWI/ADC) seen during secondary seizure stage

RESLES (Reversible Splenial Lesion Syndrome - Figure 4) also known as Mild Encephalopathy with Reversible Splenial Lesion - MERS

- Self-limiting syndrome characterised by mild encephalopathy +/- seizures following an infection (influenza, rotavirus, HHV6, SARS-CoV etc.); other presentation - delirium, ataxia, headache etc.
- Neuroimaging: characteristic lesion of restricted diffusion over the splenium of the corpus callosum, occasionally involving cerebral white matter; lesion often resolves in 2-6 weeks.
- Usually good outcome

Clinical approach :

When to suspect?

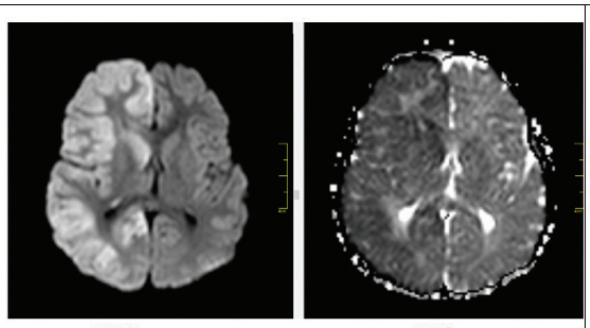
- Any children with encephalopathy ± seizures in the context of febrile illness / infection (either during or at the convalescent phase of the illness)
- Evidence of hepatopathy, coagulopathy or acute systemic inflammatory response
- After excluding CNS infection, metabolic / toxic aetiologies, inflammatory disease (e.g.: multisystem inflammatory syndrome-MISC), autoimmune or acquired demyelinating disorder

Investigations :

- CT brain may be normal (except ANE). Ideally, need MRI brain with DWI/ADC + contrast.
- Blood tests - FBC, LFT, renal profile, coagulation profile, CK, LDH, ferritin, fibrinogen, D-dimer, cytokine profile (if available)
- Infection screen (blood/CSF/nasal swab +/- other viral screen) to look for viral triggers or concomitant infection
- Consider screening for autoimmune encephalitis or systemic autoimmune disorders (e.g. SLE)
- Urgent EEG in selected cases (discuss with paediatric neurologist)

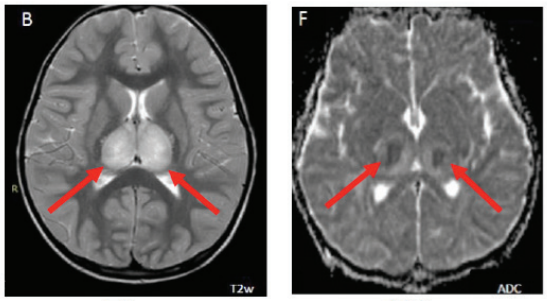
Management :

- Aggressive treatment of seizures and status epilepticus (following guidelines), although iv phenobarbitone tends to be a more effective 2nd line anti-seizure medication.
- Management of encephalopathy - consider early referral to PICU team and appropriate cerebral protection strategies (following guidelines)
- First line immunotherapy (IV methylprednisolone or IVIG) should be commenced as soon as possible, once CNS infection is ruled out or presumptively treated, preferably in consultation with a paediatric neurologist. Recent anecdotal reports - IV tocilizumab may be helpful in ANE / FIRES.



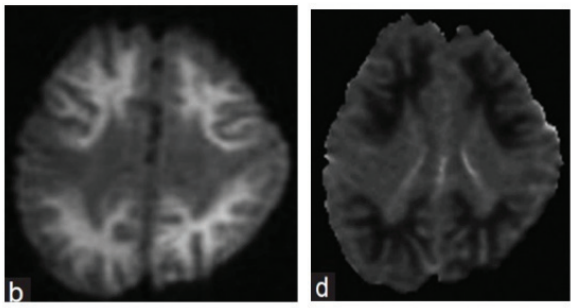
DWI ADC

Figure 1 : HHE (acute)



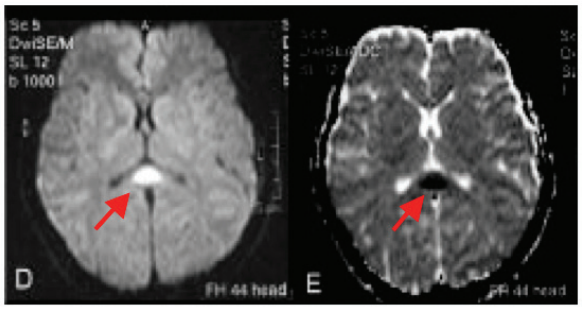
T2 ADC

Figure 2 : ANE



DWI ADC

Figure 3 : AESD



DWI ADC

Figure 4 : RESLES

Section 10

ENDOCRINOLOGY

Chapter 58:
Approach to Short Stature

Short stature can be a sign of disease, disability and social stigma causing psychological stress.

The objective of evaluation of a child with short stature is to determine whether there is a primary growth disorder and identify an underlying chronic disorder (secondary growth disorder) which needs treating.

It is important to have early diagnosis and treatment in order to achieve improved clinical outcomes

Definition:

- Definitions of growth failure:
  - Height below 3rd percentile (-2 standard deviation (SD) for age and gender).
  - Height significantly below genetic potentials (-2 SD or 10 cm below mid-parental target).
  - Abnormally slow growth velocity.
  - Downwardly crossing percentile channels on growth chart (for children above 18 months of age).
- Average height velocity at different phases:
  - Prenatal growth : 1.2 -1.5 cm per week
  - Infancy : 23 - 28 cm per year
  - Childhood : 5 - 6.5 cm per year
  - Puberty : 8.3 cm per year (girls), 9.5 cm per year (boys)
  - Measure serial heights to assess the growth pattern and height velocity.

Indications for Referral to a Paediatrician/Paediatric Endocrinologist

1. Children with intrauterine growth retardation (small for gestational age) who do not catch up to the growth curve by 2 years of age
2. Height more than 3 SD below the mean for age (Height 2 SD below the mean is slightly below 3rd centile on the percentile chart)
3. Growth velocity less than 4 cm per year between age 5 to prepubertal years
4. Projected height more than 2 standard deviations (10 cm) below the midparental height
5. No onset of puberty by 14 years of age for boys or 13 years of age for girls
6. Diagnosis of conditions approved for recombinant growth hormone therapy (see management section)

Initial screening evaluation of growth failure

- General tests:
  - FBC with differentials, renal profile, liver function test, calcium, phosphate, blood gas analysis, ESR, Urinalysis.
- Chromosomal analysis in every short girl, and in boys when chromosomal abnormality is suspected
- Endocrine tests
  - Thyroid function tests.
  - Growth factors: IGF-1 (IGFBP-3 if available)
  - Growth hormone stimulation tests if growth hormone deficiency is strongly suspected. (Refer to a Paediatric Endocrine Centre)

- Imaging studies
  - Bone age: anteroposterior radiograph of left hand and wrist.
  - CT / MRI brain (if hypopituitarism is suspected).
- • Other investigations depends on clinical suspicion.
  - iPTH, Vitamin D
  - LH, FSH, oestradiol or testosterone, 8 am cortisol, prolactin, serum and urine osmolality
  - Radiograph of the spine.
  - Further genetic testing

Differential diagnosis of short stature and growth failure

Healthy but short children
- Familial short stature
- Constitutional growth delay

Intrinsic short stature
- Small for gestational age
- Genetic syndromes
  - Down syndrome
  - Turner syndrome
  - Prader-Willi syndrome
- Skeletal dysplasia
  - Achondroplasia
  - Hypochondroplasia

Systemic diseases
- Infectious: HIV, tuberculosis
- Cardiac disease
- Renal disease
  - Renal tubular acidosis
  - Chronic renal insufficiency
- Gastrointestinal
  - Cystic fibrosis
  - Inflammatory bowel disease
- Central nervous system disease
- Chronic lung disease
- Malignancy

Endocrinopathies
- Hypothyroidism
- Hypopituitarism
  - Heredity, sporadic, idiopathic
- Isolated GH deficiency
  - Birth injury
  - Craniopharyngioma
  - Cranial irradiation
  - Brain tumours
  - Midline defects
  - Haemosiderosis
- GH insensitivity (Laron syndrome)
- Cushing syndrome, exogenous steroids
- Poorly controlled diabetes mellitus
- Precocious puberty
- Pseudohypoparathyroidism
- Pseudo-pseudohypo-parathyroidism

Non-organic aetiology
- Psychosocial deprivation
- Nutritional dwarfing

Abbreviation: *GH, Growth Hormone*

Clinical Approach to children with Short Stature

History

- Antenatal
  - Complications of pregnancy
  - Pre-eclampsia, hypertension
  - Maternal smoking, alcohol
  - Infections
- Birth
  - Gestational age
  - Birth weight and length
  - Mode of delivery (breech, forceps)
  - Apgar score
- Neonatal complications
- Developmental milestones
- Nutrition
  - General well being
  - Appetite, energy, sleep, bowel habits
  - Pattern of growth from birth
- Maternal and child relationship
- Medical history
  - Underlying illness, medications irradiation
- Family History
  - Short stature (3 generations).
  - Age of onset of puberty in family members of the same sex
  - Diseases in the family

Physical Examination

Anthropometry
- Height, weight, head circumference
- Height velocity
- Arm span
- Upper: lower segment Ratio: 1.7 in neonates to slightly <1.0 in adults

- General appearance and behaviour
- Dysmorphism
- Pubertal staging

Family Measurements

Measure height of parents for mid-parental heights (MPH)

Boys : $\frac{\text{Father's height} + (\text{Mother's height} + 13)}{2}$

Girls: $\frac{\text{Mother's height} + (\text{Father's height} - 13)}{2}$

Management

- Treat underlying cause (hypothyroidism, uncontrolled diabetes mellitus, chronic illnesses). Ensure normal nutritional status.
- For children suspected to be GH deficient, refer to Paediatric Endocrinologist for assessment and management of GH deficiency.
- Psychological support
- The Malaysian Clinical Practice Guidelines on The Use of Growth Hormone in Children and Adults (2010) recommend treatment with recombinant human growth hormone for the following conditions:
  - Paediatric GH deficiency
  - Turner syndrome
  - Small for gestational age

GH Treatment

- Subcutaneous GH should be initiated by a Paediatric Endocrinologist.
- GH dose: 0.025 - 0.05 mg/kg/day (0.5 - 1.0 units/kg/wk) SC daily at night.
- GH treatment should start with low doses and be titrated according to clinical response, side effects, and growth factor levels.
- During GH treatment, patients should be monitored at 3-monthly intervals (may be more frequent at initiation and during dose titration) with a clinical assessment (growth parameters, compliance) and an evaluation for adverse effects (e.g. impaired glucose tolerance, carpal tunnel syndrome), IGF-1 level, and other parameters of GH response.
- Other biochemical evaluations:
  - Thyroid function
  - HbA1c
  - Lipid profile
  - Fasting blood glucose
- Continue treatment till child reaches near final height, defined as a height velocity less than 2cm / year over at least 9 months (or bone age more than 13 years in girls and more than 14 years in boys).
- Treat other pituitary hormone deficiencies such as hypothyroidism, hypogonadism, hypocortisolism and diabetes insipidus

Chapter 59:
Congenital hypothyroidism

Introduction

- This chapter is based on recent *Consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism in Malaysia.*[1]
- Congenital hypothyroidism (CH) is the commonest congenital endocrine disorder and also the most preventable cause for mental retardation.
- The incidence of CH is ranging from 1 in 1170 to 3666 live births based on local studies.

Aetiology [2]

- Primary hypothyroidism (most common causes for CH)
  - Thyroid dysgenesis (60 — 70%) — due to thyroid gland development anomaly
  - Athyreosis, hypoplasia, thyroid ectopia, hemiagenesis
- Thyroid dyshormogenesis (30 — 40%) — due to impaired thyroid hormone production
  - Sodium-iodide symporter defect, thyroid peroxidase defects
  - Resistance to TSH binding or signalling
- Central hypothyroidism
  - Isolated thyroid stimulating hormone (TSH) deficiency
  - Part of combined pituitary hormone deficiency
- Peripheral hypothyroidism
  - Resistance to thyroid hormone, abnormalities of thyroid hormone transport
- Syndromic hypothyroidism e.g. Pendred syndrome
  - Transient congenital hypothyroidism

Neonatal screening for congenital hypothyroidism

- CH screening using cord blood has been the practice in Malaysia since its implementation in 2003.[1]
- Primary TSH measurement supplemented by free thyroxine (FT4) is the preferred strategy.
- Interpretation of cord blood TSH levels and subsequent actions are summarised in *Figure 1.*
- The recall should be done after 72 hours of life, usually by day 4 — 6. This is due to postnatal surge in TSH occurs within 30 minutes of life, followed by FT4 that peak at 24 — 36 hours of life, and then a rapid decline to reach a steady state only after 72 hours.
- The recall should include patients whose cord blood TSH was not available, as in home deliveries, babies born before arrival (BBA) and rejected blood samples etc.

Clinical evaluation

- Clinical features suggesting of CH:
  - Sluggishness
  - Constipation
  - Hoarseness of voice
  - Poor weight gain
  - Dry skin
  - Prolonged neonatal jaundice
  - Macroglossia
  - Umbilical hernia
  - Cold extremities
  - Wide posterior fontanelle (normal 0.5 x 0.5cm)
  - Goitre

  *Beware that majority of newborns with CH do not manifest clinical features at birth until 3 — 6 months later.

- Obtain history of risk factors for CH (maternal history of thyroid disease; use of anti-thyroid drug; excessive iodine intake e.g. seaweed; maternal iodine deficiency; parental consanguinity; family history of thyroid disease; prematurity; low birth weight infant; use of iodine antiseptic solutions).
- Other physical examinations include:
  - Growth parameters
  - Dysmorphic features
  - Features of pituitary hormones deficiency (central hypothyroidism)
  - Congenital malformation e.g. facial midline defect (cleft lip, cleft palate, nasal encephalocele), cardiac abnormality particularly atrial and ventricular septal defects, urogenital abnormalities.

Diagnosis [1,3]

- The venous TFT at Day 4-6 is confirmatory in most cases for diagnosis of CH. Please refer to *figure 2* for interpretation and recommendation of actions. For some special categories of babies, please refer to section on **Special Categorie**s.
- FT4 and TSH should not be interpreted in isolation of each other.
- The suggested thresholds of FT4 in the recommendations are based on expert opinion and only to serve as a guide. An elevated TSH is often the primary determinant in deciding treatment for *primary* hypothyroidism.
- In some cases where the results are equivocal, a decision to repeat the test and monitor is a reasonable option after discussion with the parents.

Treatment

- Treatment should be started as soon as diagnosis is made. Treatment initiation within 2 weeks of life had shown restoration to near-normal IQ in moderate and severe CH.
- Levothyroxine (LT4) is the treatment of choice for CH. A brand LT4 rather than a generic formulation is recommended.
- An initial dose of LT4 at 10-15 mcg/kg/day (maximum 50 mcg/day) is recommended, the lowest dose for mild disease and higher dose for severe disease.
  - Mild CH (FT4 > 10 pmol/L) 10 mcg/kg/day
  - Moderate CH (FT4 5–10 pmol/L) 10 mcg/kg/day
  - Severe CH (FT4 <5 pmol/L) 15 mcg/kg/day
  - Subclinical CH 5-10 mcg/kg/day
- LT4 should be administered orally in tablet form. LT4 in suspension or syrup form is not recommended.
- LT4 tablets can be crushed, mixed in small amount of water or milk, and served using a spoon. LT4 should not be served in a milk-bottle.
- LT4 is administered in a single daily dose and at a consistent timing every day to ensure compliance. It is recommended to take the medication in the morning upon awakening for all ages (expert consensus opinion).
- LT4 can be taken before, with or after food. However, intake of soy, iron or calcium supplementation within an hour of LT4 administration should be avoided.

Monitoring of treatment

- Serum FT4 and TSH should be measured before, or at least 4 hours after the last LT4 administration.
- Frequency of TFT monitoring:
  - After initiation of LT4, the first clinical and biochemical follow-up should be 1-2 weeks later. If the initial dose of LT4 is close to 15 mcg/kg/ day or 50 mcg/day, follow-up should be within 1 week of treatment initiation.
  - Subsequent clinical and biochemical evaluation should be every 2 weeks until TSH normalises.
  - Thereafter, the evaluation can be reduced to every 1 to 3 months until the age of 12 months.
  - Between the ages of 1 and 3 years, the frequency of evaluations can be lowered to every 2 to 4 months; thereafter, every 3 to 6 months until growth is completed.
- TSH normalises slower compared to FT4. The aim is to achieve normalisation of FT4 within 2 weeks of treatment, followed by normalisation of TSH within 4 weeks of treatment.
- Serum concentration of TSH should be kept within the age-specific reference range and FT4 in the upper half of the age-specific reference range. Over-suppression of TSH to <0.5 mIU/L should be avoided.
- FT4 and TSH should be interpreted together in deciding adjustment of LT4 dose.
- Evaluations should be performed at more frequent intervals if there is abnormal FT4 or TSH level, or if compliance is questioned.
- After any change in LT4 dose or LT4 formulation, extra follow-up evaluations should be done 4 to 6 weeks later until FT4 and TSH are normalised.
- Monitoring for **long term outcomes** includes:
  - Psychomotor and speech development
  - Hearing test before school age
  - Growth and puberty
  - Compliance to treatment, which is important to future cardiovascular health and pregnancy outcome.

Re-evaluation of thyroid function in congenital hypothyroidism

- All babies treated for CH will need to be re-evaluated to determine if the CH is permanent or transient and to establish a possible aetiology.
- Re-evaluation is done at or after 3 years of age when myelination in the central nervous system is complete.[4]
- At re-evaluation, LT4 is stopped for 4 weeks or phased out over 4-6 weeks. At the end of this period, venous FT4 and TSH are measured:
  - If FT4 & TSH are within the normal reference range — LT4 replacement is discontinued and TFT monitored for the next 6 months. If TFT remains normal after 6 months, the patient can be discharged.
  - If TSH is >10mIU/L — this likely indicates permanent CH. LT4 replacement is resumed, and the patient continues regular follow-up.
  - If TSH is <10 mIU/L, but more than upper limit of reference range and FT4 normal — withhold LT4 treatment for another 3-4 weeks and FT4 & TSH are re-tested. Long term LT4 replacement is indicated if there is structural abnormality of the thyroid gland, or TSH increases to >10 mIU/L, or FT4 falls to below the reference range for age, or there are symptoms and signs of hypothyroidism.
- Early re-evaluation can be done at or after the age of 6 months in a CH child who has been known to have a gland-in-situ (GIS), and requires a low thyroxine dose of less than 3 mcg/kg/day at the age of 6 months, as they are likely to have a transient form of CH.
- Re-evaluation may not be required if venous TSH has been persistently >10 mIU/L after 1 year of age despite thyroxine replacement, as this most likely indicates a permanent form of CH.
- In patient confirmed to have permanent form of CH at re-evaluation, thyroid ultrasonography is useful to determine the presence, location and anatomy of the thyroid gland. However, its accuracy is operator dependent.
- Thyroid scintigraphy may also be considered as it is a more reliable imaging modality to determine the aetiology of CH, especially in thyroid ectopia and certain cases of dyshormonogenesis.

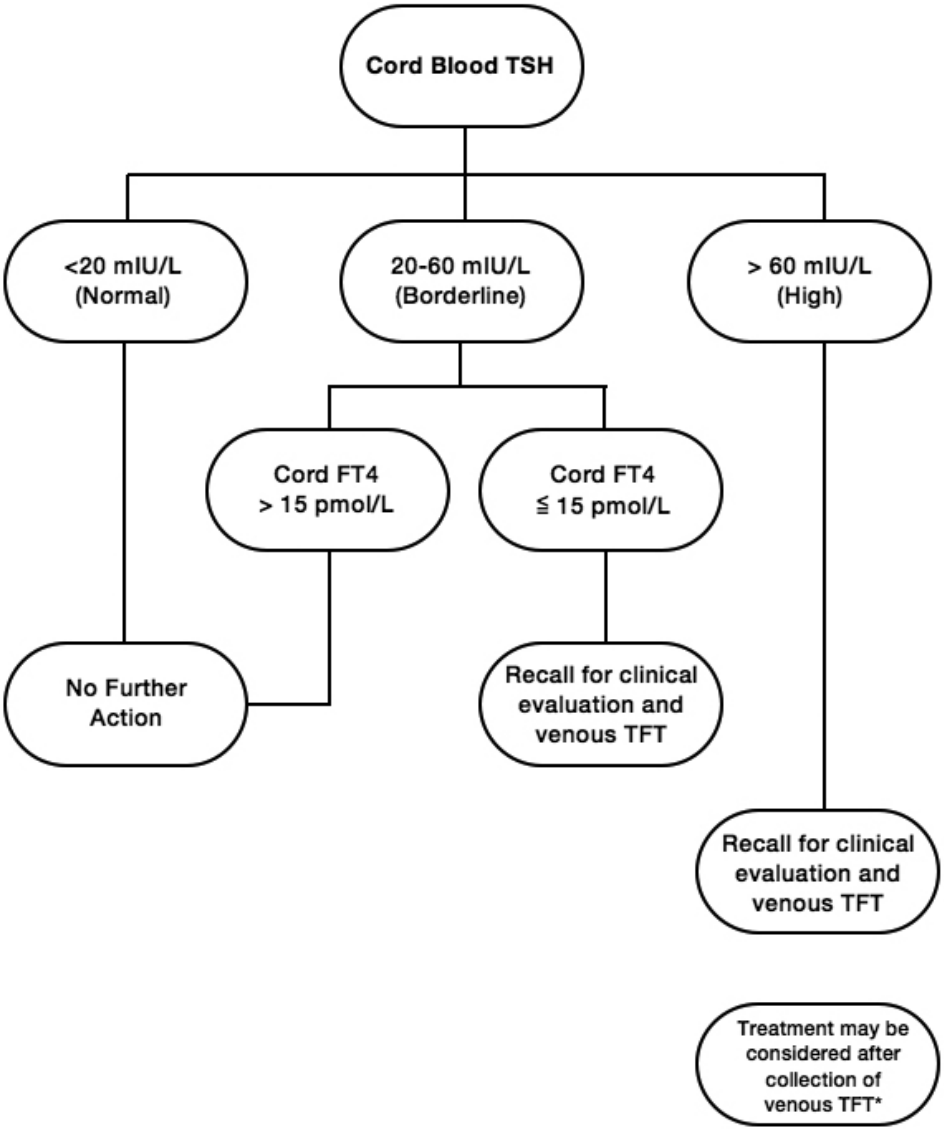
Special considerations

The following groups of neonates are at high risk for later development of congenital hypothyroidism post-screening. Even though they may have a normal screening tests, it is recommended to have their TFT repeated.[1]

- **Sick neonates**
  - Include newborns with perinatal asphyxia, sepsis, those who require respiratory or cardiovascular support, or have undergone major surgical procedures.
  - To repeat at 2 weeks after recovery from acute illness.
- **Preterm infants below 37 weeks gestation / low birth weight below 2.5kg**
  - For late preterms who are not admitted or have a short stay in hospital, TFT should be repeated 2 weeks after initial screening. This may be done as outpatient or at the Maternal and Child Health Clinic (MCHC) nearest to their homes.
  - For those who have prolonged stay in hospital, TFT should be repeated at 2 weekly interval until discharge and 2 weeks post discharge. In hospital with neonatologists or paediatrician, the interval to repeat these tests can be based on the clinical judgement and discretion of attending specialists.
  - LT4 therapy of isolated hypothyroxinaemia without clear elevation of TSH is not recommended.
- **Down syndrome**
  - TFT should be repeated at 3-4 weeks of life, even if the newborn screening result is normal.
- **Multiple births**
  - Re-testing of TFT should be done in monozygotic twins at 14 days of life. Due to mixing of foetal blood, the affected infant may not be detected by the initial newborn screening.

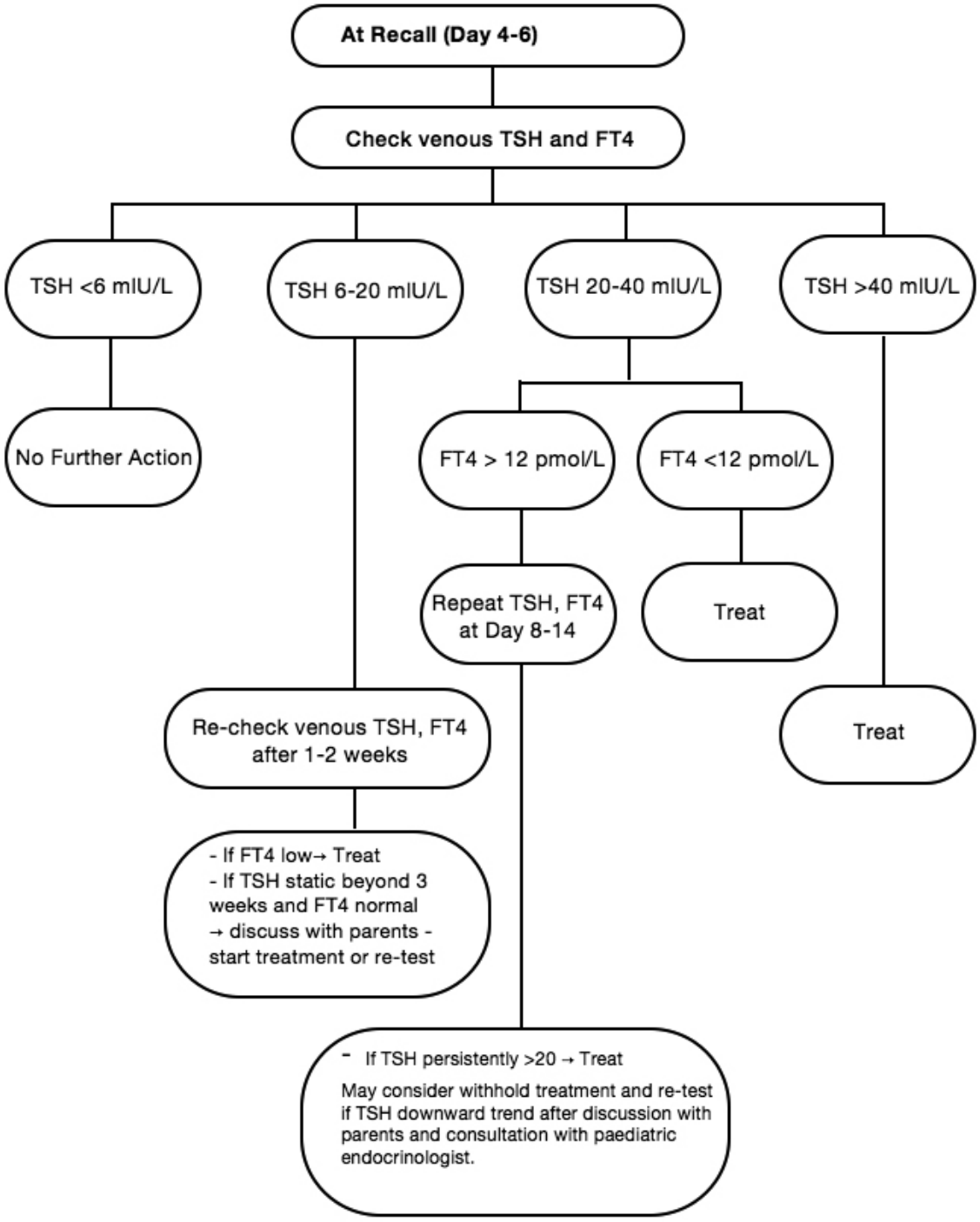
- **Infant of mother with autoimmune thyroid disease (AITD)**
  - TFT to be repeated at day 4 – 6 and at day 10 – 14 of life.
  - As the transplacental maternal autoantibodies persist for 3 — 6 months in the affected babies, newborns treated for CH due to maternal AITD should be monitored for at least 6 months. The dose of LT4 should be titrated against the TFT and tapered accordingly.
- **Congenital central hypothyroidism (CCH)**
  - Our TSH-based neonatal screening for CH will miss CCH where TSH is inappropriately low with a low FT4. CCH is much rarer compared to congenital primary hypothyroidism, but delayed diagnosis and treatment will result in severe consequences as well. Besides, majority of CCH (74-84%) is also associated with multiple pituitary hormone deficiencies.
  - Newborns with the following features are at risk of CCH:
    - Facial mid-line defect e.g. cleft palate or cleft lip, nasal encephalocoele
    - Symptoms and signs of pituitary hormones deficiency in a neonate e.g. intractable hypoglycaemia, prolonged cholestatic jaundice, micropenis
    - Ocular abnormality e.g. optic nerve hypoplasia
    - All newborns at risk of CCH should be recalled for re-test of venous FT4 and TSH at day 4-6, regardless of their initial screening results, and followed up accordingly.
    - Newborns with symptoms and signs suggestive of pituitary hormone deficiencies should have FT4 and TSH checked, in addition to other pituitary hormones.
    - In babies with CCH and concomitant ACTH deficiency, adequate glucocorticoid replacement should precede LT4 treatment to prevent adrenal crisis.
    - The starting dose of LT4 is the same as in primary hypothyroidism. Treatment is monitored by measuring FT4 and TSH and aim to keep FT4 in the upper half of the age-specific reference range.

Figure 1: Cord blood TSH interpretation and recall of patients



*In special circumstances such as in disadvantage families, logistic problems etc.

Figure 2: Interpretation of TFT at recall and decision to initiate treatment



Adapted from Consensus Guidelines on Screening, Diagnosis and Management of Congenital Hypothyroidism in Malaysia, November 2021.

Chapter 60:
Diabetes Mellitus

Introduction

- Type 1 diabetes mellitus (T1DM) is the most common type of diabetes mellitus in children and adolescents. The incidence of type 2 diabetes mellitus (T2DM) is on the rising trend among adolescents due to obesity.
- Monogenic diabetes or MODY is a familial form of diabetes that usually presents with a mild, non-ketotic diabetes presenting during adolescence or early adulthood.
- Neonatal diabetes should be suspected in infants less than 1 year old.
- Regardless of the type of diabetes, any child with severe hyperglycemia, ketonemia and metabolic abnormalities will initially require insulin therapy.

Diagnosis of T1DM

- The diagnosis of diabetes mellitus in children and adolescents should be made based on clinical features and biochemical criteria (Refer Table 2: World Health Organization diagnostic criteria*).
- Autoantibodies testing (glutamic acid decarboxylase antibody, anti-islet antibody, insulin autoantibodies and protein tyrosine phosphatase antibody, (other autoantibodies may be done if available) to confirm the diagnosis of T1DM
- The diagnosis must be confirmed by repeat blood glucose testing in the absence of unequivocal hyperglycaemia.
- The role of HbA1c alone in the diagnosis of diabetes mellitus remains unclear and diabetes cannot be excluded when the value is <6.5%.

Table 1: Symptoms and Signs of Diabetes Mellitus

Symptom and Signs Diabetes Melitus	
Polydipsia Polyuria Weight loss Enurlesis (secondary)	Vomiting Dehydration Abnormal pain Hypervenilation due to acidosis Drowsiness, coma

Table 2: WHO diagnostic criteria of Diabetes Mellitus

Diagnostic criteria of Diabetes Mellitus
• Classic symptoms[a] of diabetes or hyperglycaemic crisis, with plasma glucose concentration ≥ 11.1 mmol/L OR • Fasting plasma glucose[b] ≥ 7.0 mmol/L OR • Two hour post-load glucose ≥ 11.1 mmol/L in OGTT[c] OR • HbA1c >6.5%[d]
[a]classic symptoms consist of thirst, polyuria, polydipsia, recurrent infection and weight loss. [b]Fasting is defined as no caloric intake for at least eight hours. [c]The test should be perfomed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g. [d]The test should be perfomed in a laboratory using a method that is National Glycohaemoglobin Standardisation Programme certified and standardised to the Diabetes Control and Complications Trial (DCCT) assay

Table 3: Clinical features of T1DM and T2DM.

	T1DM	T2DM
Age of onset	6 months to young adulthood	Usually pubertal or later
Clinical presentation	Most often acute, rapid onset of symptoms	Variable: often insidious onset of symptoms
Autoimmunity	Present	No
Ketosis	Common	Rare
Body habitus	Usually lean but can be overweight following population frequency	Often overweight/obese
Acanthosis nigricans	Typically absent	Commonly present

Management

Principles of insulin therapy in T1DM

- Daily insulin dosage varies between individuals and changes over time.

Guidelines on dosage:

- During the honeymoon period (partial remission phase) total daily insulin dose is usually 0.5 IU/kg/day or less
- Prepubertal children (outside the partial remission phase) usually require insulin of 0.7–1.0 IU/kg/day.
- During puberty, requirements may rise to 1 - 2 IU/kg/day.

INTENSIVE INSULIN THERAPY

Basal-bolus regimen

- The basal-bolus regimen (intermediate-acting insulin/long-acting basal once or twice daily and rapid-acting/short-acting boluses with meals and snacks) mimics the physiological insulin secretion.
- Basal insulin constitutes about 30 - 50% of the total daily insulin dose (TDD) requirements; the remainder is pre-prandial rapid-acting or short- acting insulin.

Pump therapy

- Insulin pump therapy /continuous subcutaneous insulin infusion (CSII) offers flexibility, better metabolic control and improvement in quality of life without the need for multiple insulin injections. In toddlers, pump is a preferred method whenever affordable and expertise available.

LESS INTENSIVE INSULIN THERAPY

- Less intensive regimen consists of three or less injections a day.
- Three injections daily consist of
  - Rapid-acting/short-acting and intermediate-acting insulin pre-breakfast.
  - Rapid-acting/short-acting alone pre-lunch or pre-dinner
  - Intermediate-acting insulin pre-bed.
- Premixed insulin is not routinely recommended for T1DM because of its fixed ratio of insulin components which does not allow flexibility of dosing.

Table 4: Types of insulin preparation and action profiles for subcutaneous administration (ISPAD guideline 2022)

Insulin type	Onset of action (h)	Peak of action (h)	Duration of action (h)
Prandial insulins			
Ultra-rapid-acting analog (faster aspart)	0.1–0.2	1–3	3–5
Rapid-acting analogs (aspart, glulisine and lispro[a])	0.15–0.35	1-3	3–5
Regular/soluble (short acting)	0.5–1	2–4	5–8
Intermediate acting insulin			
NPH[b]	2–4	4–12	12–24[c]
Basal long-acting analog			
Glargine[a]	2–4	8–12	22–24[c]
Detemir	1–2	4–7	20–24[c]
Glargine U300	2–6	Minimal peak	30–36
Degludec	0.5–1.5	Minimal peak	>42

Note: All insulins used must be produced under "Good Manufacturing Practice/Good Laboratory Practice" conditions. Peak and duration of action of a specific insulin formulation is affected by the dose; that is, large doses tend to last longer than small doses.
[a]Biosimilar formulation approved in some countries.
[b]NPH: neutral protamine hagedorn insulin; isophane insulin.
[c]The duration of action may be shorter.

Insulin storage

When in use, insulin can be stored at room temperature of 25 or 30 degree Celsius for up to 4 weeks. Exposure to high temperatures should be avoided (e.g. leaving in the car compartment).

INSULIN DOSE ADJUSTMENT

- For patients with T1DM on basal bolus therapy, pre-meal insulin dose may be adjusted based on insulin to carbohydrate ratio (ICR) or insulin sensitivity factor (ISF).
- Insulin dose adjustments according to glucose trends by SMBG or CGM are important.

Insulin to Carbohydrate Ratio (ICR)

- ICR is defined as the amount of carbohydrate in grams covered by one unit (IU) of rapid-acting or short-acting insulin.
- It can be calculated by using the 500 (for rapid-acting insulin), and 450 (for short-acting insulin) rules.
- For toddlers and very young children, a 330 or 250 rule might be used instead.
- The 500 rule for rapid-acting insulin:
  ICR = 500* / (Total daily insulin)
  *450 for short acting insulin

Insulin Sensitivity Factor (ISF)

- ISF is defined as the amount of BG in mmol/L reduced by one unit (IU) of rapid-acting or short-acting insulin and used to correct hyperglycaemia.
- The 100 rule for rapid-acting insulin:
  ISF = 100* /(Total daily insulin)
  *83 for short-acting insulin

Glycaemic targets

- Target HbA1c should be less than 7%.
- SMBG targets should be 4 – 10 mmol/L with a tighter fasting range of 4-8 mmol/L.
- CGMS recovered over a 14-day period should have time spent as follows >70% between 3.9-10 mmol/L, <4% <3.9 mmol/L, <1% < 3 mmol/L, <25% > 10 mmol/L, <5% > 13.9 mmol/L

In places with limited resources and poor glucose monitoring, less stringent targets may have to be accepted.

Monitoring of glycaemic control

- Self-monitoring of blood glucose (SMBG) should be practiced by all T1DM children at least 6x per day and more frequent during sick days or during exercise.
- Diary to record glucose levels, insulin dosages and dietary details for treatment adjustments.
- To optimise basal insulin, blood testing should be done at bedtime, during the night (e.g. 3am to detect nocturnal hypoglycaemia and hyperglycaemia) and after the overnight fast (pre-breakfast).
- For adjustment of meal insulin dose, pre-meal blood testing should be done. For subsequent adjustment of meal insulin dose, blood testing should be done pre-meal and two hours post-meal to show levels of BG in response to the meal insulin.
- For glycaemic control during vigorous/prolonged exercise, blood testing should be done before, during and monitored several hours after the exercise.
- Blood testing should be done when hypoglycaemia is suspected.

Continuous Glucose Monitoring System (CGMS)

- CGMS uses minimally invasive device to measure SC interstitial fluid glucose every 1 - 5 minutes. It is preferred whenever available and affordable. Early use of CGMS in T1DM is associated with better diabetes control without frequent finger glucose pricks.

Self-monitoring of urinary or blood ketones

- Urine or blood ketones measurement should be monitored during episodes of uncontrolled hyperglycaemia, intercurrent illness (sick days) and impending ketoacidosis.

Recommendations for HbA1c measurement

- HbA1c measurement is recommended every 3 months
- The recommended HbA1c target for young people with diabetes is less than 7%.

Diet

- A balance and healthy diet for age is required with dietician involvement.
- Encourage fairly regular and consistent meals to match the insulin.
- Continuous eating pattern (grazing) should be limited.
- Carbohydrate counting should be taught to patients. Insulin dosage should match the carbohydrate intake.

Exercise

- Physical activities should be performed regularly and in a safe manner in patients with T1DM with adjustment of insulin and carbohydrate intake accordingly.
- Avoid strenuous physical activity if pre-exercise BG is high (>14mmol/L) with ketonuria or ketonaemia.
- Do not inject insulin in the site that will be heavily involved in muscular activity (e.g. not to inject in the thigh before cycling).
- Avoid physical activity exercise at peak action of insulin.
- Consider reducing evening basal insulin for prolonged exercise.
- Monitor BG before, during exercise and in evening and night to avoid nocturnal hypoglycaemia.
- Drink more water and have simple carbohydrate available.

Diabetic Education

At diagnosis - Survival skills:

- How the diagnosis has been made, simple explanation of the uncertain cause of diabetes. No cause for blame.
- The need for immediate insulin and how it will work.
- Normal blood glucose (BG) levels and glucose targets
- Practical skills insulin injections; blood and/or urine testing, reasons for monitoring.
- Basic dietary advice.
- Recognition and treatment of hypoglycaemia.
- Diabetes during sick days illnesses. Advice not to omit insulin - prevent DKA.
- Diabetes at home or at school including the effects of exercise.
- Psychological adjustment to the diagnosis.
- Details of emergency telephone contacts.

Medic alert

- Always wear the medic alert as this may be lifesaving during an emergency.

Diabetes support group & resources

- Diabetes Malaysia (Persatuan Diabetes Malaysia) , NADI, Diabetes Resource Centre at regional centre, hospitals. Referral to the social welfare for poor families
- https://diabetesmalaysia.org.my/
- https://hellotype1.com/my/
- https://mpedg.mems.my
- https://www.nadidiabetes.com/

School

- Patients should have diabetes medical management plan. The school teachers should be informed about children having diabetes.

Complications and other associated conditions

Screening complications for T1DM and T2DM vascular complications are as in table.

Table 5: Screening recommendations for vascular complications (ISPAD guideline 2022)

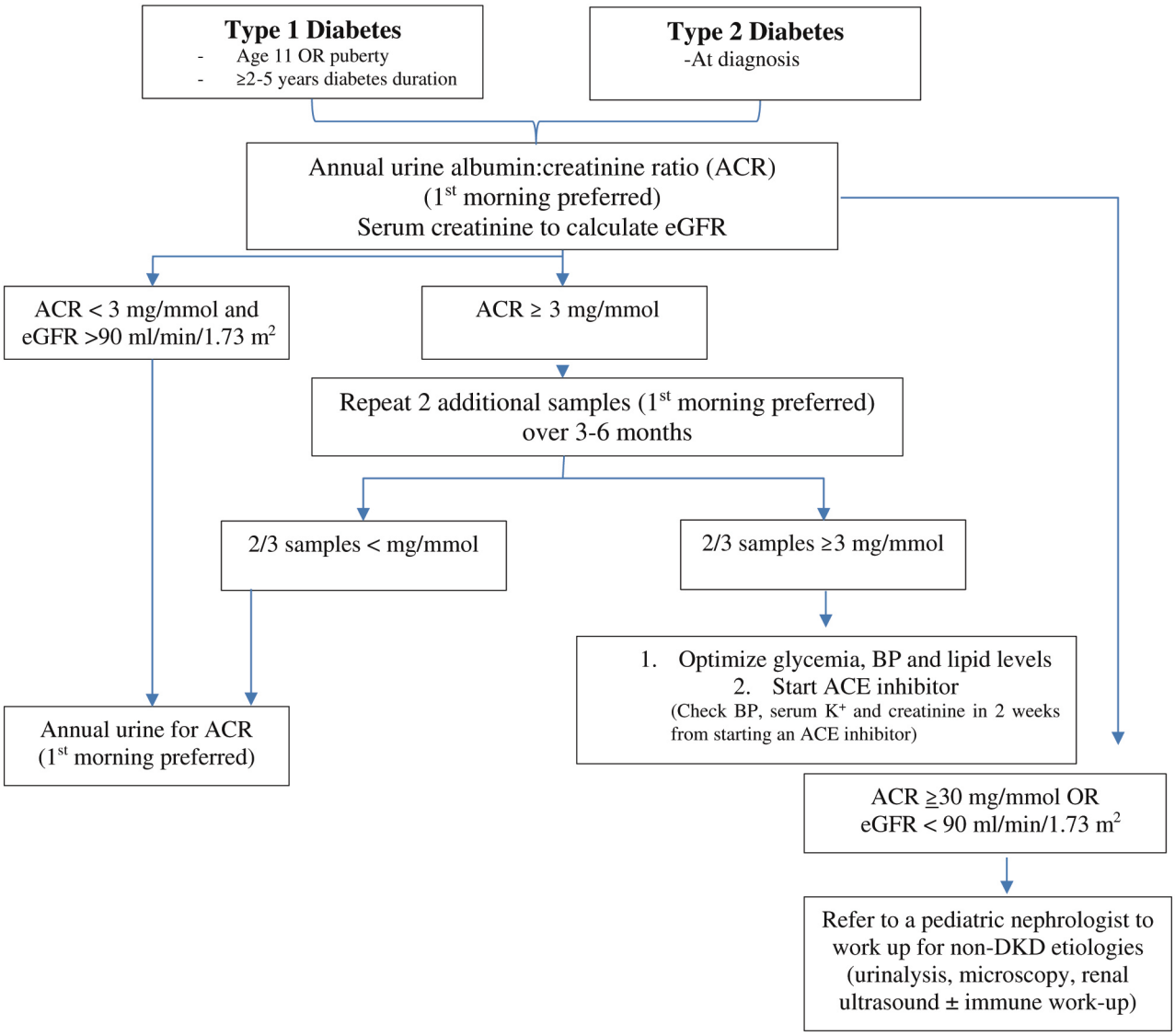
	When to commence screening?	Screening methods
Nephropathy	**T1D:** at puberty or age 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Urinary ACR Confirm with 1st morning urine sample Frequency: annually
Retinopathy	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Fundus photography or mydriatic ophthalmoscopy Frequency: every 2–3 years
Neuropathy	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	History Physical examination Clinical tests Frequency: annually
Macrovascular disease	**T1D:** 11 years with 2–5 years diabetes duration **T2D:** at diagnosis	Lipid panel every 3 years BP at least annually; ideally at every clinic visit

Microalbuminuria: 2 of 3 consecutive urine collections within 3-6 months duration should be used as evidence of microalbuminuria defined as:

→ Albumin excretion rate (AER) 20-200 mcg/min or AER 30-300 mg/day.
→ Albumin/creatinine ratio (ACR) 2.5-25 mg/mmol (males) and 3.5 – 25 mg/mmol (females) on first morning urine specimen; Random ACR is higher.
→ Albumin concentration (AC) 30-300 mg/L (on early morning urine sample).

- Abnormal screening tests should be repeated as microalbuminuria may not be persistent.
- When interpreting urine microalbuminuria, false positive results should be considered in exercise, menstrual bleeding, infections, fever, kidney diseases, marked hyperglycaemia.
- Consider screening of eGFR in T1D at puberty or from age 11 years, whichever is earlier, with 2–5 years diabetes duration.
- Consider screening of eGFR starting at diabetes diagnosis in youth with T2D.
- Consider work-up for non-diabetic kidney disease in all children and adolescents with T2D and T1D with Chronic Kidney Disease (CKD) stage A3 (UACR >300 mg/g or 30 mg/mmol) or G2-5 (eGFR <90 ml/min/1.73m^2) including urinalysis, renal ultrasound and immune work-up.
- Optimize glycemia & blood pressure to prevent the onset and progression of albuminuria.
- Consider angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in adolescents with persistently elevated albuminuria
- Monitor for changes in BP, serum creatinine and potassium within 2 weeks of initiation of an ACE inhibitor or ARB, and annually thereafter.
- Consider holding ACE inhibitors or ARB during episodes of dehydration and DKA.

Table 6: Diabetic kidney disease screening algorithm (ISPAD guideline 2022)



Blood pressure

- Blood pressure should be monitored at least annually ideally every visit.
- For people with diabetes <13 years old, hypertension is defined as average SBP and/or DBP > or equal 95th percentile for sex, age and height on three or more occasions.
- For age ≥ 13 years, hypertension is defined as average SBP and/or DBP ≥ 130/80 mm Hg.
- Initial treatment weight loss, limit salt intake, increased physical activity
- If unable to achieve normal BP after 6 months of lifestyle intervention, an ACE inhibitor or other BP lowering agent is recommended.
- ACEi is safe in children in short-term studies but not safe during pregnancy.

Lipid

- Screening for dyslipidemia is recommended soon after diagnosis when glycemia is stabilized in T1D from age 11 years.
- Non-fasting lipids screening may be obtained and if triglycerides or LDL levels are elevated, a fasting lipid profile would then be indicated.
- High LDL cholesterol is defined as >2.6 mmol/L (100 mg/dL).
- Interventions to improve glycemia, dietary changes and increased exercise should be instituted. If they do not lower LDL cholesterol <3.4 mmol/L (130 mg/dL), statins may be considered in children from age 10 years.
- Contraception counseling is required in post-pubertal adolescents who are treated with statins due to their potential teratogenicity.

TABLE 2 Recommended threshold values for different parameters for intervention and primary prevention of microvascular and CVD in children and adolescents with T1D

Threshold value	Type of intervention
<13 years: BP >90th percentile for age, sex and height ≥13 years: BP >120/80 mm Hg	Lifestyle intervention: exercise, diet and less screen time
<13 years: BP >90th percentile despite lifestyle intervention ≥13 years: BP >120/80 mm Hg despite lifestyle intervention	ACE inhibitor or other BP lowering agent If elevated albuminuria is present: ACE inhibitor or ARB
<13 years: BP >95th percentile for age, sex and height ≥13 years: BP > 130/90 mm Hg	Lifestyle intervention and ACE inhibitor or other BP lowering agent If elevated albuminuria is present: ACE inhibitor or ARB
LDL-cholesterol >2.6 mmol/L (100 mg/dL)	Dietary and lifestyle intervention
LDL-cholesterol >3.4 mmol/L (130 mg/dL)	Statin

Others

- Monitor weight, height, BMI, and puberty.
- Screening of thyroid function soon after diagnosis of diabetes in T1DM. Then every second year if asymptomatic, no goitre and thyroid autoantibodies negative. More frequent assessment if indicated.
- Screening for coeliac disease is recommended during the initial year of diagnosis for T1DM and at 2-5 years intervals (ISPAD 2022)
- More frequent assessment if there is clinical suspicion of coeliac disease or coeliac disease in first-degree relative.
- Routine clinical examination for skin and joint changes.
- Symptoms and signs of other autoimmune diseases in T1DM - Addison, autoimmune gastritis, juvenile idiopathic arthritis, other gastrointestinal diseases
- Screening for vitamin D deficiency in high-risk groups (darker skin pigmentation, coeliac disease)
- Advice on bone health to optimize calcium and vitamin D intake, avoid smoking, weight-bearing exercise.
- Prevention or cessation of smoking
- Psychological assessment and support

Table 7: Sick day management for T1DM

Sick Day Management						
Ketones		Blood Glucose				
Blood mmol/L	Urine	5.5 mmol/L	5.5 - 10 mmol/L	>10 - 14 mmol/L	>14 - 22 mmol/L	>22 mmol/L
<0.6	Negative or trace	Do not give extra insulin Recheck BG & ketones in 2 hours	No insulin adjustment needed	Add correction dose of insulin according to ISF	Give extra 5% of TDD or 0.05 IU/kg	Give extra 10% of TDD or 0.1 IU/kg *Repeat if needed*
0.6 - 1.4	Trace, small to moderate	Starvation ketones Extra carb & fluid needed	Starvation ketones Extra carb & fluid needed No insulin adjustment needed	Extra carb & fluid needed Give 5-10% of TDD or 0.05 - 0.1 IU/kg	Give extra 5 - 10% of TDD or 0.05 - 0.1 IU/kg	Give extra 10% of TDD or 0.1 IU/kg *Repeat if needed*
1.5 - 2.9	Moderate to large	High levels of starvation ketones Check BG meter Recheck BG & ketones Extra carb & fluid needed	High levels of starvation ketones Extra carb & fluid needed Give 5% of TDD or 0.05 IU/kg; rpt insulin dose when BG has risen	Extra carb & fluid needed Give 10% of TDD or 0.1 IU/kg	Give extra 10 - 20% of TDD or 0.1 IU/kg; repeat insulin dose after 2 hours if ketones do not decrease	
>3.0	Large	Very high levels of starvation ketones Check BG meter Recheck BG & ketones Extra carb & fluid needed	Very high levels of starvation ketones Extra carb & fluid needed Give 5% of TDD or 0.05 IU/kg; rpt insulin dose when BG has risen	Extra carb & fluid needed Give 10% of TDD or 0.1 IU/kg	Give extra 10 - 20% of TDD or 0.1 IU/kg; repeat insulin dose after 2 hours if ketones do not decrease	
There is an immediate risk of ketoacidosis if the blood ketone level is ≥3.0 mmol/L						

Table 8: Management of T2DM ISPAD

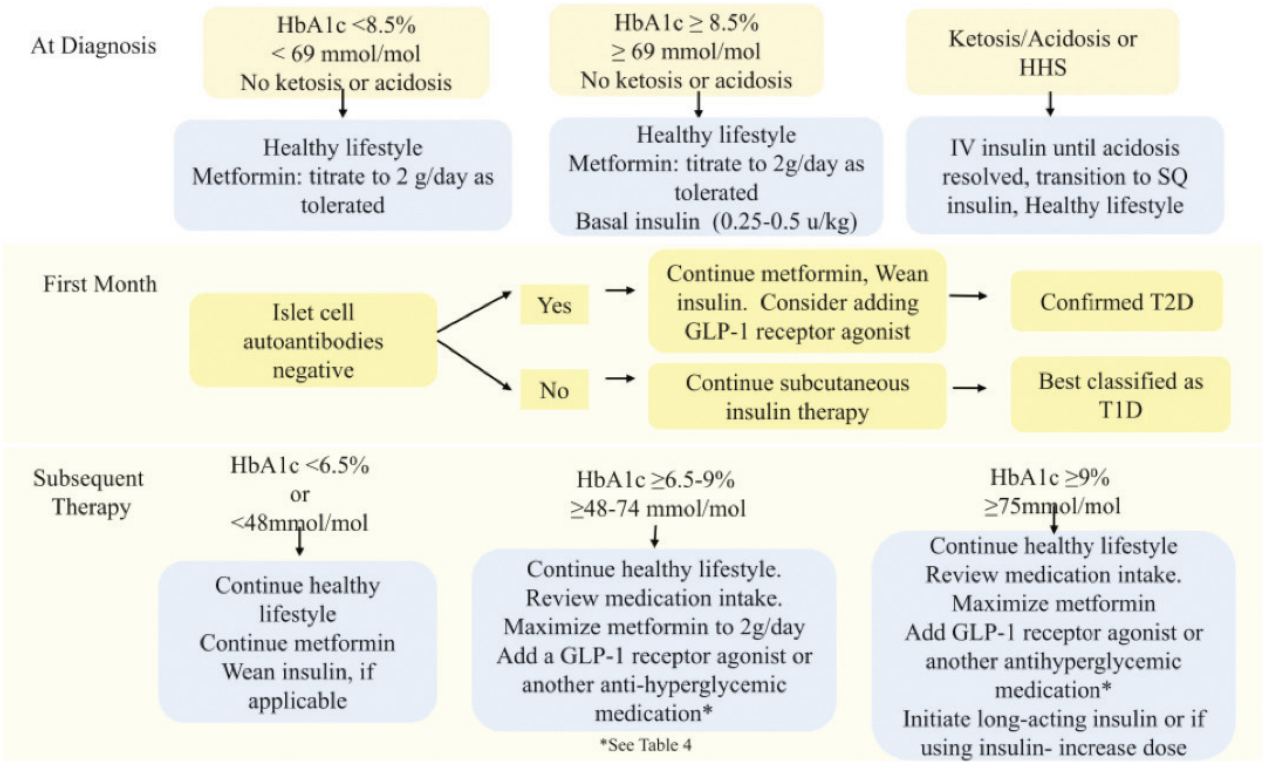


FIGURE 1 Management of T2D in Children and Adolescents. Initial management and subsequent therapy. Adapted from ADA Position Statement "Evaluation and Management of Youth-Onset Type 2 Diabetes". GLP-1, glucagon like peptide-1.

Chapter 61:
Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State

Diabetic Ketoacidosis (DKA)

The biochemical criteria for the diagnosis of DKA are:
- Hyperglycemia (blood glucose >11 mmol/L [≈200 mg/dl])
- Venous pH <7.3 or serum bicarbonate <18 mmol/L
- Ketonemia (blood ß-hydroxybuyrate (BOHB) usually ≥3 mmol/L) or moderate-large ketonuria.

DKA is categorised by the severity of acidosis which guides rehydration therapy:
- Mild (venous pH <7.3, bicarbonate <18 mmol/L)
- Moderate (venous pH <7.2, bicarbonate <10 mmol/L)
- Severe (venous pH <7.1, bicarbonate <5 mmol/L)

Goals of therapy

- Correct dehydration.
- Correct acidosis and reverse ketosis.
- Restore blood glucose to near normal.
- Avoid complications of therapy.
- Identify and treat any precipitating event.

Emergency management

- Acute management following APLS or PALS guidelines.
- Vital signs and measure weight, current weight should be used for calculations
- Insert intravenous line
- Bedside blood for glucose and ketones
- Venous blood gas, glucose, electrolytes, urea, creatinine, FBC, calcium, phosphorus, magnesium
- Assess for shock, degree of dehydration and GCS
- Start intravenous therapy following guidelines
- Urine for ketones if blood ketone not available
- Antibiotics and appropriate cultures (blood, urine, throat) if suspect infection or if critically ill child.
- If laboratory measurement of serum potassium is delayed, perform an ECG for baseline evaluation of potassium status.

** avoid unnecessary intubation unless there is severe drop in GCS compromising airway and breathing

Supportive measures

- Secure the airway and give oxygen.
- Empty the stomach via a nasogastric tube if conscious level is poor and unable to protect airway
- A peripheral intravenous catheter or an arterial catheter (in ICU) for painless repetitive blood sampling.
- Continuous cardiac monitoring to assess T waves for evidence of hyper- or hypokalaemia.
- Antibiotics for febrile patients or suspected infection.
- Do not catheterize routinely unless the child is unconscious or unable to void on demand.

Calculations
• Anion gap = (Na + K) - ($Cl + HCO_3$)
• Normal value: 12 +/- 2 mmol/L
• In DKA the anion gap is typically 20–30 mmol/L
• An anion gap > 35 mmol/L suggests concomitant lactic acidosis
• Corrected sodium (mmol/L) = measured Na + $\frac{2 \times (\text{plasma glucose} - 5.6)}{5.6}$
• Effective osmolality (mOsm/kg) = 2 x (Na + K) + plasma glucose + urea

Monitoring of DKA

Hourly (or more frequently as indicated) bedside monitoring

- Vital signs (pulse rate, respiratory rate and blood pressure)
- GCS and neurological observations for cerebral oedema
- Bedside capillary blood glucose
- Insulin dose
- Accurate fluid input (including oral fluid) and output

Two to four hourly (or more frequently)

- Blood gases
- Bedside blood ketone (capillary blood)
- Serum electrolytes, urea
- Serum calcium, magnesium and phosphorus
- Haematocrit

Fluids and Salt

- Fluid replacement should begin 1 hour before starting insulin therapy.
- The ISPAD guideline 2022 recommends for children who are volume depleted but not in shock, volume expansion (resuscitation) should begin immediately with 0.9% saline, 10 to 20 ml/kg infused over 20–30 min to restore the peripheral circulation.
- In the presence of shock, 10-20 ml/kg boluses 0.9% saline should be infused as quickly as possible
- Reassessment after each 10ml/kg bolus is important and repeated if necessary. Total bolus required is usually not > 30ml/kg in DKA without other causes of shock or additional loss of fluids.
- Subsequent rehydration and maintenance fluid should be calculated and infused over 24-48 hours.
- Clinical estimates of the volume deficit are subjective and inaccurate in DKA.
- Therefore based on the degree of acidosis, in mild DKA use 5%, moderate DKA 7% and severe 10% dehydration.
- The rate of fluid administration usually do not exceed 1.5-2x the daily maintenance requirement.
- Resuscitation boluses in another centre before assesment should be factored in the rehydration. Consider to minus the initial bolus amount from the rehydration fluids especially if excessive fluids were given.
- *After initial resuscitation fluids, rehydration fluid can be accomplished with 0.45%-0.9% or a balanced salt solution (Ringer's lactate, Hartmann's solution or Plasmalyte)* . At present there is no evidence on the use of colloid fluids

- The decision to switch solution depends on the patient's hydration status, serum sodium and osmolality.
- Calculate the corrected sodium (formula as above) and monitor changes.
- Clinical assessment of hydration status and calculated effective osmolality are valuable guides to fluid and electrolyte therapy.
- The aim is to gradually reduce serum effective osmolality to normal.
- Serum sodium level should increase simultaneously as the serum glucose level decreases
- Most DKA resolves before 24 h and remaining fluid deficits can be replaced by oral intake after transition to subcutaneous insulin.
- The ISPAD 2022 guideline suggests that calculation of fluid infusion rates for obese children do not need to follow ideal weight. However, fluid calculations should not exceed those used in adult protocols, eg 1L maximum per bolus and 500ml/hour infusion.

Insulin therapy

- Insulin therapy in DKA should begin with a rate of 0.05 - 0.1 unit/kg/hr 1 hour after starting fluid replacement therapy. The lower dose 0.05 unit/kg/hr can be used for pH >7.15 especially in children < 5 years old.
- Do not administer IV bolus of insulin at the start of therapy. It may increase the risk of cerebral oedema and exacerbate hypokalaemia.
- The dose of insulin should remain at 0.05 - 0.1 unit/kg/h until DKA resolves. For patients with marked sensitivity to insulin (e.g. young children with DKA), the dose may be decreased provided that metabolic acidosis continues to resolve.
- If no improvement is seen in pH, anion gap or blood ketones, reassess the patient, review insulin dose and consider other possible causes of impaired response to insulin such as sepsis or errors in insulin preparation, route of administration or insufficient fluids.

Adjustment of glucose administration:

- During initial volume expansion, BG falls steeply. Thereafter, it usually decreases at a rate of 2 - 5 mmol/L/hour after commencing insulin therapy.
- **When BG falls to < 17 mmol/L or falls rapidly >5mmol/L/hour**, 5% dextrose should be added to the IV fluid and then adjusted accordingly. 10% or 12.5% dextrose may be needed to prevent hypoglycaemia.

Use of SC insulin

- In situations where continuous insulin IV infusion is not possible and in children with uncomplicated mild to moderate DKA with normal circulation, hourly or 2 hourly SC rapid-acting insulin (lispro or aspart) may be as effective as IV. Dose SC 0.15 unit/kg every 2h (initiated 1 h after fluids), reduced to 0.1 unit/kg every 2 hr if BG decrease by >5mmol/L even after adding dextrose.
- SC short-acting (eg actrapid) insulin is another alternative in mild DKA when IV infusion or rapid-acting insulin is not available. Suggested starting dose 0.13-0.17unit/kg/dose every 4h. Doses are adjusted by 10-20%. Frequency may be increased every 2 or 3 hr.
- SC long-acting insulin is required to prevent rebound hyperglycaemia/ketosis.

Potassium replacement

- Children with DKA may have total body potassium deficits between 3 and 6 mmol/kg.
- Potassium replacement (refer to table) in DKA on insulin is vital and levels should be monitored closely.
- Serum potassium may decrease rapidly during treatment predisposing to cardiac arrhythmias.
- IV potassium replacement must not exceed 0.5 mmol/kg/hour.
- ECG changes may help to determine whether the child has hypo- or hyperkalaemia.
- Hypokalaemia: prolonged PR interval, T-wave flattening and inversion, ST depression, prominent U waves and apparent long QT interval.
    - Hyperkalaemia: tall, peaked and symmetrical T waves, and shortening of the QT interval.
    - If hypokalaemia persists despite a maximum rate of potassium replacement, the rate of insulin infusion may be reduced.
    - Potassium phosphate may be used together with potassium chloride (KCL) or acetate to avoid hypophosphataemia or hyperchloraemic metabolic acidosis. E.g. 20mmol/L KCL and 20 mmol/L potassium phosphate.

Potassium level	Replacement
Hypokalemia	Start potassium replacement 40 mmol/L (1.5 g KCL/500 ml) at the INITIAL volume expansion before insulin therapy.
Normokalemia	Start Potassium replacement at 40 mmol/L during rehydration concurrent with insulin.
Hyperkalemia	Start potassium replacement only after urine output is documented and when potassium is < 5.5 mmol/L.

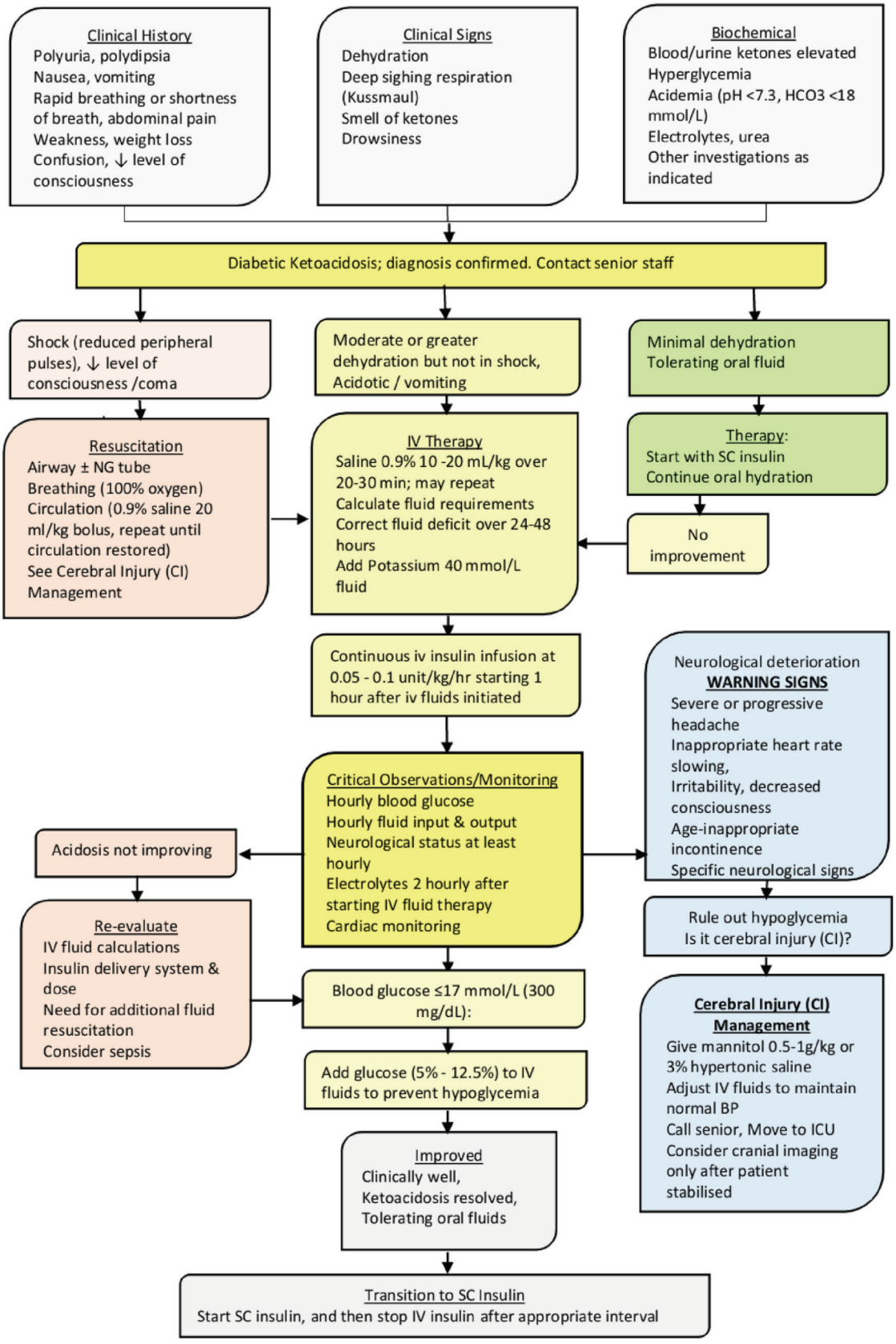
TABLE 2: Potassium replacement in DKA

Phosphate

- Continuation of intravenous therapy without food consumption >24h is a risk factor for clinically significant hypophosphataemia.
- Manifestations of severe hypophosphataemia include encephalopathy, seizures, impaired cardiac contraction, arrhythmias, respiratory failure, hemolytic anemia, myopathy, dysphagia, ileus and rhabdomyolysis.
- Severe hypophosphataemia <0.32 mmol/L with or without symptoms should be treated promptly. Insulin infusion may need to be reduced.
- ISPAD 2022 guideline recommends routine phosphate replacement to prevent hypophosphataemia is advisable while available especially in severe DKA.
- Potassium phosphate can be combined with potassium chloride or potassium acetate to provide phosphate replacement
- Monitor serum calcium and magnesium carefully during phosphate infusion.

Acidosis

- Fluid and insulin replacement will gradually reverse acidosis.
- Bicarbonate therapy may cause paradoxical CNS acidosis, hypokalaemia and increasing osmolality. Administration of bicarbonate is not recommended except in life threatening hyperkalemia or severe acidosis venous pH <6.9 that have compromised cardiac contractility.
- Important causes of persistent acidosis include insufficient fluid administration, infection/ sepsis and incorrect preparation of the intravenous insulin infusion.
- Lack of resolution of acidosis due to development of hyperchloremic acidosis is generally a benign condition and should not delay transition to subcutaneous insulin.



Algorithm 1. Treatment for DKA (ISPAD guideline for DKA 2022)

Introduction of oral fluids and transition to SC insulin injections

- Oral fluids should be introduced only with substantial clinical improvement (mild acidosis/ketosis may still be present). Persistent ketonuria may occur for several hours after serum BOHB bedside blood ketones have normalized. Hence, absence of ketonuria is not used to determine resolution of DKA.
- When oral fluid is tolerated, IV fluid should be reduced accordingly.
- When the change to SC insulin is planned, a dose of basal (long-acting) insulin should be administered in addition to rapid or short-acting insulin. Basal insulin may be given while the child is still receiving intravenous insulin infusion to facilitate transition to SC.
- The most convenient time to change to SC insulin is just before a mealtime. As intravenous insulin has a short half life, the first SC injection should be given 15-30 min (rapid-acting insulin) or 1 hour (regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed.
- Glucose is still monitored frequently at first to prevent hyper and hypoglycaemia
- Initial total insulin dose including long-acting is about 1u/kg/day, lower dose should be used in young children. Intensive insulin injections (basal bolus injections) 4 or more times per day are preferable to conventional (twice daily) injections.

Morbidity and mortality

- In national population studies, mortality rate from DKA in children is 0.15–0.30%.
- Cerebral oedema accounts for 60–90% of all DKA deaths. 10% - 25% of survivors of cerebral edema have significant residual morbidity.
- Other rare causes of morbidity and mortality include: Sepsis, hypokalaemia and hyperkalaemia, severe hypophosphataemia, hypoglycaemia, aspiration pneumonia, pulmonary oedema, adult respiratory distress syndrome (ARDS), rhabdomyolysis, acute renal failure and acute pancreatitis.

Cerebral injury

- The cause of DKA-related cerebral injury is of ongoing study. Rapid fluid administration resulting in changes in serum osmolality was initially thought to be the cause, but recent evidence suggests that cerebral hypoperfusion and the hyperinflammatory state in DKA play central roles. Risk factors include younger children, severe acidosis & dehydration at presentation, new-onset diabetes and longer duration of symptoms.
- Clinically significant cerebral oedema usually develops within the 1st 12 h after treatment has started, but may occur before treatment or rarely, as late as 24 - 48 h later. Signs that occur before treatment should not be considered in the diagnosis.

Table 3: Clinical diagnosis of cerebral edema

Diagnostic Criteria for Cerebral Oedema	
• Abnormal motor or verbal response to pain • Decorticate or decerebrate posture • Cranial nerve palsy (especially III, IV, and VI) • Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)	
Major Criteria	Minor Criteria
• Altered mentation / fluctuating level of consciousness. • Sustained heart rate deceleration (decrease > 20 bpm), not attributable to improved intravascular volume or sleep state. • Age-inappropriate incontinence	• Vomiting • Headache • Lethargy, not easily arousable • Diastolic blood pressure > 90 mmHg • Age < 5 years

Clinical diagnosis of cerebral edema

- One diagnostic criterion OR
- Two major criteria OR
- One major and two minor criteria

- These criteria have a sensitivity of 92% and a false positive rate of only 4%.
- In DKA patient with multiple risk factors to cerebral oedema, mannitol and hypertonic saline should be readily available with the dose calculated beforehand. If neurological status deteriorates acutely, treatment should be given immediately.

Treatment of cerebral oedema

- Initiate treatment as soon as the condition is suspected
- Prop up the patient by about 30 degree
- Consider reducing the rate of fluid by one-third
- Adjust fluid as needed to maintain normal blood pressure while avoiding excessive fluid administration. AVOID hypotension.
- Give mannitol 0.5 - 1 g/kg IV over 10-15 min. The effect should be apparent >15min and duration about 120 min. If no response, the dose can be repeated after 30 minutes.
- Hypertonic saline (3%) 2.5-5ml/kg over 10-15 min may be used as an alternative to mannitol or in addition to mannitol if there has been no response over 15-30min.
- Consider intubating the patient if there is impending respiratory failure.
- After treatment for cerebral oedema has been started, neuroimaging may be considered to rule out other neuro emergencies eg intracranial hemorrhage or cerebrovascular thrombosis.

Hyperglycemic Hyperosmolar State (HHS)

DKA should be distinguished from HHS, which is characterized by severe hyperglycemia and markedly increased serum osmolality without substantial ketosis and acidosis. The rate and amount of fluid required for HHS is more and insulin requirement usually less. Mixed presentation of HHS and DKA may occur and treatment should be tailored accordingly.

Pediatric Endocrine Society proposed criteria for HHS in the pediatric age range

- plasma glucose concentration >33.3 mmol/L (600 mg/dl)
- arterial pH > 7.30; venous pH > 7.25 serum bicarbonate >15 mmol/L
- small ketonuria, absent to small ketonemia*
- effective serum osmolality >320 mOsm/kg
- obtundation, combativeness, or seizures (in approximately 50%)

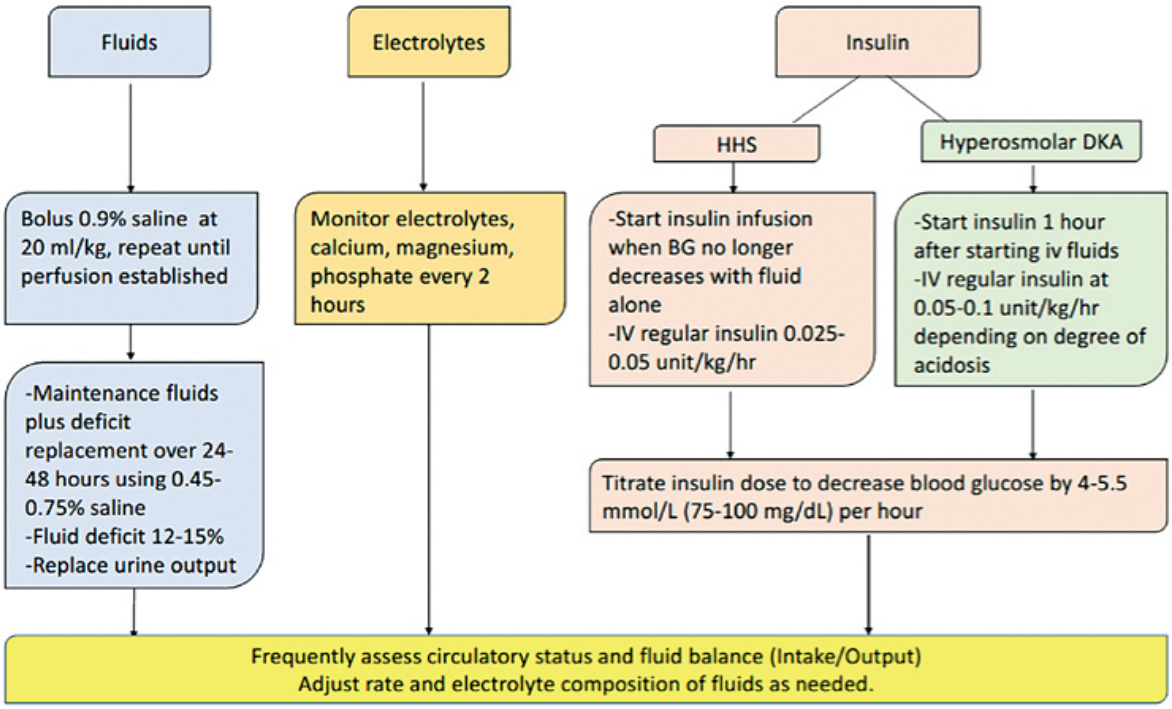


Table 4: Treatment of HHS (ISPAD guideline 2022)

Chapter 62:
Disorders of Sexual Development

Definition

- Disorders of sex development (DSD) is defined as congenital conditions in which the development of chromosomal, gonadal and anatomic sex is atypical.

DSD is a Neonatal Emergency

Major concerns in DSD patients are:-

→ Underlying medical issues:
- Dehydration, salt loss (adrenal crisis).
- Urinary tract infection.
- Bowel obstruction.

→ Decision on sex of rearing:
- Respect parents and family concerns
- Prevent gender confusion.
- Psychosocial issues

General concepts of care

- Gender assignment must be avoided before expert evaluation of patients.
- Evaluation and long-term management must be performed at a centre with an experienced multidisciplinary team (paediatric subspecialists in endocrinology, surgery, and/or urology, psychology/ psychiatry, neonatology and social work)
- Patients and family concerns (e.g. social, religion and culture) should be respected and addressed

Features that suggest DSD include :

Newborn

- Overt genital ambiguity.
- Apparent female genitalia with enlarged clitoris, posterior labial fusion or an inguino- labial mass.
- Apparent male genitalia with bilateral undescended testes, micropenis, proximal hypospadias.
- Hypospadias with undescended testes.
- Family history of DSD, e.g. Complete androgen insensitivity syndrome (CAIS).
- Discordance between genital appearance and a prenatal karyotype.

Childhood/Adolescence

- Virilization in a female
- Delayed puberty, primary amenorrhea

Disorders of Sexual Development (DSD)			
Sex Chromosome DSD	46, XY DSD		46, XX DSD
45, X Turner Syndrome 47, XXY Klinefelter Syndrome and variants 45, X/46, XY Mixed gonadal dysgnesis 46,XX/46,XY chimeric, ovotesticular DSD	*Disorders of Testicular Development* Complete gonadal dysgenesis Partial gonadal dysgenesis Gonadal regession Ovotesticular DSD	*Disorders of Androgen Synthesis/Action* Androgen synthesis defect Luteinzing Hormone receptor defect Androgen insensitivity 5 α-reductase deficiency Disorders of Anti-Mullerian hormone Timing defect Endocrine disrupters Cloacal exstrophy	*Disorders of Ovarian Development* Ovotesticular DSD Testicular DSD (SRY+, dup SOX9) Gonadal dysgenesis	*Fetal Androgen Excess* Congenital adrenal hyperplasia (CAH) 21-Hydroxylase deficiency 11-Hydroxylase deficiency Non-CAH Aromatase deficiency POR gene defect Maternal Luteoma Iatrogenic

EVALUATION

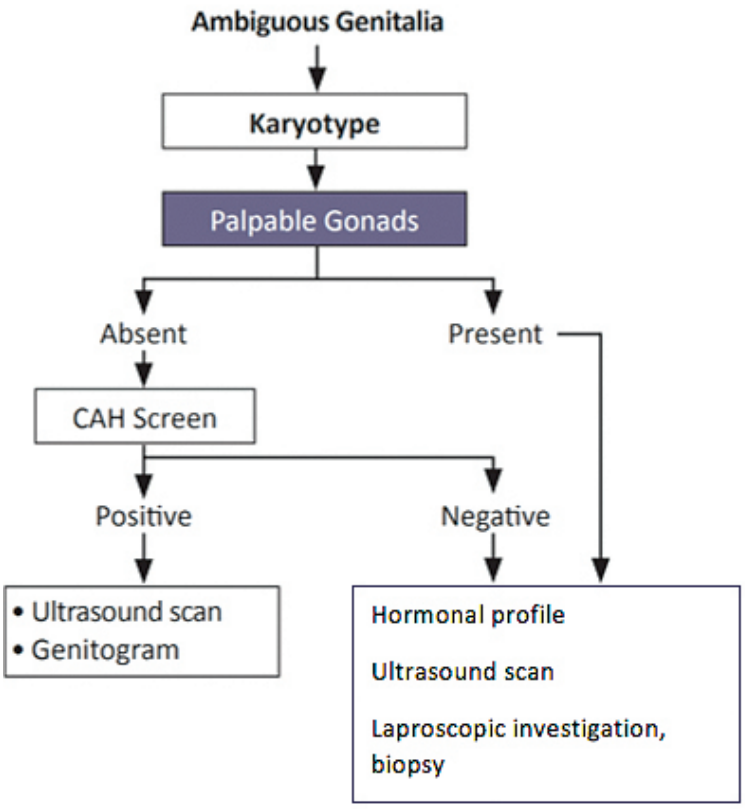
History

- Parental consanguinity.
- Obstetric : previous abortions, stillbirths, neonatal deaths.
- Antenatal : drug history, exogenous androgens, endocrine disruptors
- Family History: Unexplained neonatal deaths in siblings and close relatives, infertility, genital anomalies in the family. 3-generation family tree is required.
- Symptoms of salt wasting during neonatal period.
- Increasing skin pigmentation
- Progressive virilisation
- Abnormal pubertal development.

Physical Examination

- Blood Pressure, Hydration status
- Growth Parameters
- Hyperpigmentation.
- Dysmorphic features (Turner phenotype, congenital abnormalities).
- Cloacal anomaly.
- Appearance of external genitalia
  - Size of phallus, erectile tissue, chordae
  - Position of urethral opening
  - Labial fusion or appearance of labio-scrotal folds, rugation, pigmentation
  - Presence or absence of palpable gonads, size, position
  - Position and patency of anus.

APPROACH TO DISORDERS OF SEX DEVELOPMENT



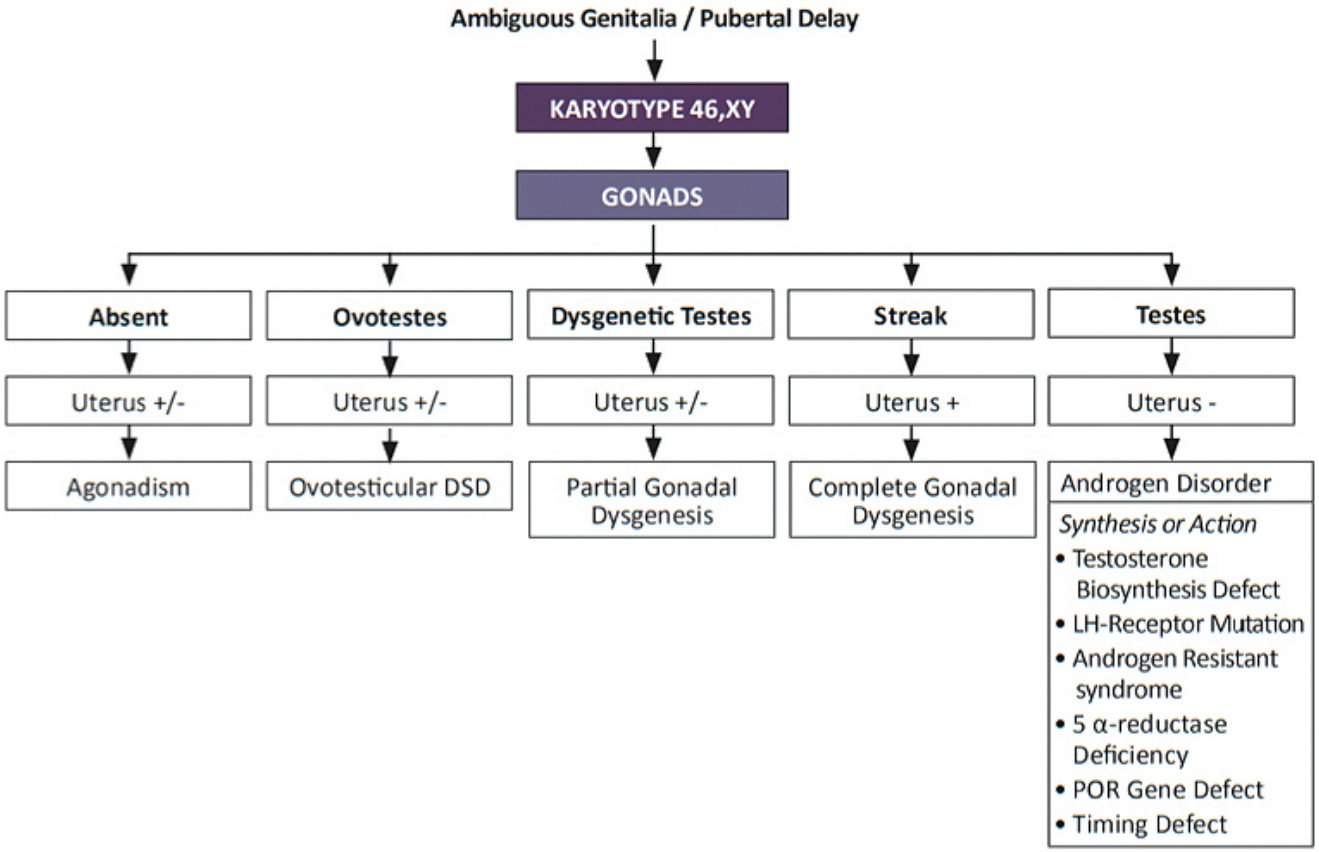
Investigations

- Chromosomal study, karyotyping with X- and Y-specific probe detection, SRY gene
- **Exclude salt losing CAH**
- Serial serum electrolytes in the neonatal period
- Serum 17-hydroxyprogesterone (taken after 72 hours of life), Renin, Cortisol
- Testosterone, LH, FSH (after 1st week of life)
- Anti-Mullerian hormone (depending on indication and availability)
- Abdominopelvic ultrasound – to look for gonads, uterus/Mullerian structures

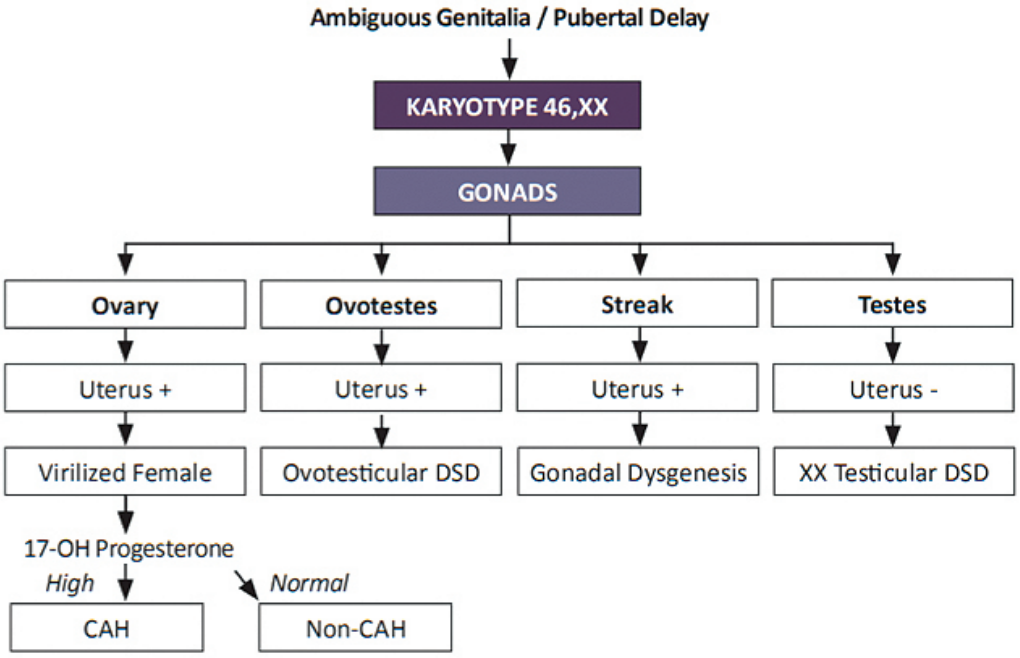
Additional investigations as indicated:

- Synacthen Test,
- hCG stimulation tests (testosterone, dihydrotestosterone (DHT), androstenodione at Day 1 & 4).
- LHRH stimulation test
- Urinary steroid analysis
- Genetic studies – gene panel or whole exome sequencing
- Further imaging studies (genitogram).
- Laproscopy and biopsy of gonads if indicated

DIAGNOSTIC ALGORITHM OF 46, XY DSD



DIAGNOSTIC ALGORITHM OF 46, XX DSD



Management

Goals

- Phenotype and psychosocial outcome concordant with assigned sex
- Preserve fertility
- Ensure normal sexual function

General management plan

- Admit to hospital. Salt losing CAH, which is life threatening, must be excluded.
- Parents of newborns with DSD should be provided with psychological support, Information should be given in a sensitive manner avoiding gender bias.
- Patient and family concerns should be respected and addressed in strict confidence. Open communication with patients and families is essential and participation in decision making is encouraged.
- When there is any doubt about sex assignment, a hasty decision must be avoided prior to expert evaluation. Do not register the child until final decision is reached.
- Patients should be managed by a multidisciplinary team involving paediatric endocrinologist, paediatric surgeon, neonatologist, psychologist and social worker. Specific management plan will depend on the underlying diagnosis.

Gender Assignment

Gender assignment and sex of rearing should be based upon the most probable adult gender identity and potential for adult function.
Factors to be considered in this decision include:-

- Diagnosis.
- Fertility potential.
- Adequacy of the external genitalia for normal sexual function. Adequate phallic size when considering male sex of rearing.
- Endocrine function of gonads. Capacity to respond to exogenous androgen.
- Parents' socio-cultural background, expectations and acceptance.
- Psychosocial development in older children.
- Decision about sex of rearing should only be made by an informed family after careful evaluation, documentation, and consultation.

Surgical management

- The goals of surgery are:
  - Genital appearance compatible with gender
  - Unobstructed urinary emptying without incontinence or infections
  - Good adult sexual and reproductive function
  - Removal of dysgenetic gonads to reduce risk of malignancy
- Only surgeons with the expertise in the care of children and specific training in the surgery of DSD should perform these procedures.
- Early genitoplasty is feasible only if the precise cause of DSD has been established and gender assignment has been based on certain knowledge of post-pubertal sexual outcome. Otherwise, surgery should be postponed as genitoplasty involves irreversible procedures such as castration and phallic reduction in individuals raised females and resection of uterovaginal tissue in those raised male.
- The procedure should be anatomically based to preserve erectile function and the innervations of the clitoris.
  → If Assigned Female surgical procedure may include
    - Removal of testicular tissue
    - Vaginoplasty

  → If Assigned Male surgical procedure may include
    - Orchidopexy
    - Removal of Mullerian structures
    - Surgical repair of hypospadias
    - Gonadectomy to be considered if dysgenetic gonads

Psychosocial support

- Psychosocial care should be an integral part of management in order to promote positive adaptation and allow parents to express and resolve their concerns
- Psychological assessment at regular intervals is recommended to screen for mental health issues such as gender dysphoria and to provide support for families.
- The issue of sex reassignment can present at various stages throughout life. It is important to assess the patient's and parents' satisfaction with the sex-assignment decision. The implications of a change in gender needs careful evaluation and planning.
- Ongoing education of both the parents and child (age-appropriate) at regular intervals is essential, because many of these patients will require surgery and hormonal therapy.

Chapter 63:
Congenital Adrenal Hyperplasia (CAH)

Neonatal diagnosis and treatment

- CAH is a group of disorders caused by a variety of enzyme deficiencies in the adrenal cortex.
- About 95% of all CAH is caused by 21-hydroxylase deficiency (21-OHD)
- The worldwide incidence in most studies ranges from 1:14,000 to 1:18,000
- 21-OHD is classified into classic and non-classic forms according to the severity of manifestations.
- The classic form is subclassified into salt-wasting and simple virilizing forms. Patients with simple virilising form may show salt loss during severe illness.
- Non-classical CAH (NCCAH) has adequate glucocorticoid and mineralocorticoid production to escape diagnosis at birth but may present with variable degrees of androgen excess later in life

Clinical presentation

Neonatal period

- Clinical presentation of 21-OHD depends on the infant's gender and severity of disease
- The clinical manifestations of 21-OHD can be as follows :

1. symptoms caused by adrenal insufficiency or salt-wasting
   - Salt loss may manifest from day 5 of life with poor feeding, vomiting, dehydration and poor weight gain. If left undiagnosed, patients can present with adrenal crisis which is life-threatening. Biochemical parameters may demonstrate hyponatremia, hyperkalemia, metabolic acidosis and hypoglycaemia.
   - Occasionally there may be delayed presentation to the second to third week of life.
2. virilization of the external genitalia due to excessive androgens
   Females
   - Clitoromegaly or phallus-like structure.
   - Displacement of the vaginal opening towards or into the urethra.
   - Posterior fusion of labia.
   - Scrotalisation of the skin of the labia majora.
   - Variable pigmentation of the external genitalia.

   Males
   - have apparently normal external genitalia with/without penile enlargement.
3. skin hyperpigmentation due to excessive ACTH.
   - Hyperpigmentation (as common as up to 90%) is seen in both genders

Childhood

- Both male and female children with NCCAH or simple virilizing CAH can present with premature pubarche, tall stature, accelerated linear growth and advanced bone age.
- Clitoromegaly (girls) and phallic enlargement (boys) may also be present

Diagnostic approach in infants with suspected 21-OHD

History

- Family history of previous unexplained neonatal death or sudden death.
- Poor feeding and poor weight gain.
- Adrenal crisis
- Skin hyperpigmentation
- Ambiguous genitalia
- Parents are generally asymptomatic

Physical examination

- Growth parameters (weight/length)
- Hyperpigmentation of the skin (axilla, lip, mouth and external genitalia)
- Ambiguous genitalia (virilization without palpable gonads)
- In a newborn with ambiguous genitalia, CAH due to 21-OHD must be excluded as it is the most common cause (virilization of external genitalia without palpable gonads).

Investigations

- Hyponatremia, hyperkalemia
- Metabolic acidosis
- Hypoglycaemia
- Renal impairment

Diagnosis of salt-wasting CAH

- Newborn infants with suspected CAH or those with siblings with CAH should be admitted.
- These infants should be observed for signs of salt wasting with regular monitoring of:
  - weight, hydration status
  - vital signs (blood pressure, heart rate), fluid balance
  - blood sugar levels.
  - serial electrolytes and renal function (initial abnormality may not be apparent in the first few days of life)
- Specific laboratory measurements which should be taken (after 48 hours of life) include :
  - 17-hydroxyprogesterone, serum cortisol 8 am (early morning), plasma renin, aldosterone and testosterone. In addition, DHEAS can be considered. These investigations may need to be sent to tertiary laboratory facilities. (e.g. IMR)
- For patients with ambiguous genitalia – additional investigations :
- Urgent karyotype
- Ultrasound to evaluate internal structure (uterus, gonads)

To confirm the diagnosis, consider standard dose ACTH stimulation test after discussion with paediatric endocrinologist. Samples should be obtained at baseline, 30 and 60 minutes after administering tetracosactide, measuring cortisol and 17OHP.

Newborn screening for CAH

Screening for 21-hydroxylase deficiency markedly reduces the time to diagnosis of infants with CAH consequently reducing morbidity and mortality.

Management of CAH

Principles of treatment

The principles of treatment for 21-OHD are to :

- supplement insufficient glucocorticoids and mineralocorticoids
- suppress excessive adrenal androgen production
- ensure normal growth and maturation

- Oral hydrocortisone should be given in 3 divided doses, in the range of 11-15 mg/m2/day to suppress excess adrenal androgen production. During infancy, higher doses of hydrocortisone may be needed to reduce markedly elevated adrenal hormone levels, but it is important to rapidly reduce the dose when target levels are achieved.
- Divided or crushed tablets of hydrocortisone should be used instead of syrup due to uneven distribution in liquid form.
- During childhood, the preferred glucocorticoid is hydrocortisone because its short half-life minimizes the adverse side effects of longer-acting, more potent ones especially growth suppression. However, in some patients who has completed their growth, long-acting glucocorticoids (e.g. prednisolone) can be considered.
- Most patients with classical CAH will require mineralocorticoid therapy in the form of oral fludrocortisone at doses of 0.05 – 2g/day in divided doses.
- During the neonatal and early infantile periods, relative mineralocorticoid resistance occurs because of immature tubular reabsorption of sodium; administration of sodium chloride in doses of 1 – 2g/day in 4 – 6 divided doses are required. Sodium chloride replacement is generally not required beyond infancy, because sensitivity to mineralocorticoid increases with age.
- Adequate instructions (verbal and written) must be conveyed to the caregivers. Written communications (letter) to relevant health care providers regarding the diagnosis/medication/ treatment strategies during acute illness should be kept by the patient/caregivers.
- All patients on glucocorticoid treatment must have medic alert (card, bracelet or pendant) with them at all times to ensure prompt treatment during emergency.
- Appropriate genetic counselling should be given to parents so that proper screening for CAH can be done for future children.

Monitoring treatment of CAH

At each visit there should be careful physical examination looking for signs of over or undertreatment:

- Height and weight should be assessed at each visit. Normal growth rate for age is a sign of adequate treatment. Overtreatment with glucocorticoids causes a reduction in growth velocity and obesity, whereas undertreatment with glucocorticoids causes adrenal insufficiency and accelerated growth velocity
- Blood pressure. As excessive mineralocorticoid increases the blood pressure, doctors should reassess the fludrocortisone and sodium dose periodically.
- Presence of hyperpigmentation, oily facial skin, acne, pubic or axillary hair which suggest undertreatment.
- Pubertal status

Periodic investigations to monitor control:

- Serum 17OHP, renin, testosterone and electrolytes
- If there are concerns of growth, a bone age should be done. Bone age acceleration indicates possibility of ongoing undertreatment.
- Consider screening for testicular adrenal rests by testicular ultrasonogram in children older than the age of 10 years.

Management of salt losing crisis

- Administration of IV normal saline (0.9%): 10-20 ml/kg over 1 hour to correct hypovolaemic shock. Subsequent rehydrating fluids should contain 0.45 – 0.9% NaCl according to serum sodium levels (with appropriate dextrose concentration in maintenance fluid).
- Administer IV hydrocortisone 100 mg/m2 stat followed by 25 mg/m2 six hourly during the acute condition.
- If hypoglycaemia is present, correct with 2 ml/kg of dextrose 10%.
- Continuous cardiac monitoring for hyperkalemic changes, and if necessary severe symptomatic hyperkalemia needs to be corrected urgently (such as resonium, nebulized salbutamol or even glucose and insulin).
- Monitor fluid input and output, vital signs, glucose level, serial serum electrolytes and daily weight.

Treatment with glucocorticoids during stress/illness

- Parents must be given clear written instruction on higher doses of hydrocortisone during stress/illness (during febrile illness (>38.5 C), when vomiting or poor oral intake, after trauma and before surgery).
- During acute illness or stress, oral glucocorticoid dose should be 2-3 times of the usual maintenance dose.
- If patients are unable to take oral steroids, parenteral hydrocortisone will be indicated. Intravenous hydrocortisone should be administered as in crisis (100 mg/m2 stat followed by 25 mg/m2 six hourly)
  If weight status is unsure a bolus dose is given as below.
  First 2 years of age: 0-25mg.
  2-8 years old: 50mg.
  Above 8 years old: 100mg.
- Patients should resume maintenance therapy promptly after illness/stress has subsided.

Feminizing surgery

- Feminizing surgery is needed usually for the severely virilised (Prader staging more or equal to 3) females.
- It should be performed by an experienced surgeon in a centre with multidisciplinary support (paediatric endocrinologists, mental health professionals, and social work services).
- The age of surgery is controversial and will depend on the local expertise.

Psychological issues

- Patients with CAH and their families should be managed sensitively to minimize the emergence of psychological issues
- Due to the effects of hyperandrogenization on the body and brain these patients are at risk of gender dysphoria and may benefit from early referral to professionals with specialised expertise in managing such problems.

Section 11

NEPHROLOGY

Chapter 64:
Acute Glomerulonephritis

Introduction

Acute glomerulonephritis (AGN) is an abrupt onset of one or more features of an **Acute Nephritic Syndrome**:

- Oedema e.g., facial puffiness
- Microscopic /macroscopic haematuria (urine: tea-coloured or smoky)
- Decreased urine output (oliguria)
- Hypertension
- High urea (Uraemia)

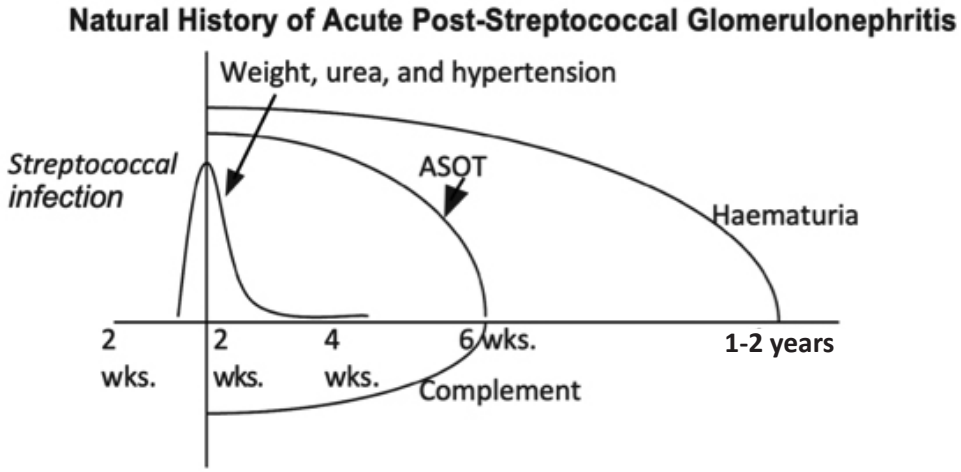
Presenting features of AGN

- Acute nephritic syndrome (most common)
- Nephrotic syndrome
- Hypertensive encephalopathy (may have seizure in posterior reversible encephalopathy syndrome(PRES)
- Pulmonary oedema
- Rapidly progressive glomerulonephritis
- Subclinical (detected on routine examination)

Causes of Acute Nephritis Syndrome
Post-streptococcal AGN
Post-infectious acute glomerulonephritis (other than Group A ß-Haemolytic *Streptococci*)
Infectious related glomerulonephritis
Henoch-Schonlein Purpura/IgA Vasculitis
IgA nephropathy
Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitides
Systemic lupus erythematosus
C3 Glomerulopathy
Primary immune-mediated glomerulonephritis
Haemolytic Uraemic Syndrome/Thrombotic thrombocytopenic purpura
Subacute bacterial endocarditis
Ventriculo-atrial shunt nephritis

POST-STREPTOCOCCAL AGN

- The is the commonest form of acute glomerulonephritis in children; especially between 6-10 years of age.
- Various pathogenetic mechanisms have been described: streptococcal nephritogenicity and molecular mimicry with the kidney ultrastructure and glomerular immune complex formation. Complement activation (especially the alternative pathway) is a key feature in post-streptococcal AGN.



Investigation findings in Post-Streptococcal AGN

- Urinalysis and culture
  - Haematuria – present in all patients
  - Proteinuria (trace to 2+, but may be in the nephrotic range; usually associated with more severe disease)
  - Red blood cell casts (pathognomonic of acute glomerulonephritis).
  - Other cellular casts
  - Pyuria may also be present
- Bacteriological and serological evidence of an antecedent streptococcal infection:
  - Raised Antistreptolysin O Titer (ASOT) (> 200 IU/ml)
  - Increased anti-DNAse B (if available) – a better serological marker of preceding streptococcal infection
- Renal function test
  - Blood urea, electrolytes, and serum creatinine
- Full blood count
  - Anaemia (mainly dilutional)
  - Leucocytosis may be present
- Complement levels
  - C3 level: low at onset of symptoms, normalizes by 6 weeks
  - C4 level: usually within normal limits in post-streptococcal AGN
- Ultrasound of the kidneys (if clinically indicated)

Management

- Strict monitoring - fluid intake, urine output, daily weight, BP *(Nephrotic chart)*
- Penicillin V for 10 days to prevent spread Group after of β - haemolytic streptococcal infection to close contacts and not help with the nephritis (give erythromycin if penicillin is contraindicated)
- Fluid restriction to control oedema and circulatory overload during the oliguric phase until child voids and blood pressure is controlled. A negative fluid balance is targeted when they are overloaded.
  - Day 1: Restrict oral fluid to nutritional needs (up to 400 mls/m²/day). Avoid intravenous fluids if child has pulmonary oedema. Target negative fluid balance
  - Day 2: 400 mls/m²/day till patient voids – (As long as patient remains in circulatory overload)
  - When child is in diuresis – free fluid is allowed
  - Diuretics (e.g. Frusemide) should be given in children with pulmonary oedema. It is also usually needed for treatment of hypertension.
- Diet – no added salt to diet. Protein restriction is unnecessary
- Look out for complications of post-streptococcal AGN:
  - Hypertensive encephalopathy usually presenting with seizures
  - Pulmonary oedema (acute left ventricular failure)
  - Acute kidney injury needing kidney replacement therapy

Management of severe complications of post-streptococcal AGN

Hypertension

- Refer to **Chapter on Hypertension in Children**

Pulmonary oedema

- Give oxygen, prop patient up; ventilatory support if necessary.
- IV Frusemide 2 mg/kg/dose stat; double this dose 4 hours later if response remains poor.
- Fluid restriction – withhold fluids for 24 hours if possible.
- Consider dialysis if no response to diuretics.

Acute kidney injury

- Mild kidney impairment is common.
- Severe persistent oliguria or anuria with uraemia is uncommon.
- Management of severe acute kidney injury: see Chapter on Acute Kidney Injury.

Indications for Kidney Biopsy

- If there is a rapid rise in creatinine to suggest Rapidly Progressive Glomerulonephritis (RPGN)
- Features suggesting a non-post-infectious AGN as the cause of acute nephritis.
- Delayed resolution
  - Low C3 > 3 months
  - Abnormal serum creatinine for > 6 weeks
  - Persistent proteinuria for > 6 months

Follow-up

- Monitor BP at every visit.
- Do urinalysis and kidney function to monitor recovery.
- Repeat C3 levels 6 weeks post event; refer to a paediatric nephrologist if remains abnormal.
- Microscopic haematuria may persist for 1 to 2 years.

Outcome

- Short term outcome: Excellent, mortality < 0.5%.
- Long term outcome: 1.8% of children develop chronic kidney disease following post-streptococcal AGN. These children should be referred to a paediatric nephrologist.

HENOCH-SCHONLEIN PURPURA NEPHRITIS (HSP Nephritis / IgA Vasculitis)

Definition

Classic tetrad:

- Palpable purpuric rash (without thrombocytopenia)
- Abdominal pain
- Arthritis/arthralgia
- Glomerulonephritis (20-55% of HSP patients)

Epidemiology

- Most common systemic vasculitis of childhood affecting small vessels.
- Predominantly aged 3-15 years; 50% < age 5 years.

Aetiology

- Underlying cause remains unknown
- Immune-mediated vasculitis
- Variety of infectious and chemical triggers proposed as a cause, up to 50% have history of preceding URTI

Pathophysiology

- Small vessel leukocytoclastic vasculitis
- Tissue deposition of IgA-containing immune-complexes

Diagnostic approach

History

- Rash
  - Palpable purpura, petechiae and ecchymoses
  - Usually symmetrical
  - Gravity/pressure-dependent areas (buttocks and lower limbs in ambulatory children)
- Arthritis/arthralgia
  - Usually affects large joints of lower limbs
  - Occasionally upper limbs
  - Usually no significant effusion or warmth
- Abdominal pain
  - Commonest complication- intussusception
  - Others- GI haemorrhage, bowel ischaemia/ perforation, pancreatitis, protein-losing enteropathy
- Unusual presentations
  - Epididymitis/orchitis
  - Pulmonary haemorrhage
  - Headaches
  - Seizures

Physical Examination

- Skin lesions
  - Palpable purpura, non-blanching
  - Can occur anywhere on the body, but usually concentrated on the lower extremities
  - Polyarthralgia
  - Abdominal pain on examination
  - Scrotal pain and swelling - 13% of boys

Laboratory Investigations

- Urinalysis
- 24-hour urine protein / urine protein creatinine ratio
- Electrolytes, urea and creatinine

Treatment approach

Symptomatic management

- Joint pain
  - Ibuprofen/ paracetamol
- Severe abdominal pain
  - Oral prednisolone
  - Intravenous corticosteroid if nausea/ vomiting present
- Renal involvement
  - Referral to paediatric nephrologist is necessary.
  - Specific treatment in patients with proteinuria and/or renal impairment may include the following:
  - Intravenous pulsed Methylprednisolone / oral Corticosteroid
  - Oral Azathioprine / Mycophenolate mofetil / Cyclosporine
  - Intravenous Cyclophosphamide
  - Angiotensin-converting-enzyme (ACE) inhibitor, angiotensin receptor blockers(ARB)

Prognosis of HSP nephritis

- Progression to End Stage Kidney Disease (ESKD):
  - 2-3% of those with initial kidney involvement, 15-30% with more severe kidney disease.
- Children at risk for progression:
  - Nephrotic syndrome
  - Kidney insufficiency

Follow-up

If initial UFEME normal/ only microscopic hematuria, monitor BP and UFEME:

- Weekly for the first month after disease onset
- Every 2 week from week 5-12
- Single reviews at 6 and 12 months
- If UFEME remains normal at 12 months, no further follow-up required.

Indications for referral to Paediatric Nephrologist

- Gross haematuria
- Acute nephritis
- Abnormal proteinuria with or without nephrotic syndrome (sub-nephrotic range inclusive)
- Presence of hypertension
- High serum creatinine

Core Messages:
• Post-Streptococcal AGN remains common especially in areas with overcrowding issues. • Generally, Post-Streptococcal AGN has a good long term kidney outcome. • IgA vasculitis runs a much more aggressive course compared to IgA nephropathy. • RPGN presentation demands fast and timely intervention to prevent nephron loss.

Chapter 65:
Nephrotic Syndrome

Diagnosis

Nephrotic syndrome is a clinical syndrome of massive proteinuria defined by

- Nephrotic range proteinuria ≥ 40 mg/m^2/hour (≥ 1 g/m^2/day) or an early morning urine protein creatinine ratio (UPCR) of ≥ 200 mg/mmol
- Hypoalbuminaemia of < 30 g/l
- Oedema

Aetiology

- **Nephrotic syndrome is caused by alteration to the glomerular filtration barrier that leads to loss of proteins in the urine.**
- More than 90% of the condition is primary. Primary nephrotic syndrome is an immune disease that could be idiopathic, a single gene disease (up to 30%) or circulating factor disease affecting the podocytes.
- Secondary nephrotic syndrome could be due to:
  - Infection (Hepatitis B, C, HIV, chronic malaria, subacute bacterial endocarditis, disseminated tuberculosis)
  - Drugs (NSAIDs)
  - Metabolic (Amyloidosis, diabetes mellitus)
  - Systemic disease like systemic lupus erythematosus, neoplasms
  - Others (severe obesity, chronic reflux nephropathy with secondary focal segmental glomerulosclerosis)

This chapter outlines the management of idiopathic nephrotic syndrome. Management of secondary forms of nephrotic syndrome should follow the management of the primary condition.

Investigations at initial presentation

- Full blood count (FBC)
- Renal profile: Urea, electrolytes, creatinine
- Liver function tests, particularly serum albumin
- Urinalysis: Quantitative urinary protein excretion
  - Spot urine protein creatinine ratio (in first morning void) or
  - Timed urine collection e.g., 24 hour urine for protein
- Lipid profile
- Other investigations would depend on the age of the patient, associated kidney impairment, gross haematuria, hypertension or features to suggest an underlying secondary cause for the nephrotic syndrome.

- These may include the following but not limited to:
  - Antinuclear factor / anti-dsDNA
  - Serum complement (C3, C4) levels
  - ASO titres
  - Ultrasound kidney ureter bladder if planned for kidney biopsy or if suspected renal vein thrombosis
  - Other tests as indicated

Kidney biopsy

- A kidney biopsy is not needed prior to corticosteroid or cyclophosphamide therapy. This is because up to 85% of children with idiopathic nephrotic syndrome have minimal change steroid responsive disease.
- Main indication for renal biopsy is **steroid resistant nephrotic syndrome**, defined as failure to achieve remission despite 4 weeks of adequate corticosteroid therapy.
- Other indications are features that suggest non-minimal change nephrotic syndrome:
  - Persistent hypertension
  - Kidney impairment, and/or
  - Gross haematuria

Definitions in nephrotic syndrome

Relapse	Urine protein ≥ 3+ (UPCR ≥ 200 mg/mmol) for 3 consecutive early morning specimens, **with or without oedema** in a child who previously achieved complete remission
Steroid sensitive nephrotic syndrome (SSNS)	Complete remission after 4 weeks of prednisolone at standard dose
Steroid dependent nephrotic syndrome (SDNS)	Two consecutive relapses during recommended prednisolone therapy or within 14 days of its discontinuation
Frequently relapsing nephrotic syndrome (FRNS)	≥ 2 relapses in the first 6-months after stopping initial therapy; or ≥ 3 relapses in any 12 months
Steroid resistant nephrotic syndrome (SRNS)	Failure to achieve complete remission despite therapy with daily prednisolone at a dose of 60 mg/m2/day for 4 weeks
SSNS Late responder	Achievement of complete remission between 4 and 6 weeks of prednisolone therapy (confirmatory period) for new onset disease
Complete Remission	Urine protein nil or trace (UPCR ≤ 20 mg/mmol) for at least 3 consecutive early morning specimens
Partial Remission	UPCR (based on first morning void or 24 h urine sample) > 20 but < 200 mg/mmol and serum albumin ≥ 30 g/l

General advice

- Counsel parents and patients (age-appropriate) about the disease particularly with regards to the high probability (85-95%) of relapse.
- Home urine albumin monitoring: once daily dipstick testing of the first morning urine specimen. The patient is advised to consult the doctor if proteinuria ≥ 3+ for 3 consecutive days.
- The child is also advised to consult the doctor should he/she become oedematous regardless of the urine dipstick result.
- Children on systemic corticosteroids or other immunosuppressive agents should be advised and cautioned about contact with chickenpox and measles. This need to be informed to the doctor urgently and if exposed, should be treated like any immunocompromised child who has come into contact with these diseases.
- In case of exposure to chickenpox in children with immunosuppressive treatment who have not been immunized against VZV, prophylactic treatment with specific Varicella-zoster Immunoglobulin (VZIG) or oral acyclovir for 5–7 days starting within 7–10 days of the exposure can be given.
- For patient who are steroid dependent, need to monitor 25-OH-vitamin D level annually, aiming for levels > 20 ng/ml (> 50 nmol/l)

Management

- Confirm that patient has nephrotic syndrome by ensuring that the patient fulfils the case definition.
- Exclude other causes of nephrotic syndrome. If none, then the child probably has idiopathic nephrotic syndrome.
- A normal protein diet with adequate calories is recommended.
- No added salt to the diet when child has oedema.
- Penicillin V dosage recommendation during oedema for children who have not complete pneumococcal vaccination
  - 1-5 years old: 125mg BD
  - 6-12 years old: 250mg BD
  - >12 years old: 500mg BD
- Fluid restriction - not recommended except in chronic oedematous states

CORTICOSTEROID THERAPY

Corticosteroid is effective in inducing remission of idiopathic nephrotic syndrome.

INITIAL THERAPY FOR NEWLY DIAGNOSED NEPHROTIC SYNDROME:

Once a diagnosis of idiopathic nephrotic syndrome has been established, oral Prednisolone should be started.

- Prednisolone at dose of 60 mg/m^2/day (maximum dose 60mg/day) **for 6 weeks**, followed by alternate day (EOD) Prednisolone at 40 mg/m^2 EOD (maximum dose 40mg EOD) **for 6 weeks** then stop.
  - Prednisolone is administered as a single dose, following food and therapy with antacids /proton pump inhibitors is not routinely needed.
  - 80% of children achieve remission (defined as urine dipstick trace or nil for 3 consecutive days) within 28 days of the corticosteroid treatment.
  - Children who fails to achieve complete remission despite 4 weeks of initial treatment with Prednisolone therapy of 60mg/m^2/day has Steroid Resistant Nephrotic Syndrome and should be referred to a Paediatric Nephrologist for further management. A kidney biopsy is warranted in these children.

RELAPSING STEROID SENSITIVE NEPHROTIC SYNDROME:

- The majority of children with nephrotic syndrome will relapse.
- These children do not need admission unless they are grossly oedematous or experience complications of nephrotic syndrome.
- Serum albumin is not required during relapse.

First Line Treatment of Relapsing Steroid Sensitive Nephrotic Syndrome

- Prednisolone at dose of 60 mg/m^2/day (maximum dose 60mg/day) **until complete remission (negative/ trace dipstick on 3 or more consecutive days)** followed by Prednisolone of 40 mg/m^2 EOD for (maximum dose 40mg EOD) for **4 weeks** then stop.
- **Tapering schedule during alternate day dosing is no longer recommended.**

Second Line Treatment of Relapsing Steroid Sensitive Nephrotic Syndrome

- In children with FRNS and SDNS, maintenance treatment is indicated once remission is achieved.
  - FRNS should be maintained with either a steroid-sparing agent or low-dose prednisolone (preferably ≤ 0.5 mg/kg EOD, maximum at 20mg after EOD.
  - SDNS children should be maintained with a steroid-sparing agent.
- Regular evaluation for significant steroid-related adverse effects is necessary while patient is maintained on prolonged low dose of prednisolone.
- Common steroid toxicity are hypertension, impaired linear growth, obesity, impaired glucose tolerance, ophthalmology complications, abdominal striae and behaviour changes.

Relapse and inter-current infections

- Most common relapse trigger is inter-current upper respiratory tract infection (URTI).
  - In children taking alternate day low dose prednisolone, this can be increased to low dose daily prednisolone (≤ 0.5 mg/kg/day, maximum at 20mg OD) at the onset of infection to prevent a relapse (for a maximum of 1 week)
  - Children not on prednisolone should also be considered for a short course of low dose daily prednisolone at the onset of URTI especially if they have a history of repeated infection-related relapses.

STEROID-SPARING AGENTS

Utility of sparing agent in rank order as tabulated below.

First Line: Cyclophosphamide or Levamisole -Initiation does not require paediatric nephrology consult if clinical indication is evident
Second Line: Either of the First Line agent not tried / Mycophenolate mofetil (MMF) / Calcineurin inhibitor e.g., Cyclosporin A / Tacrolimus / Rituximab -Nephrology consult is warranted and choice of sparing agent chosen at the discretion of the paediatric nephrologist

Cyclophosphamide therapy

- Dose: Per oral 2 mg/kg/day (maximum 150mg/day) for 12 weeks or 3 mg/kg/day (maximum 150mg/day) for 8 weeks. (Maximum cumulative dose should not exceed 168 mg/kg).
- **Begin therapy in combination with the alternate-day Prednisolone starting with a dose of 40 mg/m^{2}EOD and reducing to 10 mg/m^2 EOD until completion of the course of Cyclophosphamide therapy.**
- Three quarter of children with FRNS remains in remission after 2 years.
- Parents should be counselled about the effectiveness and major side effects; which include leukopenia, infection, alopecia, haemorrhagic cystitis, hepatic dysfunction and gonadal toxicity. Risk of azoospermia is higher in post pubertal boys. Risk of female infertility is generally lower.
- In patient who unable to tolerate or uncertain adherence to oral Cyclophosphamide, to discuss with paediatric nephrologist regarding IV Cyclophosphamide.
- Monitor full blood count and urinalysis 2 weekly.
  - While on treatment, patient should be kept well hydrated.
  - Treatment should be discontinued during significant infection, leukocyte count is ≤ 4.0 x10^9/L, neutropenia <1.5 x10^9/L or thrombocytopenia < 50 x10^9/L and therapy resumed at lower dose after recovery.

Relapse post Cyclophosphamide

- Relapse after a course of Cyclophosphamide is treated as for infrequent relapse.
- Should the relapse occur soon after a course of Cyclophosphamide when the child is still steroid toxic, or if the child again becomes SDNS/FRNS then a Paediatric Nephrology opinion should be sought for other steroid-sparing agent.

Levamisole

- Dose: 2- 2.5 mg/kg EOD (maximum 150mg/day)
- Comparative studies indicate that the risk of relapse in patients receiving Levamisole is similar to Cyclophosphamide or MMF.
- Side effects include rashes, leukopenia and raised transaminases. Rarely, anti-neutrophil cytoplasmic antibody (ANCA) positivity with related arthritis, rash and other symptoms of vasculitis may occur in 2% of children. These side-effects resolve with discontinuation of levamisole.
- Monitor full blood count and liver function test every 3-4 monthly and test ANCA antibodies yearly while on therapy.
- Therapy should be discontinued without tapering once patient is in sustained remission and steroid-free for at least 12 months.

Other Steroid-Sparing Agents (consult a paediatric nephrologist)

- Mycophenolate mofetil (MMF)
- Calcineurin inhibitors: Cyclosporin or Tacrolimus
- Rituximab

Complications of nephrotic syndrome and management

Hypovolemia

- Hypovolaemia may occur at disease onset or relapse, especially when associated with diarrhoea, vomiting or unsupervised diuretics therapy.
- Clinical features: Abdominal pain, cold peripheries, poor pulse volume, hypotension and haemoconcentration.
- Patient in shock and/or hypotensive should receive boluses 5% albumin
- (20 ml/kg over 20-30 minutes) without diuretic as per resuscitation guideline.
- Children with oedema, once the blood pressure is stabilised, human albumin 20 or 25% may be given at 0.5-1.0 g/kg over 4-6 hours, with frusemide (1-2 mg/kg IV) given in the middle/at the end, if volume has been restored and urine output insufficient.

Primary Peritonitis

- Clinical features: Fever, abdominal pain and tenderness in children with newly diagnosed or relapse nephrotic syndrome
- Investigations: Blood culture, FBC
- Treatment: Parenteral penicillin and a third generation cephalosporin

Severe Oedema without the sign of hypovolaemia

- During a relapse, patient that has mild oedema generally do not need diuretics. Oedema subsides once patient is rendered into remission following initiation of prednisolone.
- Patient with severe oedema (gross ascites, scrotal/vulval oedema or overt anasarca) may require inpatient oedema control.
- First line: Frusemide
  - There is consideration to switch from oral to IV to overcome poor gut absorption due to the oedematous state.
  - Dose: IV Frusemide 1-2 mg/kg each time and this may be repeated if necessary provided the patient is hemodynamically stable.
  - Need to monitor for hypokalaemia while on frusemide.
- Second line: If the patient does not respond well to frusemide, human albumin can be given together with it.
  - Human albumin (20 or 25%) at 0.5 - 1.0 g/kg given **together with** IV frusemide at 1-2 mg/kg. There are variations in practice: albumin may be given over 2 hours infusion followed immediately with frusemide or over 4 hours infusion with the frusemide dose given in between as well as at the end of the infusion.
- Caution: fluid overload and pulmonary oedema can occur with albumin infusion especially in those with impaired renal function. Urine output and blood pressure should be closely monitored.
- Clinical features of fluid overload : Basal lung crepitations, rhonchi, hepatomegaly, hypertension
- During relapse, serum albumin does not need to be monitored. Albumin infusion should be used judiciously and not to aim at increasing the number. As the patient achieves remission, serum albumin will normalise.
- Refractory cases may require continuous infusion of frusemide or addition of other types of diuretics such as bumetanide, thiazide, spironolactone or amiloride (sequential blockade). Nephrology consult is necessary in such cases.

Thrombosis

- Preventive anticoagulation/antiplatelet is not recommended in the acute nephrotic stage.
- If thrombotic complications occur, thorough investigation and adequate treatment with anticoagulation is usually needed. Please consult a Paediatric Nephrologist.

Acute Adrenal Crisis

- May be seen in children who have been on long term corticosteroid therapy when they undergo situations of stress e.g. acute illness /infection.
- It is important not to omit the steroid completely in children on prolonged therapy during acute illness or when they undergo surgery / trauma to prevent crisis. Sick day management should include doubling the existing steroid dose and this may be given intravenously at equivalent Hydrocortisone dose.
- In children with established acute adrenal insufficiency, regular stress doses of intravenous Hydrocortisone (2-4 mg/kg every 6 hourly; maximum 100mg QID) should be started urgently. This is adjusted according to response and reduced over 4-5 days to oral maintenance dose. Hydration status should be maintained and standard treatment of the acute illness (antimicrobial therapy inclusive) instituted. Consult endocrinologist.

A Paediatric nephrology consultation is recommended if:

- Age <12 months or >12 years
- Persistent hypertension
- Elevated creatinine despite correction of hypovolaemia
- Low C3 or C4 titre
- Unclear of clinical presentation / dilemma between nephrotic and nephritis with nephrotic range proteinuria. (e.g. gross haematuria, intravascular fluid overload with hypertension, kidney impairment)
- Steroid resistance
- Needing steroid sparing agents beyond oral Cyclophosphamide/Levamisole.

STEROID RESISTANT NEPHROTIC SYNDROME (SRNS)

- Those who do not achieve complete remission within 4 weeks prednisolone at a dose of 60 mg/m^2/day for 4 weeks is deemed as steroid resistant.
- Up to 10% of children with SSNS may eventually present with Late Resistance.
- These children needs to be under Paediatric Nephrology follow up.

Possible outcomes at 4 weeks of prednisolone at standard dose:
1. Complete remission ⟶ **SSNS**
2. No remission ⟶ **SRNS**
3. Partial remission

For 2&3: Allowed another 2 weeks of observation (*Confirmatory period*) with the daily prednisolone ± 3 pulses of IV Methylprednisolone 500 mg/m2 and Renin-angiotensin-aldosterone inhibitor (RAASi)

Possible outcomes at the end of the *Confirmation period*:
1. Complete remission ⟶ **Late responder SSNS**
2. Partial / No remission ⟶ **SRNS**

- SRNS: Refer for kidney biopsy. Specific treatment depends on the histopathology.
- Genetic testing is required in congenital/infantile nephrotic syndrome (onset < 3 months and within first year of life respectively), nephrotic syndrome with extra renal features, familial steroid resistance, non-response to therapy with calcineurin inhibitor and prior to kidney transplantation.
- Immunosuppressants used for SRNS are Cyclosporin, Tacrolimus, Mycophenolate mofetil, Cyclophosphamide infusion, IV Methylprednisolone (Mendoza) and biologic agents such as Rituximab infusion. With time, more novel therapeutic strategies may be available.

General management of the nephrotic state

- Control of oedema; patient may need regular diuretics (Frusemide/Bumetanide ± Thiazide/ Amiloride/ Spironolactone).
- Restriction of dietary sodium.
- Antiproteinuria ± blood pressure control with ACE inhibitor or Angiotensin II receptor blocker (ARB). Blood pressure and creatinine monitoring is necessary 1-2 weeks after initiation of ACE inhibitor / ARB.
- Penicillin prophylaxis in oedematous state.
- Monitoring:
  - Kidney function, liver function, calcium, phosphate, urine protein and therapeutic drug monitoring if applicable at 3 monthly interval.
  - Lipid profile, thyroid function test (TFT) and 25-OH-Vitamin D assay annually or as clinically indicated.
  - L-thyroxine treatment and lipid lowering agent (statin) to be consider based on TFT and lipid profile result.
- Dysgammaglobulinaemia is common in nephrotic state but this does not warrant routine monitoring unless in the event of recurrent infections.
- Nutrition: normal caloric and dietary protein intake, as appropriate for age with salt restriction.
- Response to immunosuppression remains the most important predictor of long term kidney outcome. Children with persistent proteinuria may develop decline in kidney function with time.

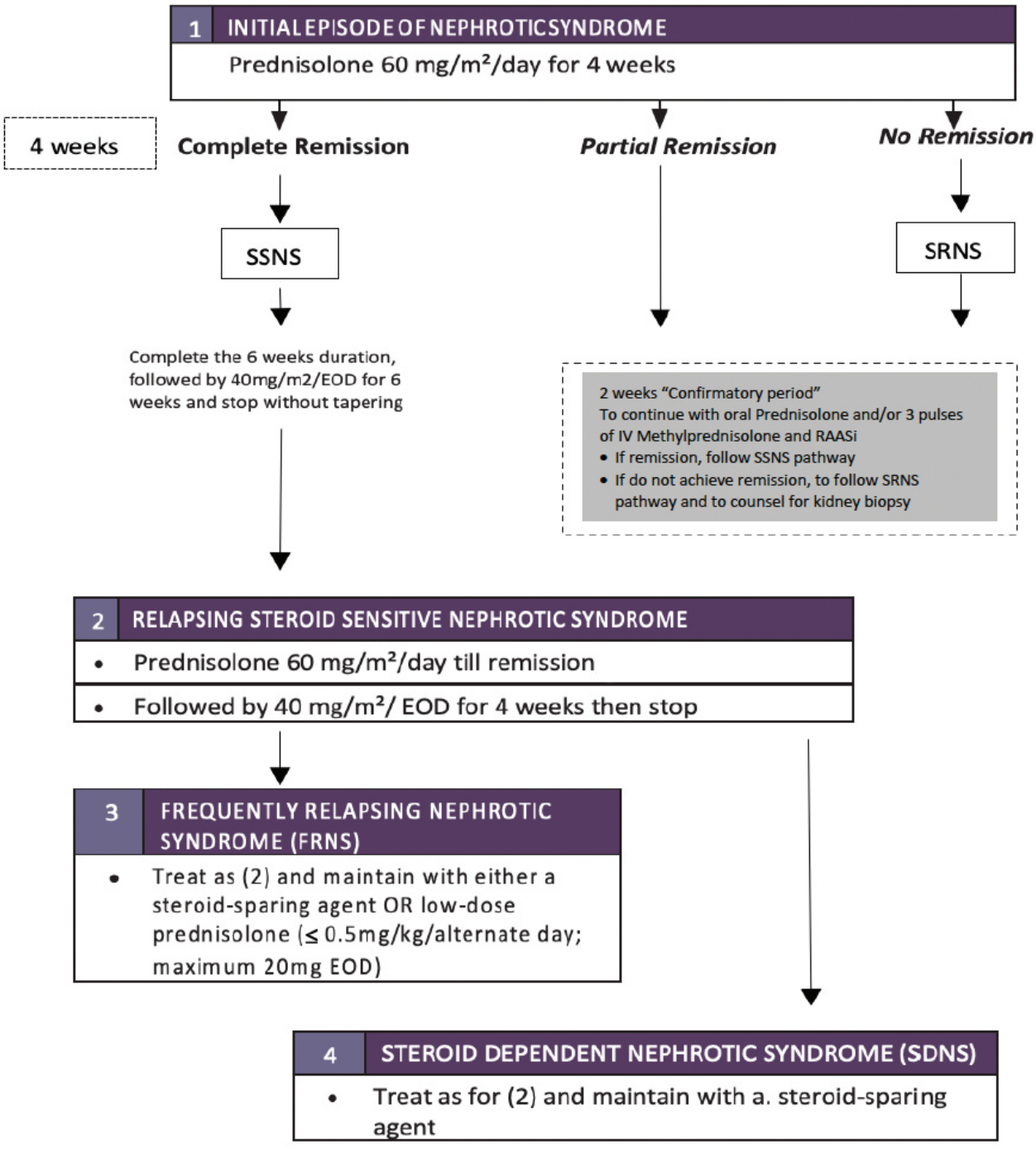
Vaccination and Nephrotic Syndrome

Immunisation:

- Give live vaccines 4 weeks after cessation of corticosteroid therapy, 3 months after cessation of Cyclosporin/MMF/Cyclophosphamide and 6 months post Rituximab.
- Other types of vaccines (non-live) may be administered when the child is in remission.
- Pneumococcal vaccine should be administered to all children with nephrotic syndrome.
- Patient receiving immunosuppressants should be prioritised to receive the COVID vaccine and the additional/booster dose.

Core Messages:
• Most children with idiopathic nephrotic syndrome demonstrates steroid responsiveness • Children on steroid should be monitored for steroid toxicity • Steroid unresponsiveness predicts future decline in kidney function

MANAGEMENT OF NEPHROTHIC SYNDROME



Renin-angiotensin-aldosterone inhibitor (RAASi)

Chapter 66:
Acute Kidney Injury (AKI)

Definition

- Abrupt (within hours) decrease in renal function, with both injury (structural damage) and impairment (loss of function) as measured by a rapid decline in glomerular filtration rate.
- Potentially reversible
- Evolving definition *(AKIN, pRIFLE, KDIGO)*. However, most widely accepted definition is KDIGO whereby measurement of serum creatinine and urine output are necessary to stage the degree of AKI.

Stage	Serum creatinine (SCr) µmol/L	Urine output
1	Increase to 1.5 to 1.9 times from baseline, OR increase of ≥ 26.5 umol/L	< 0.5 ml/kg/hour for 6 to 12 hours
2	Increase to 2 to 2.9 times from baseline	< 0.5 ml/kg/hour for ≥ 12 hours
3	Increase > 3 times from baseline, OR SCr ≥ 353.6 µmol/L OR Initiation of renal replacement therapy, OR eGFR < 35 ml/min per 1.73m^2 (< 18 years)	< 0.3 ml/kg/hour for ≥ 24 hours, OR anuria for ≥ 12 hours

Risk factors of developing AKI:

- vasopressor use
- invasive mechanical ventilation
- percent fluid overload
- post cardiac surgery patient
- oncology children with high risk for tumour lysis syndrome
- pre-existing renal disease
- use of nephrotoxic drugs

Biomarkers for AKI

- Urea is an unreliable marker for AKI as it is secreted and reabsorbed at tubular level, hence not accurately reflecting renal function.
- Similarly, serum creatinine is also unreliable as it is secreted at tubular level. However, this remains the best marker for kidney function since it is universally available in most hospitals and inexpensive despite its limitation.
- Novel biomarkers in research include neutrophil gelatinase–associated lipocalin (NGAL), cystatin C and kidney injury molecule (KIM-1).

Clinical features

- Oliguria (< 300 ml/m^2 /day; < 1 ml/kg/hour in neonates, < 0.5 ml/kg/hour in children)
- Anuria (< 100ml/day)
- Seizures – secondary to hypertensive encephalopathy/uremic encephalopathy
- Acute pulmonary oedema
- Electrolyte derangement – hyperkalaemia, hyperphosphataemia, hypocalcaemia, high anion gap metabolic acidosis

Common causes of AKI

Pre-renal

- Absolute decrease in extracellular fluid volume (Gastrointestinal losses, haemorrhage)
- Decreased renal blood flow (cardiac failure, renal artery stenosis)
- Altered intrarenal haemodynamics (drug-induced e.g. NSAIDS, Calcineurin inhibitor, ACEI, sepsis, hypercalcaemia, hepatorenal syndrome)

Intra-renal

- Glomerular disorders (glomerulonephritis, thrombotic microangiopathies)
- Tubulointerstitial disorders
- Acute tubular necrosis (hypoxic-ischaemic injury, aminoglycosides, chemotherapy)
- Toxin (myoglobin, haemoglobin)
- Venom (bee sting)
- Infection, pyelonephritis
- Tubular obstruction [crystals due to uric acid (tumor lysis syndrome), calcium oxalate, acyclovir, methotrexate, myoglobin]

Post-renal

- Anatomic obstruction (bladder outlet e.g., pelvic tumour, ureteral stones or stricture, posterior urethral valves, acute obstruction in solitary kidney)

Investigations

- Full blood count
- Renal profile, serum electrolytes
- Serum albumin, calcium, phosphate
- Blood gases
- Urinalysis

The following investigations in suspected underlying cause:

- Full Blood picture- e.g. Microangiopathic haemolytic anaemia (MAHA)
- Urine electrolytes (paired sample with serum) – FENa, urine osmolality
- Kidney imaging – ultrasound
- Complements, ANA, anti-dsDNA, serological etc.

Management of AKI

- Treat early as it may prevent further complications
- Remove offending cause or treat underlying aetiology
- Dialysis if indicated (Refer chapter acute dialysis)

Hypovolaemia/Intravascular depletion

- Aggressive fluid therapy. Administration of intravenous (IV) fluid bolus with normal saline (10 to 20 ml/kg over 30 minutes) may prevent more severe intrinsic AKI.
- Aim to achieve euvolaemic state

Euvolaemia

- Ensure balance input and output

Hypervolaemia

- Clinical features (hypertension, displaced apex beat, increase JVP, hepatomegaly, basal crepitations etc.),
- Monitor input output balance, daily weight, central venous pressure (CVP) if possible.
- Calculation of percentage of fluid overload
- Fluid restriction
  - If necessary to give fluid, restrict to insensible loss (400 ml/m^2/day) initially. This includes oral and intravenous fluids
  - Further fluid target should be based on regular clinical assessment
- Diuretics
  - High dose IV frusemide 2-5 mg/kg/dose slow infusion
    Do not exceed the rate of 4mg/min
  - Continuous infusion 0.5-2 mg/kg/hour
- Refractory pulmonary oedema: dialysis

Hypertension

- Usually related to fluid overload and/or alteration in vascular tone.
- Antihypertensives – preferably short-acting antihypertensive as it is easily titrated compared to long-acting.
- A diuretic is usually needed
  **Caution with the use of ACE-I in AKI as it may worsen it (> 20% increment post commencement warrants for stopping ACE-I)*

Hyperkalemia

- Definition: when serum K^+ > 6.0 mmol/L (neonates) and > 5.5 mmol/L (children)
- To perform urgent ECG first to look for Tall tented T wave, prolonged PR interval, widening QR complexes, flattened P wave, Sine wave, VF or asystole

- Treatment of Hyperkalemia

  - Do a 12-lead ECG and look for hyperkalemic changes. If ECG is abnormal or plasma K^+ > 7 mmol/L, connect patient to a cardiac monitor and give the following in sequence:
    i. IV 10% Calcium gluconate 0.5 - 1.0 ml/kg (1:1 dilution) over 5 -15 mins (immediate onset of action)
    ii. IV Dextrose 0.5 g/kg (2 ml/kg of 25%) over 15 – 30 mins
    ± IV Insulin 0.1 unit/kg (onset of action 30 mins)
    iii. IV 8.4% Sodium bicarbonate 1 ml/kg (1:1 dilution) over 10 - 30 mins (Onset of action 15 - 30 mins)
    iv. Nebulized 0.5% Salbutamol 2.5 - 5 mg (0.5 - 1ml: 3ml 0.9% Saline) (Onset of action 30 mins)
    v. Calcium polystyrene sulphonate
    Child: Oral 0.5-1 g/kg daily in divided dose (e.g. 0.25 g/kg/dose 4 times per day), max 60g per day
    Neonate: Rectal
    OR
    Sodium polystyrene sulphonate
    Child: Oral 0.5-1 g/kg daily in divided dose (e.g. 0.25 g/kg/dose 4 times per day), max 60g per day
    Neonate: Rectal

  - In patients with serum potassium between 5.5 - 7 mmol/L without ECG changes, give calcium or sodium polystyrene sulphonate
  - If insulin is given after dextrose, monitor for hypoglycaemia
  - Dialyse if poor or no response to the above measures

Nutrition

- AKI is a hypercatabolic state
- The aim is to provide adequate nutrition
- Caloric and protein: provide age appropriate suggest diary intake
- Commence enteral feeding as soon as possible
- Should caloric intake be insufficient due to fluid restriction, commence dialysis.

Prevention of AKI

- Optimal blood pressure control
- Avoid nephrotoxic medications
- Renal adjusted dose for specific drugs

Neonatal AKI

- Serum creatinine at birth reflects maternal creatinine and this decline with time.

Definition of neonatal AKI :

Neonatal AKI is defined as an creatinine greater than 133 umol/L (1.5 mg/dL) or an increase of at least 17 to 27 umol/L per day (0.2 – 0.3 mg/dL) from a previous lower value.

"Red flags" / Risk factors for neonatal AKI includes:

- Outborn delivery
- Preterm delivery
- Hypoxic insult / Resuscitation with adrenaline
- Need for surgical intervention
- Hyperbilirubinemia
- Exposure to nephrotoxic agent

Estimation of Glomerular filtration rate

$$\text{Schwartz/Brion eGFR (ml/min/1.73m2)} = \frac{33\ (\text{Preterm}) \times \text{Height (m)}}{\text{Serum Creatinine (mg/dL)}} \quad \frac{45\ (\text{Term}) \times \text{Height (m)}}{\text{Serum Creatinine (mg/dL)}}$$

$$\text{Schwartz/Brion eGFR (ml/min/1.73m2)} = \frac{29.2(\text{Preterm}) \times \text{Height (cm)}}{\text{Serum Creatinine (µmol/L)}} \quad \frac{39.8\ (\text{Term}) \times \text{Height (cm)}}{\text{Serum Creatinine (µmol/L)}}$$

To adjust for Height to cm and Serum Creatinine to SI unit umol/l

Much progress made in the last decade to mitigate AKI in the NICU. These include usage of caffeine among premature infants, theophylline in neonates with hypoxic-ischaemic encephalopathy and active surveillance program of nephrotoxic drugs use in the NICU.

Core Messages:

- AKI is potentially reversible and aggressive management is warranted to mitigate this
- Children with severe AKI requires long term surveillance as they are at risk of chronic kidney insufficiency
- Neonates are special group at risk for AKI and it is important to identify this early as neonatal AKI may lead to nephron loss and risk of CKD later.

Chapter 67:
Acute Dialysis

Introduction :

The purpose of dialysis:

- To remove endogenous and exogenous toxins
- To maintain fluid, electrolyte, and acid-base equilibrium until kidney function improves

Criteria or indications for initiation of acute dialysis
• Symptomatic uraemia (encephalopathy, coagulopathy, neuropathy, or pericarditis) • Severe metabolic acidosis or severe electrolyte derangements (hyperkalaemia, symptomatic hypo/hypernatremia, symptomatic hypocalcaemia with hyperphosphatemia) refractory to treatment • Severe overload in the presence of oligo-anuria not responsive to diuretics (daily % fluid overload (FO) > 10-15% with increased ventilatory requirements) • Inborn errors of metabolism: neonatal hyperammonaemia or acute metabolic crisis • Intoxication /poisoning (ethylene glycol, methanol, isopropanol, valproic acid, salicylate) • Need for high volume infusions even if AKI is not severe e.g., intravenous immunoglobulin or repeated blood transfusions in an oliguric child • Increased nutritional needs in a catabolic septic child with AKI • Others: tumour lysis syndrome

$$* \% FO = \frac{\text{total fluid input (L)} - \text{total fluid output (L)} \times 100}{\text{admission weight (kg)}}$$

Modalities of acute dialysis or kidney replacement therapy (KRT):

- peritoneal dialysis (PD)
- haemodialysis (HD)
- continuous renal replacement therapy (CRRT)

When considering the initiation of KRT, identification of patient characteristics that may preclude one or more of the modalities is necessary:

- Size of the patient: at some centres, equipment, personnel, and supplies may not be available for HD or CRRT in infants and small children
- Haemodynamic stability: HD may be difficult to perform in haemodynamically unstable patients
- Abdominal or diaphragmatic pathology may preclude the use of PD
- Lack of vascular access precludes the use of HD and CRRT
- The anticipated duration of KRT and presence of any concurrent coagulopathy

Acute PD

Types of Catheter Access:

- A formal Tenckhoff catheter surgically inserted (open) or percutaneously inserted by the bedside by trained personnel.
- Acute stiff PD catheter.
- Improvised PD catheters e.g. chest tubes, multipurpose drainage catheters, adult sized central venous lines, nasogastric tubes, and Foley's urinary catheter.

Contraindications to Acute PD:

Absolute:

- Abdominal wall defects, fungal peritonitis, abdomen compartment syndrome

Relative:

- Perforated bowel/viscus, recent abdominal surgery, paralytic ileus, difficult ventilation/on HFOV, abdominal wall hernias, abdominal wall cellulitis/burns, pleuroperitoneal fistula

Sites of insertion (single catheter insertion):

- The most appropriate site of catheter insertion will depend on the overall clinical setting.
- Recommended insertion sites for bedside percutaneous placement of a PD catheter are shown in the diagram:

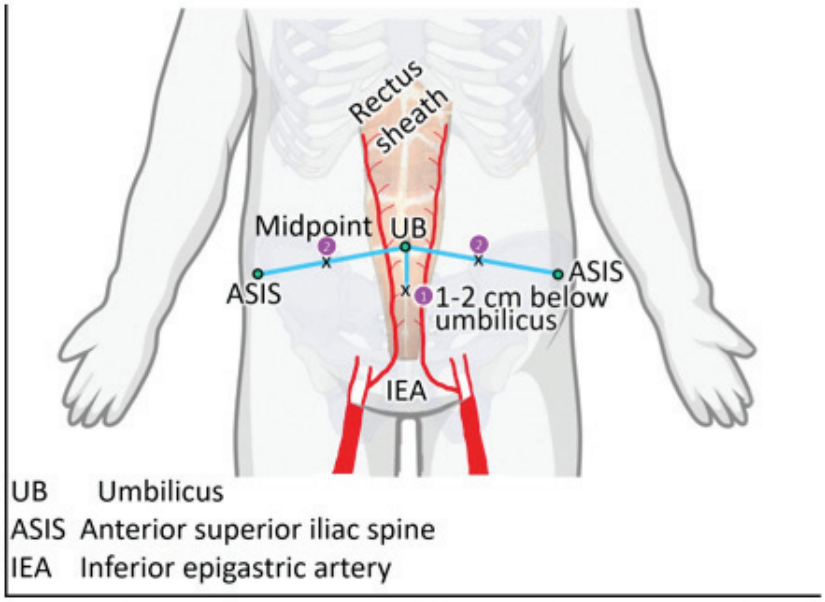


Figure 1 The relationship of the inferior epigastric artery with site of insertion

1. In the midline,1 to 2 cm below umbilicus (in small children/infants, this space may be limited and occupied by the bladder) or
2. Midpoint between the umbilicus and anterior superior iliac spine of the hip, on either side
   - The inferior epigastric artery, which lies within the rectus muscle, is usually running medial to the landmarks in 2.
   - Ensure that the catheter is inserted way below any enlarged spleen or liver, and the bladder must be catheterised.

Continuous Flow Peritoneal Dialysis (CFPD):

> Therapy with this technique in children warrants consultation with a paediatric nephrologist

- Two catheters are necessary for this technique.
- Surgical assistance may be required for catheter insertions.
- CFPD on average is 3-5 times more effective for clearance and ultrafiltration than conventional PD.
- CFPD requires a second catheter to be placed in the peritoneal cavity for continuous flow of dialysate through the abdomen.
- The exact technique differs according to the method used and catheters of appropriate diameter and length are required.
- The potential sites are marked in the diagram on the previous figure 1
- Ideally, both the catheters should be directed away from each other.

Procedure of PD catheter insertion:

- Obtain consent for peritoneal dialysis and catheter insertion.
- Prophylactic antibiotics are recommended prior to catheter insertion, if not already on treatment antibiotics.
- Empty the bladder or catheterise in an unconscious / ill patient if not already placed.
- Perform the procedure under strict aseptic technique and apply sedation based on local protocol.
- Assemble PD lines and spike fluids with additives as indicated.
- Clean the area with povidone iodine/chlorhexidine and drape the patient.
- Infiltrate the insertion site and subcutaneous tissue with local anaesthetics.

Technique of insertion of different PD catheters	
Acute stiff PD catheter *(applicable to improvised catheter such as chest tube)*	
1	Advance the large bore cannula (18-20G) perpendicularly until the peritoneum is breached (a 'give" is felt). Connect to the dialysate bag and instil 10-20 ml/kg dialysate to help prevent traumatic puncture of the underlying viscus by creating a false ascites.
2	Check catheter for any breakages (by withdrawing the stylet) before insertion.
3	Make a small skin incision (slightly smaller than the diameter of the catheter) using a size 11 straight surgical blade) and avoid cutting the muscle layer.
4	Introduce the catheter with the stylet perpendicular to the abdominal wall while controlling the length with the dominant hand, until the peritoneum is pierced.
5	The stylet is then withdrawn, and the catheter gently pushed in, directing it caudally towards the pelvic cavity until all the perforations are well within the peritoneal cavity
Catheter insertion using the Seldinger technique *(applicable for soft PD catheter, multi-purpose drainage catheter or adult-sized double lumen central venous catheter)*	
1	Various commercial kits and sizes are available. In resource limited situation, improvisation should be considered.
2	Advance the large bore cannula (18G or larger) perpendicularly until the peritoneum is breach (a 'give" is felt). Connect to the dialysate bag and instil 10-20 ml/kg dialysate to help prevent traumatic puncture of the underlying viscus by creating a false ascites
3	Thread and advance the guide wire through the cannula aiming towards the pelvic cavity.
4	Remove the cannula. Make a skin nick. Ensure the exit site is kept as small as possible to minimise risk of leak. Over the guide wire, introduce the dilator.
5	Subsequent steps can be either: a. <u>Soft PD catheter</u>: • Introducer in the soft PD catheter set comes with an overlying peel-away sheath. Once the introducer is inserted remove the dilator and guide wire while retaining the sheath in the abdomen. • Introduce the soft PD catheter through the sheath into the abdominal cavity directing it to the pelvic cavity until the external cuff fits snugly at the skin. • Peel off the sheath leaving the catheter in situ. Two operators needed to perform this step. Secure the catheter with the cuff slightly buried with a purse string suture. b. <u>Multi-purpose drainage e.g., "pigtail" catheter and the double lumen central venous catheter</u>: • For the multi-purpose drainage e.g., "pigtail" catheter and the double lumen central venous catheter, introduce the dilator over the guide wire to dilate the track and remove leaving the guide wire in place. • Insert the catheter over the guide wire and direct it to the pelvic cavity. Then, the guide wire is removed leaving the catheter in situ. Secure the catheter with a purse string suture.
6	Cover the site with dry gauze and secure with plaster. If there is staining or bleeding seen, this needs to be dealt with immediately.
7	Connect the catheter to the PD line; this may be improvised using consumables available in the unit if commercial ready-to-use device (Y set) is not available. The entire system i.e., the dialysate, catheter and drainage bag should be connected in a closed circuit and three-way taps applied to ease operation. For small fill volumes (≤ 100ml), a buretrol or chamber can be used to measure this volume accurately.

Further additives to PD fluid:

- Heparin (500 unit/L) can be added into the PD fluid to prevent fibrin clots.
- Antibiotics can be added to PD fluid to treat PD peritonitis.
- Once serum potassium falls below 4 mmol/l, potassium chloride (KCL) (4 mmol/L) should be added. (*1 gm of KCL in 10 ml ampule is equivalent to 13.3 mmol of potassium. Hence adding 3 ml to 1 litre would result in dialysate with 4.0 mmol/L of potassium).*
- If bicarbonate solution is used as PD fluid, Dextrose (1-4%) would need to be added to aid ultrafiltration.

The acute PD prescription
Fill Volume (FV) • Start at 10-20 ml/kg and observe for discomfort, cardiorespiratory deterioration or leakage from catheter exit site. • The volume can be increase gradually to a maximum of 30-40 ml/kg or 800-1000 ml/m^2, if tolerated. • FV should not exceed 800 ml/m2 in < 2 years

PD Solution
• Type of PD solution
  • Standard commercially available lactate-based: 1.5%, 2.5%, 4.25% dextrose.
  • Bicarbonate dialysate, useful if lactic acidosis is a significant problem e.g. in sepsis associated with lactic acidosis, hepatic failure or inborn errors of metabolism.
• PD is usually initiated with dextrose 1.5% concentration; higher concentration is required if more rapid ultrafiltration is desired.
• Watch out for hyperglycemia, hypotension, or hypovolaemia with the use of more hypertonic PD solution.

Duration of PD • The duration of PD depends on the needs of the patient – usually continuous throughout a full 24 hour period. • Close monitoring for peritonitis, electrolytes, drug dosages and therapeutic drug monitoring, should be conducted when providing acute PD.
Note: • *In centres with continuous renal replacement therapy (CRRT), the bicarbonate solution used for CRRT can be used.* • *In centres where this is not readily available, the assistance of the pharmacist is required to constitute a physiological dialysis solution. For example, dialysis fluid can be made by adding 50% Dextrose to either Ringer's Lactate, Plasmalyte B or Hartmann's solution*

Monitoring while on PD:

- Input / output chart, vital signs and PD chart should be kept up to date – close monitoring is mandatory to achieve and maintain normotension and euvolaemia.
- Check for exit site leaks and effluent turbidity – if present, this must be noted to the doctor immediately. Send PD fluid for cell count and culture and sensitivity if effluent is turbid and antibiotics should be initiated - *decision to continue PD would then need to be evaluated.*
- Blood urea, serum electrolytes, and creatinine should be requested according to clinical context; these should be reviewed by the doctor once ready. These should be measured 12-hourly for the first 24 hours and once daily, as indicated.

Commonly used Intraperitoneal (IP) antibiotic dosing recommendations for treatment of peritonitis			
	Intermittent therapy (1 exchange daily for minimum 6 hours)	Continuous therapy (All exchanges)	
		Loading dose	Maintenance dose
Aminoglycosides			
Amikacin	2 mg/kg daily	Not advised	
Gentamicin	0.6 mg/kg daily	Not advised	
Cephalosporins			
Cefazolin	15 mg/kg daily (for long dwell) 20 mg/kg daily (for short dwell)	500 mg/L	125 mg/L*
Cefepime	1000mg daily	500 mg/L	125 mg/L*
Cefotaxime	500-1000mg daily	No data	
Ceftazidine	1000-1500mg daily (for long dwell) 20 mg/kg daily (for short dwell)	500 mg/L	125 mg/L*
Cefriazone	1000mg daily	No data	
Penicillins			
Amoxicillin	No data		150 mg/L
Ampicillin Ampicillin/ Sulbactam	4g daily	 1000mg/500mg	125 mg/L 133.3mg/66.7mg
Cloxacillin	1000-1500mg daily (for long dwell) 20 mg/kg daily (for short dwell)	500 mg/L	125 mg/L*
Penicillin G	No data	50,000 unit/L	25,000 unit/L
Others			
Imipenem Cilastatin	500mg alternate exchange	250 mg/L	50 mg/L
Meropenem	500mg daily (for long dwell in APD) 1000mg daily (for short dwell in CAPD)		125 mg/L
Ciprofloxacin	No data		50 mg/L
Vancomycin**	15-30 mg/kg every 5-7 days*** for CAPD 15 mg/kg every 4 days for APD	20-25 mg/kg	25 mg/L
Fluconazole	150-200mg every 24-48h (Oral route preferred)	No data	

**Increase in doses by 25% may be needed for patients with significant residual kidney function*
***IP Vancomycin should be administered intermittently*
****Supplemental doses may be needed for APD patient and dwell time of at least 6 h is preferred*
This table is not exhaustive, please refer to guidelines for antibiotic/antimicrobial dosing not listed here

Acute haemodialysis and CRRT:

- Vascular access is the key component of these modalities, and a wide variety of temporary vascular catheters are available in the market.
- Prescription for acute HD should be discussed with the paediatric nephrologist.
- Biohazard serology (Hepatitis B, Hepatitis C, HIV) must be screened for prior to initiation of either therapy.
- Complications include blood vessel thrombosis, haemorrhage, catheter related blood stream infection and introduction of air emboli.
- Acute HD is efficient for rapid solute clearance and ultrafiltration especially in life threatening hyperkalaemia, drug toxicity and tumour lysis syndrome.
- CRRT has the ability to control UF separately from solute removal, hence allowing greater flexibility within the prescription i.e.:
  - better uraemia control in metabolic crisis and poisoning
  - there is usually no need for fluid restriction, allowing for adequate nutrition
  - allows for large volume infusions (medication/blood products)
- The main disadvantages are:
  - requires trained personnel for safe and proper provision of CRRT/HD
  - cost (filters/dialysate)
  - anticoagulation is required to prevent filters from clotting

Longer term kidney replacement therapy and dialysis access occlusion

- For children who continue to require longer term kidney replacement therapy or progress to end stage kidney failure, occlusion of dialysis access (Tenckhoff/tunneled catheter) is a common mechanical complication.
- Fibrinolytic agents (urokinase/streptokinase) have a role in catheter salvage – the use of these would warrant consultation with a paediatric nephrologist.

Core Messages:

- Although various modalities of kidney replacement therapies have been described, they may not be readily available in reality.
- Nevertheless, PD is feasible even in resource limited setting and improvisation of techniques is possible to allow delivery of care.
- An attempt of dialysis should be offered to any child with AKI unless contraindicated.

Chapter 68:
Neurogenic Bladder

Introduction

- Neurogenic bladder is bladder dysfunction caused by pathology of the brain or spinal cord.
- The risk of serious complications is high and can be prevented with proactive management.

Multi-disciplinary approach

- Management of patients with spinal dysraphism is long-term. It often requires a multidisciplinary team that will look into all aspects of care including
  - Cognitive impairment, neurological deficits, and seizures
  - Bladder and bowel management
  - Chronic kidney disease (CKD)
  - Foot and leg deformity
  - Welfare and school placement

Causes of Neurogenic Bladder
Neural tube defects (NTD) such as myelomeningocele • The prevalence of NTD in Malaysia is 0.42 per 1000 live births and is associated with maternal folate deficiency. • It may require early repair.
Tethered cord syndrome • Characterized by onset of lower limb weakness and bladder dysfunction during pubertal growth spurt. • Tissue attachments caused by spina bifida occulta or prior myelomeningocele repair prevent the spinal cord from moving as the vertebra elongates, resulting in mechanical stretching and ischaemic injury. • It involves the level of spinal cord distal to S2 by thickened filum terminale and low-lying conus.
Acquired conditions • Spinal cord infection, injury or tumor.
Brain pathology • Cerebral palsy, tumours.
Other non-neurological conditions • Anorectal malformation, cloacal anomaly, bladder exstrophy and posterior urethral valves (PUV).

- Level of spinal cord lesion, clinical neurological deficit and voiding habits are not reliable predictors of the severity of bladder dysfunction, pattern of detrusor-sphincter dysfunction, and subsequent risk of renal damage.

Clinical evaluation of newborn

- The goal of initial evaluation is to determine the underlying cause of neurogenic bladder and other disability, and risk stratification of the patient.

Complete neonatal history and physical examination.

- Neonate has not passed urine within 24 hours of life or has poor and dribbling urine stream
- Palpable bladder
- Examination of the external genitalia
- Examination of the back for sacral pit, tuft of hair, flattened buttocks, absence of upper gluteal cleft, under-developed lower limbs, and other stigmata
- Parent circumstances and receptiveness

The initial investigations include

- Renal profile
- Ultrasound (US) of the kidneys, ureter, and bladder
- Ultrasound spine may be performed within the first 6 months of life, as the incompletely ossified posterior vertebral arch provides an acoustic window. MRI spine is preferred in children older than 6 months if indicated.
- Micturating cystourethrogram (MCUG) is rarely indicated unless other conditions such as PUV need to be rule out

Late presentation features include

- Bladder stone
- Urine retention, urinary incontinence, poor urine flow (dribbly and straining)
- Recurrent urinary tract infection (UTI)
- US findings of bilateral hydronephrosis, hydroureter, and thickened bladder

Management

The aims of management are:

- Low pressure storage of urine in order to protect the upper urinary tract
- Complete bladder emptying in order to prevent recurrent UTI and bladder stones
- Continence, allowing integration in school and community

Proactive Management for neonate with myelomeningocele
• Early clean intermittent catheterization (CIC) • CIC every 4-6 hours as it leads to better acceptability from parents and child who get used to the routine. Parents may decrease frequency of CIC if post-void residual urine is minimal. It is often difficult to initiate CIC in older children and there is evidence that proactive management preserves kidney function, reduces renal scarring rate and results in fewer bladder augmentation procedures. • Antibiotic treatment of symptomatic UTI • Anticholinergic if upper tract dilatation or high pressure bladder

Expectant Management for neonate with spinal bifida occulta

These children have wet nappies due to reflex detrusor contraction.

- In children with no upper tract dilatation on ultrasound, expectant management include regular monitoring.
- CIC and anticholinergic medication are only commenced when there is upper tract dilation on ultrasound, or UTI.

Other voiding methods using manual suprapubic pressure on bladder (Crede method) or Valsalva are not recommended as bladder emptying is incomplete, and these methods worsen upper tract reflux and dilatation.

How to initiate CIC
1. CIC should be commenced once the diagnosis is confirmed or after child has undergone surgical repair of myelomeningocele. 2. Trained health care professional explains indication and technique of CIC.
Procedure
1. Assemble all equipment: Appropriate sized catheter (hydrophilic, gel reservoir and non-coated catheter), lubricant, small mirror (for girls), and kidney dish. 2. Wash hands with soap and water. 3. Clean the urethral orifice with clean water.
For boys:
1. Use one hand to lift the penis and stretch the urethral. 2. Lubricate the catheter, with lignocaine gel or K-Y jelly. 3. Use the other hand to insert the catheter into the urethra. 4. Advance catheter with gentle firm pressure until catheter tip reaches bladder and urine begins to drain through the catheter. There may be some resistance as the catheter tip reaches the bladder neck. 5. If there is resistance to insertion – slightly withdraw the catheter, stretch penis further, and apply gentle perineal pressure before inserting the catheter again.
For girls:
1. Use one hand to separate labia. 2. Lubricate the catheter, with lignocaine gel or K-Y jelly. 3. Use the other hand to insert the catheter into the urethra. 4. Advance catheter with gentle firm pressure until catheter tip reaches bladder and urine begins to drain through the catheter.
For both boys and girls
1. Urine may be drained into a kidney dish or directly into the toilet bowl. 2. Once urine stops flowing, the catheter should be rotated and for further urine drainage and then withdrawn slowly. 3. Wash hands after upon completion.
How to select correct catheter size?
Newborns : 5-6 Fr Older Children: 8-10 Fr Adolescents : 12-14 Fr

How often should CIC be performed?
1. Start with CIC 5-6 times per day – morning upon walking up, mid-morning, during school recess, before lunch, before teatime, after dinner and just before bedtime. 2. Parent may decrease frequency of CIC if post-void residual is minimal.
Can catheters be reused?
1. Clean re-used supplies do not increase the likelihood of UTI. 2. After using a catheter, rinse it well under running tap water, air dry and store in a clean and dry container.
Alternative to CIC: Vesicostomy 1. In children who develop recurrent UTI if parents are unable to perform CIC 2. In patients with elevated bladder pressure despite compliance to CIC 3. In patients with multiple other disabilities which increase caregiver burden

Follow up care

- Review medical history, symptomatic UTI
- Monitor blood pressure, growth
- Optimize bladder management, bladder diary, CIC
- Optimize bowel management
- Renal profile, Urinalysis, Urine culture in suspected febrile or symptomatic UTI
- Ultrasound kidney ureter bladder
- Urodynamic study
- *Tc99 dimercaptosuccinic acid* DMSA scan if recurrent febrile UTI
- Check the need of antibiotic prophylaxis, anticholinergic medication, surgeries

Urodynamic Studies

- A video urodynamic study is a specialized test to evaluate bladder pressures during bladder filling and voiding phases. However, if video facilities are unavailable, a prior MCUG can be combined with a urodynamics study to improve interpretation.

Timing of urodynamic study

- A baseline urodynamic study is indicated in all children with neurogenic bladders. However, because of limited availability of this procedure, children should be referred earlier for urodynamic studies when they have the following findings:
  - Recurrent UTI
  - Upper urinary tract dilatation on ultrasound
  - Incontinence despite CIC
  - Thickened bladder wall
  - Raised serum creatinine

Antibiotic prophylaxis

- The incidence of bacteriuria may be as high as 76% among patients who perform regular intermittent catheterization.
- Untreated bacteriuria seldom leads to symptomatic infection or upper tract deterioration
- Long-term antibiotic prophylaxis may reduce the risk of symptomatic UTI, this needs to balance against the risk of antibiotic resistance.
- Antibiotics prophylaxis can be stopped for most of the infants once parents are comfortable with CIC.
- Explore other causes of recurrent UTI such as tight foreskin, constipation, poor compliance to CIC and elevated bladder pressure

Anticholinergic Medication

- Anticholinergics agents inhibits binding of acetylcoline to its muscarinic receptors resulting in relaxing effect on urinary bladder.

When to start anticholinergic?

- Upper tract dilatation or high-pressure bladder

Oxybutynin Hydrochloride

- Dosage is 0.3-0.5 mg/kg/day in 2-3 divided doses
- It is safe in infants < 1 year of age
- Side effects: constipation, feeling warm, cognitive and behaviour changes

Other anticholinergic medication includes

- Tolterodine, Solifenacin, Fesoterodine, Propiverine hydrochloride and Mirabegon

Intravesical Botulinum Toxin A

- May be used in patients unable to tolerate the side effects of anticholinergic medication and as a temporizing measure before bladder augmentation.
- It improves bladder compliance, increase bladder compliance, increase bladder capacity, inhibit detrusor overactivity, prevent detrimental remodelling and fibrosis of bladder.
- Its effect last 8-15 months and would need repeat injections

Overnight bladder drainage

- Overnight bladder drainage reduces frequency of UTI, improves upper tract dilatation and is an alternative to bladder augmentation in children with poorly compliant bladder in early stage of CKD.

Bladder augmentation

- Surgical reconstruction should be considered in symptomatic children with unfavorable urodynamic parameters such as poor bladder compliance and detrusor leak point pressure > 40 cm H2O.
- Bowel segments (ileum/sigmoid colon) or Native ureter may be used to increase bladder capacity.
- Creation of catheterisable channels (Mitrafanoff) using the appendix, ileum or sigmoid colon may facilitate CIC.

Neurogenic Bowel

- Neurogenic bowel dysfunction coexists with neurogenic bladder and manifests as constipation with or without soiling.
- Patients should be encouraged to evacuate their bowels with any of the following treatment modalities.

Behaviour modification

- Position: Footstool to ensure knees are higher than hips. Lean forward and put elbows on knee. A toilet ring should be placed over the toilet seat if needed.
- Toilet sits: up to 5 minutes, 1-3 times per day.
- Chart or diary: to reinforce positive behaviour and record frequency of bowel movement.

Dietary modification

- Increasing dietary fiber, sugar free Nutri fiber

Medications

- Osmotic laxatives: Lactulose, Polyethylene glycol (Macrogol)
- It binds water, soften stool and activate bowel movement
- As sufficient amount of liquid in the colon is needed for the medication to be effective, the patient should be encouraged to drink enough water
- Other laxative: Bisacodyl
- Enema: Glycerin enema
- How to use Glycerin enema?
  - Child should lie on his/her side with legs pulled up
  - Squeeze liquid into rectum and remove
  - Dosage: Pre-school children 5ml, School-aged children 10ml
  - Child presses buttocks together for 15-20 minutes before heading to the toilet

Colonic irrigation

- Retrograde/Antegrade continence enema.

Other Aspects of Care

- Children with neurogenic bladder and intact cognition should be encouraged to receive education in a regular school.
- Communicate with school authorities to encourage integration of students with spinal dysraphism with other able-bodied students.
- This is because lack of formal education and school leaving certificate prevents entry into vocational or tertiary education and limits the patient's potential to be self-sufficient.

Prevention of Neural Tube Defects (spina bifida)

- Folate supplementation during the periconceptional period prevents spina bifida.
- It is recommended that all women of child bearing age should receive at least 0.4mg of folic acid daily.
- Women with previous pregnancy affected by a neural tube defect should receive 4mg OD.

Chapter 69:
Urinary Tract Infection and Vesicoureteric Reflux

Introduction

- Urinary tract infection (UTI) comprises 5% of febrile illnesses in early childhood; before age 2 years, 2.1% of girls and 2.2% of boys will have had a UTI.
- UTI is an important risk factor for the development of hypertension, kidney failure and end stage kidney disease.

Definition

- *Urinary tract infection* is growth of bacteria in the urinary tract or combination of clinical features and presence of bacteria in the urine.
- *Significant bacteriuria* is defined as the presence of > 10^5 colony forming units (cfu) of a single organism per ml of freshly voided urine (Kass).
- *Acute pyelonephritis* is bacteriuria presenting clinically with fever > 38°C and/or loin pain and tenderness. It carries a higher risk of kidney scarring.
- *Acute cystitis* is infection limited to the lower urinary tract presenting clinically with acute voiding symptoms: dysuria, urgency, frequency, suprapubic pain or incontinence.
- *Asymptomatic bacteriuria* is presence of bacteriuria in the urine in an otherwise asymptomatic child.

Atypical UTI :
• Clinically ill child /septicaemic • Poor urine flow • Abdominal mass • Elevated creatinine • Failure to respond to antimicrobial within 48 hours of initiation • Non-Escherichia Coli infection
Recurrent UTI:
• 2 or more episodes of UTI with acute pyelonephritis • 1 episode of UTI with acute pyelonephritis plus one or more episode of UTI with cystitis • 3 or more episodes of cystitis

Clinical Presentation

- Symptoms depend on the age of the child and the site of infection.
- In infants and toddlers: signs and symptoms are non-specific e.g. fever, vomiting, irritability, jaundice and failure to thrive.
- UTI should be considered in children with unexplained fever.
- Symptoms of lower UTI such as pain with micturition and frequency are often not recognized before the age of two.

Physical Examination

- General examination, growth, blood pressure.
- Abdominal examination for distended bladder, ballotable kidneys, fecal masses, genitalia, and anal tone.
- Examine the back for any spinal lesion.
- Look for lower limb deformities or wasting (to suggest possibility of neurogenic bladder).

Diagnosis

- Accurate diagnosis is extremely important as false diagnosis of UTI would lead to unnecessary interventions that are potentially harmful and costly.
- The diagnosis is best made with a combination of culture and urinalysis.
- **The quality of the urine sample is of crucial importance.**

Urine specimen transport

- If collected urine cannot be cultured within 4 hours; refrigerate specimen 4^0C or add a bacteriostatic agent e.g. boric acid (1.8%)
- Use container pre-filled with boric acid and fill urine to required level.

Urine testing

- Rapid diagnosis of UTI can be made by examining the fresh urine with urinary dipstick and microscopy. However, where possible, a fresh specimen of urine should be sent for culture and sensitivity.

Management

- All infants with febrile UTI should be admitted and intravenous antibiotics started as for acute pyelonephritis.
- In patients with high risk of serious illness, it is preferable that the urine sample should be obtained first; however, treatment should be started even if urine sample is unobtainable.

Antibiotic prophylaxis

- Routine prophylaxis whilst awaiting investigations is not recommended but may be indicated following severe infections or recurrent UTIs while awaiting investigations.
- Recent evidence has shown that antimicrobial prophylaxis does reduce the risk of febrile or symptomatic UTI in children with VUR III or IV but has no significant effect on the incidence of renal scarring.
- Hence antibiotic prophylaxis should be considered in the following:
  - Infants and children with recurrent symptomatic UTI
  - Infants and children with VUR grade III and above

Collection of Urine

Suprapubic aspiration (SPA)

- Best technique ("gold standard") of obtaining an uncontaminated urine sample.
- Any gram-negative growth is significant.
- Technique: Refer Practical Procedures

Catheterisation

- Sensitivity 95%, specificity 99%, as compared to SPA.
- Low risk of introducing infection but have higher success rates and the procedure is less painful compared to SPA.

Clean catch urine specimen

- Recommended in a child who is bladder trained/continent.
- In younger pre-continent infant, Voiding Stimulation Technique facilitates faster clean catch by triggering involuntary voiding reflexes in the newborn (The Quick-Wee® method)

Bag urine specimen

- High contamination rate of up to 70%.
- Negative culture excludes UTI in untreated children.
- Positive culture should be confirmed with a clean catch or SPA.

** Note: When it is not possible to collect urine by non-invasive methods (clean catch/ voiding stimulation technique), catheterisation or SPA should be used. Please refer to section on Procedures.

Sensitivity and specificity of various tests for UTI		
Test	**Sensitivity % (range)**	**Specificity % (range)**
Leucocyte esterase (LE)	83 (67-94)	78 (64-92)
Nitrite	53(15-82)	98 (90-100)
LE or nitrite positive	93 (90-100)	72 (58-91)
Pyuria	73 (32-100)	81 (45-98)
Bacteria	81(16-99)	83 (11-100)
Any positive test	99.8 (99-100)	70 (60-90)

Antibiotic Treatment for UTI

UTI (Acute Cystitis)
PO Trimethoprim(TMP) 4 mg/kg/dose twice a day (max 300mg daily) for 3 days
PO Trimethoprim/Sulphamethoxazole 4mg/kg/dose(TMP) twice a day for 3 days
PO Nitrofurantoin 0.75-1 mg/kg/dose four times a day for 3 days
Note:

- *Cephalexin, cefuroxime and amoxicillin can also be used especially in children who had prior antibiotics.*
- *A single dose of antibiotic therapy is not recommended.*

Upper Tract UTI (Acute pyelonephritis)
Children under 3 months
Intravenous

- Cefotaxime 50 mg/kg (neonate) two to three times a day OR
- Ceftriaxone 50-75 mg/kg once a day

Children aged 3 months and over
Oral antibiotic

- Cephalexin 10-15 mg/kg three times a day
- Co-amoxiclav 15-25 mg/kg twice a day

Intravenous antibiotic (if vomiting, unable to take oral antibiotics or severely unwell) for children aged 3 months and over.

- Co-amoxiclav 25 mg/kg three times a day
- Cefuroxime 25 mg/kg three times a day
- Ceftriaxone 50-75 mg/kg once a day
- Gentamicin 5 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration

Antibiotic course length

- Oral 7 to 10 day course
- Intravenous- antibiotics should be reviewed 48 hours and stepped down to oral antibiotics where possible, for a total of 10 days.

Asymptomatic bacteriuria
No treatment recommended

Antibiotic Prophylaxis for UTI

UTI Antibiotic Prophylaxis

PO Cephalexin 12.5 mg/kg On Night (ON) (max 125mg ON)
PO Trimethoprim/Sulphamethoxazole 2 mg/kg (TMP dose) ON
PO Trimethoprim 2 mg/kg ON (max 100mg per dose)
PO Nitrofurantoin 3 months to 11 years: 1-2 mg/kg ON,
12 years to 15 years: 50mg to 100mg ON

Note:

- Antibiotic prophylaxis is not routinely recommended in children with UTI
- Prophylactic antibiotics should be given for 3 days with MCUG done on the second day.
- A child develops an infection while on prophylactic medication, treatment should be with a different antibiotic and not a higher dose of the same prophylactic antibiotic.

Recommendations for imaging

- Children with Atypical UTI should undergo ultrasound during the acute infection.
- Otherwise, in our local setting, all children with febrile UTI should undergo ultrasound kidney, urinary tract and bladder within 6 weeks.
- Micturating cystourethogram (MCUG) should not be routinely performed but guided by ultrasound findings. It should be considered in children with Atypical UTI /Recurrent UTI as well.
- Radionuclide imaging *(Tc99 dimercaptosuccinic acid DMSA)* identifies scarring and should be arranged for children with Atypical UTI /Recurrent UTI 6 months post infection.
- Other modalities such as *Diethylenetriaminepentaacetic Acid* DTPA or *Tc-99m mercaptoacetyltriglycine* MAG3 scans may be indicated following ultrasound.

Preparation for Micturating cystourethogram (MCUG)

- Trimethoprim 4 mg/kg BD for 3 days (one day before, on the day of and one day after the procedure) should be given as periprocedural antibiotic prophylaxis. (Adjust to 2 mg/kg BD for 3 days if eGFR < 15 ml/min/1.73m^2)
- If oral medication is not feasible, alternative such as IV/IM Gentamicin may be given before the procedure.
- IV/IM Cefuroxime/Ceftriaxone should be considered in children with kidney impairment and dose adjusted appropriately

Measures to reduce risk of further infections

- Children who have had a UTI should be encouraged to have adequate fluid intake.
- Children who have had a UTI should have ready access to clean toilets when required and should not be expected to delay voiding.
- Constipation should be avoided.
- In boys with recurrent UTI and high grade reflux, circumcision is beneficial to reduce the risk of UTI.

UTI and bladder bowel dysfunction (BBD)

- BBD describes a spectrum of lower urinary symptoms accompanied by faecal elimination issues that manifest primarily by constipation and/or encopresis.
- Increased rectal faecal load can affect bladder emptying and/or storage by:
  1. mechanical compression, resulting in decreased bladder capacity that can cause urge incontinence and frequency
  2. changing the physiological neural stimuli of the bladder and pelvic floor muscles, leading to progressively decreased urge to evacuate, chronic bladder spasms, insufficient emptying, and significant post-void urine volumes.
- Treatment of BBD includes high fibre diet, use of laxatives, timed frequent voiding, regular bowel movement and adequate position and toilet posturing.

VESICOURETERIC REFLUX

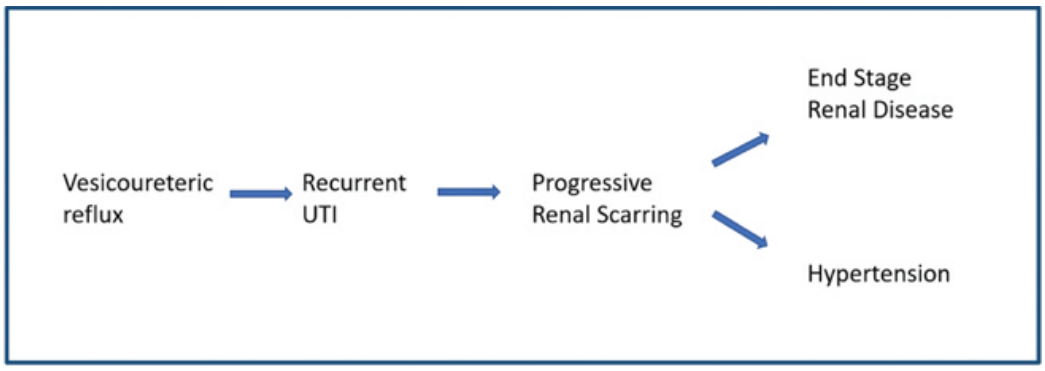
Definition

- Vesicoureteric reflux (VUR) is defined as the retrograde flow of urine from the bladder into the ureter and collecting system.
- In most individuals VUR results from a congenital anomaly of ureterovesical junction (primary VUR), whereas in others it results from high pressure voiding secondary to posterior urethral valve, neurogenic bladder or voiding dysfunction (secondary VUR).

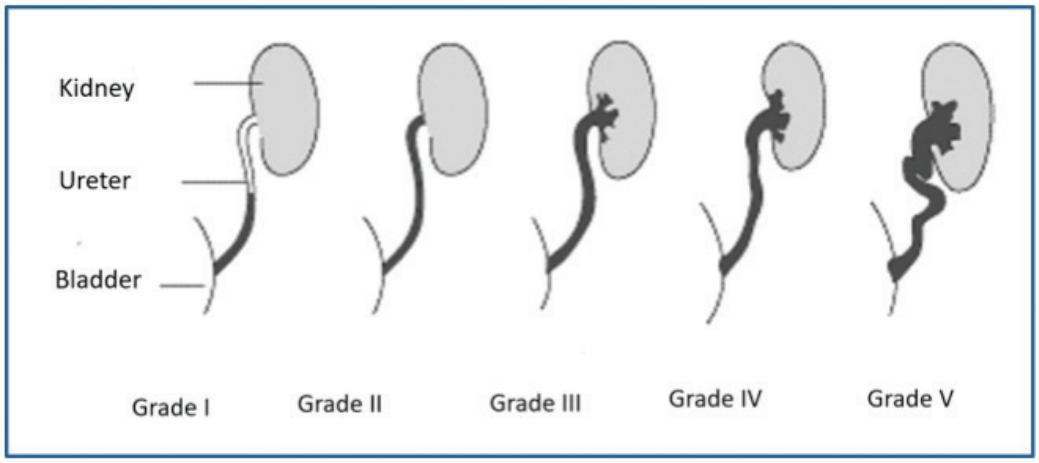
Significance of VUR

- Commonest radiological abnormality in children with UTI (30 – 40%).
- Children with VUR are thought to be at risk for further episodes of pyelonephritis with potential for increasing renal scarring and renal impairment (reflux nephropathy).

NATURAL HISTORY OF VESICOURETERIC REFLUX



CLASSIFICATION OF VESICOURETERIC REFLUX ACCORDING TO THE INTERNATIONAL REFLUX STUDY COMMITTEE



Management

- Antibiotic prophylaxis: refer to antibiotic prophylaxis section above.
- Surgical management or endoscopic treatment is considered if the child has recurrent breakthrough febrile UTI.

Referral To Paediatric Nephrology/Urology In UTI

- Significant hydronephrosis on ultrasound in the absence of reflux on MCUG
- Bilateral reflux nephropathy
- Children with dysfunctional voiding patterns in association with recurrent urinary tract infection
- Recurrent urinary tract infections despite antibiotic prophylaxis
- Severe vesicoureteric reflux (Grade III or above)

Long Term Follow-Up In UTI

Children with kidney scarring requires blood pressure monitoring.

- Assessment during follow-up includes height, weight, blood pressure and routine test for proteinuria. Repeat urine culture only if symptomatic.

Core Messages:

- Infants and young children with unexplained fever should have urine tested for UTI.
- Diagnosis of UTI should be unequivocally established before a child is subjected to invasive and expensive radiological studies.
- Antibiotic prophylaxis should not be routinely recommended following first-time UTI.

Chapter 70:
Perinatal Urinary Tract Dilatation

Terminology includes

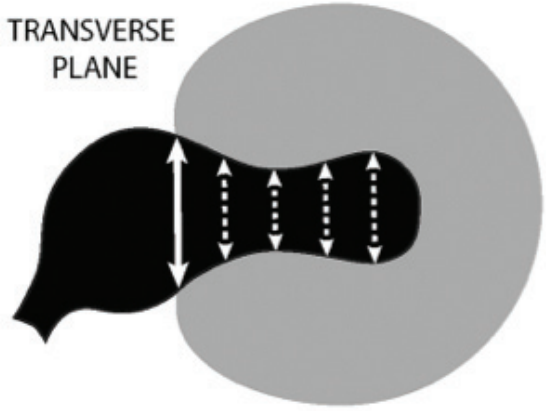
- Antenatal hydronephrosis, antenatal/fetal urinary tract dilatation
- Postnatal urinary tract dilatation

Epidemiology

- Perinatal detection of urinary tract dilatation (UTD) is a common, reported in up to 5% of pregnancies.

Definition

- Sonographic imaging should include measurement of antero-posterior renal pelvis diameter (APRPD) as visualized on a transverse plane.



- The largest APRPD should be used for UTD classification, and in this example, the largest measurement is indicated with a solid line, which is located at the junction of intra-renal and extrarenal pelvis.

- Normal APRPD range
  - Before 28-week gestation: Less than 4 mm
  - After 28-week gestation : Less than 7 mm
  - Postnatal : Less than 10 mm

- The new UTD classification system combines the features of the Society for Fetal Urology (SFU) grading system, and the APRPD system allowing for risk stratification and recommendations for further evaluation.
- During ultrasound (US) kidney ureter bladder scan, the following findings should be documented:
  - Renal pelvis dilatation, APRPD
  - Central calyceal dilatation
  - Peripheral calyceal dilatation
  - Renal parenchymal abnormalities such as cortical thinning, increased echogenicity or cystic dysplasia
  - Ureteric dilatation, including distal ureter diameter
  - Bladder abnormalities such as wall thickening, dilated posterior urethral or ureterocele

Aims of evaluation of patient with perinatal UTD

- To identify children with congenital anomalies of the kidneys and urinary tract (CAKUT) who are at risk of long-term complications and may require surgery.
- To avoid over-investigation of a larger group of children who may have transient or physiological UTD.
- Antenatal evaluation of UTD facilitates perinatal counselling on prognosis and immediate postnatal management

Causes of perinatal UTD
Transient or Physiological UTD (50-70% of patients) • May be due to high fetal urine flow, or kinks in the ureter during early development that resolve as the child grow older. • More likely with mild renal pelvis dilatation. • Absence of red flag signs such as maternal oligohydramnios, renal parenchyma thinning or bladder wall thickening.
Pelviureteric junction obstruction (PUJO) (10-30% of patients) • It is suspected when there is a renal pelvis dilation, without ureteric dilatation.
Vesicoureteric reflux (VUR) (10-40% of patients) • The degree of renal pelvis dilatation does not correlate with reflux grade, and a normal postnatal ultrasound (US) does not rule out presence of reflux.
Multicystic dysplastic kidney (2-5% of patients) • It is diagnosed in the presence of a small kidney, multiple non-communicating renal cysts and no discernible renal parenchyma.
Posterior urethral valves (PUV) (1-5% of patients) • This is a urological emergency. • It is suspected in a male-child, when there is bilateral renal pelvis dilatation, ureteric dilatation, distended thick-walled bladders, dilated posterior urethra and maternal oligohydramnios

Antenatal management

- The goal of antenatal management of an unborn child with perinatal UTD is identification of the high-risk infant, provision of perinatal counselling and planning immediate postnatal management.
- In the absence of any maternal indications, severe maternal oligohydramnios, or other fetal abnormalities, pregnancy should be carried to full term, allowing normal labour.

Immediate postnatal evaluation

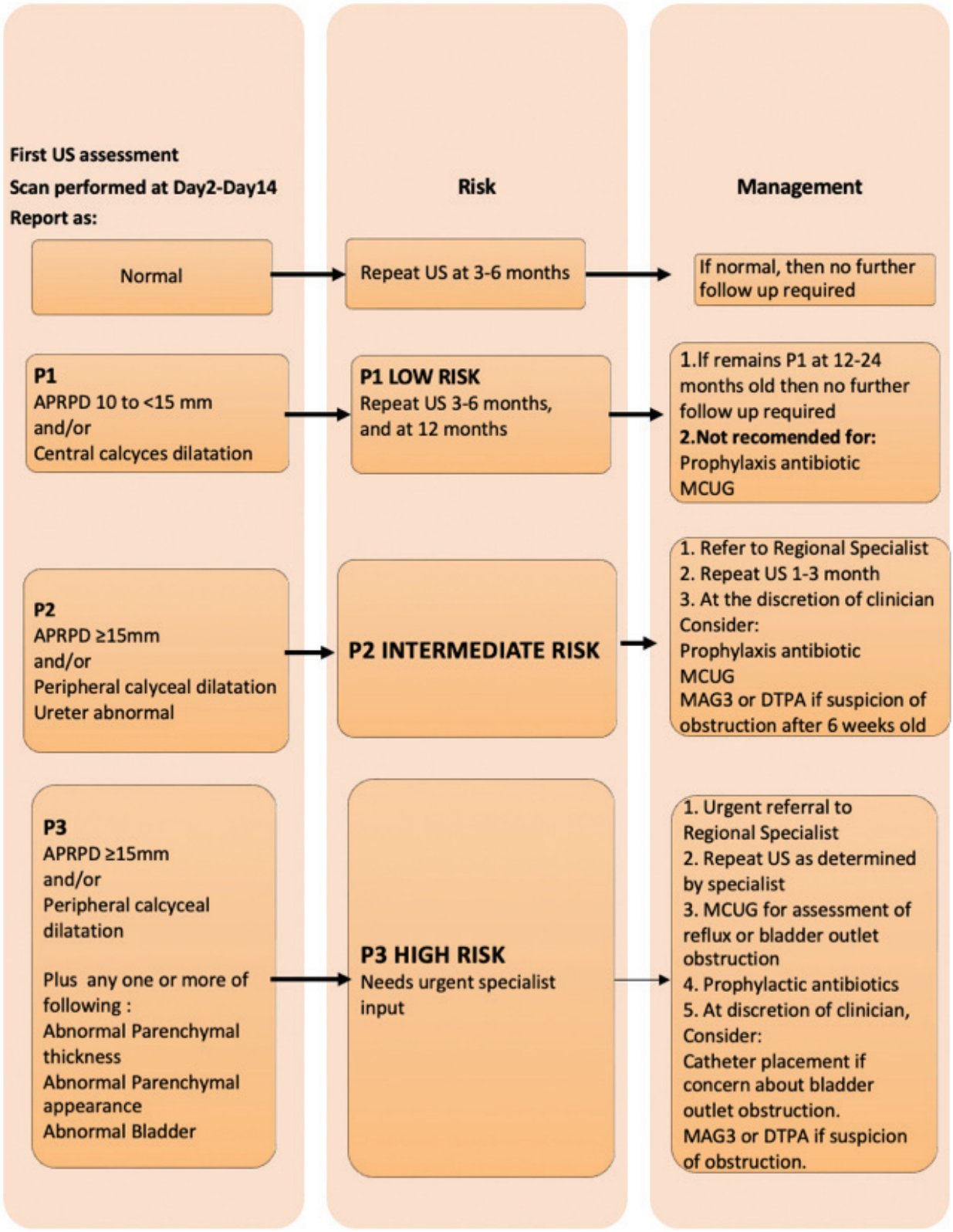
"Red Flags":
• History of oligohydramnios • Abdominal wall abnormality • Palpable bladder or kidneys • Urinary tract infection • Stigma of spina dysraphism • Cortical thinning, reduce corticomedullary differentiation • Single kidney with UTD • Bilateral UTD • Rapidly raising serum creatinine • Neonates not passing urine in the first 24 hours
Infant with any of the red flag needs urgent regional specialist input (Urology/Surgeon/Paediatric Nephrology)

- In neonate who has not passed urine within the first 24 hours of life, or has poor and dribbling urinary stream, it is advisable that:
  - Catheterisation with a stiff, short, and well-lubricated 5-8 Fr umbilical catheter tube or nasogastric tube is performed
  - Antibiotic treatment is initiated
  - The urine output and renal profile monitored for post-obstructive diuresis and electrolyte imbalance.

Postnatal Management

- Initial investigations required for neonates
  - Urine culture if clinical suspicion of urinary tract infection.
  - Renal profile at 24-48 hours of life
  - Further imaging as illustrated in the guide below.

Postnatal management of Perinatal UTD in the absent of red flag



Regional Specialist could be either from Urology/ Surgery/ Paediatric Nephrology

Radiological investigations
Diuretic renography in perinatal UTD **A diuretic renogram should be performed when PUJO or vesicoureteric junction obstruction is suspected.** • Tc-99m Mercaptoacetyltriglycine (MAG3) and Diethylenetriaminepentaacetic Acid (DTPA) nuclear renograms are dynamic scans that provide information on relative kidney function and drainage of the upper urinary tracts. • MAG3 has higher kidney uptake because it is cleared predominantly by tubular secretion, making it suitable for use even in neonates, patients with obstructive uropathy and patients with kidney impairment. • DTPA is cheap and widely available. It is cleared predominantly by glomerular filtration, making it suitable for use in older children with normal kidney function. • To obtain optimal results, it is best performed after 6 weeks of life, allowing for maturation of neonatal kidneys. In patients with severe hydronephrosis and cortical thinning, the test may be performed earlier. • The infant should be prepared for the procedure with adequate hydration and bladder catheterization. A distended bladder delays upper tract drainage leading to a false positive report.
Micturating cystourethrogram (MCUG) • MCUG is indicated in infants with suspected VUR or PUV and to look for abnormalities such as ureterocele or an ectopic ureter. • Refer chapter on Urinary Tract Infection, Practical Procedures

Antibiotic prophylaxis

- Refer chapter on Urinary Tract Infection

Other investigations

- Other investigations may be necessary in situations where a diagnosis is still unclear. These tests are often invasive and should be done in a specialist setting.
  - **Cystoscopy** may be performed to look of PUV, ectopic ureter insertion and ureterocele.
  - **Retrograde pyelogram** may be done when multi-level ureteric obstruction is suspected such as concurrent PUJO and vesicoureteric junction obstruction.
  - **Magnetic resonance urography (MRU)**
    - In the evaluation of complex duplication or renal fusion anomalies
    - To look for site of ectopic ureter insertion
    - To identify ureters of poorly functioning kidney and to locate occult upper pole moieties.

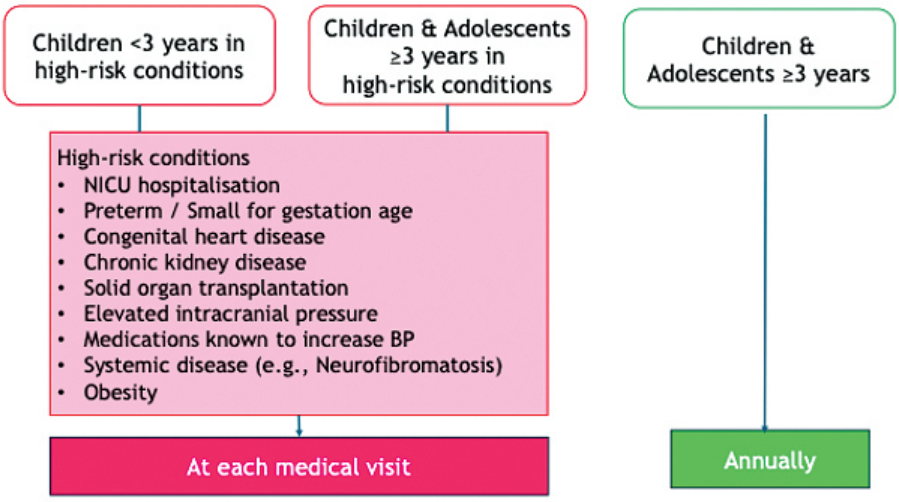
Chapter 71:
Hypertension (HTN) in Children

Definition

Table 1. Definitions of Blood Pressure (BP) Categories and Stages		
	For Children Aged 1-13 years	For Children ≥13 years
Normal BP	<90th percentile	<120/<80 mmHg
Elevated BP	≥90th percentile to <95th percentile or 120/80 mmHg to <95th percentile (whichever is lower)	120/<80 to 129/<80 mmHg
Stage 1 HTN	≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mmHg (whichever is lower)	130/80 to 139/89 mmHg
Stage 2 HTN	≥95th percentile +12 mmHg, or ≥140/90 mmHg (whichever is lower)	≥140/90 mmHg

Normative BP Tables (See Chapter on Normal Values in Children)

BP Measurement: Who and When?



BP Measurement Technique

- Choose an appropriately sized cuff (Cuff width covers ≥ 40% of the upper arm and cuff length covers 80%-100% of the circumference of the arm.)
- Measure BP with the child in a seated position and their arm supported, after he or she has been sitting quietly for 3-5 minutes (for an infant, lying supine).
- Auscultatory or validated oscillometric device can be used for office BP measurement in children and adolescents
- If BP level > 90th percentile on oscillometric devices, confirmatory measurement shold be obtained by ascultation.
- For the diagnosis of hypertension, office BP should be elevated on at least 3 different visits

Diagnosis

A diagnosis of HTN is made if a child or adolescent has BP readings > 95th percentiles on 3 different visits.

Ambulatory Blood Pressure Monitoring (ABPM)

ABPM may be indicated for the following purposes:
- Confirmation of HTN.
- Differentation between sustained hypertension and white coat HTN.
- Detection of masked HTN.
- Evaluation of BP in patients with chronic diseases associated with HTN.
- Determination of the effectiveness of antihypertensive treatment.

White Coat Hypertension

Clinic BP readings consistently ≥ 95th percentile but normal BP outside the clinic setting or normal ambulatory BP.

Masked Hypertension

Normal clinic BP measurement but abnormal ambulatory BP.

Primary Hypertension

Children (≥ 6 years of age) and adolescents do not require an extensive evaluation for secondary causes of HTN if one or more of the following factors are present:
- a positive family history of HTN
- overweight or obese
- absence of history or physical findings suggestive of a secondary cause of HTN

Secondary Hypertension

- It is vital to identify causes of secondary HTN as resolution of HTN may occur after adequate treatment of underlying disease(s), hence avoiding the need for prolonged drug therapy.

Causes of Secondary Hypertension in Children

Kidney disease
- Glomerulonephritis
- Pyelonephritis-related kidney scarring
- Acute kidney injury
- Congenital anomalies of kidney and urinary tract (CAKUT)
- Polycystic kidney disease
- Obstructive Uropathy

Renovascular
- Renal artery stenosis
- Thrombosis of renal artery and vein
- Haemolytic uraemic syndrome

Endocrine
- Cortisol/glucocorticoid excess
- Aldosterone/mineralocorticoid excess
- Catecholamine excess
- Congenital adrenal hyperplasia
- Thyroid disease
- Hypercalcemia

Cardiovascular
- Coarctation of aorta
- Takayasu arteritis

Central nervous system
- Pain
- Convulsions
- Increased intracranial pressure
- Guillain-Barre syndrome
- Dysautonomia

Malignancy
- Wilms' tumour
- Neuroblastoma
- Pheochromocytoma

Pharmacology
- Sympathomimetics
- Corticosteroids
- Stimulants
- Caffeine

Others
- Obstructive sleep apnoea
- Bronchopulmonary dysplasia

Clinical Evaluation

A complete history and examination is needed to identify the underlying cause and to assess for "red flags" that may indicate hypertensive emergency.

"Red flag" symptoms and signs	
Red Flags	**End Organ Dysfunction**
Nausea and/or vomiting Headache Visual disturbance Behavioural change Altered mental status / Drowsiness Seizure	Hypertensive encephalopathy
Fundoscopy: Retinal haemorrhage, cotton wool lesions, papilloedema	Hypertensive vascular changes Increase intracranial pressure
Chest pain Breathlessness Edema Gallop rhythm Cardiomegaly Pulmonary edema	Cardiac failure

Investigations

Preliminary investigations may include:

- Urine dipstick for proteinuria and hematuria
- Urine culture for infection
- Full blood count
- Blood urea, serum creatinine and electrolytes
- Thyroid stimulating hormone
- Abdominal, kidney and urinary tract ultrasound
- Fasting lipid profile
- Fasting blood sugar (±HbA1c)

Further investigations may be conducted after discussion with a paediatrician or relevant subspecialty experts:

- Glomerulonephritis screen (e.g.: C3, C4, ANA, ANCA)
- Plasma renin and aldosterone
- Renal colour Doppler ultrasonography
- Tc-99m Dimercaptosuccinic acid scan (DMSA)
- Urine and plasma cathecholamines or metanephrines
- Urinary free cortisol and plasma cortisol
- Sleep study
- Genetic study

Echocardiography

- To be performed to assess for cardiac target organ damage at time of consideration of pharmacologic treatment of HTN.

Treatment Approach

The treatment goal should be a reduction of SBP and DBP to < 90th percentile and < 130/80 mmHg in adolescents ≥ 13 years old.

A. Non-pharmacologic therapy or Therapeutic Lifestyle Changes

- Exercise
- Weight loss
- Low-salt or no-added-salt diet
- Avoidance of smoking (in teens)

B. Pharmacologic therapy

Initiate pharmacologic therapy in children and with one or more of the following conditions:

- HTN with failed lifestyle modifications
- Symptomatic HTN
- Stage 2 HTN without a clearly modifiable factor (eg.obesity)
- Any stage of HTN associated with chronic kidney disease or diabetes mellitus.
- Hypertensive end-organ damage, most often left ventricular hypertrophy (LVH).

Drug choice should be targeted to the child's underlying pathophysiology and presence of concurrent disorders.

- A child with HTN associated with CKD and proteinuria, diabetes mellitus and microalbuminuria, an Angiotensin converting enzyme inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) is the most appropriate first-line agent
- A child with HTN and migraine a beta-blocker or calcium channel blocker is the most appropriate agent
- A child with corticosteroid-induced HTN, a diuretic most appropriate
- A child with HTN and heart failure, consider beta-blocker (e.g., Bisoprolol)

Oral Antihypertensive Medications			
Drug	**Initial dose**	**Maximum dose**	**Dosing interval**
ACE Inhibitor			
Captopril	Infants: 0.05mg/kg/dose Children: 0.5mg/kg/dose	6mg/kg per day 6mg/kg per day	Daily to 4 times a day 3 times a day
Enalapril	≥1mo: 0.08mg/kg/dose (up to 5mg per day)	0.6mg/kg per day (up to 40mg per day)	Daily to twice a day
ARBs			
Irbesartan	6-12y: 75mg per day ≥13y: 150mg per day	150mg per day 300mg per day	Daily Daily
Losartan	≥6y: 0.7mg/kg (up to 50mg)	1.4mg/kg (up to 100mg)	Daily
Valsartan	≥6y: 1.3mg/kg (up to 40mg)	2.7mg/kg (up to 160mg)	Daily
Thiazide diuretics			
Hydrochlorothiazide	1mg/kg per day	2mg/kg per day (up to 37.5mg/day)	Daily to twice a day

Oral Antihypertensive Medications			
Drug	**Initial dose**	**Maximum dose**	**Dosing interval**
Calcium channel blockers			
Amlodipine	1-5y: 0.1mg/kg ≥6y: 2.5mg	0.6mg/kg (up to 5mg per day) 10mg	Daily Daily
Felodipine	≥6y: 2.5mg	10mg	Daily
Nifedipine	0.25mg/kg	0.5mg/kg/dose (up to 10mg)	3 to 4 times a day
Beta blockers			
Atenolol	0.5-1mg/kg per day	2mg/kg per day (up to 100mg per day)	Daily or twice a day
Metoprolol	0.5-1mg/kg per day (up to 25mg)	6mg/kg per day (up to 200mg per day)	Daily or twice a day
Propranolol	1mg/kg/dose	2mg/kg/dose (up to 640mg per day)	2-3 times a day
Peripheral Alpha-blockers			
Prazosin	0.05-0.1mg/kg	0.5mg/kg	3 times a day
Vasodilator			
Minoxidil	0.2mg/kg	50-100mg per day	Daily to 3 times a day

y year
Note: Newer antihypertensive agents not mentioned in the table (eg: Bisoprolol), Clonidine may be used in difficult to manage cases or special population (CKD) but with consultation from the relevant subspecialties.

Hypertensive Emergencies

Hypertensive emergency is defined as an acute severe symptomatic elevation in BP with evidence of potentially life-threatening symptoms or target organ damage. BP is commonly elevated far above the level of stage 2 HTN.

Hypertensive urgency is defined as an acute severe elevation in BP **WITHOUT** severe, life-threatening symptoms or evidence of acute target organ damage.

Hypertensive encephalopathy is characterized by severe BP elevation with cerebral edema and neurological symptoms of lethargy, coma, and/or seizures. It can be produced with no extreme BP elevations when the HTN appears as a sudden onset, since the autoregulation of cerebral flow is not able to control the rapid BP increment.

Management Principles of Hypertensive Emergencies

- Admit patient to ICU/HDW for close monitoring/support of the vital organs.
- Establish vascular access.
- Continuous BP monitoring, preferably via intra-arterial catheter.
- Urine output monitoring.
- Manage any serious complications before or as hypertension is being treated.
- In the case of hypertensive encephalopathy, neuroimaging is required.
- Treatment strategy is directed at lowering BP promptly but gradually. (A sudden decrease can lead to neurological complications such as intracranial bleeding. Avoid short acting Nifedipine as this may precipitate a sudden uncontrolled drop in BP).
- **The initial goal of therapy is to reduce the BP not more than 25% of the planned reduction over the first 8 hours. Thereafter, the remaining reduction is achieved gradually over the next 24 hours.**
- **The target BP in such situation generally should be at the 90th- 95th percentile.**
- Children with a hypertensive emergency should always be treated with intravenous medications. Continuous infusion is safer than bolus.
- Hypertensive urgencies can be treated by oral medications.

Antihypertensive Medications for Hypertensive Emergencies and Urgencies

Drug	Class	Route	Dose	Onse of action	Comment
Labetalol	α- and β - adrenergic blocker	IV bolus IV infusion	0.2-1mg/kg/dose (up to 40mg per dose) 0.25-3mg/kg/hr	5- 10 mins	Contraindicated in asthma, heart failure and may cause bradycardia.
Hydralazine	Direct vasodilator	IV bolus IV infusion	Initial: 0.1- 0.2 mg/kg/dose every 4 to 6 hr; increase as required to 0.2-0.6mg/kg/dose every 4 to 6 hr (up to 20 mg per does) 12.5-50mcg/kg/hr (Max 3mg/kg in 24 hrs for children > 1 month)	10 mins	Tachycardia, vomiting, flushing, vomiting
Nicardipine	Calcium channel blocker	IV bolus IV infusion	30mg/kg/dose 0.5- 4mg/kg/min	5 - 15 mins	Reflex tachycardiac Increases cyclosporine and tacrolimus levels
Frusemide	Loop diuretics	IV bolus	0.5- 5mg/kg/dose	within mins	Hypokalemia. Useful in volume hypertension
Nifedipine	Calcium channel blocker	Oral	0.25mg/kg/dose	20-30 mins	May cause unpredictable hypotension, reflex tachycardia
Captopril	ACEI	Oral	0.1-0.2mg/kg/dose	10-20 mins	Contraindication in suspected bilateral renal artery stenosis
Minoxidil	Direct vasodilator	Oral	0.1-0.2mg/kg/dose	5-10 mins	Fluid retention

Core Messages:

- Appropriate technique of BP measurement is important to obtain accurate readings.
- Early pharmacotherapy intervention in children who fails lifestyle modification improves long term cardiovascular outcomes.
- Hypertensive emergencies should be treated with intravenous agents whenever possible.

Chapter 72:
Chronic Kidney Disease (CKD) in Children

Definition

Definition: Children who suffer from CKD are those with abnormalities in renal structure or function that persists for more than 3 months. CKD patients have long-term morbidity & mortality as well as linked to a much-reduced quality of life.

Criteria for CKD is either of the following presentations for > 3 months (KDIGO 2024).

1. Glomerular filtration rate (GFR) < 60 ml/min/1.73m^2
2. One or more markers of kidney damage:
   - Albuminuria (ACR ≥ 3 mg/mmol) or proteinuria
   - Urine sediment abnormalities
   - Persistent haematureia
   - Electrolyte and other abnormalities due to tubular disorders
   - Histology abnormalities
   - Structural abnormalities detected by imaging
   - History of kidney transplant

Staging of CKD (KDIGO 2024)

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk. GFR, glomerular filtration rate.

Risk for CKD progression

Caveat: This staging does not apply to children less than 2 years old due to ongoing renal maturation. A healthy newborn would have an eGFR estimated between 20-60 ml/min/1.73m^2 that will continue to rise to finally achieve adult normal values by the age of 1-2 years old.

1. Evaluation of cause
Causes of CKD

Congenital Anomalies of Kidney & Urinary Tract (CAKUT)	Vesicoureteric reflux (VUR) Posterior urethral valves (PUV) Hypoplastic Kidney(s) Obstructive uropathy
Glomerulonephritis	Nephrotic Syndrome Systemic Lupus Erythematosus (SLE) IgA Nephropathy
Cystic kidney disease	Autosomal recessive Polycystic Kidney Disease (ARPKD) Autosomal dominant Polycystic Kidney Disease (ADPKD) Nephronophthisis
Others	Ischaemic insult to the kidneys

2. Evaluation of GFR

- Evaluate using serum creatinine and a GFR estimating equation

Estimation of GFR (eGFR) in children aged 1-17 years old
Schwartz (2009):

$$eGFR\ (ml/min/1.73m^2) = \frac{41.3 \times Height\ (m)}{Serum\ Creatinine\ (mg/dl)}$$

To adjust for Height to cm and Serum Creatinine to SI unit umoi/l

$$eGFR\ (ml/min/1.73m^2) = \frac{36.5 \times Height\ (m)}{Serum\ Creatinine\ (\mu mol/l)}$$

Reference MDCALC Revised Schwartz Equation for Glomerular Filtration Rate (GFR) 2019

- Using additional test (such as creatinine clearance) in specific circumstances when eGFR on serum creatinine is less accurate.

3. Evaluation of Albuminuria/ Proteinuria

Initial screening in a morning spot urine sample
- Urine albumin-creatinine ratio (UACR)
- Urine protein-creatinine ratio (UPCR)

Clinical Features

It can vary extensively in relation to both the causes and complications of CKD.

Strategies to retard CKD progression

1. Optimal blood pressure

- Monitor BP every health encounter
- DASH diet (Dietary Approach to Stop Hypertension) that promote low sodium, low saturated fat, low sugar, high vegetable and fruit intake
- Optimal blood pressure control helps to retard 50% of annual reduction in eGFR

2. Reduce microalbuminuria / proteinuria

- Monitor for urine microalbuminuria / proteinuria
- ACE inhibitor / ARB are both renoprotective by reducing the proteinuria independent of BP lowering.

3. Correct Metabolic acidosis
4. Prevent anaemia
5. Manage acute insult that could cause further deterioration of GFR promptly, e.g., dehydration, UTI, sepsis, urinary tract obstruction, nephrotoxic medication

Complications of CKD

1. Metabolic acidosis

- Adversely causes bone resorption and growth retardation.
- Monitor blood gases.
- Aim for a serum bicarbonate level 22-25 mmol/l.
- Treatment: Oral sodium bicarbonate 1-2 mmol/kg/day.

2. CKD-Mineral and bone disorder

- Altered calcium-phosphate homeostasis and vitamin D metabolism can lead to bony deformities and abnormal growth.
- Monitor serum Ca^{2+}, PO^{4-}, albumin, ALP, PTH assay
- Keep serum phosphate and calcium within the age-appropriate normal range.

i. Treatment for hyperphosphatemia
   a. Review diet intake/ inorganic phosphate (food additives)
   b. Phosphate binders: (to be crushed and take together with meals)
      - Calcium-base phosphate binders: Calcium carbonate, Calcium acetate
      - Non-calcium phosphate binders: Sevelamer, Lanthanum carbonate, Sucroferric oxyhydroxide

ii. Treatment for hypocalcemia:
   - Vitamin D analogue: calcitriol, alfacalcidiol, paracalcitol
     Intravenous calcitriol in hemodialysis patient

iii. Treatment of Vitamin D deficiency:
   - Prevalence is higher within the CKD population hence native Vitamin D supplementation (cholecalciferol) is relevant.
   - Monitor for persistent elevated parathyroid hormone levels; for this, administer active Vitamin D such as calcitriol instead.
   - Dose for treatment of vitamin D deficiency as illustrated in the table below. Modest high dose preparation (e.g. 25,000 IU capsule) may be applied mainly to non-adherence issue.

Suggested treatment dose of Vitamin D supplementation in children with CKD		
Intensive replacement phase (3 months)		
Age	**25(OH)D**	**Vitamin D dose**
< 1 year		600 IU/ day*
> 1 year	< 50 nmol/L	4000 IU/ day
	50-75 nmol/L	2000 IU/ day
Monitor serum calcium, phosphate, albumin, ALP 1-3 monthly *Recheck Vitamin D level*		
Maintenance Phase		
< 1 year	> 75 nmol/L	400 IU/day
> 1 year	> 75 nmol/L	1000-2000 IU/ day

*In infants < 1 year, a fixed dose is recommended irrespective of the level of vitamin D

- Treatment of Secondary hyperparathyroidism
  - Calcimimetic (e.g., Cinacalcet) is effective to treat the disease
  - Total/ subtotal parathyroidectomy may be indicated in severe cases

3. Anemia (Renal anemia)

   - Defined as a haemoglobin level below 11 g/dL.
   - Mainly caused by erythropoietin deficiency and/or iron deficiency.
   - Treat for erythropoietin deficiency after excluding other causes.
     Erythropoietin stimulating agents options:
     i. Erythropoietin (alfa/beta)
     ii. Darbepoietin alfa
     iii. CERA (Continuous Erythropoietin Receptor Activator)

   - Iron deficiency is defined as a serum ferritin below 100 ng/mL and a transferrin saturation (TSAT) below 20%.
     Treatment options:
     i. Oral iron supplement
     ii. Parenteral iron (Iron (III)-hydroxide sucrose complex, Iron (III) hydroxide dextran, ferric derisomaltose, ferric carboxymaltose) in CKD cases with limited intestinal iron absorption or no response to oral iron supplement.

4. Stunted growth

   - Poor growth is common in children with chronic kidney disease due to poor appetite & protein-energy wasting.
     In cases with fluid restriction, energy-dense formula milk or fortification of milk feeds may be considered based on their requirement as below:

     i. Infants: Fortification of breast milk or infant formula with protein powder, glucose polymer or fat emulsion (Precaution: The renal solute load could be too high).
     Alternative is the low solute, high energy formula with low levels of protein, potassium, and phosphate but its availability is limited by its high cost.
     ii. Older children: Energy-dense renal formula
     Consider gastrostomy feeding for children with poor oral intake, preferably with overnight infusion feeding to optimize growth as much as possible.
   - Children with chronic kidney disease can be considered for growth hormone treatment if they still have persistent growth failure even after optimal nutrition intake.

Energy and protein requirements for infants, children and adolescents with CKD 2-5D (0-18 years) as per recommendation by the Paediatric Renal Nutrition Task Force 2020.

AGE	SDI for energy (kcal/kg/day)		SDI Protein (g/kg/day)
1 month	93 - 107		1.52 - 1.8
2 months	93 - 120		1.4 - 1.52
3 months	82 - 98		1.4 - 1.52
4 months	82 -98		1.3 - 1.52
5 months	72 - 82		1.3 - 1.52
6-11 months	72 - 82		1.1 -1.3
12 months	72 - 120		0.9 - 1.14
	MALE	FEMALE	
2 years	81 - 95	79 - 92	0.9 - 1.05
3 years	80 - 82	76 - 77	0.9 - 1.05
4-6 years	67 - 93	64 - 90	0.85 - 0.95
7 - 8 years	60 -77	57 - 75	0.9 - 0.95
9 - 10 years	55 -69	49 - 63	0.9 - 0.95
11 -12 years	48 -63	43 - 57	0.9 - 0.95
13 - 14 years	44 - 63	39 - 50	0.8 - 0.9
15 - 17 years	40 -55	36 - 46	0.8 - 0.9

Follow Up

All children with CKD should be under the care of a paediatric nephrologist.

1. Monitoring of
   - BP and growth
   - Dietary intervention
   - Urine FEME, full blood count, renal profile, serum alkaline phosphatase, calcium & phosphate, venous blood gas and serum bicarbonate

     Frequency:
     - Stage 3 - Three to four monthly
     - Stage 4 - Two to three monthly
     - Stage 5 - One to two monthly
2. Stage 4 CKD: Predialysis education programme allows discussion to take place on suitable kidney replacement modalities (kidney transplant/peritoneal dialysis/ haemodialysis)
3. Stage 5 CKD: Timely initiation of dialysis before patient develops significant uraemic symptoms prevents morbidity and mortality.

Core Messages:
• Children with structural as well as functional abnormalities of the kidneys are at risk of developing CKD • Medical care incorporates active management to delay progression of CKD

Chapter 73:
Congenital anomalies kidney and urinary tract (CAKUT)

Introduction

- CAKUT accounts for 20-25% of birth defects
- It arises from disruption of normal nephrogenesis as early as five weeks gestation
- The pathogenesis of kidney parenchymal malformations is thought to be multifactorial, involving genetic and environmental factors (gestational diabetes mellitus, maternal diet, medications, and substance abuse)
- Genetic mutations association is up to 20% of cases
- CAKUT causing high incidence of chronic kidney disease (CKD) and end stage kidney disease (ESKD) in 30-50% children and is essential to diagnose early to minimize kidney damage

Type of CAKUT

A. Obstructive uropathy

a. Posterior urethral valves (PUV)

- Obstructive membranes that develop in the urethra in male infants
- Incidence reported to be 1:5000 - 1:8000 births and in males only
- Most common cause of lower urinary tract obstruction
- 30-70% of patient's progress to ESKD despite surgical correction at birth
- Antenatal detected urinary tract dilatation (UTD) and history of oligohydramnios
- Present with palpable abdominal mass, urinary tract infection and voiding dysfunction (urinary frequency, poor urine stream, urinary Incontinence) in older boys

Management:

- MCUG is the gold standard for diagnosis
- Early referral to paediatric urology/paediatric surgical team for surgical intervention (fulguration, vesicostomy)
- Close monitoring of the renal profile, electrolytes, and ultrasound kidney ureter bladder scan (US KUB)

Complications:

- Concentrating defects
- Salt wasting
- Poor growth
- Urinary tract infection (UTI)
- Chronic kidney disease

b. Pelvic-ureteric junction obstruction (PUJO)

- Incidence 1:1500- 1:2000 births
- 75% are unilateral
- Male predominance
- Caused by intrinsic stenosis or extrinsic compression of the ureter at the pelvic-ureter junction
- Imaging: US KUB, MAG3/DTPA
- Referral to paediatric urologist/paediatric surgical team for evaluation
- Close monitoring of the UTI, renal profile, electrolytes, and US KUB

B. Renal aplasia/hypoplasia/dysplasia/oligonephronia

a. Multicystic dysplastic kidney (MCDK)

- Nonfunctioning dysplastic kidney with multiple cysts
- Around 60% of MCDK involute in 5 years
- Commonly associated with vesicoureteric reflux (VUR)
- The risk of malignancy and hypertension is comparable to general population
- Serial US KUB to monitor contralateral compensatory hypertrophy
- DMSA is recommended

b. Hypoplastic dysplastic kidney

- Can be unilateral or bilateral involvement
- Infants with bilateral kidneys involvement (kidney shape and tissue differentiation are abnormal and reduced number of nephrons) may have impaired kidney function at birth
- Commonly associated with duplex kidney, megaureter and VUR
- Serial US KUB to monitor contralateral compensatory hypertrophy
- DMSA is recommended

c. Renal agenesis

- Absent of kidney
- Important to look for non- renal anomalies association: Renal-Coloboma Syndrome, Branchio-Oto-Renal Syndrome
- Bilateral renal agenesis is fatal and is commonly associated with Potter syndrome (flattened nose, recessed chin, prominent epicanthal folds, and low-set abnormal ears, pulmonary hypoplasia, wide hands, and rocker-bottom feet)
- Serial US KUB to monitor contralateral compensatory hypertrophy
- DMSA to confirm diagnosis

d. Reflux nephropathy (refer Chapter on Urinary tract infection and Vesicoureteric reflux)

Red flag signs for early referral to paediatric specialists (urology/surgical/nephrology):
• Elevated creatinine • Hypertension • Proteinuria • Recurrent urinary tract infection • Worsening of upper tract dilatation • Contralateral normal kidney not growing as per expectation • Bladder abnormality • Voiding dysfunction

History and Examination:

- Detailed maternal and pregnancy history
- Pulmonary evaluation in fetuses with oligohydramnios
- Dysmorphism (trisomy 13 and 18, Turner syndrome)
- Ear abnormalities - Branchio-Oto-Renal Syndrome, Diabetic embryopathy
- Abdominal examination to look for mass (enlarged kidneys due to obstructive uropathy), deficient abdominal wall musculature (Prune belly syndrome)
- Urogenital anomalies: undescended testes (Prune belly syndrome), Anorectal malformation
- Spine

Postnatal work up:

- Serum creatinine should be taken after 24-72 hours of life (it usually reflects mother's creatinine)
- US KUB
- The following investigations are done when indicated
  - MCUG (micturating cystourethrogram)
  - MAG3 (Mercaptoacetyltriglycine)/ DTPA (Diethylenetriaminepentaacetic Acid)
  - DMSA (Dimercaptosuccinic acid)

Follow up:

- Patient with unilateral kidney involvement should be followed up at least yearly with renal profile, urine FEME (proteinuria), blood pressure and growth parameter. US KUB evaluation is tailored to individual circumstances.
- Patients with bilateral kidney involvement should be followed 3-6 monthly with renal profile, urine FEME (proteinuria), blood pressure and growth parameters in the first year of life and after which the frequency should be tailored based on kidney function and other clinical factors. US KUB evaluation is tailored to individual circumstances.

Core Messages:
• CAKUT is the most frequent cause of CKD in children • Early detection and proper management may retard the progression of kidney damage • Monitor for red flag signs and complications to enable early referral to the relevant specialities.

Section 12

HAEMATOLOGY ONCOLOGY

Chapter 74:
Approach to a Child with Anaemia

Refer Chapter 1: Normal Values in Children for Hematological Parameters for Varying Ages

IRON DEFICIENCY ANAEMIA

Laboratory findings

- Red cell indices: Low MCV, Low MCH values
- Low serum Iron, High TIBC
- Low serum ferritin

Causes of Iron Deficiency Anaemia

- Chronic blood loss
- Increase iron demand – prematurity, growth
- Malabsorption
- Worm infestation
- Inadequate dietary intake

Treatment

- Nutritional counselling
  - If breastfed, maintain breastfeeding
  - Use iron fortified cereals
- Oral iron medication
  - Give 6 mg/kg/day of elemental iron
  - Continue for 6-8 weeks after haemoglobin level is restored to normal
  - Dose calculation depends on the elemental iron in the preparation
- Syrup FAC (Ferrous ammonium citrate): the content of elemental iron per ml depends on the preparation available, (usually 86 mg/5ml)
- Tablet Ferrous fumarate 200 mg has 65 mg of elemental iron per tablet

Consider the following if failure to response to oral iron:

- Non-compliance
- Inadequate iron dosage
- Unrecognized blood loss
- Impaired GI absorption
- Incorrect diagnosis
- Rare conditions e.g. IRIDA (Iron Resistant Iron Deficiency Anaemia- these patients are resistant to oral/im iron, may partially respond to parenteral iron)

Blood transfusion

- Generally, blood transfusion is NOT required in chronic Iron Deficiency Anaemia unless patient is
  - In overt cardiac decompensation
  - Severely symptomatic (e.g. FTT, poor weight gain).
- In patients with chronic anaemia, it is usually safe to plan the transfusion the next morning (during working hours) and take necessary blood investigations prior to transfusion (e.g. FBP, Hb analysis, HIV etc.)
- In severe anaemia (Hb < 4 g/dL) low volume RBC cells (< 5mls/kg) is preferred. It might be necessary to transfuse slowly over 4-6 hours with IV Frusemide (1mg/kg) midway.

HEREDITARY SPHEROCYTOSIS

Pathogenesis

- Due to the inheritance of a defective structural protein (spectrin) in the RBC membrane producing spheroidal and osmotically fragile RBCs
- These RBCs are trapped and destroyed in the spleen --> shortened RBC life span
- Degree of clinical severity is proportional to the severity of RBC membrane defect
- Inheritance: AD in 2/3; AR or de novo in 1/3

Clinical features – can be mild, moderate and severe

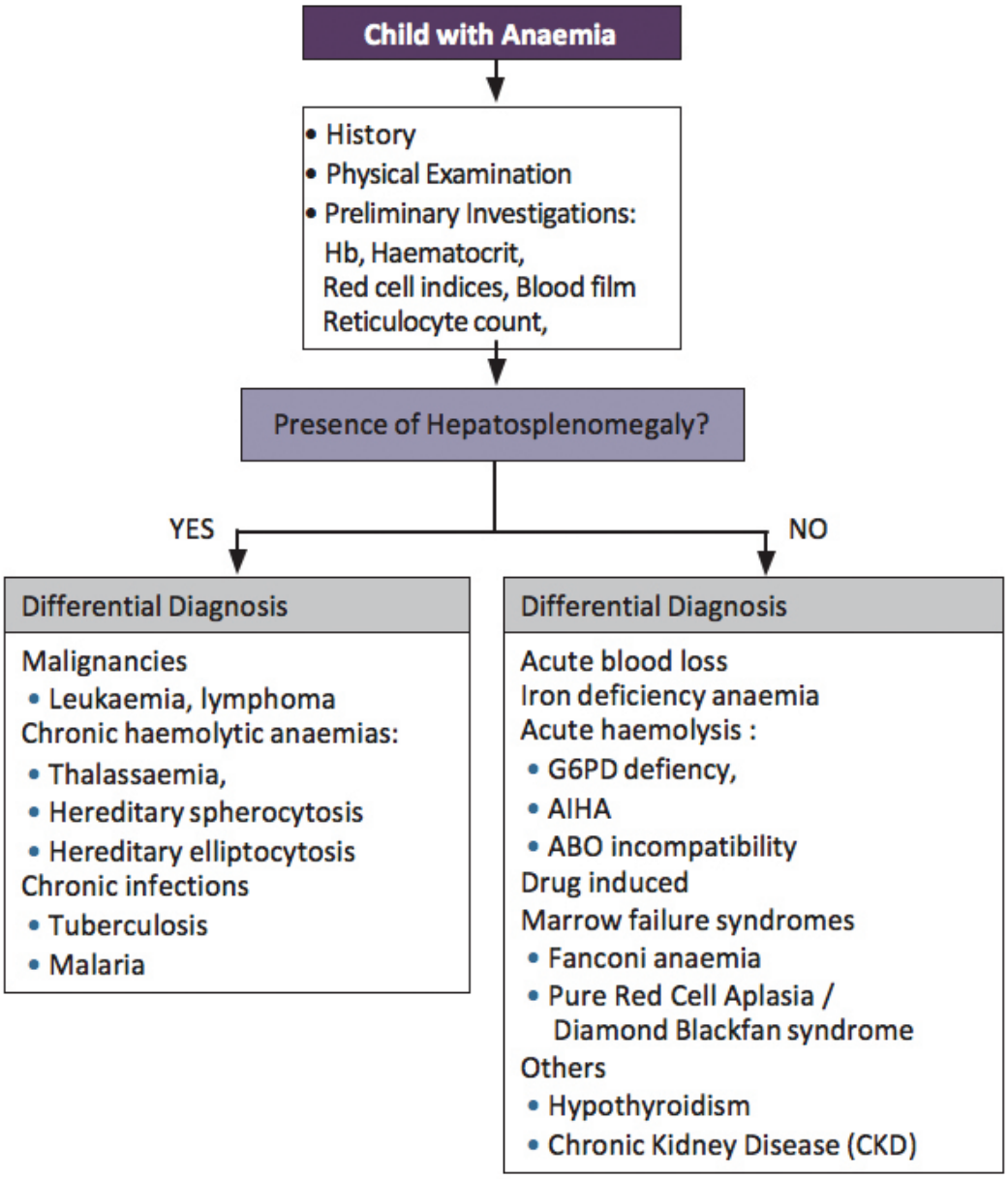
- Anaemia
- Intermittent jaundice
- Splenomegaly
- Haemolytic crises
- Pigment gallstones in adolescents and young adults
- Aplastic crises with Parvovirus B19 infections
- Megaloblastic crises (All patients should receive folate supplement) Rare manifestations
- Leg ulcers
- Spinocerebellar ataxia
- Myopathy
- Extramedullary haematopoietic tumours

Investigations in children with Suspected Spherocytosis
Reticulocytosis
Microspherocytes in peripheral blood film
Osmotic fragility is increased
Elevated MCHC
Normal direct antiglobulin test
Autohaemolysis is increased and corrected by glucose

Treatment

- Folic acid supplements
- Splenectomy
  - To be delayed as long as possible.
  - In mild cases, avoid splenectomy unless gallstones developed
- Splenectomy is avoided for patients < 5 years age because of the increased risk of post-splenectomy sepsis due to capsulated bacteria. For patients planned for splenectomy, give pneumococcal, haemophilus and meningococcal vaccination 4-6 weeks prior to splenectomy and prophylactic oral penicillin given post-splenectomy for life.

APPROACH TO CHILDREN WITH ANAEMIA



HAEMOLYTIC ANAEMIA IN CHILDREN

1. Haemolysis refers to the increased breakdown of red blood cells (RBC) or shortening of RBC survival from the usual 120 days, leading to increased production of unconjugated bilirubin and jaundice clinically. As the RBC survival decreases, the bone marrow responds by increasing RBC production, so there is increased reticulocytosis.
2. 3 cardinal sign to confirm haemolysis

    a. Anaemia
    b. Hyperbilirubinaemia
    c. Reticulocytosis

3. Children with haemolytic anaemia usually present with pallor, lethargy, and fatigue. Other indicators include darkened urine, scleral icterus, and jaundice.
4. Other important history

    - Family history of gallstone disease, splenectomy with family history of Hereditary Spherocytosis
    - Recurrent pain in Sickle Cell Disease
    - Bleeding, oncological, rheumatological (joint pain, rashes etc), menstruation, and the birth history are important.
    - Current and past medications including any supplements are also important as oxidant drugs can cause haemolysis, especially in patients with G6PD deficiency

5. Full Blood Count + differential counts, Peripheral Blood Film (PBF) and reticulocyte count are essential in diagnosing haemolytic anaemia. Some other important investigations are serum bilirubin, Coombs Test and Lactate Dehydrogenase (LDH).
6. Haptoglobin is not well synthesized in infants and is an acute phase reactant, and thus is not helpful in evaluating autoimmune haemolytic anaemia, but can be used for older children
7. G6PD levels can be falsely normal during an acute haemolytic episode because reticulocytes have higher G6PD activity than mature red blood cells, which necessitates repeat testing after the resolution of haemolysis, if there is high clinical suspicion of G6PD deficiency.
8. In case of autoimmune haemolytic anaemia, screen for Primary Immunodeficiency Disorder and rheumatologic disease (frequently indicated in teenager females).

Figure 1: Approach to Haemolytic Anaemia

Management

1. Management of haemolytic anaemia will be dependent on the underlying cause.
2. For warm autoimmune haemolytic anemia (Warm AIHA), corticosteroids are the mainstay of therapy. You may consult Paediatric Hemato-oncologist before starting oral prednisolone 1-2mg/kg/day and taper down slowly over 4-6 months. Approximately 80% of patients have a good initial response to corticosteroid.
3. In refractory cases, when haemoglobin has not been stabilized over 10g/dL within 3-4 weeks post initiation of treatment, or when there is difficulty in weaning the child off steroids, second line options include rituximab (anti-CD20 antibody), splenectomy, and immunosuppressive agents (includes azathioprine, cyclosporine, cyclophosphamide, etc.)
4. For cold AIHA, it is usually occurs following a viral infection. Therapy is generally supportive by keeping the child warm and use in-line blood warmer during transfusion. Autoantibody is transient and recurrence is rare.
5. In Autoimmune Haemolytic Anaemia, if the patient is clinically stable and responding to therapy, transfusions may not be required.
6. When the anemia is severe and becomes symptomatic (neurologic signs such as confusion), transfusion is urgently required. When compatible units cannot be located, clinicians and transfusion specialist should cooperate and do not delay the transfusions.
7. If there is presence of microangiopathic haemolytic Anaemia in PBF with thrombocytopenia and acute renal failure, think of Haemolytic Uremic Syndrome. It is life threatening. Treat the underlying infection and require close monitoring in ICU setting. The patient may need renal replacement therapy.

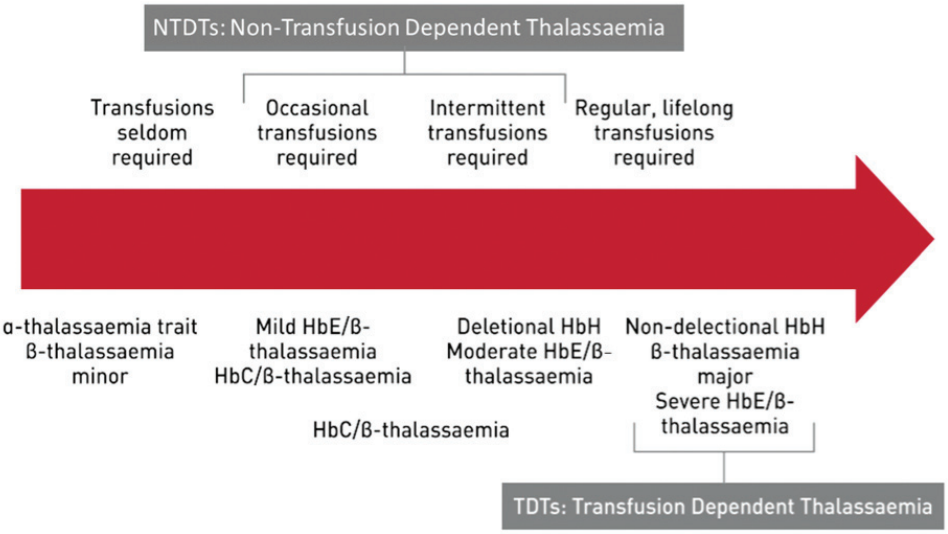
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Chapter 75:
Thalassaemia

- The term 'thalassaemia' refers to a group of blood diseases characterised by decreased or absent synthesis of one or more of the normal globin chains.
- According to the chain whose synthesis is impaired, the thalassaemias are called α, β, γ, δ, δβ or εγδβ thalassaemias.
- The most relevant types are α and β thalassaemias, resulting from the decrease of one of the two types of polypeptide chains (α or β) that form the normal adult human haemoglobin molecule (Hb A, α2β2).
- As autosomal recessive conditions, heterozygotes of either α or β thalassaemia are usually asymptomatic and require no treatment.
- Homozygotes and compound heterozygotes for thalassaemia alleles result in thalassaemia syndromes or diseases.
- In addition, interactions of thalassaemia and corresponding haemoglobinopathies e.g. Hb E, Hb C or Hb S with β thalassaemia or Hb Constant Spring (Hb CS) with α thalassaemia also give rise to various thalassaemia syndromes.
- Currently, based on their clinical severity and transfusion requirement, these thalassaemia syndromes can be classified phenotypically into two main groups (as shown in figure 1);
- Transfusion-Dependent Thalassaemias (TDTs)
- Non-Transfusion-Dependent Thalassaemias (NTDTs)

Figure 1: Phenotypic classification of thalassaemia syndromes based on clinical severity and transfusion requirement.



- The TDTs require regular blood transfusion to survive and without adequate transfusion support, they would suffer several complications and a short life span.
- This category includes patients with β thalassaemia major, severe Hb E/β thalassaemia, transfusion -dependent Hb H disease or Hb H hydrops fetalis and surviving Hb Bart's hydrops fetalis.
- The groups of NTDT patients include β thalassaemia intermedia, Hb E/β thalassaemia and Hb H disease.

β thalassaemia

- β thalassaemia includes three main forms:
  - thalassaemia major
  - thalassaemia intermedia and
  - thalassaemia minor also called 'β thalassaemia carrier', 'β thalassaemia trait' or'heterozygous β thalassaemia.
  - Subjects with β thalassaemia major are homozygotes or compound heterozygotes for β0 or β^+ genes.
  - Subjects with thalassaemia intermedia are mostly homozygotes or compound heterozygotes
  - Subjects with thalassaemia minor are mostly heterozygotes.

Clinical diagnosis

- Clinical presentation of β thalassaemia major usually occurs between 6 and 24 months of age with severe microcytic anaemia, mild jaundice and hepatosplenomegaly.
- Affected infants fail to thrive and become progressively pale.
- Feeding problems, irritability, recurrent bouts of fever due to a hypermetabolic state or intercurrent infection, and progressive enlargement of the abdomen caused by spleen and liver enlargement may occur.
- The clinical picture in patients who are untreated or poorly transfused, is characterised by;
  - growth retardation
  - pallor
  - jaundice
  - poor musculature
  - genu valgum
  - hepatosplenomegaly
  - leg ulcers
  - Development of masses from extramedullary haematopoiesis, and skeletal changes resulting from expansion of the bone marrow. Skeletal changes include;
    - deformities in the long bones of the legs
    - typical craniofacial changes: thalassaemic facies (bossing of the skull, prominent malar eminence, depression of the bridge of the nose and hypertrophy of the maxillae, which tends to expose the upper teeth).

α thalassaemia

- α-thalassaemias are inherited disorders characterised by reduced or suppressed production of α globin chains.
- The human α globin genes are duplicated and located at the telomeric end of the short arm of chromosome 16.
- α thalassaemia is caused most commonly by deletions of large DNA fragments that involve one or both α globin genes.

Hb H disease:

- When there are deletions or non-deletional abnormalities of three globin genes, the affected individual would have only one functional gene.
- In general, patients with non-deletional Hb H disease have more severe disease than patients with deletional for example, co-inheritance of Hb Constant Spring and the deletion of two α genes results in a severe form of Hb H disease in which up to 20% of patients require frequent blood transfusion and splenectomy.
- Hb H disease patients with certain non-deletional mutations, specifically Hb Pak Num Po (ααPNP), Hb Quong Sze (αQZα) or Hb Adana (αCD59α) have a severe phenotype that mimics that of α thalassaemia major:
  - early onset of anaemia (at birth or within 6 month of birth)
  - marked anaemia (Hb <50 g/l)
  - huge hepatosplenomegaly
  - failure to thrive.

Hb Bart's hydrops fetalis:

- the most severe clinical manifestation of α thalassaemia, is generally associated with the absence of all four α globin genes, severe fetal anaemia and death in utero.

DIAGNOSIS OF THALASSAEMIA

- The diagnosis of thalassaemia relies on measuring red blood cell indices and haemoglobin analysis and assessing the clinical severity of anaemia.
- Molecular genetic testing may be useful for predicting the clinical phenotype and enabling presymptomatic diagnosis of at-risk family members and prenatal diagnosis.
- The diagnostic criteria for thalassaemia and hemoglobinopathies are summarized in Figure 2.

Figure 2: Summary of diagnostic methods for thalassaemia and hemoglobinopathies. DCIP = dichlorophenolindophenol; Hb =haemoglobin; MLPA = multiplex ligation-dependent probe amplification. QTL = quantitative locus; PRC = polymerase chain reaction; RBC = red blood cells; RDB = reverse dot blot; TI = thalassaemia intermedia;TM = thalassaemia major.

		β-TM	β-TI	HβE / βThal		HbH
Hb levels		<5g/dL	~7 – 10 g/dL	Mild	9 – 12 g/dL	2.6 – 13.3 g/dL
				Moderately/ Severe	6 – 7 g/dL	
				Severe	4 – 5 g/dL	
BLOODSMEAR	**Low Hb Production**	Red cell hypochromia microcytosis, Target cells				
	Haemolysis	Irregularly crenated RBC, increased reticulocytes [5 – 10%]				
	Ineffective erythropoiesis	Nucleated RBC, Basophilic stripling				
	Special Features	+Numerous F-cells/ Acid elution	+F-cells/ Acid Elution	+DCIP staining [HbE] +F-cells/ Acid Elution		HbH inclusion bodies
Haemoglobin study		HbF up to 100% HbA2↑	HbF 10 – 50% [up to 100%] HbA2 > 4%	HbE [40 – 60%] HbF [60 – 40%] ±HbA [with β-thal] HbA2↑		Variable HbH [0,8 – 40%] HbA2↓ the presence of a-variants e.g. Hb CS, Hb PS etc.
DNA analysis		• Common known mutations of both β0 and β – thal mutations in population specific set can be done by PCR based methods. • For rare or unusual mutations, direct sequencing or array analysis is required • Other analysis for β-TI included α- and β- globin rearrangements, Xmn I polymorphism and other QTLs for γ-globin expression				Gap-PCR developed for 7 common α-thal deletions and RDB for non-deletional mutations. For unknown mutations, MLPA analysis and sequencing required

TREATMENT OF THALASSAEMIA

Blood transfusions

- The aim of blood transfusion in thalassaemia is to deliver an effective and safe transfusion regimen while minimizing the burden of transfusion therapy on everyday life.
- An effective transfusion regimen will result in:
  - good growth and development
  - good energy levels
  - sufficient suppression of intra and extramedullary haematopoiesis.
- Blood transfusion therapy is decided upon the following criteria:
  - Confirmed diagnosis of thalassaemia.
  - Laboratory criteria:
  - Haemoglobin level (Hb) <70 g/L on 2 occasions, > 2 weeks apart (excluding all other contributory causes such as infections)
- Clinical criteria irrespective of haemoglobin level: Haemoglobin > 70 g/L with any of the following:
  - Significant symptoms of anaemia
  - Poor growth/failure to thrive
  - Complications from excessive intramedullary haematopoiesis such as pathological fractures and facial changes.
  - Clinically significant extramedullary haematopoiesis

Key recommendation

- The diagnosis of thalassaemia should be confirmed with appropriate clinical and laboratory methods before the onset of transfusions .
- Before first transfusion, extended red-cell antigen typing of patients at least for D, C, c, E, e and Kell and if available a full red-cell pheno/genotype should be performed.
- Leucodepleted packed red cells should be used where available.
- Transfusions should be performed every 2–4 weeks, maintaining pre-transfusion haemoglobin above 9.0–10.5 g/dL or up to 11.0–12.0 g/dL for patients with cardiac complications.
- A record of red-cell antibodies, transfusion reactions and annual transfusion requirements should be kept for each patient.

Iron overload and iron chelation

- Major cause of iron overload
  - Blood transfusion therapy in TDT,
  - Increased GI absorption in NTDT.

Diagnosis and monitoring of iron overload

The diagnosis and monitoring of iron overload are based on the complementary use of the following parameters:

Serum ferritin

- Serum ferritin (SF) concentration is measured at least every 3 months (1–3 months).
- Target value is currently between 500 and 1000 µg/L.
- Measuring the trends in SF is a more reliable indicator for adjusting therapy than the use of single values.

Liver iron concentration

- Liver iron concentration (LIC) is measured by magnetic resonance imaging (MRI)-based methods.
- Normal LIC values are up to 1.8 mg/g dry weight.
- Sustained high LIC above 15 mg/g dry weight have been linked to worsening prognosis, liver fibrosis progression, or liver function abnormalities.
- The frequency of LIC assessment should be guided by its level and its rate of change:
  - Stable levels in the range 3–7 mg/g dry weight (dw): Every 1 or 2 years
  - Levels >7 mg/g dw: yearly
  - Levels falling rapidly or <3 mg/g dw: 6–12 monthly

Myocardial iron

- Myocardial iron is assessed by T2* cardiac MRI .The frequency of cardiac MRI scan should be guided by myocardial iron level, for example:
  - Stable T2* >20 ms: 2 yearly
  - T2* 10–19 ms: yearly
  - T2* <10 ms: 6 monthly

  It is particularly important to measure cardiac function when cardiac iron is high (eg, T2* <10 ms), as this is associated with a high risk of deteriorating function and heart failure and requires urgent intensification of chelation.

Target organ function and other parameters

- Patients should be also regularly screened for iron-mediated damage including cardiac dysfunction, diabetes, hypothyroidism, hypoparathyroidism, and hypogonadotropic hypogonadism.

Iron chelation therapy

The aims of iron chelation therapy are as follows:

- *Prevention therapy:* to maintain safe levels of body iron at all times, by balancing iron intake from blood transfusion with iron excretion by chelation (iron balance).
- *Rescue therapy:* to remove excess iron stored in the body.
- *Emergency therapy:* to urgently intensify iron chelation in case of iron-induced heart failure.
- *Dose adjustment of therapy:* to adjust dosing and treatment regimens to changing circumstances identified by careful monitoring of body iron and its distribution; monitoring is important to avoid:
  - under-chelation with increased iron toxicity; or
  - over-chelation and increased chelator toxicity.
- *Adherence to therapy:* to adhere to prescribed regular regimen; intermittent high-dose chelation can induce negative iron balance but does not provide continuous protection from labile iron and also risks increased toxicity from the iron chelator.

Key points and recommendations

- Uncontrolled transfusional iron overload increases the risks of heart failure, endocrine damage, liver cirrhosis, and hepatocellular carcinoma .
- Chelation therapy is an effective treatment modality in improving survival, decreasing the risk of heart failure, and decreasing morbidities from transfusion-induced iron overload .
- Chelation therapy at the correct doses and frequency can balance iron excretion with iron accumulation from transfusion
- Direction of change in body iron in response to transfusion and chelation can usually but not always be estimated from the trend in serum ferritin.
- Prevention of iron accumulation using chelation therapy is preferable to rescue treatment because iron-mediated damage is often irreversible, and removal of storage iron by chelation is slow—particularly after it has escaped the liver.
- Response to chelation is dependent on the dose applied and the duration of exposure.
- Response to chelation is affected by the rate of blood transfusion
- Cardiac iron accumulates later than liver iron, and is rare before the age of 8 years, affecting a subset of patients.
- Chelation of storage iron from the liver tends to be faster than from myocardium
- Cardiac storage iron concentration is directly related to the risk of heart failure, which can be reliably estimated by MRI (e.g. cardiac T2*), provided the centre performing the measurement uses a validated method that has been independently calibrated.
- Chelation can reverse iron-mediated cardiac dysfunction rapidly (within weeks) by rapid chelation of labile iron, if 24 hours chelation cover is achieved.
- Chelation therapy removes myocardial storage iron slowly (months or years).
- Over-chelation increases side effects from chelation therapy, and doses should therefore be decreased as serum ferritin or liver iron levels fall (demonstrated most clearly with DFO).
- The optimal chelation regime must be tailored for the individual and will vary with their current clinical situation.
- Chelation therapy will not be effective if it is not taken regularly—a key aspect of chelation management is to work with patients to optimize adherence.

Parameters	Desferal (Desferrioxamine)	Exjade FCT (Deferasirox)	Ferriprox, L1 (Deferiprone)
Dose range (mg/kg/day)	30 – 60 5-7 times/week	14 – 28	75 – 100 (in three divided doses)
Administration	Slow subcutaneous infusion over 8-12 hrs for 5 nights per week	Convenient film-coated daily dose	Oral three times daily dose
Iron excretion	Urine, stool	Stool	Urine
Monitoring	➢ Auditory / eye assessment	➢ Serum creatinine, ALT & proteinuria monthly ➢ Auditory & eye assessment annually	➢ FBC & differentials weekly ➢ ALT every 3 months
Side effects	➢ Local reaction, allergy ➢ Ocular, auditory, bone growth retardation	➢ Gastrointestinal symptoms ➢ Increased creatinine ➢ Increased in hepatic enzymes	➢ Gastrointestinal symptoms ➢ Arthralgia ➢ Agranulocytosis/neutropenia

Haemopoietic stem cell transplantation (HSCT)

- In thalassemia patients, HSCT is cost-effective when compared to life-long supportive therapy
- HSCT should be offered to thalassemia patients and their parents at an early age, before complications due to iron overload have developed, if an HLA identical sibling is available.
- Either bone marrow or cord blood from an HLA identical sibling can be used.
- A matched unrelated donor can be used, provided that high compatibility criteria for both HLA class I and II loci are present.
- Haploidentical HSCT in thalassemia can be considered in experienced HSCT centres in the context of well-designed clinical trials.
- Myeloablative conditioning regimens should always be used for standard transplantation.
- Post-transplant care should include all transplant and thalassemia related complications.

Chapter 76:
Immune Thrombocytopenia

Immune Thrombocytopaenia (ITP) is an acquired isolated thrombocytopenia due to immune-mediated destruction of otherwise normal platelets at a rate that exceeds production. It is a diagnosis of exclusion, patient with ITP should have normal history and examination aside from bleeding symptoms, normal FBC and other investigation aside from thrombocytopenia.

Nomenclature

- Newly diagnosed ITP – remission occurs before 3 months (50-70%)
- Persistent ITP – low platelet count beyond 3 months – 1 year (20-30%)
- Chronic ITP – symptoms persist beyond 1 year (10-20%)

Grading of Disease Severity

- *Mild (77% of children)*
  - Few petechiae
  - Small (<5cm) bruises
  - Epistaxis, stopped by applied pressure within 20 minutes.
- *Moderate (20% of children)*
  - Numerous petechiae
  - Large (>5cm) bruises.
  - Epistaxis longer than 20 minutes.
  - Intermittent bleeding from gums, lips, buccal, oropharynx or gastrointestinal tract.
  - Hypermenorrhagia, haematemesis, haematuria, melena – without hypotension and falling Hb<20g/l
- *Severe (3% of children)*
  - Epistaxis requiring nasal packing or cautery.
  - Continuous bleeding from gums, buccal, oropharynx. Suspected internal
  - haemorrhage (lung, muscle, joint).
  - Hypermenorrhagia, haematemesis, haematuria, melena – leading to hypotension and falling Hb>20g/l
- *Life-threatening (rare, 0.1%-0.9% of children)*
  - Intracranial haemorrhage or continuous or high volume bleeding resulting in hypotension or prolonged capillary refill and requiring fluid resuscitation or blood transfusion

Pathogenesis

- ITP is an autoimmune disorder characterized by autoantibody mediated immunologic destruction of normal platelets (mainly occurring in the spleen), in response to an unknown stimulus.

Clinical Manifestations

- Onset is usually abrupt / acute.
- Duration from onset of thrombocytopenia to normalisation of platelet counts can be a few days to 6 months (average 3 weeks).
- Majority will give a history of a viral infection in the preceding 2-4 weeks.
- Spectrum of bleeding severity ranges from cutaneous bleeding, i.e., petechiae --> mucosal bleeds (gum bleeds, epistaxis, gross haematuria)
  --> life threatening bleeds i.e. intracranial haemorrhage.

Diagnosis and Investigations

- Diagnosis is based on:
  - History
  - Physical examination
  - absence of hepatosplenomegaly or lymphadenopathy.
- Blood counts:
  - isolated thrombocytopenia, with normal haemoglobin and white cell count.
- PBF:
  - normal apart from reduced, occasional larger platelets, no abnormal cells.
  - Other tests may be indicated when there is atypical presentation. The tests would depend on the differential diagnoses suspected in the thrombocytopenic child.
  - Bone marrow examination is not necessary to diagnose ITP if the treating physician is certain that the personal history, family history, physical examination, complete blood count, and peripheral blood smear are typical of ITP.
- Examples of abnormalities that might indicate an alternate diagnosis rather than ITP are:-
  - Fever or bone or joint pain
  - A family history of low platelets or easy bruising
  - Risk factors for HIV
  - Skeletal or soft-tissue morphologic abnormalities
  - Non-petechial rash
  - Lymphadenopathy
  - Abnormal Hb, WBC count, or morphology not typical of ITP

Management

- Most children remit spontaneously.
- The platelet count is usually < 20 x 10^9/L at diagnosis.
- 70% achieve a platelet count > 50 x 10^9/L by the end of the 3rd week without treatment

- Consider hospitalization in:
  - Severe life-threatening bleeding (e.g. ICH) regardless of platelet count.
  - Platelet count < 20 x 10^9/L with evidence of bleeding.
  - Platelet count < 20 x 10^9/L without bleeding but inaccessible to health care.
  - Lack of confidence in homecare.
- Advise:
  - Precaution with physical activities especially small children.
  - Avoid contact sports.
  - Seek immediate medical attention if significant bleed.
  - Avoid aspirin /NSAIDs.
- Treatment is generally indicated if there is:
  - Life threatening bleeding episode (e.g. ICH) regardless of platelet count.
  - Platelet count < 20 x 10^9/L with mucosal bleeding.
  - Platelet count < 10 x 10^9/L with any bleeding.
- Choice of treatment includes:
  - Oral Prednisolone 2 mg/kg/day for 14 days then taper off over 5 days
  - (regardless of response)
  - Oral Prednisolone 4 mg/kg/day for 3 - 4 days
  - IV Immunoglobulin (IVIG) 0.8 g/kg/dose for a single dose, round up to the nearest bottle to avoid wastage

- Notes regarding treatment:
  - Treatment do not resolve the condition faster, but can temporarily raise the platelet count much quicker compared to no treatment. There is no evidence that these treatment reduce bleeding complications/mortality/influence progression to chronic ITP.
  - Side effects of IVIG are:-common (15 - 75%): fever, flushing, headache, nausea, aseptic meningitis and possible transmission of blood borne infections e.g. Hepatitis C (older preparations).
  - Steroids should not be continued if there is no response or if there is a rapid relapse after withdrawal. The long-term side-effects in a child outweigh the benefits.
  - Treatment is directed at the clinical status of the patient i.e. treat the child, not the platelet count.
- Intracranial Haemorrhage (ICH)
  - Is the most feared complication of ITP.
  - Incidence in a child with ITP is between 0.1 - 0.5%.
  - The risk is highest with platelet count < 20 x 10^9/L, history of head trauma, aspirin use and presence of cerebral arteriovenous malformation.
  - 50% of all ICH occurs after 1 month of presentation, 30% after 6 months.
  - Early treatment with steroid or IVIG may not prevent late onset ICH.
- Emergency treatment
  - Emergency treatment of ITP with severe bleeding, i.e. severe epistaxis or gastrointestinal bleed causing drop in Hb or ICH includes:
    - IV Methylprednisolone 30 mg/kg/day for 3 days.
    - IVIG 0.8g - 1g/kg as a single dose – calculated to nearest bottle of IVIG. (usually 3 grams/bottle)
    - Combination of IVIG and methylprednisolone in life threatening conditions.
    - Platelet transfusion in life threatening haemorrhage: 8 - 12 units/m2 BSA (2 to 3 folds more than usual units) as the platelets will be consumed by the haemorrhage to form blood clots and will reduce further circulating platelets.
    - Consider emergency splenectomy if other modalities fail.
    - Neurosurgical intervention maybe indicated in ICH.

Second-Line Therapies for Children

- In children with ITP lasting ≥3 months who have non-life-threatening mucosal bleeding and/or diminished health-related quality of life and do not respond to either IVIG or steroid, the ASH guideline panel suggests the following options for second-line therapies presented in the order they should be pursued :
  - Thrombopoietin receptor agonist (eltrombopag or romiplostim)
  - Rituximab
  - Splenectomy

Chapter 77:
Haemophilia

- Haemophilia is a group of inherited blood disorders in which there is a life-long defect in the clotting mechanism.
- The most common types of haemophilia are:
  - Haemophilia A (factor VIII deficiency)
  - Haemophilia B (factor FIX deficiency).
- They are inherited as X-linked recessive traits; therefore, males are affected and females are carriers.
- Females can be affected as well.
- In 30% of cases, no family history is obtainable because of spontaneous new mutation.

CLINICAL PRESENTATION

- Person with haemophilia (PWH) can present with the following symptoms:
  - easy bruising in early childhood
  - 'spontaneous' bleeding particularly into the soft tissues, muscles, joints and gums
  - excessive bleeding following trauma or surgery
  - A newborn or infant with haemophilia can present with spontaneous intracranial bleed.
  - A child may also present with post-vaccination or vitamin K injection haematoma.
- A positive family history is present in two-thirds of patients while another one-third may have spontaneous mutation.
- The most common site of bleeding in haemophilia is the joints (70 - 80%), especially hinged joints (e.g. ankles, knees and elbows).
- Bleeding is considered:
  - serious if it occurs in the
  - joints (haemarthrosis)
  - muscles, especially deep compartments (iliopsoas, calf and forearm)
  - mucous membranes in the mouth, gums, nose and genitourinary tract
- life-threatening if it occurs in the
  - neck or throat (including floor of the mouth)
  - intracranial
  - gastrointestinal

Diagnostic Investigations:

PT	APTT	Platelet count	Possible diagnosis
Normal	Prolonged	Normal	Haemophilia A or B
Normal	Normal or prolonged	Normal or reduced	Von Willebrand Disease (VWD)
Normal	Prolonged	Normal or reduced	Platelet defects

- If APTT is prolonged & there is positive family history of haemophilia, proceed to perform FVIII or FIX factor assay based on Haemophilia type in the family.
- Otherwise, mixing study should be done first.

Mixing study results		Interpretation
Immediate	2-hour incubation	
Corrected	Corrected	Factor deficiency
Corrected	Not corrected	Time dependent inhibitor e.g. FVIII inhibitor
Not corrected	Not corrected	Immediately acting inhibitor e.g. Lupus anticoagulant antibody

Classification of haemophilia and clinical presentation

Severity	Clotting factor level	Bleeding manifestations
Severe	<1 IU/dL (<0.01 IU/ml) or <1% of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable haemostatic challenge
Moderate	1 - 5 IU/dL (0.01 - 0.05 IU/ml) or 1 - 5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5 - 40 IU/dL (0.05 - 0.40 IU/ml) or 5% to <40% of normal	Severe bleeding with major trauma or surgery; spontaneous bleeding is rare

- Cascade genetic screening for haemophilia should be offered to at least first- & second-degree female relatives if the mother of persons with haemophilia (PWH) is a confirmed carrier.
- Further Investigations
  - Hepatitis B surface antigen, anti HBS antibody
  - Hepatitis C antibody
  - HIV serology

Treatment

- Factor replacement therapy, non-pharmacological & adjunctive treatments are essential in preventing joint damage & other potential serious & life-threatening events in haemophilia.

PROPHYLAXIS

- The optimal approach to haemophilia treatment is using prophylactic therapy to prevent bleeds & chronic joint damage, hence reducing short & long-term complications.
- Prophylaxis should be given to all persons with severe haemophilia even at a low dose.
- Primary prophylaxis is preferred in PWH & should commence after first large joint bleed, intracranial bleed, severe intramuscular bleed or before age 3 years old, whichever comes first.
- Prophylactic therapy regimens in haemophilia

Protocol	Dosage
High dose prophylaxis; Malmo protocol	25 - 40 IU/kg three times/week for haemophilia A 30 - 50 IU/kg twice/week for haemophilia B
Intermediate dose prophylaxis; Utrecht protocol	15 - 25 IU/kg two to three times/week for haemophilia A 30 - 50 IU/kg once or twice/week for haemophilia B (after first/second joint bleed or two bleeds per month)
Low dose prophylaxis	10 IU/kg two times/week for haemophilia A 20 U/kg once/week for haemophilia B (secondary prophylaxis)

* The above are doses and frequencies are for standard half-life of factor FVIII and FIX.
  - Extended half-life of FVIII is available in the country and can achieve similar efficacy when be given in less frequency

MANAGEMENT OF BLEEDING EPISODES

- The desired factor level is dependent on site & severity*; usually it is given until bleeding resolves.
- Factor replacement should precede investigation & aim to achieve desired factor level as shown in the Table below e.g. 100%=IU/dL for life-threatening bleed in head, neck & gastrointestinal tract.
- Suggested plasma peak levels & duration of treatment for acute bleeding in specific sites & surgeries.

Type of Haemorrhage	Haemophilia A		Haemophilia B	
	Desired level (IU/dL)**	Duration (Days)	Desired level (IU/dL)**	Duration (Days)
Joint				
	40 - 60	1 - 2, may be longer if response is inadequate	40 - 60	1 - 2, may be longer if response is inadequate
Superficial muscle/ no neurovascular compromise (except iliopsoas)				
	40 - 60	2 - 3, sometimes longer if response is inadequate	40 - 60	2 - 3, sometimes longer if response is inadequate
Iliopsoas and deep muscle with neurovascular injury, or substantial blood loss				
• Initial • maintenance	80 - 100 30 - 60	1 - 2 3 - 5, sometimes longer as secondary prophylaxis during physiotherapy	60 - 80 30 - 60	1 - 2 3 - 5, sometimes longer as secondary prophylaxis during physiotherapy
Central Nervous System/head				
• Initial • maintenance	80 - 100 50	1 - 7 8 - 21	60 - 80 30	1 - 7 8 - 21
Throat and neck				
• Initial • maintenance	80 - 100 50	1 - 7 8 - 14	60 - 80 30	1 - 7 8 - 14
Gastrointestinal				
• Initial • maintenance	80 - 100 50	7 - 14	60 - 80 30	7 - 14
Renal				
	50	3 - 5	40	3 - 5
Deep laceration				
	50	5 - 7	40	5 - 7
Surgery (major)				
• Pre-op • Post-op	80 - 100 60 - 80 40 - 60 30 - 50	1 - 3 4 - 6 7 - 14	60 - 80 40 - 60 30 - 50 20 - 40	1 - 3 4 - 6 7 - 14
Surgery (minor)				
• Pre-op • Post-op	50 - 80 30 - 80	1 - 5, depending on type of procedure	50 - 80 30 - 80	1 - 5, depending on type of procedure

*Table is based on country with no resource constraint.
**IU/dL=%

A formula for dose of factor concentrate calculation is as follows:

$$\text{Dose required} = \frac{(\text{desired \% rise - baseline level}) \times (\text{kg body weight})}{K}$$

For severe haemophilia, the baseline level is assumed to be 0%.
K = 2.0 for plasma-derived FVIII (Haemophilia A) or 1.5 for recombinant FVIII
1.0 for plasma-derived FIX (Haemophilia B) or 0.6 for recombinant FIX

Special precautions on certain bleeding sites.

Intracranial haemorrhage (ICH)
- Give factor replacement before suspected bleed is confirmed by CT scan

Iliopsoas bleed
- Symptoms: Pain/discomfort in the lower abdomen/upper thighs
- Signs: Hip flexed, internally-rotated, unable to extend
- Ultrasound / CT scan to diagnose.
- Early referral to Physiotherapy
- Repeat U/S to assess progress.

Haematuria
- Bed rest.
- Hydration (1.5 x maintenance).
- Monitor for first 24 hours: UFEME & Urine C&S.
- If bleeding persists for > 24 hours, start factor concentrate infusion.
- Perform KUB & Ultrasound of the kidneys.

- **DO NOT** give anti-fibrinolytic drugs (tranexamic acid) because this may cause formation of clots in the tubules which may not recanalize.

MANAGEMENT OF INHIBITOR

- These are antibodies directed against the exogenous factor VIII or IX neutralizing the clotting activity.
- Overall incidence is 15-25% in haemophilia A and 1-3% in haemophilia B.
- Presence of inhibitors should be suspected in the following situations:
  - poor response to replacement therapy
  - recovery assays are not as expected
  - increase bleeding episodes despite optimal prophylaxis
- Inhibitor should be screened:
  - at regular interval
    - for children-once every five exposure days until 20 exposure days, then every 10 exposure days between 21 & 50 exposure days, then at least twice a year until 150 exposure days, there after yearly.
    - for adults with >150 exposure days, every 6 - 12 months
  - after intensive treatment for >5 days, within 4 weeks of the last infusion
  - prior to surgery
- Treatment of bleeding episode in Haemophilia A and B with inhibitor
  - The main treatment option for bleeding episodes in PWH with inhibitors is bypassing agents e.g. rFVIIa (recombinant Factor VII activated) or aPCC.(activated Prothrombin Complex Concentrate).
  - These agents bypass the coagulation pathway that normally utilises FVIII.
  - rFVIIa and aPCC are equally effective and well tolerated with no increase in thromboembolic risk.

The doses:
- rFVIIa is 90 - 120 µg/kg rounded up to the nearest vial size, given every 2-3 hours until haemostasis achieved.
- Equivalent effectiveness and safety have been demonstrated with a single dose of 270 µg/kg vs three doses of 90 µg/kg.
- aPCC can be used at doses of 50 - 100 IU/kg given every 8 - 12 hours, but should not exceed 200 IU/kg/day.

IMMUNE TOLERANCE INDUCTION (ITI)

- Primary goal of treatment haemophilia with inhibitor is eradication of inhibitor by ITI.
- Consultation with Paediatric Haematologist is necessary for planning of ITI.
- Initiation of ITI should be postponed until the inhibitor titre has dropped to <10 BU (Bethesda Unit).
- An inhibitor titre of <10 BU before ITI initiation positively affects both the likelihood of success and the time required to achieve tolerance.
- Do consider starting ITI regardless of the inhibitor titre if:
  - the inhibitor titre does not fall below 10 BU within a 1- to 2-year period of close observation or
  - a severe life- or limb-threatening bleeding event occurs
- Prerequisite for starting ITI to ensure no interruption of treatment for best response:
  - commitment from PWH with inhibitor/care giver
  - good venous access
  - adequate budget

Supportive Treatment

Analgesia
- There is rapid pain relief in haemarthroses once missing factor concentrate is infused.
- If analgesia is required, avoid intramuscular injections.
- Do not use aspirin or the non-steroidal anti-inflammatory drugs (NSAIDS) as they will affect platelet function.
- Paracetamol with or without opioids can provide adequate pain control.

Dental care
- Good dental hygiene is important as dental caries are a regular source of bleeding.
- Dental clearance with factor replacement will be required in severe cases.

Immunisations
- All immunizations should be given as per scheduled and given subcutaneously.
- Avoid given factor replacement on the same day of immunization as it post the risk of inhibitor development.

Haemophilia Society
- All haemophiliacs should be registered with a patient support group e.g. Haemophilia Society.
- They should have a medic-alert bracelet/chain which identifies them as haemophiliacs and carry a book in which the diagnosis, classification of severity, types of bleeds and admissions can be recorded.

Novel therapies and advances in Haemophilia treatment
- Non-factor replacement e.g Emicizumab given subcutaneously, indicated for prophylaxis both for haemophilia A with and without inhibitor.
- Other non-factor replacement like futisiran, concizumab and Anti-TFPI are in the pipeline.
- Gene therapy-provide cure for haemophilia.

Chapter 78:
Oncology Emergencies

METABOLIC EMERGENCIES

Tumour Lysis Syndrome

Tumour lysis syndrome
Characterised by: Hyperuricemia Hyperkalemia Hyperphosphatemia Hypocalcemia

Introduction

- Pathophysiology:
  Massive tumour cell death
  --> rapid release of intracellular metabolites
  --> exceeds excretory capacity of the kidneys
  --> acute kidney injury (AKI)
- More common in lymphoproliferative tumours with abdominal involvement (e.g. lymphoma, leukaemia)
- Beware of giving steroids in any patients with suspected leukaemia!!!
- Can occur spontaneously even before any chemotherapy is started

Characterised by:

- Hyperuricemia: Breakdown of intracellular purines in DNA increase uric acid
- Hyperkalaemia can occur secondary to
  - Tumour cell lysis
  - Renal failure from uric acid nephropathy or hyperphosphatemia
- Hyperphosphatemia with associated hypocalcaemia.
  - Most commonly occurs in lymphoproliferative disorders as phosphate content in lymphoblasts are 4 times higher than in normal lymphocytes
- Tissue damage from $CaPO_4$ precipitation (When Ca X PO_4 > 60mg/dl)
- Hypocalcaemia leads to altered sensorium, photophobia, neuromuscular irritability, seizures, carpopedal spasm and GIT symptoms

Risk factors for Tumour lysis syndrome	
Patient Factors Hyperuricaemia Dehydration Reduced urine output Acute kidney injury Acidic urine Rarely: underlying disease e.g. HPT (Hypertension), CKD (Chronic Kidney Disease)	*Tumour Factors* Bulky disease, i.e. ALL, Lymphoma Exquisitively chemosensitive tumours

Renal failure - cause of renal failure in the patient with TLS is multifactorial:-

- Uric acid, phosphorus and potassium are excreted by kidneys
- Lactic acidosis will facilitate uric acid crystallization and uric acid obstructive nephropathy.
- Increased phosphorus excretion causes calcium phosphate precipitation in microvasculature and tubules.
- Risk increases if renal parenchyma is infiltrated by tumour, e.g. in abdominal or renal lymphoma or ureteric obstruction from tumour compression/lymph nodes.

Management (Prevention):

- To be instituted in every case of acute leukaemia or lymphoma prior to induction chemotherapy.
- Hydration: Ensure adequate hydration in all patients.
- In high risk patients, hyper hydration of 125ml/m^2/hr or 3000ml/m^2/day .
- NO ADDED POTASSIUM in drip.
- Allopurinol 10mg/kg/day, max 300mg/day.
- Rasburicase in patients with high risk of developing TLS. (No allopurinol in these patients).
- Alkalization of urine with sodium bicarbonate is no longer advocated.

- HCO_3 makes uric acid more soluble.
- However,
  - Calcium phosphate precipitates in alkaline urine (esp. if pH >8).
  - Alkalinisation may aggravate hypocalcaemia.
- Xanthine, hypoxanthine and allantoin precipitation is not affected by pH.

- May have to delay chemotherapy until metabolic status stabilizes
- Close electrolyte monitoring: BUSE, Ca^{2+}, PO_4, uric acid, creatinine, HCO_3
- Strict I/O charting. Ensure adequate urine flow once hydrated. May require frusemide.

Management (Treatment)

- Treat hyperkalaemia as per institution protocol– kalimate/ resonium/ lytic cocktail.
- Diuretics as required.
- Treatment of hypocalcaemia depends on the phosphate level:
  - If phosphate is raised, correct the high phosphate.
  - If phosphate is normal /symptoms of hypokalaemia, give IV calcium correction.
  - If hypocalcaemia is refractory to treatment, exclude associated hypomagnesaemia.
- Definitive treatment of established TLS is dialysis
  - Haemodialysis most efficient at correcting electrolyte abnormalities.
  - Peritoneal dialysis is not effective in removing phosphates.

OTHER METABOLIC EMERGENCIES:

Hyponatraemia

- May occur in acute myeloid leukaemia (AML)
- Can occur as part of SIADH

Hypernatremia

- May occur in patients with Diabetes Insipidus due to brain tumours, LCH, etc.

Hypokalaemia

- Common in AML
- Due to rapid cellular generation which leads to uptake of potassium into cells
- Intracellular K+ 30-40 X higher than extracellular K^+
- Therefore hypokalaemia may develop after chemotherapy

Hypercalcaemia

- Associated with NHL (Non Hodgkin Lymphoma), Hodgkin lymphoma, rhabdoid tumours, alveolar rhabdomyosarcoma, etc.
- Treatment:
  - Ensure adequate hydration
  - IV Frusemide (which increases calcium excretion)

HAEMATOLOGICAL EMERGENCIES

Hyperleukocytosis

- Defined as TWBC > 100,000/mm^3 in patients with acute leukaemia.
- Symptoms are related to leukostasis, especially in acute monocytic leukaemia.
  - LUNGS: Pulmonary infiltrates causing dyspnoea, hypoxaemia and right ventricular failure
  - CNS: causing headache, papilledema, seizures, haemorrhage or infarct.
  - Other complications: renal failure, priapism, dactylitis.
- Mechanism:
  - Excessive leukocytes form aggregates and thrombi in small veins causing obstruction.
  - Worsens when blood is viscous.
  - Excessive leukocytes competes for oxygen; damages vessel wall causing bleeding.

Management

- Adequate hydration/ hyper hydration at 125mls/m2/hour
  - Facilitate excretion of toxic metabolites.
  - Reduce blood viscosity.
- Avoid increasing blood viscosity
  - Exercise caution in use of packed cell transfusion and diuretics.
- During induction in patients with hyperleukocytosis, keep platelet count >20 000/mm³ and coagulation profile near normal.
- Exchange transfusions and leukopheresis should not be used alone as rapid rebound usually occurs. Concurrent chemotherapy should therefore be initiated soonest possible.

Coagulopathy

- AML (especially AML M3) is associated with an initial bleeding diathesis
- Consumptive coagulopathy is due to release of a tissue factor with pro-coagulant activity from cells
- The use of all-trans retinoic acid (ATRA) has circumvented this complication
- Management
  - Platelet transfusions: 6 units/m² should increase platelets by 50,000/mm³
  - Fresh frozen plasma (FFP) or cryoprecipitate
  - Vitamin K

Other haematological emergencies

- Thrombocytopenia
- Severe anaemia

SUPERIOR VENA CAVA OBSTRUCTION

- Especially in newly diagnosed NHL/Hodgkin Lymphoma/acute leukaemia.
- Rarely, malignant teratoma, thymoma, neuroblastoma, rhabdomyosarcoma or Ewing's sarcoma may present with anterior or middle mediastinal mass and obstruction.
- 50% associated with thrombosis.
- Presentation: shortness of breath, facial swelling, syncope.

Management

- Recognition of symptoms and signs of SVC obstruction.
- Avoid sedation and general anaesthesia --> significant risk of circulatory collapse or respiratory failure with general anaesthesia or sedation.
- Avoid upper limb venepunctures as may cause bleeding due to increased intravascular pressure / aggravate SVC obstruction.
- Tissue diagnosis should be established by the least invasive method possible.
- Consider obtaining diagnosis by BMA, biopsy of superficial lymph node under LA or measurement of serum markers, e.g. alpha-fetoprotein.
- If tissue diagnosis impossible, treat empirically based on the most likely diagnosis.
- Chemotherapy and radiotherapy may make histologic diagnosis difficult (as early as 48 hours) --> biopsy as soon as patient is fit / safe.
- NHL - Primary mode of treatment is with steroids and chemotherapy.
- Consider radiotherapy for symptomatic treatment in severe cases.

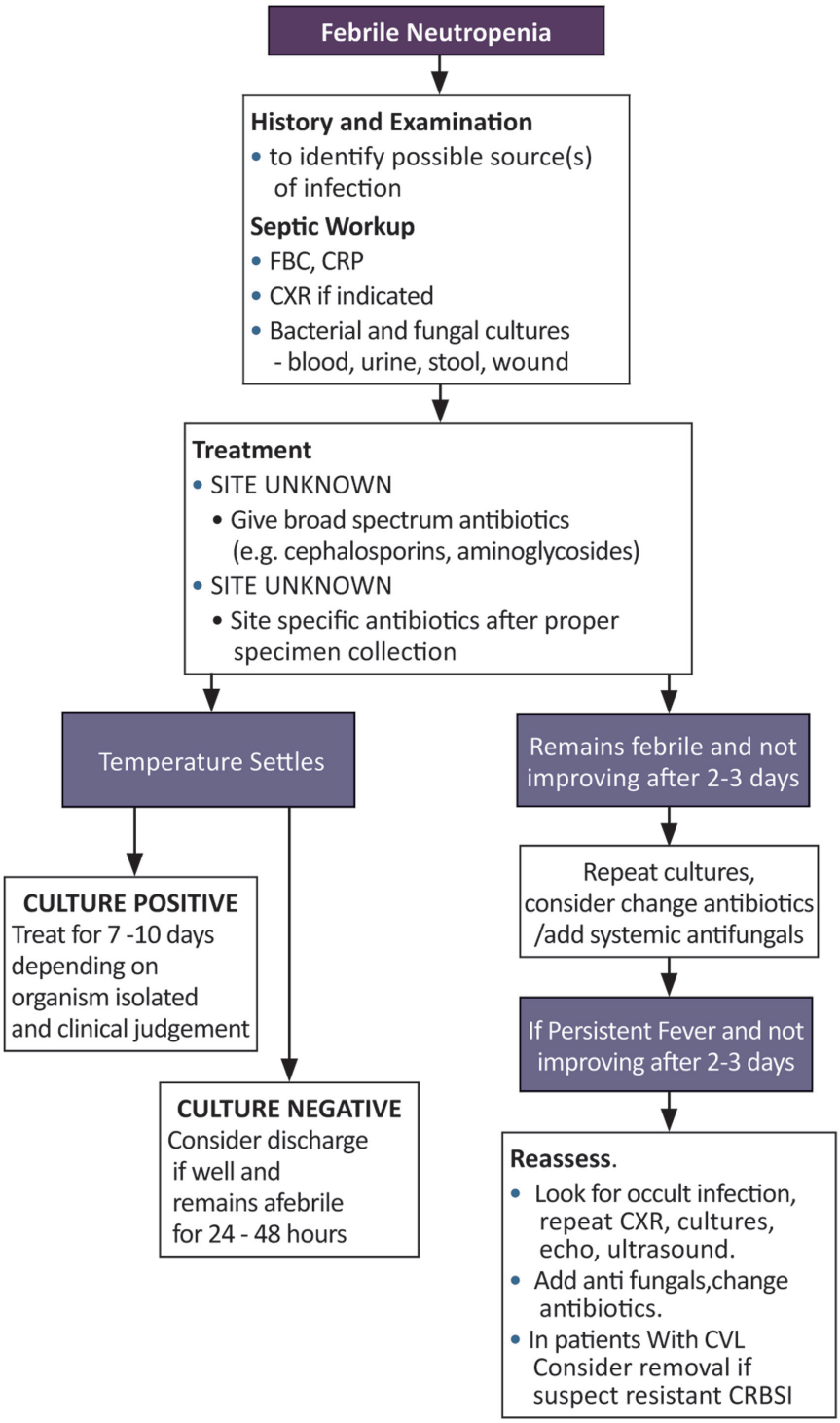
INFECTION

Febrile neutropenia

- Febrile episodes in oncology patients must be treated with urgency especially if associated with neutropenia. Usually bacteraemia or dissemi- nated fungal infections occur when the absolute neutrophil count (ANC) <500 /mm³.
- Risk increases maximally if ANC < 100 /mm³ and greatly reduced if the ANC > 1000 /mm³.

Management (Refer Algorithm on next page)

APPROACH TO CHILD WITH FEBRILE NEUTROPENIA



Other considerations:
- If central venous line (CVL) is present, culture from both lumens; add anti-Staph cover e.g. Cloxacillin.
- Repeated physical examination to look for new signs and symptoms or clues to possible sources.
- Close monitoring of patient's well-being --> vital signs, perfusion, BP, I/O.
- Repeat cultures if indicated.
- Investigative parameters, FBC, CRP, BUSE as necessary.
- In presence of oral thrush or other evidence of fungal infection, start antifungals.
- Monitor renal function closely as some patients may have recently been given potentially nephrotoxic chemotherapy, e.g. cisplatin.

Typhlitis

- A necrotizing colitis localised to the caecum occurring in neutropenic patients.
- Bacterial invasion of mucosa causing inflammation --> full thickness infarction and perforation.
- Usual organisms are Clostridium and Pseudomonas.
- X-ray shows nonspecific thickening of gut wall --> pneumatosis intestinalis
  +/- evidence of free gas in abdomen.

Management
- Usually conservative with broad spectrum antibiotics covering gram -ve organisms and anaerobes (use metronidazole).
- Mortality 20-100%.
- Criteria for surgical intervention:
  - Persistent gastrointestinal bleeding despite resolution of neutropenia and thrombocytopenia and correction of coagulation abnormalities.
  - Evidence of perforation.
  - Clinical deterioration suggesting uncontrolled sepsis (controversial).

NEUROLOGICAL COMPLICATIONS

Spinal Cord Compression

Prolonged compression leads to permanent neurologic sequelae
- Epidural extension: Lymphoma, neuroblastoma and soft tissue sarcoma.
- Intradural: Spinal cord tumour.

Presentation
- Back pain: localized or radicular, aggravated by movement, straight leg raising, and neck flexion.
- Later: weakness, sensory loss, loss of bladder and bowel continence
- Diagnosed by MRI or CT.

Management
- Urgent laminectomy (if deterioration within 72 hours)
- If paralysis present > 72 hours, chemotherapy is the better option if tumour is chemo sensitive, e.g. lymphoma, neuroblastoma and Ewing's tumour. This avoids vertebral damage. Onset of action of chemotherapy is similar to radiotherapy.
- Prior IV Dexamethasone 0.5mg/kg 6 hourly to reduce oedema. Caution when dealing with possible lymphoma.
- +/- Radiotherapy.

Increased Intracranial Pressure (ICP) and brain herniation

- Cause: Infratentorial tumours causing blockage of the 3rd or 4th ventricles such as medulloblastomas, astrocytomas and ependymomas
- Signs and symptoms vary according to age/site
  - Infant - vomiting, lethargy, seizures, symptoms of obstructive hydrocephalus and increased head circumference.
  - Older children - early morning headaches +/- vomiting, poor school performance.
  - Cerebellum: ipsilateral hypotonia and ataxia.
  - Herniation of cerebellar tonsil: head tilt and neck stiffness.
  - Tumours near 3rd ventricle: craniopharyngioma, germinoma, optic glioma, hypothalamic and pituitary tumours --> visual loss, increased ICP (intracranial pressure) and hydrocephalus.
  - Aqueduct of Sylvius obstruction due to pineal tumour: raised ICP, Parinaud's syndrome (impaired upward gaze, convergence nystagmus, altered pupillary response).

Management

- Assessment of vital signs, look for focal neurological deficit.
- Look for evidence of raised ICP (bradycardia, hypertension and apnoea).
- Look for evidence of herniation (respiratory pattern, pupil size and reactivity).
- Dexamethasone 0.5 mg/kg QID to reduce oedema.
- Urgent CT to determine cause.
- Prophylactic antiepileptic agents.
- **LUMBAR PUNCTURE IS CONTRAINDICATED**
- Decompression – i.e. shunting +/- surgery.

Cerebrovascular accident (CVA)

- Can result from direct or metastatic spread of tumour, antineoplastic agent or haematological abnormality.
- L-Asparaginase is associated with venous or lateral and sagittal sinus thrombosis caused by rebound hypercoagulable state.
- AML especially APML (acute promyelocytic leukaemia) associated with DIVC (disseminated intravascular coagulation) and CVA, due to the release of procoagulants.

Management

- Supportive.
- Use of anticoagulant potentially detrimental.

MISCELLANOUS EMERGENCIES

Acute Pancreatitis

- Should be considered in patients on L-Asparaginase and steroids and complaining of abdominal pain.
- Careful examination plus measurement of serum amylase and ultrasound abdomen.

ATRA (all-trans retinoic acid) syndrome

- Characterised by: fever, respiratory distress, oedema, pleural/pericardial effusion, and hypotension.
- Pathophysiology: due to leukostasis associated with ATRA induced multiplication and differentiation of leukaemic promyelocytes.
- Treatment: Dexamethasone 0.5-1mg/kg/dose bd, maximum dose 20 mg bd.

Chapter 79:
Acute Lymphoblastic Leukaemia

- Acute lymphoblastic leukaemia (ALL) is the most common childhood malignancy, representing nearly one third of all paediatric cancers.
- Peak age: 2 – 5 years old; Male: Female ratio of 1.2:1

Presentation

- Signs and symptoms which reflect bone marrow infiltration by malignant cells causing anaemia, neutropenia, thrombocytopenia and extramedullary disease.
- Common signs and symptoms:
  - Pallor
  - Bleeding/ bruising
  - Prolonged or unremitting fever
  - Lymphadenopathy
  - Hepatosplenomegaly
  - Bone pains
  - Persistent back pain
- Less common signs and symptoms:
  - CNS involvement: headache, nausea, vomiting, lethargy, irritability, seizures, spinal cord compression due to spinal mass.
  - Unilateral/bilateral painless testicular enlargement
  - Skin manifestations e.g. skin nodules
  - Cough/difficulty breathing
- Differential Diagnosis:
  - Acute myeloid leukemia (AML)
  - Aplastic anaemia
  - Rheumatic disease i.e. Juvenile Idiopathic Arthritis, SLE
  - Metabolic disease i.e. Gaucher
  - Myelodysplastic syndrome
  - Viral infection e.g. EBV or CMV
- Initial investigations:

  For diagnosis
  - Full Blood Count (FBC) may have anaemia and/thrombocytopenia
  - Total White Count (TWC) may be normal, low or high
  - Peripheral blood film (PBF) may shows blast cells, therefore absent of blast in PBF does not rule out ALL.
  - Bone Marrow Aspirate (Bone Marrow Aspiration) and trephine biopsy smear
  - Immunophenotyping
  - Cytogenetics
  - Molecular mutation studies
  - Cerebral Spinal Fluid (CSF) examination for blast cells

  For assessment and monitoring
  - CXR to look for mediastinal masses
  - Tumour lysis profile: BUSE especially serum K+, serum Creatinine, Uric Acid, PO4, Ca2+, HCO3
  - Lactate dehydrogenase (LDH) – assess degree of leukaemic cell burden and risk of tumour lysis
  - Coagulation profile if the child is toxic or bleeding.
  - Blood cultures and septic workup if febrile.
  - Hepatitis B/C, HIV and VZ IgG screen pre transfusion and pre treatment.
  - Repeat BMA and CSF examinations will be done at protocol defined intervals.

Prognosis

- Overall cure rates for childhood ALL are over 80%.
- Generally depends on:- Prognostic groups, based on clinical and laboratory features.
- Patient should receive treatment in centres with paediatric oncologists
- Availability of other special diagnostic tests
- Use of standard treatment protocols
- Level of supportive care available
- Unfavourable if there are clinical features indicating high risk
  - Age > 10 years old and infants
  - Very high WBC count at diagnosis
  - Molecular characteristics of the leukaemic blasts, e.g. Philadelphia chromosome t (9; 22) (q34; q11); BCR-ABL; P185BCR-ABL tyrosine kinase.
  - Day 8 peripheral blast cell count > 1000 x 10^9/L.
  - Poor response to induction chemotherapy based on subsequent BMA/ MRD (Minimal Residual Disease) reassessment where available.

Treatment

- The regimes or treatment protocols used vary according to treating institutions:
  - BFM – Germany protocol
  - MRC – UK protocol
  - MASPORE (Malaysia-Singapore)
  - CCG/COG – USA protocol
- Generally, chemotherapy regimen consists of Induction, CNS treatment/prophylaxis, Consolidation/ intensification and Maintenance phases.
- Duration is for a total of 2 years (MRC-UK is 2 years for girls and 2.5 years for boys).

Maintenance therapy

- Maintenance therapy usually starts about 2 weeks after completion of consolidation/intensification regime. For all patients, the total duration of therapy including Maintenance is 24 months (104 weeks) from start of therapy at initial diagnosis.
- General guidelines for children with ALL on maintenance chemotherapy
  - Check height, weight and calculate surface area (BSA/m^2) every visit and adjust drug dosages accordingly.
  - To calculate BSA = √ [Height (cm) x Weight (kg) / 3600]
  - Check FBC fortnightly for the first 1-2 months after starting maintenance chemotherapy, and monthly after that if stable
  - Consider doing BMA if counts are repeatedly low or relapse suspected. 2/3 of relapses occur within the first year of stopping treatment. CNS relapse usually manifests as headache, vomiting, abnormal sensorium or hypothalamic symptoms (hyperphagia and abnormal weight gain). Testicular relapse presents as painless testicular swelling, usually unilateral.
- Different institutions and protocols have different regimes for maintenance chemotherapy. So it is important to know the requirements of the various protocols
- As a general rule, chemotherapy is adjusted to maintain
  - TWC at 1.5 - 3 X 10^9/L
  - ANC (Absolute Neutrophil Count) at or more than 0.5 X 10^9/L
  - ALC (Absolute Lymphocyte Count) at or more than 0.3 X 10^9/L
  - PLT (platelet) at or more than 50 X 10^9/L
- If TWC < 1.5 x 10^9/L or ANC < 0.8 x 10^9/L or ALC < 0.8 x 10^9/L or platelets < 75 x 10^9/L:
  - Reduce tablet 6-mercaptopurine (6-MP) and oral methotrexate (MTX) dose by 50%
- Once counts are above those levels:
  - Increase 6-MP and MTX back to 75% of normal dose.
  - Review the patent in 1 week
- If counts are acceptable, increase back to 100% of normal dose.

- If ANC < 0.5 x 10^9/L or ALC 0.2 X 10^9/L or platelets < 50 x 10^9/L:
  - Stop both drugs
- Restart drugs at 50% dose once neutrophil count have recovered > 0.5 x 10^9/L
- Increase back gradually to 75% and later 100% if counts are acceptable

- Febrile infections:
  - If the blood counts are sufficient and the patient is in good general conditions, therapy should be resumed (possibly at reduced dose) when the patient has been free from fever for one day.

- Liver toxicity:
  - GOT/GPT > 10- 20 x UNL and rising (steadily high levels can be tolerated) and/or bilirubin > 3 x UNL.
    - Consider dose reduction or stop 6-MP and MTX.
    - Investigate for causes of liver dysfunction and monitor LFT.
  - Restart at reduced dose and increase as tolerated

- Mucositis:
  - Usually related to MTX and may mainly develop when the MTX dose is high or in patients with Down Syndrome.
  - Reduce MTX dose while keeping 6-MP until improvement and restart at full dose.
  - Initate supportive treatment with mouthwash and antifungal treatment.

- Severe diarrhoea and vomiting:
  - Stop both drugs.
- Restart at 50% dose when better and return to full dose when tolerated

- Anaemia:
  - Hb is usually stable during maintenance chemotherapy, although repeatedly low Hb alone may be due to 6MP intolerance.
  - Some patents may require transfusion if anaemia occurs early in the course of maintenance therapy.
- Standard doses of 6-MP and MTX are to be maintained as much as possible. The dose ratio 6-MP:MTX should usually be 2.5:1.
- Consider sending blood for Thiopurine Methyltransferase (TPMT) enzyme deficiency screening if available.
- Children with homozygous TPMT deficiency can have profound myelosuppression due to 6-MP.

Cotrimoxazole

- Routinely used as prophylaxis for PJP (Pseudomonas jiroveci) except 1 week prior to and during high dose methotrexate therapy
- In the event of chronic cough or unexplained tachypnoea, consider PJP
- If CXR shows interstitial pneumonitis: -
  - send nasopharyngeal secretions for PCP (Pneumocystis pneumonia)
  - Antigen detection e.g. Immunofuorescent test (IFT) or PJP PCR detecton
  - Treat empirically with Cotrimoxazole (20 mg/kg/day in divided doses)
  - PJP should be treated for a total of 2 weeks

Complications

- Complications of oncologic emergencies can be seen before, during and after treatment. (see Chapter on Oncologic Emergencies)
- During treatment, once discharged from oncology ward, care givers must be able to recognise signs and symptoms that require urgent medical attention, especially infections as they can be life threatening.
- Infections must be taken seriously (even while on maintenance therapy) as evidence suggests that patients are still immunocompromised up to 3 months after discontinuing chemotherapy.

Infections

- refer also **Chapter on Oncologic Emergencies** – febrile neutropenia
- If there is significant fever (Temperature ≥ 38.5°C x 1 or ≤ 38°C x2, one hour apart) and neutropenia, stop all chemotherapy drugs and admit for IV antibiotics.
- Take appropriate cultures and CXR if indicated and give IV antibiotics immediately without waiting for specific bacteriological confirmation.
- Use a combination of aminoglycosides and cephalosporins to cover both gram negative and gram positive organisms.
- If nosocomial infection is suspected, use the appropriate antibiotics according to your hospital's culture sensitivity pattern.
- Any fever developing within 24 hours of central venous line access should be treated as CRBSI (Catheter-related bloodstream infection).
    - Common organisms are the gram positive cocci.
    - Consider adding cloxacillin to the antibiotic regime.
- Assume multiresistant bacterial sepsis when dealing with patients presenting with septic shock, especially if recently discharged from hospital.
    - Vancomycin is indicated if there is a long line (Hickman) or chemoport in-situ or if MRSA or coagulase negative *Staphylococcus* infections are suspected.
- Antifungal therapy may be indicated in prolonged neutropenia or if there is no response to antibiotics or if fungal infection is suspected.
- Early and aggressive empirical therapy without waiting for blood culture results will save lives.

Varicella and Measles

- Are life-threatening infections in the immunocompromised children.
- Reinforce this information on parents when they come for follow-up.
- If a patient is significantly/directly exposed (e.g. in the same room > 1 hour with an index case of varicella/measles including 3 days prior to clinical presentation) they are at increased risk of developing these infections.
- MEASLES: Give Measles Human broad-spectrum immune globulin IM 0.5ml/kg (may be divided into 2 separate injection sites) on the same day.
- VARICELLA / Chickenpox: Chemotherapy must be stopped on suspicion of exposure.
- If patient develops varicella, chemotherapy should be withheld and recommenced 2 weeks after the last vesicle has dried.
- For patients who develop varicella:
    - Admit, isolate and treat immediately with IV acyclovir.
    - May switch to oral acyclovir until the lesions are healed.
    - Usual treatment duration is about 10 days.
- For exposed patients: who are VZ IgG negative at diagnosis, on chemotherapy or within 6 months of stopping chemotherapy:-
    - VZIG should be given within 7 days of contact, if available
    - If VZIG not available, consider starting oral acyclovir as post-exposure prophylaxis
        - Monitor for signs of overt varicella infection

Vaccinations

Children on chemotherapy should not receive any vaccinations.
Continue their immunisation programme from where they left off after 6 months off chemotherapy.

Section 13

GASTROENTEROLOGY

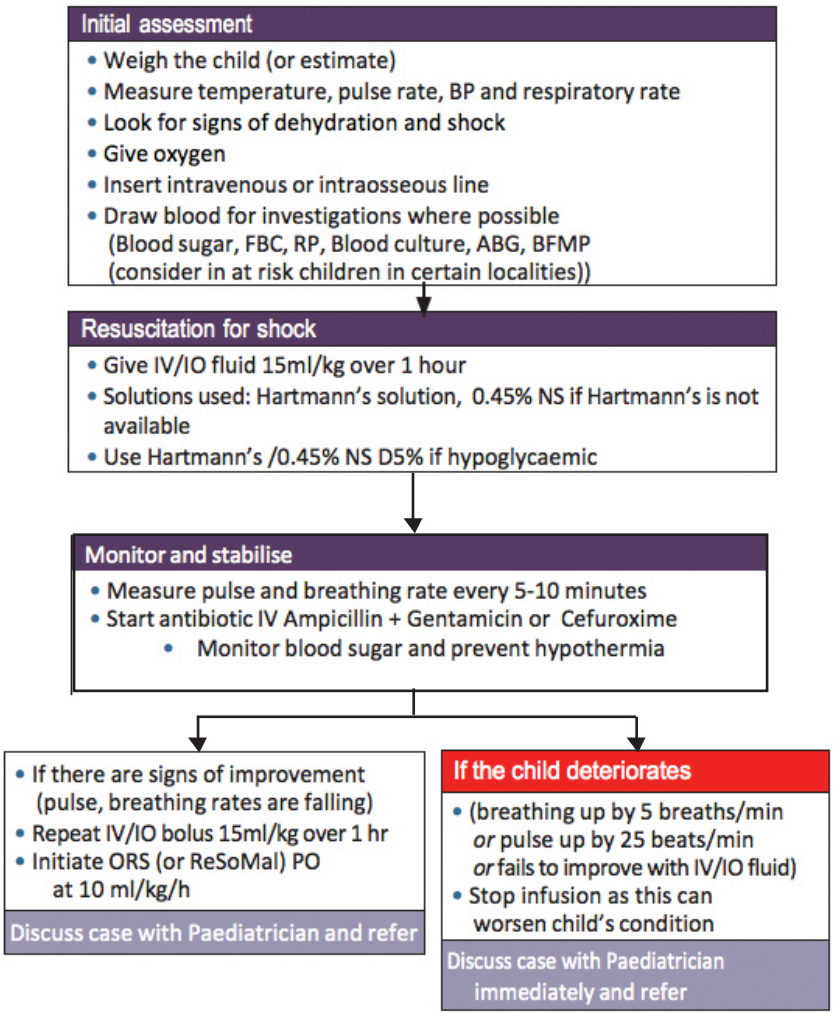
Chapter 80:
Approach to Severely Malnourished Children

RESUSCITATION PROTOCOL FOR CHILDREN WITH SEVERE MALNUTRITION

Diagnosis of severe malnutrition:

- Weight-for-length/height < -3SD (wasted) or
- Mid-upper arm circumference < 115mm or
- Oedema of both feet (kwashiorkor with or without severe wasting)

*Children with severe acute malnutrition (SAM) with loss of appetite or any medical complication should be admitted for inpatient care.



Time Frame for the management of a child with complicated severe acute malnutrition

	Stabilisation		Rehabilitation
	Day 1 – 2	Day 3 – 7	Weeks 2 – 6
1. Hypoglycaemia	→		
2. Hypothermia	→		
3. Dehydration	→		
4. Electrolytes	→	→	→
5. Infection	→	→	
6. Micronutritrients	No iron →	→	With iron →
7. Initiate feeding	→	→	
8. Catch-up feeding			→
9. Sensory stimulation		→	→
10. Prepare for follow-up			→

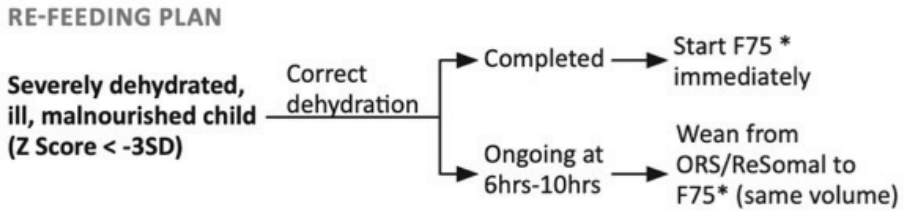
General management

- Hypoglycaemia: treat with IV 2-3ml/kg D10% bolus, or give 10% glucose or sucrose solution by nasogastric tube if no IV access. Continue IV drip or feeding to prevent recurrence.
- Hypothermia: Rewarm the child, make sure child has clothes, cover with warmed blanket.
- Dehydration: Dehydration tends to be overdiagnosed and its severity overestimated in children with SAM. Assume all children with watery diarrhea and reduce urine out have some dehydration. Do not use IV route for rehydration unless in cases of shock. Rehydrate slowly with oral or NG with oral rehydration solution (ReSoMal if available) 5ml/kg every 30 min for first 2 hours, then 5--10ml/hr up to max 12 hours). Close monitoring of weight gain, respiratory rate, pulse rate, urine frequency, enlarging liver size and stool frequency. Stop ReSoMal if signs of overhydration.
- Electrolyte imbalance: Deficiencies of potassium and magnesium may take 2 weeks to correct. Consider to give extra potassium (3-4mmol/kg/day) and magnesium (0.4-0.6mol/kg/day).
- Infection: Cover with broad-spectrum antibiotics (Penicillin or ampicillin + gentamicin or Cefuroxime). Metronidazole may be given in addition. Treat other infection appropriately (meningitis, pneumonia, malaria, parasitic infestation), e.g.: consider Cloxacillin if there are skin lesions / 3rd generation cephalosporins if meningitis is suspected.
- Micronutrient deficiencies are common. Consider:
  - Vitamin A (if available, all SAM should receive single dose)
    - < 6 months 50000 IU
    - 6 – 12 months 100000 IU
    - > 12 months 200000 IU

  (To give vitamin A on day 1 and repeat same dose on day 2 and 14 if there are signs of Vitamin A deficiency (xerophthalmia, corneal clouding or ulceration, Bitot's spot) or the child has complicated measles)
  - Thiamine 1-2mg/kg daily for 2 weeks
  - Iron 2-3mg/kg daily
  - Folic acid 5mg on day 1, then 1 mg daily
  - Multivitamin 5mls daily
  - Zinc (consider esp if child has diarrhoea)
  - < 10kg 10mg dly for 10-14days,
  - >10kg 20mg dly for 10-14days
- Initiate feeding and catch-up growth feeding: As below

Re-feeding severely malnoursihed children

This protocol is based on WHO protocol for feeding SAM in infants and children



Starter feed with F75 based on IMCI protocol

- Feeds at 75-100kcal/kg/day (< 100kcal/kg/day in the initial phase).
- Protein at 1-1.5 g/kg/day.
- Total volume 130mls/kg/day (if severe oedema, reduce to 100mls/kg/day).

How to increase feeds?

- Increase F75 gradually in volume, e.g. 10 ml/kg/day in first 3-4 days
- Gradual decrease in feeding frequency: 2, then 3 and 4 hourly when improves.
- Calculate calorie and protein content daily
- Consider F100 catch up formula when
  - Calories 130/kcal/kg/day-140kcal/kg/day.
  - Child can tolerate orally well, gains weight, without signs of heart failure.

Note:

1. *In a severely oedematous child this process might take about a week.*
2. *If you do not increase calories and proteins the child is not going to gain weight and ward stay will be prolonged.*

Monitoring

- *Avoid causing heart failure*
  - Suspect if: sustained increase (> 2 hrs) of respiratory rate (increases by 5/min), and / or heart rate by 25/min from baseline.
  - If present: reduce feed to 100ml/kg/day for 24 hr then slowly increase as follows:
  - 115ml/kg/day for next 24 hrs; then 130ml/kg/day for next 48 hrs.
  - Then increase each day by 10 mls.
- *Ensure adequate weight gain*
  - Weigh child every morning before feeds; ideal weight gain is > 10g/kg/day.
- If poor weight gain < 5g/kg/day do a full reassessment.
- If moderate weight gain (5-10g/kg/day) check intake or check for infection.
- Watch for secondary infection.
- Watch for refeeding syndrome - hypokalemia, hypophosphatemia and hypomagnesaemia.

Introducing Catch up Growth formula (F100)

- Gradual transition from F75 to F100 (usually over 48-72 hours).
- Increase successive feed by 10mls till some feeds remains uneaten.
- Modified porridge or complementary food can be used, provided they have comparable energy and protein levels.
- Gradually wean to normal diet with unlimited frequent feeds at 150-220 kCal/kg/day.
- Offer protein at 4-6 g/kg/day.
- Continue breast feeding if child is breastfed.

Note: If child refuses F75/F100 and is too vigorous for forced RT feeding, then give normal diet. However must calculate calories and protein (as above).

Discharge criteria

- Not oedematous.
- Gaining weight well.
- Afebrile.
- Has completed antibiotics.
- Aged ≥ 12 months (caution < 12 months: A Specialist opinion is required before discharge).

In situation where patient need to be transferred to district facilities, make sure:

- Provide a clear plan on how to feed and how to monitor progress.
- Provide a dietary plan with adequate calorie and protein requirements.
- A follow up appointment with a Paediatrician.

Recipes for starter and catch-up formulas			
	F-75 (starter)	F-100 (catch-up)	F-135 (catch-up)
Dried skimmed milk (g)	25	80	90
Sugar (g)	100	50	65
Vegetable oil (g)	30 (or 35 ml)	60 (or 70 ml)	85 (or 95 ml)
Electrolyte/mineral solution* (ml)	20	20	20
Water: make up to	1000 ml	1000 ml	1000 ml
Contents per 100ml			
Energy (kcal)	75	100	135
Protein (g)	0.9	2.9	3.3
Lactose (g)	1.3	4.2	4.8
Potassium (mmol)	4.0	6.3	7.7
Sodium (mmol)	0.6	1.9	2.2
Magnesium (mmol)	0.43	0.73	0.8
Zinc (mg)	2.0	2.3	3.0
Copper (mg)	0.25	0.25	0.34
% energy from protein	5	12	10
% energy from fat	36	53	57
Osmolarity (mOsmol/L)	413	419	508

*If a commercially prepared electrolyte and mineral powder is used, follow the manufacturer's instructions. If it is not available, give potassium, magnesium and zinc separately eg: add 22.5 ml of potassium chloride solution (100 g potassium chloride in 1 litre of water) instead into F-75/F-100/F-135. Give the 1.5% zinc acetate solution by mouth at 1 ml/kg per day. Give 0.3 ml/kg of 50% magnesium sulfate intramuscularly once to a maximum of 2 ml.

Preparation

- Using an electric blender: place some of the warm boiled water in the blender, add the milk powder, sugar, oil and electrolyte/mineral solution. Make up to 1000 ml, and blend at high speed.
- If no blender is available, mix milk, sugar, oil and electrolyte/ mineral solution to a paste, and then slowly add the rest of the warm boiled water and whisk vigorously with a manual whisk.
- Store made-up formula in refrigerator.

*Alternative recipes: (other milk sources)

F-75 starter formulas (make up to 1000 ml)

- Full-cream dried milk 35 g, 100 g sugar, 20 g (or ml) oil, 20 ml electrolyte/ mineral solution.
- Full-cream milk (fresh/ long life) 300 ml, 100 g sugar, 20 g (or ml) oil, 20 ml electrolyte/mineral solution.

F-100 catch-up formulas (make up to 100 ml)

- Full-cream dried milk 110 g, 50 g sugar, 30 g (or ml) oil, 20 ml electrolyte/ mineral solution.
- Full-cream milk (fresh / long life) 880 ml, 75 g sugar, 20 g (or ml) oil, 20 ml electrolyte/mineral solution.

Chapter 81:
Gastro-Oesophageal Reflux Disease (GORD)

Introduction

- Gastro-oesophageal reflux (GOR) is the passage of gastric contents into the oesophagus with/without regurgitation and vomiting.
- This is a normal physiological process occurring several times per day in healthy children.
- Gastro-oesophageal reflux disease (GORD) in paediatric patients is present when reflux of gastric contents is the cause of troublesome symptoms and/or complications.

Symptoms and Signs:

- Symptoms and signs associated with reflux vary by age and are nonspecific.

Table 1: Symptoms and signs that may be associated with GORD in infants and children 0 to 18 years old

Symptoms	Signs
General • Discomfort/irritability* • Failure to Thrive • Feeding refusal • Dystonic neck posturing (Sandifer syndrome)	General • Dental erosion • Anaemia • BRUE (brief resolved unexplained event)
Gastrointestinal • Recurrent regurgitation with/without vomiting in the older child • Heartburn/chest pain # • Epigastric pain# • Haematemesis • Dysphagia/odynophagia	Gastrointestinal • Oesophagitis • Esophageal stricture • Barrett oesophagus
Airway* • Wheezing • Stridor • Cough • Hoarseness	Airway* • Apnoeic spells • Asthma • Recurrent pneumonia associated with aspiration • Recurrent otitis media

If excessive irritability, pain, airway signs and symptoms is the single manifestation without overt regurgitation, it is unlikely to be related to GORD.

Typical symptoms of GORD in older children besides recurrent regurgitation

Warning signals requiring investigation in infants with recurrent regurgitation or vomiting:

- Symptoms of gastrointestinal obstruction or disease
  - Bilious vomiting.
  - GI bleeding: hematemesis, melaena.
  - Consistently forceful vomiting.
  - Onset of vomiting > 6 months or persistent > 12-18 months of age.
  - Constipation.
  - Chronic diarrhoea.
  - Abdominal distension.

- Symptoms suggesting systemic or neurologic disease
  - Hepatosplenomegaly.
  - Bulging fontanelle.
  - Macro/microcephaly.
  - Seizures.
  - Genetic disorders (e.g., Trisomy 21).
  - Other chronic disorders (e.g., HIV).
- Nonspecific symptoms
  - Fever.
  - Lethargy.
  - Failure to thrive.

Investigations

GORD is often diagnosed clinically and does not require investigations.

- Indication for further investigations:
  - If its information is helpful to define difficult or unusual cases.
  - If of value in making treatment decisions.
  - When secondary causes of GORD need to be excluded especially in severely affected patients.
- Oesophageal pH metry
  - The severity of pathologic acid reflux does not correlate consistently with symptom severity or demonstrable complications.
  - To correlate persistent troublesome symptoms (e.g., cough, chest pain) with acid reflux episodes.
  - For evaluation of the efficacy of acid suppression therapy.
  - Clinical utility of pH monitoring for the diagnosis and management of extraesophageal complications of GOR is limited.
- Multichannel intraluminal oesophageal pH impedance study (MII)
- It is becoming the cornerstone of assessment of GOR.
- More sensitive tool compared to pH metry as it detects both acid and non-acid reflux.
- MII can also differentiate among liquid, gas or solid reflux.
- Indications for MII:
  - To correlate persistent troublesome symptoms with both acid and nonacid reflux and to select those infants and children with extraoesophageal symptoms in whom GOR is an aggravating factor.
  - Clarify the role of acid and non-acid reflux in the aetiology of oesophagitis and other signs and symptoms suggestive for GORD.
  - For evaluation of the efficacy of acid suppression therapy.
  - To differentiate different entities like non erosive gastroesophageal relux disease (NORD), hypersensitive oesophagus and functional heartburn in patients with normal endoscopy.
- However, there is insufficient evidence to support the use of MII as a single technique for the diagnosis of GORD in infants and children.
- Barium Contrast Radiography
  - Not useful for the diagnosis of GORD as it has poor sensitivity and specificity but is useful to confirm or rule out anatomic abnormalities of the upper gastrointestinal (GI) tract.
- Nuclear Scintigraphy
  - Not recommended for the routine evaluation of GORD in children.
  - May have a role in the diagnosis of pulmonary aspiration in patients with chronic and refractory respiratory symptoms. A negative test does not rule out possible pulmonary aspiration of refluxed material.
  - May be helpful in assessing other factors that may aggravate GORD such as delayed gastric emptying.

- Oesophageal manometry
  - Not sufficiently sensitive or specific to diagnose GORD.
  - Useful in suspected motility disorder e.g. achalasia or other motor disorders of the oesophagus that may mimic GORD.
- Endoscopy and Biopsy
  - Not for diagnosis of GORD.
  - To assess severity of GORD like evidence and extent of reflux oesophagitis.
  - To identify or rule out other causes of oesophagitis including eosinophilic oesophagitis which do not respond to conventional anti reflux therapy.
  - To diagnose and monitor other GORD complications like oesophageal stricture and Barrett's oesophagus.
- Empiric Trial of Acid Suppression as a Diagnostic Test
  - Expert opinion suggests that in an older child or adolescent with typical symptoms of GORD, an empiric trial of 2-4 weeks of proton pump inhibitors (PPI) is justified.
  - However, improvement of heartburn, following treatment, does not confirm a diagnosis of GORD because symptoms may improve spontaneously or respond by a placebo effect.
  - No evidence to support an empiric trial of acid suppression as a diagnostic test in infants/young children where symptoms of GORD are less specific.
  - Trial of acid suppression should not be used as a diagnostic test for GORD in patients presenting with extraesophageal symptoms
  - Exposing them to the potential adverse events of PPI is not the best practice. Look for causes other than GORD before making such a move.

Treatment

- Physiologic GOR does not need medical treatment.
- Symptoms are often nonspecific especially during infancy; many are exposed to anti-reflux treatment without any sufficient evidence.
- Should always be balance between intended improvement of symptoms with risk of side-effects.

Suggested Schematic Therapeutic Approach

- Parental education, reassurance & observe.
- Lifestyle changes – avoid smoking including passive smoking.
- Dietary management
  - Avoid overfeeding or overeating.
  - To modify feeding volumes and frequency according to age and weight.
  - Use of a thickened formula (or commercial anti regurgitation formulae) may decrease visible regurgitation but does not reduce in the frequency of oesophageal reflux episodes.
- There may be association between cow's milk protein allergy and GORD.
  - Therefore, infants with GORD that are refractory to conventional anti reflux therapy may benefit from a 2 weeks trial of elimination of cow's milk in diet with an extensively hydrolyzed protein formula that has been evaluated in controlled trials.
  - Usually there may be other atopic symptoms or family history of atopy in these patients.
- No evidence to support the routine elimination of any specific food in older children with GORD.

- Position during sleep
  - Prone positioning decreases the amount of acid oesophageal exposure measured by pH probe compared with that measured in the supine position.
  - However, prone and lateral positions are associated with an increased incidence of sudden unexpected death in infancy (SUDI).
  - Therefore, in most infants from birth to 12months of age, supine positioning during sleep is recommended.
  - Prone or left lateral sleeping position and/or elevation of the head of the bed for adolescents with GORD may be of benefit.
- Buffering agents (some efficacy in moderate GORD, relatively safe).
  - Antacids only in older children.
  - Buffering agents e.g. alginate are useful on demand
    - Chronic use of buffering agent is not recommended for GORD because some have absorbable components that may have adverse effects with long-term use.
- Prokinetics
  - Treat pathophysiologic mechanism of GORD.
  - However, there is insufficient evidence of clinical efficacy to justify the routine use of metoclopramide, erythromycin, or domperidone for GORD.
  - Baclofen may be useful in those children in whom other pharmacological treatments have failed. Beware of its side effects.
- Proton Pump Inhibitors (PPI) (drug of choice in severe GORD).
  - Histamine-2 receptor antagonists are less effective than PPI.
    - Histamine-2 Receptor Antagonists (H2RAs).
      - Exhibit tachyphylaxis or tolerance (but PPIs do not)
      - Useful for on-demand treatment
    - Proton Pump Inhibitors
      - Administration of long-term acid suppression without a diagnosis is inadvisable.
      - When acid suppression is required, the smallest effective dose should be used.
      - Most patients require only once-daily PPI; routine use of twice-daily dose is not indicated.
      - The potential adverse effects of acid suppression, including increased risk of community-acquired pneumonias and GI infections, need to be balanced against the benefits of therapy.

- Antireflux surgery (either open or laparoscopic surgery) including fundoplication.
- May be of benefit in selected children with chronic-relapsing GORD.
- Indications include:
  - failure of optimal medical therapy, dependence on long-term medical therapy,
  - significant non-adherence with medical therapy, or
  - life threatening complications eg: pulmonary aspiration of refluxate.
- Please take note children with underlying disorders predisposing to the most severe GORD e.g. neurological impairment are also at the highest risk for operative morbidity and postoperative failure.
- It is essential therefore to rule out all non-GORD causes of the child's symptoms, confirm the diagnosis of chronic relapsing GORD, discuss with the parents the pros and cons of surgery and to assure that the caregivers understand the potential complications, symptom recurrence and sometimes the need to be back on medical therapy.

Chapter 82:
Chronic diarrhoea

Introduction

WHO defines persistent or chronic diarrhoea as an episode of diarrhoea that begins acutely and lasts for 14 days or more. The main complication results from chronic diarrhoea is malnutrition.

Mechanisms of diarrhoea:

- Osmotic e.g. Lactose intolerance
- Secretory e.g. Cholera
- Mixed secretory-osmotic e.g. Rotavirus
- Mucosal inflammation e.g. Invasive bacteria, Inflammatory Bowel Disease
- Motility disturbance

Table 2: Comparison between Osmotic and Secretory Diarrhoea

Parameter	Osmotic diarrhoea	Secretory diarrhoea	Mixed
	Carbohydrate load retains water in gut lumen	Gut mucosa secretes water into gut lumen	
Stool volume	10-20 ml/kg/day (<. 200ml/day)	20 ml/kg/day (>200ml/days)	
Stool Osmolality	> 400	Up to 300	
Stool Sodium	< 70 mmol/l	> 70 mmol/l	
Stool Potassium	< 30 mmol/l	> 40 mmol/l	
Osmotic Gap	> 135 mOsm/l	< 50 mOsm/l	
Stool pH	<5.6	> 6.0	
Stool reducing substance	Positive	Negative	
Response to fasting	Diarrhoea stops	Diarrhoea continues	Reduced
Severe metabolic acidosis			If positive suggests structural defect

Adapted from Auth MKH, et al., Investigation of chronic diarrhoea. Paediatrics and Child Health 2016 & Paediatric gastrointestinal disease: Pathophysiology, diagnosis, management. Edited by W.A. Walker, P.R. Durie, J.R. Hamilton, JA. Walker-Smith and J.B. Watkins, 1,785 pp., 2 vol. Philadelphia: B C Decker Inc., 1991.

Table 1: Causes of chronic diarrhoea according to age.

Causes of chronic diarrhoea beyond infancy
INFECTION
Bacteria: Shigella, Salmonella*, C. jejuni, E. coli, Clos. difficile, Aeromonas, Yersinia, Mycobacterium tuberculosis
Virus: Rotavirus, Adenovirus, cytomegalovirus, HIV
Parasites: Cryptosporidium, Giardia, Entamoeba histolytica, Isospora
Small bowel bacterial overgrowth
Post enteritis syndrome*
Tropical sprue
FOOD-SENSITIVE DISEASES
Chronic non-specific diarrhoea (toddler's diarrhoea)*
Lactose intolerance
Allergic and eosinophilic enteropathies
Coeliac disease
Sucrose-isomaltase deficiency
IMMUNE-MEDIATED DISORDERS
Inflammatory bowel disease*
Coeliac disease
Primary immunodeficiency: common variable immunodeficiency, severe combined immunodeficiency, IgA deficiency
AIDS enteropathy
Autoimmune enteropathy including IPEX and APECED
ANATOMIC ABNORMALITIES
Malrotation
Short gut syndrome
Intestinal lymphangiectasia
PANCREATIC INSUFFICIENCY
Cystic fibrosis
Schwachman-Diamond syndrome
PRIMARY METABOLIC DISEASES
Mitochondrial cytopathies
Mucopolysaccharidosis syndromes
Congenital disorders of glycosylation
MALIGNANCY
Gastrinoma (Zollinger-Ellison syndrome)
VIPoma
Carcinoid syndrome
Small bowel lymphoma
Multiple endocrine neoplasia (MEN)
OTHERS
Irritable bowel syndrome*
Factitious diarrhoea or Munchausen's syndrome
Laxative abuse
Nonabsorbable dietary substitutes: sorbitol, Olestra
Polypopsis syndromes
Hirschsprung's disease
Constipation with overflow incontinence*
Hyperthyroidism

Causes of chronic diarrhoea in infancy	
NORMAL VILLOUS-CRYPT ARCHITECTURE	**CRYPT-VILLOUS STRUCTURAL ABNORMALITY**
Ion transport defects	Microvillous inclusion disease
Congenital chloride-losing diarrhoea	Tufting enteropathy
Congenital sodium diarrhoea	Abetalipoproteinemia
Other transporters	Hypobetalipoproteinaemia
Ileal bile salt receptor defect	Chylomicron retention disease
Acrodermatitis enteropathica	Autoimmune enteropathy/IPEX
Carbohydrate	Primary lymphangiectasia
Glucose-galactose malabsorption	Congenital enterocyte heparin sulfate
deficiency	
Congenital sucrose-isomaltase deficiency	Allergic enteropathy*
Protein	Primary immunodeficiency
Cow's milk protein allergy*	Syndromic diarrhoea (trichohepatoenteric
syndrome)	
Enterokinase deficiency	
Lysinuric protein intolerance	
Pancreas	
Exocrine pancreatic insufficiency	
Congenital lipase deficiency	
Congenital amylase deficiency	
Anatomic	
Congenital short bowel syndrome	
Hirschsprung's enterocolitis	* Common causes of chronic diarrhoea
Enteric endocrine dysgenesis	

Approach:

- Work-up for the diagnosis
- Identify and manage the complications
- Manage the underlying disease

Clinical Assessment:

Implications of some aspects of the medical history in children with chronic diarrhea	
Line of Questioning	Clinical Implication
Onset	
• Congenital	Chloridorrhea, Na+ malabsorption
• Abrupt	Infections
• Gradual	Everything else
• With introduction of wheat cereals	Coeliac disease
Stool Characteristics	
• Daytime only	Functional diarrhoea (chronic nonspecific diarrhoea of childhood)
• Nocturnal	Organic aetiology
• Blood	Dietary protein intolerance (e.g., milk), inflammatory bowel disease
• White/light tan colour	Absence of bile; Coeliac disease
• Family history	Congenital absorptive defects, inflammatory bowel disease, coeliac disease, multiple endocrine neoplasia

Dietary History	
• "Sugar-free" foods	Fructose, sorbitol, or mannitol ingestion
• Excessive juice	Osmotic diarrhoea/chronic nonspecific diarrhoea
• Raw milk	Brainerd diarrhoea
• Exposure to potentially impure water source	Chronic bacterial infections (eg, Aeromonas), giardiasis, cryptosporidiosis, Brainerd diarrhoea
Travel history	Infectious diarrhoea, chronic idiopathic secretory diarrhoea
Failure to thrive/weight loss	Malabsorption, pancreatic exocrine insufficiency, anorexia nervosa
Previous therapeutic interventions (drugs, radiation, surgery, antibiotics)	Drug side effects, radiation enteritis, postsurgical status, pseudomembranous colitis (C. difficile), post-cholecystectomy diarrhoea
Secondary gain from illness	Laxative abuse
Systemic illness symptoms	Hyperthyroidism, diabetes, inflammatory bowel disease, tuberculosis, mastocytosis
Intravenous drug abuse, sexual promiscuity (in adolescent/child's parent)	HIV disease
Immune problems	HIV disease, immunoglobulin deficiencies
Abdominal pain	Obstruction, irritable bowel syndrome, inflammatory bowel disease
Excessive flatus	Carbohydrate malabsorption
Leakage of stool	Faecal incontinence (consider occult constipation)

Physical examination

- Growth chart, muscle bulk (mid-arm circumference), subcutaneous fat (triceps skin-fold thickness)
- Vital signs
- Pubertal stage, psychomotor development
- Mucous membrane: hydration status, ulcers etc
- Signs of nutrient deficiencies
- Abdominal distension in malabsorption syndromes or small bowel bacterial overgrowth
- Abdominal tenderness in an inflammatory state
- Perianal disease in inflammatory bowel disease
- Extraintestinal signs

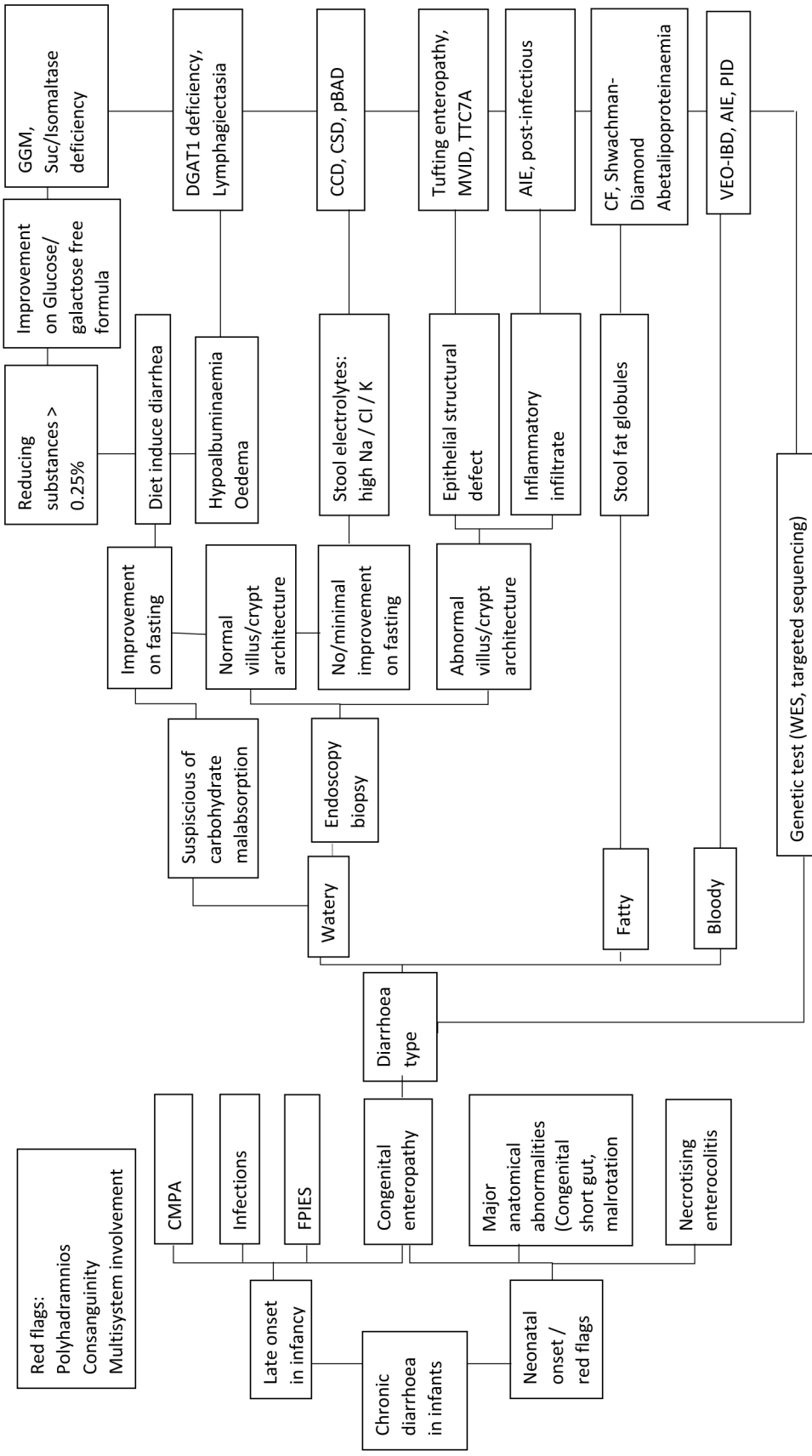
Investigations

Stools
Culture for bacteria Viral study Clostridium difficile toxin Microscopy for parasitic ova and cyst Electrolyte content and osmolarity Reducing substances (correlate with dietary intake) Fat globules Elastase (not available in Malaysia) Calprotectin Lactoferrin
Bloods
FBC – anaemia and thrombocytosis RBC characteristics – vitamin B12 or folate deficiency in malnutrition TWC and differential and immunoglobulin analysis – immune disorders ESR, CRP, Ferritin - inflammation Tissue transglutaminase immune globulin A antibody – coeliac disease (low total IgA level may result in a false-negative test) Albumin – low dietary protein intake, protein-losing enteropathy Coagulation screen, Vitamin ADEK – fat malabsorption Iron studies, Zinc, Lipid profile
Imaging
Contrast studies (Upper GI barium studies to study gross anatomy of upper GI tract) CT scan abdomen
Others
Sweat test
Upper GI endoscopy and small bowel biopsy for histology and electron microscopy
Colonoscopy and biopsy for histology
Rectal biopsy
Primary Immunodeficiency Disease screening
Genetic test

Management of chronic diarrhoea

- Initial resuscitation, correct any fluid and electrolyte abnormalities, hypoglycaemia and prevent hypothermia.
- Identify and treat the underlying cause. Specialist referral if necessary.
- Nutritional assessment and rehabilitation.
- Evaluation of stool output with no feeding for at least 24 hours. If diarrhea stop indicate osmotic diarrhea (diet-induced).
- In cases of lactose intolerance, breastfeeding should be continued unless there are persistent symptoms with perianal excoriation and failure of adequate weight gain. Formula-fed infants should be placed on lactose-free formula for 3-4 weeks.
- Consider treatment with protein hydrolysate in post-enteritis syndrome.
- Suspect monosaccharide intolerance if diarrhoea continues even with lactose-free formula or with glucose-containing oral rehydration solution. Treatment includes bowel rest, parenteral nutrition and gradual introduction of feed.
- Initiate cautious feeding once the child is stabilized
- Some suggested plans for initial feeding are:
  - √ Frequent (every 2–3 h) oral small feeds
  - √ Consider nasogastric feeding if the child is eating ≤ 80% of the amount
  - √ Start at 25-50kcal/kg/day then slowly step up to 100-130 kcal/kg/day or more
  - √ Protein: 1–1.5 g/kg/day and gradually step up.
  - √ Total fluid should base on non-oedematous weight
- Beware of refeeding syndrome in those with severe weight loss and those with prolonged IV hydration.
- Serial monitoring and necessary correction of serum electrolytes is required in the early stage of nutritional recovery.
- Phosphate supplementation is usually recommended. (*Refer Ch 80: Approach to Severely Malnourished Children*)
- Consider micronutrient supplementations in children with chronic diarrhoea and malnourishment, e.g. vitamin A, zinc, thiamine, iron, folate etc.

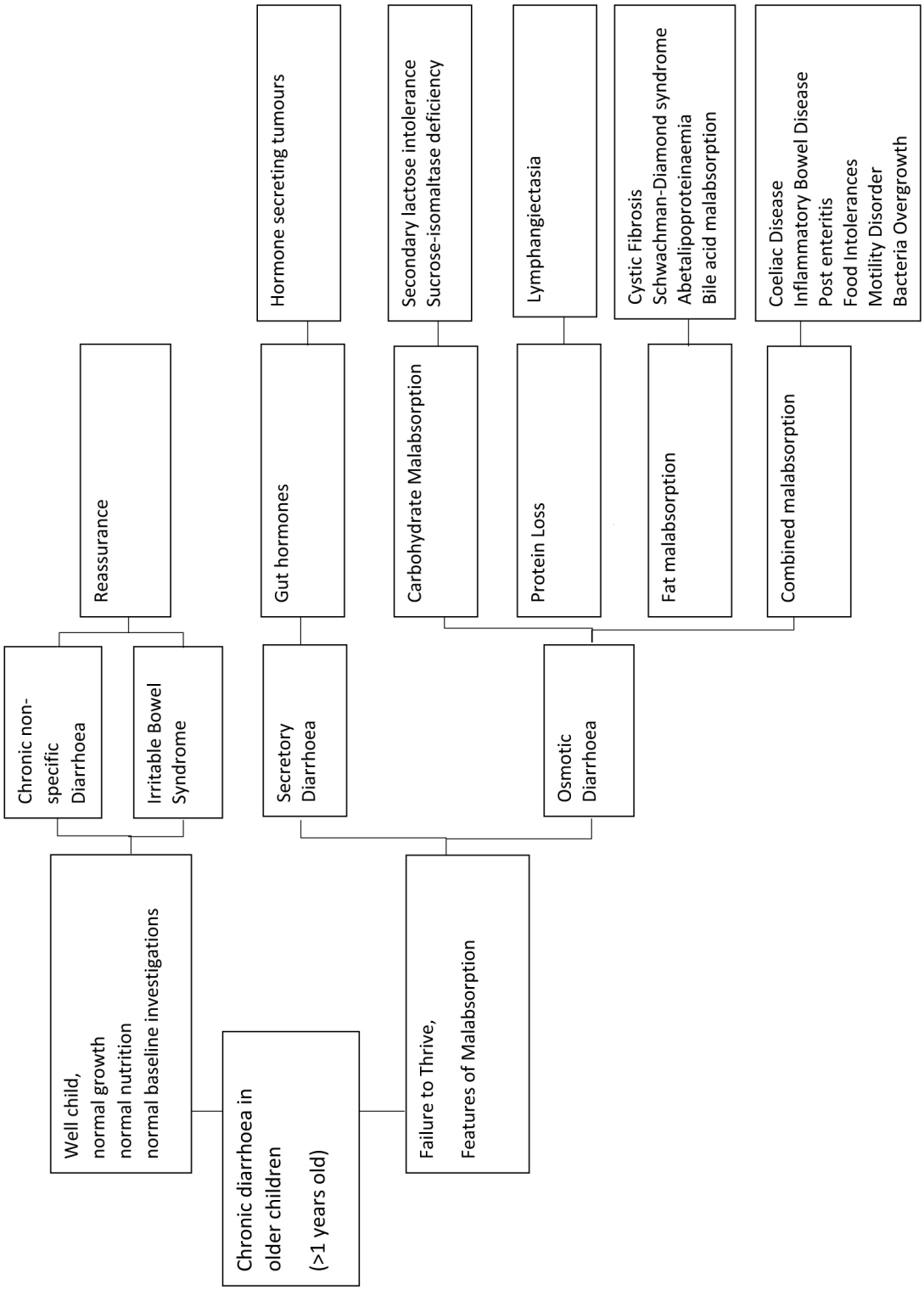
Algorithm for Approach to Chronic Diarrhoea in Infancy



CMPA: Cow's milk protein allergy, FPIES: Food protein induced enterocolitis, GGM: Glucose-galactose malabsorption, DGAT1: diacylglyceroltransferase 1, CCD: Congenital chloride diarrhea, CSD: Congenital sodium diarrhea, pBAD: Primary bile acid diarrhea, MVID: Microvillus inclusion disease, TTC7A: tetraticopeptide repeat domain 7A, AIE: Autoimmune enteropathy, CF: cystic fibrosis, VEO-IBD: very early onset inflammatory bowel disease, PID: primary immunodeficiency disorder

Adapted from Thiagarajah et al. Advances in Evaluation of Chronic Diarrhea in Infants. Gastroenterology 2018

Algorithm for Approach to Chronic Diarrhoea in Older Children (>1 years old)



Chapter 83:
Functional Constipation (FC) in Children

- **Definition:** constipation in the absence of underlying organic disease[7].
- It is the cause of childhood constipation in 95% of cases[7]
- Diagnosis is based on history and physical examination.
- **Diagnostic criteria based on ROME IV** [1,2,3]:

Must include **1 month of at least 2** of the following in infants up to 4 years of age, children and adolescent:

1. 2 or fewer defecation per week
2. History of excessive stool retention
3. History of painful or hard bowel movements
4. History of large diameter stools
5. Presence of a large faecal mass in the rectum

In toilet trained children, the following additional criteria may be used

6. At least 1 episode/ week of incontinence after the acquisition of toileting skills
7. History of large diameter stools which may obstruct the toilet

*After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Organic Causes of Constipation[9]

Anatomic malformations of the colon and rectum	Imperforate anus Anal or colonic stenosis Anteriorly displaced anus
Spinal cord abnormalities	Meningomyelocele, Spinal cord tumour or trauma Tethered cord
Metabolic conditions	Hypothyroidism Hypercalcemia Hyperkalaemia Diabetes Mellitus Diabetes Insipidus
Neuropathic/ Myopathic gastrointestinal disorders	Hirschsprung disease Internal anal sphincter achalasia Visceral myopathy/neuropathy
Drug use/toxin exposure	Opiates Phenobarbital Anticholinergics Attention-deficit/hyperactivity disorder (ADHD) drugs Antacids and sucralfate Antidepressants Antihypertensives Lead toxicity
Other systemic disorders	Coeliac disease Cystic fibrosis Cow's milk protein allergy Connective tissue disorder Mitochondrial disorders Psychiatric disorders

Physiology of Normal Defaecation[7]

The physiology of normal defaecation depends on the interplay of multiple factors:

- Stool is moved through the distal colon by peristaltic contractions of the bowel wall.
- This movement is influenced by colonic tone, which in turn is influenced by diurnal variation and the gastro-colonic reflex (altered colonic tone in response to a meal).
- Once the stool enters the recto-sigmoid junction, distension of the rectal wall results in reflex rectal contraction with concomitant relaxation of the internal anal sphincter.
- Stool is therefore presented to the anal canal and enters the "firing position".
- Stool is perceived in the anal canal, and a decision to expel or withhold the faeces is made.
- Interruptions at any stage during this process may lead to constipation.
- The commonest interruption is a painful stimulus perceived during defecation at around the time of toilet training (e.g. anal fissure), change of diet or infections[9]. Other interruption for older child includes acute events such moving house, starting nursery/school, fears and phobias, major change in family, taking medicines[4].
- Once the painful stimulus has occurred, the child may learn that voluntary withholding of stool prevents recurrence of the painful stimulus.
- This may lead to a vicious cycle of stool- withholding →faecal impaction → further stool- withholding→ further faecal impaction →overflow faecal incontinence.
- Prolonged faecal impaction can lead to chronic rectal distension and eventual loss of normal rectal sensation.
- This can lead to further impaction of stool and megarectum.

Potential Alarm Features In Constipation[2]

- Passage of meconium >48 h in a term newborn
- Constipation starting in the first month of life
- Family history of Hirschsprung's disease
- Blood in the stools in the absence of anal fissures
- Failure to thrive
- Bilious vomiting

Clinical Assessment[7]:
Key features in the history

- Delay in passage of meconium (possibility of Hirschsprung disease)
- Age at onset of symptoms and the initial triggering event: typically 2-4 years old for functional constipation, around the age of toilet training
- Consistency/nature of stool: infrequent, very large stool (large enough to block the toilet) is common chronic FC.
- Painful or bloody stools: differential diagnosis includes anal fissure, perianal group A streptococcal infection, etc.
- Abdominal pain: a very common symptom in children for many organic and functional disorders. Many constipated child may have Recurrent Abdominal Pain (RAP), which may be relieved by the periodic passage of large stool.
- Stool withholding behaviour: voluntary stool withholding may manifest as unusual behaviour, which may be mistaken for straining.
- Soiling: occurs as a result of involuntary passage of liquid stool around faecal impaction in the rectum. It is almost always associated with psychological distress in the child/family.

- Diet: may have history of anorexia, poor energy intake and poor fluid intake. Low fibre intake is common.
- Urinary symptoms: urinary tract infections, urinary frequency and nocturnal enuresis are common in chronically constipated children.
- Family history of constipation/irritable bowel syndrome (IBS)

Key points in examination

- **General health, nutritional status and growth.**
- **Abdominal palpation:** this reveal a faecal mass in at least half of all chronically constipated children. The size of the mass reflects the extent of rectal/colonic involvement.
- **Perianal inspection:** to look for signs of soiling, inflammation, anal fissure or congenital abnormalities such as anterior anus.
- **Rectal examination:** unlikely to add further useful information if clinical features are typical of functional chronic constipation. However, if clinical features are suggestive of underlying organic pathology (e.g. Hirschsprung disease, anal stenosis particularly in infancy), a single rectal examination is indicated to assess tone, calibre, position and the presence of stool in the rectum.
- **Neurological assessment:** inspection of the lumbar-sacral spine and examination of the lower limbs is essential.

Investigation:

- Investigations are generally NOT indicated if the history and examination are typical of FC.
- The following investigation can be considered but should NOT be routine:
  - √ **Abdominal radiograph:**
    Useful to demonstrate spinal abnormalities and to delineate extend of faecal loading (when abdominal examination is not conclusive). Should NOT be routine due to high radiation dose.
  - √ **Bowel transit studies:**
    To assess segmental colonic transit time by measuring the position of swallowed radio-opaque markers on plain abdominal radiographs. This is done at centre with gastroenterology services.
  - √ **Anorectal manometry:**
    To assess the normal relaxation of the internal anal sphincter in response to rectal distention. This test is invasive, not readily available in most centres.
  - √ **Full thickness rectal biopsy:**
    Diagnostic of Hirschsprung disease and indicated only if there is strong clinical suspicion.
  - √ **Electrolytes, micronutrients, endocrine assessment:**
    Iron deficiency is common in childhood constipation. Electrolytes (e.g. hypercalcemia) and endocrine abnormalities (e.g. hypothyroidism) should be considered if history and examination are suggestive.
  - √ **Allergy:**
    In children with atopic features and evidence of proctitis or perianal erythema, investigation for cow's milk allergy/allergic colitis should be considered.

Management:
Non-pharmacological management

1. **Explanation of normal bowel function.**
   Careful explanation of this process to the parents and child help the family understand the disorder and aids compliance with therapy. A basic understanding of the pathophysiology may also relieve tensions in family associated with blame and guilt.
2. **Diet/fluids and exercise.**
   A normal fibre diet is recommended, along with adequate fluid. Dietary fibre/bulking agents help retain water in the gut lumen by osmosis, and stimulate peristalsis by adding bulk to the stool. Regular exercise promotes intestinal peristalsis and helps with bowel transit.
3. **Behavioural advice.**
   Gaining a child trust is important. Time needs to be spent reassuring children about their condition and the treatment. The psychological principle of ignoring failure and rewarding success is important. Anything that helps relax the child will help with the defecation problem, whether it is fear of pain or persistent soiling. Conflict should be avoided.
4. **Toilet training.**
   Regular toileting is a crucial part of the management. Children need to be encouraged to sit on the toilet on waking, after all meals, and before bed. The peak stimulant effects is in the morning and after breakfast there will be an enhanced gastro-colonic reflex. It is important the child has a comfortable position, e.g. toilet seat with foot support. It must be stressed to the parents that this is the most important part of the child's management. It is important that the child sits on the toilet for long enough.
5. **Simple reward schemes. Reward schemes can be highly effective in the behavioural management.**
   The star chart can be used but any attractive variations of this can be used to appeal to each particular child (e.g. sticker charts, computer game time). Rewards can be given for compliance at first (e.g. sitting on toilet twice a day after breakfast and tea), and later rewards are given for success (e.g. bowel openings into the toilet).

Pharmacological management:

1. Stool disimpaction in the presence of faecal impaction/megarectum[1,2,3,4,6,7]. Can be done outpatient or inpatient, via oral or per rectal routes.
   Disimpaction is important to facilitate normal defecation dynamics and then give a sufficiently high laxative dose to ensure regular emptying[7].
   Increased soiling is often seen during the early phase of disimpaction6[6,7].
   Review children undergoing outpatient disimpaction within 1 week3.

Faecal disimpaction			
Outpatient	High dose PEG[1] (e.g Forlax PEG 4000 10g)	1-1.5g/kg/day (for 3-6 days)[1]	Each sachet to be diluted in at least 50ml of water.
	Enema[1] (please refer to table for maintenance treatment).	once per day (for 3-6 days) if PEG is not available[1]	May exacerbate the stool-withholding behaviour and/or toilet phobic behaviour[7].
	**Oral therapy is preferred than enema.*		
Inpatient	High dose PEG[8] (e.g Fortrans PEG 4000 64g with electrolytes)	1.5–4 g/kg[8]	
	Pico-salax[8] (stimulant and osmotic laxatives) Content: Sodium picosulfate 10mg, Citic acid 12g, Magnesium oxide 3.5g	¼ to 1 sachet in 2 divided doses8 depending on age and body weight followed by large amount of clear fluids.	Use with caution in renal failure (↑Mg). Each sachet to be diluted in 150ml of water*.
	**As per bowel cleansing protocol before endoscopic procedure (varies from hospital to hospital)*		

2. Maintenance therapy when the child is not faecally impacted and after faecal disimpaction to prevent re-accumulation of faeces using a variety agents[1,2,3,4,6,7]
   - **Long-term** regular use of laxatives is essential to maintain well-formed stools and prevent recurrence of faecal impaction; intermittent use may provoke relapses[6]
   - Maintenance treatment should continue for at least 2 months. All symptoms of constipation symptoms should be resolved for at least 1 month before discontinuation of treatmen[t1].
   - Treatment should be decreased gradually[1,6], over a period of months, according to response. Some children may require laxative therapy for several years[6].
   - During the developmental stage of toilet training, medication should only be stopped once toilet training is achieved[1,6].

Maintenance therapy: Oral Laxatives				
Class	**Drug/Dosage Form/Strength**	**Drug Action**	**Dose**	**Side effects/ remarks**
Osmotic Laxative	Lactulose	Non-absorbable semi-synthetic disaccharide, produces an osmotic diarrhoea of low faecal pH and discourages proliferation of ammonia-producing organisms[6]	0.5ml/kg 12H oral[5] Child 1-11 months: 2.5 ml bd* Child 1-4 years: 2.5 - 10 ml bd* Child 5-17 years: 5 - 20 ml bd* *Adjusted according to response[6].	Flatulence, bloating and crampy abdominal pain May take up to 48 hours to act[6].
	Polyethylene glycol (PEG): PEG 4000 (e.g Forlax ,1 sachet =10g) *PEG3350 not available in MOH formulary*	Increase osmotic pressure of intestinal lumen resulting in osmotic diarrhea.	**Maintenance:** 0.2-0.8g/kg/day. Recommended to start at 0.4g/kg/day **Faecal disimpaction:** 1-1.5g/kg/day (maximum of 6 consecutive days)[1]	Dissolve the contents of the sachets in at least 50 ml of water* Takes 24 - 48 hours to work* *according to product leaflet
Stimulant laxative	Bisacodyl Tablet-5mg	Increase intestinal motility Tablets act in 10-12 hours; suppositories act in 20-60 minutes[6]	Oral[5]: Child 1-5 years: 5-10mg od Child >5 years: 10-20mg od	*Used in combination with an osmotic laxative such as lactulose6
	**Oral therapy is preferred than enema.*			
Bulk-forming laxative	Isphagula Husk *(not available in MOH formulary)*	Relieve constipation by increasing faecal mass which stimulate peristalsis[6]	Child 1 month – 5years: ½-1 level spoonful bd* (prescribed by Dr only) Child 6-11 years : ½-1 level spoonful bd* Child 12-17 years : 2 level spoonful bd* **1 level spoonful=5ml spoon, to be taken with at least 150ml water*	Use with caution in younger child. Adequate fluid intake must be maintained to avoid in intestinal obstruction[6]

Maintenance therapy: Rectal laxatives/enemas				
Class	**Drug/Dosage Form/Strength**	**Drug Action**	**Dose**	**Side effects/ remarks**
Faecal Softener (Lubricant)	Glycerin (Glycerol) Liquid Paraffin	Softened stool by decreasing surface tension and increasing penetration of intestinal fluid into faecal mass.	*Child 1–11 months: 1 g *Child 1–11 years: 2 g *Child 12–17 years: 4 g *As required per rectal[6].	
		Lubricate and soften impacted faeces and promote a bowel movement6	1ml/kg od (adult 30-45ml)[5]	Anal seepage and the risks of granulomatous disease of the GI tract or of lipoid pneumonia on aspiration[6].
Stimulant laxative	Bisacodyl Suppository-5mg& 10mg	Increase intestinal motility Tablets act in 10-12 hours; suppositories act in 20-60 minutes[6]	Suppository (Not per kg)5: Child <1 year: 2.5mg od Child 1-5 years: 5mg od Child >5 years: 10mg od	Abdominal cramp. Avoid in intestinal obstruction[6].
	Poor effectiveness when not used with other agents for bowel disimpaction[8].			
Osmotic	NaCl[1]		Neonate <1 kg: 5 mL >1 kg: 10 mL1 >1 year old: 6 mL/kg once or twice/day[1]	
Faecal softener (lubricant/ osmotic Laxative	Glycerin 25% and NaCl 15% enema (Ravin enema) Enema 20ml (5g/20ml ampoule)	Glycerin lubricate and soften impacted stool. NaCl is the bile salt involved in maintaining the osmotic pressure of blood and fluid changes	Suppository: *1 enema as required *product leaflet	

#Fleet enema (sodium biphosphate 16%, sodium phosphate 6% rectal solution) is not to be used for treatment of constipation. It is meant for bowel cleansing before colonic surgery, colonoscopy or radiological examination to ensure bowel is free of solid contents.

Indications to refer for specialist advice:[7]

- Children in whom aggressive bowel clearance, e.g. Foltran/Pico-Salax, needs to be considered.
- Children in whom significant behaviour/ psychosocial problems are impacting the management of their constipation.
- Failure to respond to high doses of laxatives.
- Persistent soiling despite laxatives.
- Structural/ physical cause cannot be excluded.
- Concern regarding nutrition/ poor growth.
- Anal fissure or rectal prolapse if there is failure to be cured by a reasonable course (3 months) of laxatives.

Chapter 84:
Prolonged Jaundice and Neonatal Cholestasis

Prolonged Jaundice

Introduction:

- Prolonged jaundice is defined as visible jaundice that persists beyond 14 days in a term baby and 21 days in a preterm baby.
- Most neonatal jaundice is usually self-limited and resolved within 7-10 days postnatally.
- Infants who develop recurrence or new onset of jaundice warrant further investigations and treatment.

Importance of early review:

- To identify overt pathological causes (clinical assessment – sepsis, haemolysis, inborn errors of metabolism (IEM), endocrine disorders)
- For identification of occult infection – e.g., urinary tract infection
- To exclude neonatal cholestasis
- Risk of bilirubin-induced neurological dysfunction (BIND) – e.g. Crigler Najjar syndrome

Causes of prolonged neonatal jaundice:

The aetiology of jaundice is classified into unconjugated (table 1) or conjugated hyperbilirubinemia.
In babies with conjugated hyperbilirubinemia, which is defined as a serum c***onjugated bilirubin concentration greater than 25 micromol/l or greater than 20 percent of total bilirubin***, a prompt referral to Pediatrics unit is needed to delineate the cause.
(Conjugated neonatal hyperbilirubinemia is discussed under the heading of Neonatal Cholestasis)

Causes of unconjugated neonatal hyperbilirubinemia	
Inadequate breastfeeding – inadequate nutrition and dehydration	<u>Lactational failure:</u> Risk of hypovolemia and hypernatremia Jaundice due to slower bilirubin elimination and increases enterohepatic circulation of bilirubin. <u>Address maternal breastfeeding complications:</u> breast engorgement, cracked nipples, maternal fatigue, and stress. Late premature and small gestational age - ineffective suck due to immature oro-buccal coordination and swallowing mechanism.
Breast milk jaundice	The commonest cause of persistent benign neonatal hyperbilirubinemia Typically presented after 5 days of life, peaks within 2 weeks after birth and progressively declines to normal levels over 3-12 weeks The level should be monitored - remains unconjugated and the level does not increase. Cause by hydrolysis of beta -D- glucuronic acid by Beta-glucosidase from breast milk led to increase in intestinal absorption of unconjugated bilirubin Polymorphic mutation of the UGT1A1 gene (UGTA1*6 genotype). Continuing breastfeeding is recommended.
Infection (e.g. urinary tract infection (UTI))	Increased in oxidative stress to neonatal red blood cells, hypovolemia due to poor feeding
Ileus, intestinal obstruction, Pyloric stenosis	Increase in the enterohepatic circulation

Table 1: Causes of unconjugated (indirect) hyperbilirubinemia

Causes of unconjugated neonatal hyperbilirubinemia	
Congenital hypothyroidism	Decreased in bilirubin clearance
Haemolysis, e.g., inherited red blood cell (RBC) membrane defects e.g.: spherocytosis, erythrocyte enzymatic defects e.g.: G6PD deficiency, RBC isoimmunization (Rh or ABO incompatibility)	Increase bilirubin production
Inherited UGT1A1 disorders Crigler-Najjar syndrome (I and II), Gilbert syndrome (GS)	Crigler Najjar (CN) CN I – AR inheritance, most severe form of inherited UGT1A1 disorders (absent of UGT1A1 activity) CN II – AR, AD low UGT1A1 activity , less severe than CN-I. Often responds to phenobarbitone. More common. GS: reduced production of UGT1A1 for conjugation of bilirubin due to mutations in the UGT1A1 gene
History of polycythemia	Infants of GDM mothers, cephalohaematomas (sequestration of blood within a closed space)

Approach:

ALL babies must be screened and referred to a medical facility (with a medical officer or specialist) for prolonged jaundice (visible jaundice) at day 14 for term babies (> 37 weeks) and day 21 for preterm babies.

Clinical assessment:

History:
Risk factors and warning symptoms:
Maternal risk factors: Maternal blood group O, rhesus D (RhD) negative, previous prolonged jaundiced baby, diabetes, firstborn child
Baby's risk factors: prematurity, small for gestational age
Infection: Presence of risk factors - sick contact, history of intrapartum/postnatal infection, concurrent fever

The onset of jaundice: Early onset jaundice within first 24 hour of life may indicate pathological jaundice
Feeding: Breastfeeding, frequency, technique, eagerness to feed (thirsty), vomiting
Activity: Poor feeding, weak cry, lethargy, irritability, seizures
Reduce urine output, dark urine
Stool colour: Ask for the baby's stool color. Always inspect the stool colour and (+/- oily stool) during each consultation.
Drugs history: antibiotics (ceftriaxone, sulfamethoxazole), parenteral nutrition, antiepileptics, diuretics

Examination:
Standard physical assessment and look for red flag signs as below:

Growth failure
Jaundice, Pallor
High-pitched cry, temperature instability, lethargy, dehydration,
Neurological: muscle tone abnormalities, hyperexcitable neonatal reflexes (bilirubin-induced neurologic dysfunction, BIND)
Hepatosplenomegaly

Investigations

Serum bilirubin (Total and the split bilirubin levels (direct and indirect)
Full blood count (FBC) with retic count / full blood picture (FBP), blood group , Coomb's test
Liver function test (Total protein, serum albumin, ALT, AST, ALP)
Thyroid function test
Urine FEME, Urine C&S
G6PD screen (if cord G6PD screen not available)

Other specific investigations based on history and clinical findings (see also the topic on neonatal cholestasis when the serum bilirubin is suggestive conjugated hyperbilirubinemia)

Management of indirect hyperbilirubinemia

- Management of the patient will be according to the underlying cause
- Phototherapy, if required (TB level above photo level according to gestational age)
- Continue breastfeeding; optimize feeding if the baby is formula fed
- Traditional and alternative medicines are not encouraged
- Exposing baby to sunlight is ineffective and may be harmful (dehydration and sunburn)
- Phenobarbitone (increases conjugation and excretion of bilirubin) is not recommended for routine use due to its potential side effects. It may be reserved for cases with partial response to conventional management in suspicion of CN syndrome and Gilbert syndrome.

Management of Prolonged Neonatal Jaundice for Babies ≥ 35 weeks by Risk Groups (at the point of diagnosis in any health facilities)

High Risk	Moderate Risk	Low Risk
Positive Clinical Features/ Lab Results • ILL/ Septic Looking • Respiratory Distress • Poor Feeding • Lethargy • Poor Perfusion	Positive Clinical Features/ Lab Results • Conjugated Hyperbilirbubinaemia • Severe Jaundice- TSB > 300µmol/L • New Onset Jaundice (esp after Day 7) • Pale Stools • Dark Yellow Urine (stains diapers) • Poor Weight Gain • Hepatosplenomegaly *To also consider:* • Bottle fed > 50% • Jaundice >1 mth not investigated before • Other suspected medical condition • Significant family history	Positive Clinical Features/ Lab Results • None, i.e. • Well babies with good weight gain, exclusively breast fed (or >50%), bright yellow stool with normal physical examination • Breast milk jaundice
		Management
Management	Management	Can be managed and followed up at primary care level or hospitals without specialists. *Term babies >37 wks* Day 14: • S. Bilirubin with Direct/ Indirect bilirubin *If still jaundice, Day 21:* • S. Bilirubin with Direct/ Indirect bilirubin, • FBC + reticulocytes • UFEME + microscopy • Free T4, TSH *Preterm babies ≥ 35 to < 37 weeks* To work up 1 week later than term babies.
• Stabilize Airway, Breathing, Circulation • Refer to Paediatrician Immediately	• Refer to Paediatric Team • Same day or next working day	

Well, low risk babies DO NOT need heel prick capillary bilirubin till jaundice resolves. Warning signs for parents and RME (routine medical examination) at 1 mth and 2 mths in health clinics, looking at the same clinical features be a good safety netting.*
Refer to Paediatric Team if conjugated hyperbilirubinaemia, warning signs*, SB> 300umol/L, abnormal lab results, jaundice more than 2 months or any features in the high or moderate risk category.
**Unwell, pale stool, dark yellow urine, new onset of jaundice, persistent jaundice > 2 months*

Adapted from Paediatric Protocols For Malaysian Hospitals, 4th Edition (2018), Malaysian Paediatric Association for Kementerian Kesihatan Malaysia.

Neonatal Cholestasis (NC)

Unlike unconjugated hyperbilirubinemia, neonatal cholestasis is ALWAYS pathological.

Can be classified into biliary causes (obstructive, large extrahepatic, or small intrahepatic bile ducts) or hepatocellular causes (defect in membrane transport, embryogenesis, metabolic dysfunction etc.).
Cholestatic jaundice must be considered in jaundiced babies presenting with acholic stools and dark urine.

Evaluation of NC should be taken in a staged approach guided by a focused and detail history, physical examination and supported by targeted laboratory and radio-imaging studies.
Identifying one possible cause does not exclude co-existent pathology. E.g., it is entirely possible to have both CMV and biliary atresia as dual pathologies.

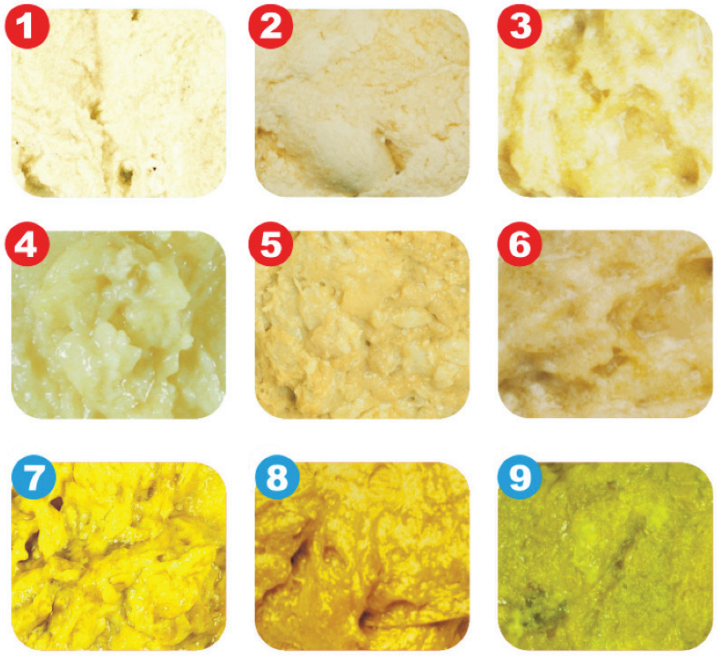
Approach:

History
Perinatal infection, perinatal ultrasound (Fetal detail scan) report, maternal infective screening/ immunization
Complications of pregnancy - Cholestasis of pregnancy (PFIC, mitochondrial disease)
Consanguinity, history of similar problems among family members (autosomal recessive conditions)
Acute fatty liver in pregnancy – Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
Low /Normal birthweight
Newborn screening – Cord TSH, G6PD status
Vitamin K administration
Consanguinity & family history eg: stillbirths, liver disease in siblings – Genetic or IEM

Jaundice - severe haemolysis (ABO incompatibility) – inspissated bile syndrome with acholic stools
Delayed meconium emission, diarrhea (infection, PFIC)
Vomiting – metabolic disturbances, intestinal obstruction, raised intracranial pressure
Diarrhoea
Urine color – dark urine (hyperbilirubinemia, dehydration)
Excessive bleeding – rashes
Behaviour – sleeping a lot, lethargy, poor feeding, floppy, irritability
Seizures
Abnormal body temperature – fever, hypothermia
Weight gain – poor in severe cholestasis, genetic or metabolic diseases

Infant stool color chart

Education should be given to parents to properly observe the stool color of their newborns during the 1st month of life. Parents are advised to bring their infants to medical attention when abnormal stool colours (1-6) are observed.



Examination

General well-being, activity level (vigor and tone)
Growth and muscle mass
Pallor, Jaundice
Tachypneic –chest infection, acidosis
Dysmorphisms (Alagille syndrome facies – broad nasal bridge, triangular facies, deep-set eyes - may not be obvious during early infancy), Down syndrome, cleft lip, cleft palate, facial malformations), Zellweger syndrome
** Examine family members in certain genetic conditions (e.g., Alagille syndrome with autosomal dominant inheritance)
Skin: Bruising, petechiae, rashes
Abdomen: Dilated veins, hepatomegaly including its consistency, splenomegaly, ascites
Heart: Cardiac murmurs, dextrocardia, dextroposition
Ophthalmological assessment – cataract, posterior embyrotoxon, macular cherry-red spots
Joints and limbs – Joints contracture (Niemann Pick type C)
Hypoplastic genitals (micropenis in hypopituitarism)
Hypotonia / encephalopathy
Stool and urine inspection – pale colour, oily stool, dark urine **(CRUCIAL)**

Laboratory test

Should be targeted towards: evaluate condition severity, confirming a clinically suspected diagnosis or excluding a condition for which there is an available treatment.

Initial investigations:

Well looking infant

FBC/FBP, Split bilirubin - total and direct bilirubin, Liver function test (LFT) including gamma glutamyl transpeptidase (GGT), renal function test, random blood sugar (RBS), coagulation screen (PT/INR & APTT), Thyroid function test (TFT) (fT4 and TSH), Urine FEME, Urine culture, urine reducing sugar,TORCHES IgM, ultrasound abdomen (fasting for at least 4 hours, assess hepatic size, echogenicity, anatomic abnormalities of bile ducts, gallbladder, vessels e.g. portal vein, hepatic veins, hepatic artery, spleen, pancreas & kidneys)

Sick infants

In addition to the above investigations, consider blood gas, serum ammonia, lactate, C reactive protein (CRP), blood culture, serum ferritin, lipid profile (triglycerides)

*** Alkaline phosphatase (ALP) is elevated in infants due to osteoblast activity, and therefore GGT is more specific to liver disorder.

Subsequent investigations to be considered :

Causes	Investigations
Obstruction / Anatomical / Bile duct pathologies **Biliary atresia**	• Elevated ALP and GGT • US abdomen: Obstruction or dilatation of the biliary tree, absence of common bile duct, small/ contracted/ irregular walled or absent gall bladder, triangular cord sign – echogenicity of the anterior wall of the right portal vein on transverse or longitudinal view, enlarged periportal lymph node, hepatic artery/portal vein ratio. • Hepatobiliary scintigraphy (HIDA) (technetium Tc99m iminodiacetic acid analogues) • Liver biopsy • Intraoperative cholangiogram (gold standard)
Choledochal malformation (Choledochal cyst) Inspissated bile Congenital gallstones Caroli disease Neonatal sclerosing cholangitis Syndromic/Non-syndromic bile duct paucity Spontaneous perforation of the bile duct Tumour (eg: hepatoblastoma)	• Ultrasound – evaluating dilatation of the intrahepatic and extrahepatic duct, gall bladder, liver parenchymal lesion(s), kidneys (cyst) • Liver biopsy
Infection Bacterial: Sepsis, UTI Viral and Protozoan: TORCHES -Toxoplasma, Rubella, Cytomegalovirus, Herpes simplex (I and II), Syphilis Other viruses: Parvovirus B19, HHV-6, VZV, HIV, Adenovirus, Coxsackie-virus Parvovirus, EBV	• TORCH IgM • RPR/VDRL • Septic work-up (blood culture, urine culture, +/- CSF culture) • CMV – Blood/Plasma CMV PCR, Urine CMV Ag • Blood serology IgM or PCR of other viruses
Endocrine Panhypopituitarism Hypothyroidism Hypocortisolism	• TFT • Early morning serum Cortisol level • Serum IGF-1, GH

Causes	Investigations
Inherited Metabolic Conditions Galactosemia* Hereditary Tyrosinemia 1* Citrin deficiency (SLC25AJ3)* Bile acid synthesis disorders Peroxisomal disorders Congenital disorders of glycosylation Dubin -Johnson (ABCC2), Rotor syndrome Fatty acid oxidation defects Mitochondrial disease Transaldolase deficiency Glycogen storage disease Gaucher's disease Hereditary Fructose Intolerance Organic acidemia Lipid metabolism: Niemann-Pick, Wolman's disease *- more common treatable causes of inherited metabolic disease-causing NC.	• Blood gas - pH • Serum lactate • Plasma glucose - hypoglycemia • Serum ammonia - hyperammonemia • Serum ketone or Ketonuria +/- • Coagulation profile • Serum amino acid • Urine organic acid • Urine for succinyl acetone • Blood spot for acylcarnitine & amino acid profile • Total galactose & galactose-1-phosphate uridyltransferase (GALT) • Serum alpha fetoprotein • Lipid profile • *** to consult genetic/ metabolic pediatrician for other specific investigations
Genetic Alagille syndrome (ALS) Progressive familial intrahepatic cholestasis Arthrogryposis renal dysfunction cholestasis (ARC) syndrome Chromosomal - Down syndrome (Trisomy 21) Alpha 1 antitrypsin deficiency (A1ATD) Cystic fibrosis (CF)	• Chromosome study • JAG 1 gene mutation for Alagille syndrome • Sweat test • A1-Antitypsin level and phenotype (extremely rare in Malaysia) • *** to consult genetic/ metabolic pediatrician for other specific investigations
Alloimmune / Autoimmune Neonatal lupus erythematosus Gestational alloimmune liver disease Hemophagocytic lymphohistiocytosis (HLH) Neonatal hepatitis with autoimmune hemolytic anaemia	• Autoimmune panel (ANA etc) • FBP, Blood group and Coombs' test • Serum ferritin • Serum triglycerides • FBP, BMA
Drugs/ Toxins Parenteral Nutrition (PN) related cholestasis Fetal alcohol syndrome Herbal products Drugs (Ceftriaxone, chloral hydrate, erythromycin, isoniazid, rifampicin, tetracycline,)	History of recent drug exposure Diagnosis by exclusion of other causes
Others Idiopathic neonatal hepatitis Malignancy (neonatal leukaemia) Intestinal obstruction Cholestasis in premature infants	

Salient features of certain causes in well appearing infants

Biliary atresia	Commonest: • form of chronic obstructive cholestasis in infancy • indication for liver transplant in children Affects 1 in 8000-12000 live births worldwide (around 1:10000 in Malaysia). A fibro-Inflammatory disease of the biliary tree occurs perinatally (acquired) or congenital (embryogenic). Classified according to the morphological abnormalities (Type I, IIa, IIb and III). It can be syndromic and associated with splenic malformation (biliary atresia splenic malformation, BASM). Well-appearing infant – acholic stool and dark urine Early treatment (Kasai's portoenterostomy) in the first 45-60 days of life improves transplant-free survival up to 75-90% Nutrition is of upmost important: fat-soluble vitamin supplementation, medium chain triglyceride (MCT)-rich formula.
Choledochal cyst	Although there are some distinctions between ultrasound findings of BA and choledochal cyst (dilated or cystic duct, no atretic gall bladder), careful evaluation for BA should still be carried out due to resemblance of US finding (e.g. BA Type 1) and possible dual pathologies.
Infection: Congenital CMV	Most common congenital infection. Most newborns affected are asymptomatic, but some may present with low birth weight, microcephaly, chorioretinitis, deafness and periventricular calcifications. Hallmark of liver related problems are hepatosplenomegaly and cholestasis.
Endocrine	Hypothyroidism – mothers with thyroid condition High TSH, low FT4 Panhypopituitarism: Cholestasis, hypoglycemia, shock due to adrenal insufficiency. Micropenis in boys. Some infants have associated septo-optic dysplasia in which MRI brain is required. Cholestasis resolves with hormonal replacement.
Alagille syndrome	Autosomal dominant, most common familial intrahepatic cholestasis. Confirmed by JAG1 and NOTCH2 genes mutations. Clinical features: Alagille facies, posterior embryotoxon, butterfly vertebrae, renal disease, cardiac defects. Liver pathology – Paucity of interlobular ducts leading to cholestasis with occasional acholic stool, elevated GGT and transaminases.
Citrin deficiency	An important treatable cause of neonatal hepatitis among Asians. Investigations MAY yield elevated total blood galactose but normal galactose-1-uridyl transferase (GALT) (i.e. secondary Galactosemia). Elevated citrulline in plasma amino acids and dried blood spot amino acids . Treatable with galactose free formula (if there is secondary galactosaemia) with medium chain triglyceride (MCT) supplementation

Progressive Familial Intrahepatic Cholestasis (PFIC)	Low or normal GGT, out of proportion of cholestasis – except for PFIC 3 in which GGT is elevated PFIC type 1 (ATP8B1), PFIC type 2 (ABCB11), PFIC type 3 ABCB4, PFIC 4 (TJP2 deficiency), PFIC 5 - FXR liver disease (FXR), PFIC 6 (MYO5B), PFIC 7 (USP53). PFIC 2 and 3 affect only the liver whereas others may have multisystem involvement.
Bile acid synthetic disorders (BASD)	Rare, Low or normal GGT with inappropriately low serum bile acid in the background of cholestasis. Diagnosis by genetic study and urine bile acid analysis by FAB-MS (test not available in Malaysia). Most of the BASDs can be treatable with end products of bile acid synthesis – cholic acid and chenodeoxycholic acid (not available in Malaysia)
Idiopathic neonatal hepatitis syndrome	Cause unknown

Salient features of certain causes in Ill appearing infants

Sepsis – e.g., bacterial infections (gram-negative septicemia, urinary tract infection)	Timely administration of antimicrobial agent(s) is important to prevent progression of sepsis
Congenital infections	Presentation: around 5-14 days, usually small for gestational age (SGA), Possible: microcephaly, rashes, chorioretinitis, cataracts, brain abnormalities - calcification, heart - PDA, Hepatomegaly, splenomegaly, elevated aminotransferases, High ferritin, Coagulopathy, Check for serology/PCR of particular pathogens
Metabolic diseases *(E.g., Galactosemia, Hereditary fructose intolerance, aminoacidopathies, organic acidurias, urea cycle defects)*	Presentation – Variable, neonatal to early infancy, +/- SGA, positive family history, CNS and head anomalies. Poor feeding, vomiting, lethargy, coagulopathy, hypoglycemia, transaminitis, +/- high ferritin, AFP and lactate with high anion gap metabolic acidosis
Gestational alloimmune liver disease (GALD)	Presentation: At birth or later. Small for gestational age, prematurity +, oligohydramnios, multi-system involvement, ascites, usually no organomegaly, hypoglycemia, progressive cholestasis, coagulopathy, ALT normal/low (<100IU/L), serum ferritin (>800 ng/mL), extremely high AFP
Panhypopituitarism	Endocrinopathies (hypoglycemia), neurologic complications
Hemophagocytic Lymphohistiocytosis (HLH)	Presentation: Variable, at birth. Bone marrow suppression, hepatomegaly, splenomegaly, hypoglycemia, transaminitis, high ferritin and triglycerides, low fibrinogen, usually normal range AFP

Imaging:

- Chest X-ray, Spine X-ray – bony deformities, butterfly vertebrae (ALS), abnormal heart shadow
- Ultrasound abdomen – Liver parenchyma, biliary duct (intrahepatic, common bile duct, gallbladder), vessels – portal vein, hepatic artery, hepatic vein, spleen, pancreas and kidneys. (US cannot exclude biliary atresia but it's helpful in detecting anatomical pathology like choledochal cyst)
- Scintigraphy – Technetium-99m labeled iminodiacetic acid (HIDA scan) BA – sensitivity (83-100%), specificity (33-80%). Hardly use nowadays as repeated fresh stool examination provide similar sensitivity and specificity.
- Echocardiography – septal defects, peripheral pulmonary artery stenosis, etc

** remember to supplement intravenous hydration with dextrose when the babies are fasting for the imaging study due to the risk of hypoglycemia, especially in high-risk babies suspected of, e.g., IEM, hepatic dysfunction, etc.

Liver biopsy: Percutaneous liver biopsy for histopathology examination. It may be helpful in diagnosing certain diseases, assessing condition severity and provide prognosis.

Sometimes referral to other specialties are necessary, eg: ophthalmology to look for cataract, posterior embryotoxon, chorioretinitis, cherry red spots, optic nerve hypoplasia & hearing assessment for congenital CMV infection.

Paediatric surgical consult (esp pale stool and dark urine, anatomical anomalies from ultrasound abdomen)

Referral to a Paediatric Gastroenterology service should be considered early when there is progression of liver disease or liver failure.

Treatment: (management of the causative disease and complications)

Optimize the nutrition
- Provide adequate calories to support growth
- May consider high carbohydrate, normal protein, and medium chain triglycerides (MCT)-based diet (Caloric 125% of RDA, protein 2-3gm/kg/day)
- Micronutrient supplementation, especially fat-soluble vitamins (Vitamin A, D, E, K) e.g., Appeton infant drop
- Sometimes, a referral to a dietitian is necessary
- Consider enteral nutrition or parenteral nutrition in infants with inadequate intake or increased metabolic demand
- Special diet consideration in certain metabolic diseases

Specific therapies may be directed at any identifiable underlying cause. **Most idiopathic neonatal hepatitis have spontaneous resolution.**

<u>Examples:</u>
Infection – broad-spectrum antibiotics, +/- antiviral (acyclovir)
Inspissated bile syndrome - Ursodeoxycholic acid (10-20mg/kg/day in 2 divided doses)
Galactosemia – Galactose- free diet (soy-based formula)
HT1 - NTBC 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione).
PN-associated cholestasis – provide balanced nutrition, wean off PN or modify PN esp. lipid content; and ursodeoxycholic acid
Hypothyroidism – Oral L- thyroxine

Treatment of complications:
Coagulopathy: Oral, subcutaneous, IM, intravenous vitamin K (0.3mg/kg/dose daily)
Pruritus: Ursodeoxycholic acid (UCDA), Rifampicin (need to monitor LFT due to potential hepatoxicity), Cholestyramine (bile acids binder)

Others:
Avoidance of hepatotoxins
Vaccination (routine as per national immunization schedule and consider extra protective vaccination)
Screening for portal hypertension and hepatocellular carcinoma during follow up
Monitor neurodevelopment
Provide family support
Referral to a liver transplant center for assessment when the disease worsens

"Time Sensitive" cases that require prompt diagnosis and urgent medical attention -

- Cholestasis with pale stool – e.g., biliary atresia (commonest, baby typically appear well, early Kasai's procedure before 60 days of life results in a better patient outcome)
- Inherited metabolic disorders, e.g., Galactosaemia, HT1
- Sepsis, sepsis-like presentation (GALD)
- Endocrine – hypothyroidism, panhypopituitarism

All babies with prolonged jaundice should be seen at least one more time, before the age of 6 weeks to ensure resolution of jaundice.

Chapter 85:
Evaluation and Management of Children With Liver Disease

Paediatric Acute Liver Failure

Paediatric acute liver failure is a complex, rapidly progressive clinical syndrome with significant morbidity and mortality. A timely, age-based diagnostic approach could establish an etiology and treatment decisions. The interval between clinical presentation and clinical outcome, spontaneous recovery, orthotopic liver transplant (OLT), or death can be as early as hours to days.

Paediatric Acute Liver Failure (PALF) criteria

i. Acute onset of liver disease without evidence of chronic liver disease (within 8 weeks of onset)
ii. Biochemical evidence of severe liver injury (Hepatocellular injury and biliary dysfunction)
   - Coagulopathy not corrected by vitamin K
   - Prothrombin time (PT) > 15 seconds or INR > 1.5 with evidence of hepatic encephalopathy (HE) or PT > 20s or INR > 2 with or without encephalopathy

Neonatal Acute Liver Failure (NALF) criteria

The criteria for Neonatal acute liver failure is the same as PALF definition except that the INR is reset at > 3.0 (Normal newborn INR may extend up to 2.0, and premature newborns may have an INR >2.0)

Acute on chronic liver failure (ACLF)

Acute deterioration of the liver functions because of a precipitating factor in the background of chronic liver disease (Wilson disease, autoimmune hepatitis, cryptogenic, Budd chiari syndrome, IEM, etc.). To date, there is no universal definition describing ACLF in children. Clinical manifestations include jaundice, coagulopathy, ascites, and/or encephalopathy. Common precipitating triggers are bacterial infection, sepsis, viral (HAV, HEV), and drugs. ACLF carries high 28 days mortality, and there is no proven treatment other than OLT.

Causes of NALF

Table 1: Causes of NALF and their features.

	Gestational alloimmune liver disease (GALD)	Viral infection	Haemophagocytic Lymphohistiocytosis (HLH)	Mitochondrial Hepatopathy
Age at presentation	Usually at birth and almost always < 3 days	5-14 days	Variable	Variable (1st week to months)
Premature birth	Most (70-90%)	Usual population incidence	Not common	Not common
History of sibling death	Common	Almost never	Uncommon	25% risk in full siblings
Oligohydramnios	Most (70-90%)	Rare	Rare	Uncommon
IUGR	Most (70-90%)	Rare	Rare	Possible (20-30%)
Multiorgan involvement	Renal tubular dysplasia	HSV - brain	Bone marrow	Possible (20-30%)
Multiorgan involvement	Renal tubular dysplasia	HSV - brain	Bone marrow	CNS, heart
Ascites	Common (40-60%)	Rare	Uncommon	Uncommon
Patent ductus arteriosus	Most (70-90%)	Never	Never	Never
Hepatomegaly	Uncommon (10-20%)	Common	Common	Common
Splenomegaly	Uncommon (10-20%)	Mild	Common	Uncommon
Hypoglycemia	Usual	Common	Common	Usual
Coagulopathy	Profound (INR – 4-10)	Moderate to profound	Moderate to profound	Moderate to profound
Metabolic acidosis	No	No	No	Yes
Cholestasis	Progressive	Minimal at presentation	Moderate to severe	Moderate
ALT	Typically low or normal (<100 IU/L)	Typically high often > 1000IU/L	Typically high often> 1000IU/L	Typically high often 100-500 IU/L
AFP	Almost always high (> 80,000ng/mL in term neonate); typically, > 300,000 ng/mL	Almost always normal (<80,000ng/mL in term neonates)	Almost always normal (<80,000ng/mL in term neonates)	Variable elevation
Ferritin	Almost always > 800 ng/mL and <7000	Often very high (>20,000 ng/mL)	Very high (>20,000ng/mL)	Variable elevation
Lactate pyruvate molar ration and ketone body ratio	Normal	Normal	Normal	Abnormal

Adapted from S.A Taylor and PF Whitington, Liver Transplantation 22 677-685 2016 AASLD.

Other causes of NALF

- Sepsis
- Giant cell hepatitis with autoimmune hemolytic anaemia
- Inherited Metabolic conditions – Galactosaemia, Hereditary fructose intolerance (AR, aldolase B deficiency), hereditary tyrosinaemia type I, mitochondrial depletion syndrome
- Tumor – massive liver hemangioma, neonatal leukaemia

Specific management of NALF according to causes:

- GALD -
- Investigation: Labial salivary gland biopsy, MRI liver (T2*)
- High-dose intravenous IgG (IVIG) (1gm/kg body weight) – Suspected case in which work up in progress
- Confirmed diagnosis: Double-volume exchange transfusion with repeat high-dose IVIG
- High risk of recurrence therefore affected mothers with infants with NH-GALD are to be given high dose IVIG antenatally in subsequent pregnancies.
- Viral (HSV-associated NALF) – IV acyclovir
- Galactosaemia – Lactose-free formula
- Hereditary fructose intolerance – avoidance of fructose and sucrose
- Hereditary tyrosinaemia type 1 – NTBC (Nitisinone), restriction of phenylalanine and tyrosine.
- Sepsis: Antimicrobial (Board spectrum and +/- antiviral, iv acyclovir)

Evaluation Of Paediatric Acute Liver Failure (PALF)

Aim:

- Rapid identification of a cause for effective treatment
- Prognosticate the natural progression of the disease for decisions on emergency liver transplantation

Aetiology of PALF (According to age)

- Certain conditions are more common in selected age group in which helps to scale down the list of pathological causes.

Table 2a: All ages

Infectious Viruses Hepatitis A (HAV) Hepatitis B(HBV) Hepatitis E (HEV) Herpes simplex virus Parvovirus B-19 Adenovirus Dengue virus Epstein Barr virus Human Herpesvirus -6 (HHV-6) Enterovirus (echovirus, coxsackie A & b) Sepsis – Gram-negative organism Neisseria meningitides Brucellosis, Coxiella burnetii (Q fever) Plasmodium falciparum Entamoeba histolytica	Often associated with a prodrome. Test – usually serological markers eg: IgM against HAV, HEV, HSV, EBV, CMV etc, HBsAg, HB core IgM, and/or plasma PCR (DNA/RNA). Blood culture
Immunologic Immune dysregulation Haemophagocytic lymphohistiocytosis (HLH) Coeliac disease Autoimmune hepatitis Multisystem inflammatory syndrome in Children (MIS-C)	Elevation of autoimmune markers high total protein, high IgG level, HLH – fever, hepatosplenomegaly, high ALT/AST, cytopaenia, hyperferritinemia (often >5000ng/mL), hypofibrinogenemia, high sCD25. Can be primary HLH or secondary (triggered by viral infection)
Metabolic Mitochondrial disease (hepatopaties)	Lactic acidosis, multi-systemic involvements
Vascular Hypoperfusion of the liver (shock, sepsis, cardiac dysfunction, Veno-occlusive disease (VOD), Budd Chiari syndrome (BSC)	Systemic hypotension with multiorgan dysfunction VOD: Hepatic sinusoidal obstruction, after exposure to chemotherapy for hematopoietic stem cell transplantation. Symptoms include weight gain, hepatomegaly, ascites and hyperbilirubinemia. BCS – uncommon cause of ALF. Ultrasound abdomen and doppler.

Toxin/ Drugs Paracetamol Isoniazid (idiosyncratic) Pyrazinamide Propylthiouracil (idiosyncratic) Halothane (idiosyncratic) Valproate acid (idiosyncratic) Carbamazepine (idiosyncratic) Lamotrigine (idiosyncratic) Amoxicillin-clavulanate, Rifampicin Nitrofurantoin (idiosyncratic) Amiodarone (idiosyncratic) Herbal Cocaine, ecstasy (3,4 – methylenedloxyamphetamine MDMA) Amanita phalloides (mushroom)	Paracetamol toxicity Acute single ingestion > 150mg/kg Chronic ingestion> 90mg/kg /day; > 15mg/kg every 4 hourly for > 1 day Risk factor: Concomitant use of other drugs that alter hepatic metabolism, prolonged fasting, younger age, prolonged exposure and delayed presentation Need to get a thorough history. Marked elevation ALT and AST with mildly raised bilirubin. Stage 1: (<24H from ingestion) Nonspecific nausea, vomiting, abdominal pain. Near normal/ normal lab test. Stage II (24-72h from ingestion) RUQ pain, LFT, INR elevations. Stage III (73-96h) Severe liver dysfunction (jaundice, coagulopathy, metabolic acidosis with high anion gap) HE, AKI, multiorgan failure. Stage IV (>96h) Recover phase. Clinical and biochemical symptoms improve.Rx with NAC (refer to chapter on acute poisoning) Valproate: Undiagnosed mitochondrial disease (Alpers -Huttenlocher disease) causes hepatotoxicity from valproate
Others Indeterminate Leukaemia	Indeterminate:(causes not identified despite extensive diagnostic work up (25-40%), next generation sequencing may be of help. Leukaemia: high fever, organomegaly, high uric acid and LDH with abnormal blood film. Malignant infiltration to liver is a contraindication to OLT.

Table 2b: Infants and toddlers

Inherited Metabolic Disease Galactosaemia Hereditary Tyrosinaemia type I (HT-1) Lysosomal storage disease - Niemann-Pick type C Mitochondrial Hepatopathies (MH) Urea Cycle Defects (eg: ornithine transcabamylase deficiency) Fatty acid oxidation disorders (FAOD) Recurrent PALF	Galactosaemia: AR. Impaired galactose-1-phosphate uridyltransferase (GALT). ALF in infants consuming breast milk and lactose-containing formula. Associated with gram-negative sepsis. Urine for reducing sugar - a simple and good screening test. GALT quantitative assay in RBCs (sampling before any RBC transfusion) HT-1: AR, deficiency of fumarylacetoacetate hydrolase (FAH), profound coagulopathy with normal/ near normal transaminase. Elevated urine succinylacetone. Niemann Pick type C – associated with progressive neurological disease. Mitochondrial hepatopathies (MH): Dysfunction of hepatocyte mitochondria resulting in hepatocyte injury, steatosis, or ALF. Multisystemic involvement, lactic acidosis. (Most of the MH are contraindicated for OLT due to multisystemic involvement) Urea cycle defects: Most presented withhyperammonemia, neurologic symptoms and liver dysfunction, OTC deficiency: X-linked recessive, hyperammonemia. Ammonia scavengers and protein intake restriction. FAOD: (AR) Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, fatty acid transportation defects, beta-oxidase enzymes defects. ALF is triggered by febrile illness, fasting, and dehydration with hypoketotic hypoglycemia. Hyperammonemia and cardiomyopathy may occur. (Reyes-like syndrome). Urine organic acid, plasma carnitine, and acylcarnitine profiles (preferably taken during a crisis), functional studies in cultured skin fibroblasts, or genetic studies. Management includes continuous iv glucose infusion, L-carnitine administration, and avoidance of lipids and some medications e.g., valproic acid and salicylates. Recurrent PALF: can be due to metabolic, toxin or immune relate. Occasionally fever triggered ALF due to mutation in certain genes eg:NBAS, SCYL1 and RINT1.
Immune-mediated/ Autoimmune Autoimmune Hepatitis – type II Multisystem inflammatory syndrome in Children (MIS-C) HLH	Raised inflammatory markers

Table 2c: Older children and adolescents

Metabolic Wilson disease (WD) Mitochondrial disease (Fatty oxidation defects)	WD: Coombs negative hemolytic anaemia, marked hyperbilirubinemia, low serum ceruloplasmin, normal or low ALP, low uric acid, marked serum copper > 200µg/dL, Kayser Fleischer rings (50%), elevated dry weight liver copper. Rx: copper chelation with penicillamine / zinc.
Immune-mediated/ Autoimmune Autoimmune Hepatitis (AIH) (I or II)	AIH - Antinuclear antibody (ANA), anti-smooth muscle (SMA), Liver kidney microsomal (LKM), +/- hyperimmunoglobulin G, liver biopsy. Treatment - corticosteroids, azathioprine.
Drugs / toxins Alcohol Paracetamol Cocaine, ecstasy (3,4 – methylenedloxyamphetamine MDMA) Herbal remedy	Drug history and drug levels

Table 2: Causes and description of conditions associated to age group.

Assessment of PALF

Assessment should begin with comprehensive clinical history and physical examination.

i. HISTORY

- Symptoms of acute hepatitis
  - o fatigue, malaise, nausea, and abdominal pain/discomfort
  - o +/- jaundice, dark urine, pale stool
- Other associated symptoms (varies based on age and aetiology)
- fever
- anorexia, vomit, diarrhoea, bloody stool
- headache
- conjunctivitis
- irritability / confusion
- rashes
- respiratory symptoms, sore throat

- Drug history (including supplement and traditional medicine, illicit drug use, and alcohol intake for older children/ adolescents), recent travel history, sick contact history, family history (autoimmune, liver disease, recurrent neonatal death, recurrent abortions, consanguinity)
- Pre-existing developmental delay, history of altered mental status or behavioural change

ii. PHYSICAL EXAMINATION

- May be normal in the early stages of Acute Liver Failure
- Initial, and serial neurological examinations should be performed to assess mental (e.g., attentiveness, confusion, orientation) and neurological signs of hepatic encephalopathy (e.g., brisk reflexes, Babinski sign)
- Hepatic encephalopathy grading
- Signs suggestive of an underlying chronic liver disease
  - growth failure, dysmorphism
  - portal hypertension (abdominal varices, hepatosplenomegaly, ascites, peripheral oedema)
  - digital clubbing, rachitic rosary
  - skin xanthomas, spider angiomas

Red flags of worsening liver disease: Salient features

- Persistent jaundice with impalpable liver or a liver of reducing size, with progressive decline in serum aminotransferase levels
- Encephalopathy, may worsen quickly (needs frequent review).
- Increasing lethargy or occasional hallucinations.
- Symptoms may be subtle and not detectable by clinical assessment but are apparent to family members:
  - personality changes: e.g. irritable /apathetic (young children), aggression, irritability, euphoria, apathy (older).
  - intellectual deterioration, insomnia, sleep inversion.
- Bruising, petechiae or bleeding from deranged clotting unresponsive to intravenous vitamin K.
- Failure to maintain normoglycemia (which aggravates encephalopathy) or presence of hyperammonaemia.
- Increased intracranial pressure (fixed dilated pupils, bradycardia, hypertension or papilloedema).

Assessment of encephalopathy

Young children (age < 4 y)

Grade	Mental status	Reflexes	Neurological signs	EEG changes
Early (Stage 1 and 2)	Inconsolable crying, sleep reversal, inattention to task	Unreliable/ normal or hyperreflexia	Difficult to test. Responses may be delayed, and attention span shortened	Normal or mild slowing
Mid (stage 3)	Somnolence, stupor, combativeness	Unreliable – can be decreased, absent or increased	Difficult to test. Progressive decrease in response to external stimuli	Mild or moderate background abnormality with slowing
Late (stage 4)	Comatose, arouses with painful stimuli or no response	Unreliable – can be decreased, absent or increased	Decerebrate or decorticate	Severe attenuation or slowing

For children (>4 y)

Table 3: Stages of encephalopathy

Stage	Mood and mental status	Reflexes	Neurological signs	EEG changes
Stage 1 (prodomal)	Mood swing: euphoria/ depression; mild confusion, slowness of mentation and affect, slurred speech; disordered sleep	Normal or hyperreflexic	Tremor, apraxia, impaired handwriting	Normal or diffuse slowing
Stage 2	Accentuation of Stage 1; lethargy, moderate confusion, inappropriate behaviour; inability to maintain sphincter control	Hyperreflexic	Ataxia, dysarthria	Abnormal, generalised slowing
Stage 3, stupor	Marked confusion; sleepy but arousable; incoherent speech	Hyperreflexic	Rigidity	Abnormal, generalised slowing
Stage 4, coma	Marked confusion; sleepy but arousable; incoherent speech May or may not respond to painful stimuli	Usually absent	Decerebrate or decorticate	Abnormal, very slow

Adapted from J.E. Squires et al, JPGN Volume 74, Number 1, January 2022 North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

D. INVESTIGATIONS

i. Initial clinical testing:

- Liver function: PT / INR / Bilirubin (total and fractionated) / Total Protein and Albumin / Glucose / Ammonia and lactate
- Multisystem assessment: RP /Ca / Mg /PO4 /FBC /Amylase / Blood Gas
- Liver injury: ALT / AST / GGT / Ferritin

** To monitor regularly (at least daily) and watch out for worsening liver disease

ii. Investigations of aetiology:

1. Infection :

- Blood Culture / Urine Culture
- Hepatitis A IgM
- Hepatitis B surface Antigen (HBsAg)
- Hepatitis C Antibody
- Hepatitis D IgM (if HBsAg positive)
- Hepatitis E IgM
- Cytomegalovirus IgM
- Herpes virus IgM
- Epstein Barr Virus IgM
- Parvovirus IgM
- Adenovirus PCR
- SARS-COV2 PCR +/- SARS-COV2 Antibody
- Respiratory panel multiplex PCR (Influenza, Parainfluenza, RSV) - if there is respiratory symptom
- Stool for multiplex PCR -GI pathogens (rotavirus / norovirus / adenovirus / enterovirus) and culture (E. Coli, Salmonella, Shigella) - if there is GI symptoms
- Dengue serology
- Leptospira IgM

Other infectious agent:

- Astrovirus, Bocavirus, HHV7, Metapneumovirus, Sapovirus, Campylobacter, Yersinia

2. Autoimmune panel :

- IgG (+/- IgG4 subclasses)/IgA/IgM
- Anti-Nuclear Antibody (ANA)
- Specific Liver Antibodies (anti-smooth muscle antibodies (SMA), anti – liver kidney microsomal antibody type 1 (anti LKM-1)
- Complement (C3 and C4)

3. Metabolic :

- Plasma amino acid
- Urine organic acid, urine succinylacetone
- Acylcarnitine profile
- Serum Ceruloplasmin and Copper
- 24-urine for copper (with and without penicillamine challenge)
- Alpha fetoprotein
- +/- blood galactose, GALT enzyme

4. Toxicology :

- Paracetamol level
- Salicylate level

5. Others :

- Full blood picture
- Iron studies and Ferritin
- Lipid profile (triglyceride)

iii. Imaging:

- Ultrasound abdomen
- Chest X-ray
- +/- echocardiography

iv. Liver biopsy - percutaneous approach - high bleeding risk ; transjugular approach if feasible (drawback – suboptimal tissue sample, technically challenging)

E. MANAGEMENT

i. General management:

- **Early referral to intensive care unit with paediatric intensivist if patient condition worsens or progress to liver failure**
- Closely monitored in quiet darkened room with head end elevated at 30° and head in neutral position (to decrease intracerebral pressure and minimize cerebral irritability)
- Place pads on bed rails to prevent injury from aggressive, combative and forceful movements
- DO NOT sedate unless already ventilated because it may precipitate respiratory failure and death
- Maintain oxygenation
- Frequent neurological observations (1-4hourly)
- Give Vitamin K (IV or Subcutaneous) to correct prolong PT. To correct prolong INR in the event of bleeding or optimization for invasive procedures. Despite abnormal INR, most of the patients with PALF maintain normal hemostasis and therefore bleeding often precipitated by low platelets counts and sepsis. Platelet count should be maintained ≥ 50 x109 /dl.
- Overzealous blood product transfusion may cause transfusion-related lung injury and fluid overload.
- If frank bleeding (GIT / Oral) occurs, consider prudent use of FFP 10ml/kg and cryoprecipitate 5ml/kg.
- Prophylactic H2 antagonist or proton pump inhibitor or oral antacid to prevent gastric/duodenal ulceration
- Full septic screen(excluding Lumbar Puncture), CXR should be obtained. Treat sepsis aggressively with broad spectrum antibiotics (aerobic and anaerobic cover, monitoring level of aminoglycosides accordingly due to potentially of acute kidney injury (hepatorenal syndrome) in ALF. Antiviral (acyclovir) should be considered in neonates and infants.

ii. Fluids

Aim to maintain hydration & renal function while reducing the risk of cerebral oedema.

- Maintain euvolemia; consider 80% of normal maintenance if condition progressed further.
- Maintenance fluids consist of Dextrose 10% in 0.45% or 0.90% Normal saline. Maintain glucose levels between 4-8 mmol/l.
- A central vein catheterization is necessary for high glucose concentration delivery.
- Check capillary blood sugar every 2-4 hourly (maintain ≥ 4mmol/l).
- Strict monitoring of urine output & fluid balance (catheterization if necessary).
- Aim urine output > 1ml/kg/hour. A reduction in urine output (<1ml/kg/hour) may indicate AKI and continuous filtration should be considered to prevent acidosis and volume overload.
- Consider checking urinary electrolytes; serum urea, creatinine, electrolytes, and osmolarity.
- Maintain sodium requirements 2-3 mmol/kg/day. Treat hyponatremia when Na < 120 mmol/l or symptomatic.
- Renal dysfunction - Possible causes: hepatorenal syndrome, dehydration, low CVP, low cardiac output, nephrotoxic medication exposure (e.g. NSAIDs). Consider haemofiltration or dialysis (discuss with nephrologist/intensivist)
- In the presence of persistent hypotension (decreased SVR) – might consider IV noradrenaline infusion followed by vasopressin analogues. May consider IV hydrocortisone in cases suspected of adrenal insufficiency.
- Ammonia lowering measures – protein restriction, bowel decontamination with lactulose

iii. Nutrition

- Provide adequate energy intake to avoid catabolism. Enteral feeding is preferred over total parenteral nutrition (with lipids). * lipids are avoided in mitochondrial disease and fatty acid oxidation defects.
- If the patient progresses to HE, consider stopping oral protein. Gradually reintroduce at 0.5-1g/kg/day, then 1-2g/kg/day either enterally or parenterally.
- Maintain normal Na, K, Mg, Phosphate and calcium.
- Bowel decontamination : Lactulose (1-2ml/kg every 4-6hourly) to produce 3-4 loose stools per day. Consider Rifaximin or neomycin if available.
- Low copper diet for suspected Wilson disease

iv. Medications

- *Try to avoid any nephrotoxic and hepatotoxic agents*
- *IV N-acetylcysteine (NAC)* is indicated if paracetamol poisoning in paediatrics (history and high index of suspicion are very important as most of the time blood paracetamol levels are already normal by the time the patient presents to hospital with liver failure). *NAC did not improve 1-year survival in non-paracetamol PALF. 1-year liver transplant free survival was significantly lower with NAC, particularly among those < 2 years old. (Squires RH, Dhawan A, Alonso E, et al. Hepatology 2013 April; 57(4):1542–1549.)*
- *Antibiotics: Combination that provides a good cover against gram-negative organisms and anaerobes e.g. cefotaxime and metronidazole if no specific infective agent is suspected (e.g. Leptospira. Mycoplasma).*
- *Antiviral: Acyclovir is recommended in neonates and small infants with ALF due to the possibility of HSV infection.*
- *Antifungal if clinically suspected.*
- *Suspected autoimmune/immune-mediated – corticosteroids, other immunomodulating therapies*
- *Suspected Wilson disease – zinc gluconate, trientine*
- *Amanita phalloides poisoning – iv benzylpenicillin (high dose)*

To consult hepatologist if in doubt

v. Clinical pearls in comatose patient

- In the presence of sudden coma, consider intracranial bleed: request a CT brain.
- Patients with Grade 3 or 4 Encephalopathy require mechanical ventilation to maintain normal cerebral perfusion pressure. Sedation may use a combination of opioid (morphine or fentanyl) and benzodiazepines (midazolam).
- Try to avoid peak end-expiratory pressure of >8cm H_2O (may increase ICP); $PaCO_2$ should be kept within 4-4.5 kPa.(30-35mmHg). Extended hypocapnia may risk patient of hypoxia.
- Raised Intracranial pressure : consider mannitol (rapid bolus 0.5g/kg as a 20% solution over 15 minutes; can be repeated if serum osmolality is < 320 mOsm/l), or induction of hypernatremia using hypertonic saline (Na > 145mmol/L) and mild cerebral hypothermia (32-35'C) in refractory high ICP.
- Inotropic support could be used to increase mean arterial blood pressure for optimal cerebral perfusion pressure.

vi. Liver Support Therapies

- Act as a bridge to liver transplant (discuss with Paediatrics intensivist and /or nephrologist)
- Removing toxins and inflammatory mediators which could lead to multiorgan failure
- May consider total plasma exchange or continuous venovenohemofiltration (CVVHDF)

vii. Liver transplantation

- Only definitive treatment that improves survival in PALF

Table 4: King's College Hospital Criteria for Liver Transplantation :

Non Paracetamol Acute Liver Failure	Paracetamol Induced Acute Liver Failure
• INR >6.5 or: • 3 of the following 5 criteria: - Patient age <10 or >40 - Serum bilirubin > 300 µmol/l - Time from onset of jaundice to the development of coma >7 days - INR >3.5 - Non A Non B hepatitis, Drug toxicity	• Arterial pH < 7.3 (after fluid resuscitation) OR • All 3 of the following criteria: - INR >6.5 - Serum creatinine > 300µmol/l - Encephalopathy (grade III or IV)

Table 5: Contraindications for liver transplantation :

Absolute	Relative
• Fixed and dilated pupils • Uncontrolled sepsis • Systemic mitochondrial / metabolic disorders • Severe respiratory failure • Hepatocellular carcinoma (HCC) with extrahepatic disease and rapid progression • Nieman Pick Disease Type-C • Severe portopulmonary hypertension not responsive to medical therapy	• Increasing inotropic requirements • Infection under treatment • Cerebral perfusion pressure <40mmHg > than 2 hours • History of progressive or severe neurologic disorder • Haemaphagocytic Lymphohistiocytosis • Hepatocellular carcinoma (HCC) with venous invasion and rapid disease

Prognosis of PALF

Maximum INR reached during the illness is the most sensitive predictor of outcome. INR > 4 is associated with the poorer outcome without OLT, whereas for paracetamol overdose, metabolic acidosis (pH <7.3) after the second day of overdose and adequately hydrated is associated with high mortality.

Evaluation and management of children with chronic liver disease (CLD) and end-stage liver disease (ESLD)

Patients with chronic liver disease may progress to end-stage liver disease in childhood or adolescents, depending on the natural progression of the disease and its aetiology. Sometimes, patients may present with complications on initial medical attention with unsuspected chronic liver disease or incidental findings from abnormal liver function tests or during the physical examination for unrelated complaints.

Infections Viral (chronic hepatitis B, Hepatitis C)
Anatomical Biliary atresia
Genetic Congenital hepatic fibrosis Caroli disease Alagille syndrome
Inherited metabolic liver disease Wilson disease Progressive familial intrahepatic cholestasis Glycogen storage diseases Lipid storage disorders Peroxisomal disorders Tyrosinemia
Autoimmune Autoimmune hepatitis Autoimmune sclerosing cholangitis
Vascular Budd Chiari syndrome Sinusoidal obstructive syndrome Portal vein thrombosis
Others Drug-induced liver injury NASH Cryptogenic (indeterminate)

Table 6: Common causes of liver cirrhosis

Complications of chronic liver disease

Often varies according to aetiology.

General complications:

1. Nutritional aspect:
   - Poor appetite
   - Failure to thrive, muscle mass wasting (sarcopenia)
   - Macronutrient and micronutrient deficiencies (Water soluble and Fat-soluble - vitamins A, D, E, and K)
   - Fat malabsorption

2. Infections:
   - Ascending cholangitis (fever, worsening jaundice, abdominal pain) , spontaneous bacterial peritonitis (fever, abdominal pain, abdominal tenderness, altered sensorium in a background of patient with existing ascites with no evidence of viscus perforation)
   - Cirrhosis – associated immune recurrent chest infections, urinary tract infections.
3. Portal hypertension (PHT):
   - Varices – esophageal, fundal and rectal, Porto hypertensive gastropathy
   - Hepatic hydrothorax
   - Splenomegaly, hypersplenism, functional asplenia
   - Hepatorenal syndrome
   - Hepatopulmonary syndrome
   - Porto pulmonary hypertension
4. Cirrhotic Cardiomyopathy
5. Metabolic bone disease- osteopenia, osteoporosis, rickets
6. Endocrine complications: adrenal insufficiency and delayed puberty
7. Electrolytes imbalance – hyponatremia, hypophosphatemia, renal impairment
8. Psychological complications: Emotional and mental stress – mood difficulties, post-traumatic stress disorder, poor adherence to medications
9. Socio-economy implications
10. Neurocognitive and developmental delay / Poor academic performance – chronic hyperammonemia
11. Haematological – leukopaenia, thrombocytopaenia, anaemia
12. Malignancy – hepatocellular carcinoma

Management of CLD – General and management of complications:

- Due to the logistic circumstances and geographical distribution of patients and limited paediatric gastroenterologists services in the country, patients are often co-managed with local paediatricians.
- Management of CLD is holistic and involves a multidisciplinary approach.

During follow-up:

- New cases: Baseline investigations and specific investigations to delineate cause.
- Monitoring of blood pressure, pulse rate, oxygen saturation
- Anthropometry – height, weight, and mid-arm circumference

Baseline investigations and assessment:

- Bloods: Full blood count, full blood picture, liver function test including ALT, AST, ALP, GGT, coagulation profile, random blood sugar
- Urine analysis: (Wilson's disease – microscopic hematuria, proteinuria)
- Ultrasound abdomen – Regular (1-2x per year) in cases with high risk of malignancy e.g. HT1, hepatitis B/C infection
- Elastography eg: Fibro scan
- PELD, MELD score
- Referral for orthotopic liver transplantation assessment esp when liver function deteriorates

General Management of CLD/ESRD:
Nutritional rehabilitation

- Importance of maintaining optimal nutrition – prevent further liver injury and improve post-OLT outcomes.
- Mechanism of malnutrition – insufficient intake, increased nutritional requirements, impaired nutrient absorption, and altered metabolism.
- Discuss with dietitian to optimize the child's nutrition
  - Energy: Infants 120-150 kcal/kg
    Older children: 130-150% of estimated energy requirement for age
  - Protein: Infants: 3-4 gm/kg
    Older children 130-150% of recommended nutrient intake
- o Anthropometry: Height, weight (can be affected by ascites, organomegaly), head circumference (for below 2 years old), mid-upper arm circumference (MUAC), and triceps skin fold.
- Dietary assessment (clinical progress, intake, social factors, and ongoing issues)
- Mode of feedings: Oral (preferred), tube (nasogastric or gastrostomy), parenteral nutrition
- Formulas feeds, and supplements containing Medium -chain triglycerides (MCT)
- Examples of strategies toimprove nutrition:
  - Concentrating feeds, use nutrient-dense feeds (meals and snacks) and supplementation of fat-soluble vitamins (Vitamin A, D, E, K), water-soluble vitamins, and trace elements. e.g. zinc.
  - Conditions associated with pancreatic enzymes insufficiency may need supplementation with pancreatic enzymes.
  - Branched chain amino acids (BCAA) may prevents muscle wasting and hyperammonemia

Vaccinations

As per national immunization schedule
For Hep B protection, preferably aim for anti-HBs level > 100mIU/mL
Other recommended vaccines: Hepatitis A, meningococcal, seasonal flu, varicella zoster and pneumococcal vaccine.

Management of complications

- **Ascites**
  - Result of fluid retention and low albumin
  - Indicates decompensation in CLD and need for OLT
  - Risk of bacterial peritonitis, splinting of the diaphragm, loss of appetite
  - Management:
  - Optimization of calorie and protein intake
    Diuretics
    - Potassium-sparing diuretics (aldosterone antagonist): Spironolactone 3mg/kg/day in 3-4 divided doses (up to 6mg/kg/day, max dose 400 mg/day)
    - Loops diuretics – Frusemide 1-2mg/kg/dose if no effective diuresis on monotherapy
  - Paracentesis (up to 50ml/kg; with close monitoring of urine output) – indicated in tense ascites causing respiratory embarrassment (with replacement - intravenous human albumin 20% 5ml/kg over 2 hours)

- **Pruritus**
  - Pruritogens – bile acids, lysophosphatidic acid, endogenous opiates, and progesterone derivatives.
  - Common in PFIC, Alagille syndrome, primary sclerosing cholangitis
  - Can be very distressing, refractory pruritus is an indication of OLT
    Common medical management of cholestatic pruritus
    - Topical: Emollient (skin moisturizer)
    - Antihistamine – chlorpheniramine (use with caution in < 2 year old)
    - Ursodeoxycholic acid (10mg/kg/dose twice a day)
    - Rifampicin (4-10mg/kg/day)(Need to monitor LFT)
    - Cholestyramine (bile salt binders)
    - Naltrexone (0.1-0.5mg/kg)

- **Metabolic bone disease (Hepatic osteodystrophy)**
  - Regular bone mineral density scan (BMD) (dual-energy X-ray absorptiometry scan (DEXA) and monitoring of serum 25-hydroxy vitamin D (25OHD) – targeting level > 50nmol/L.
  - Vitamin D (ergocalciferol, vitamin D2 or cholecalciferol, vitamin D3) (high dose) and bisphosphonates

- **Variceal bleeding (overview of management)** (Refer to chapter Approach to Gastrointestinal Bleeding)
  - Life-threatening condition (Resuscitation and support – Airway, breathing, circulation)
  - Intravenous access (at least 2 large bores venous access
  - Supplemental oxygenation and airway protection (significant hemodynamic instability, intoxicated, agitated or unable to protect own's airway)
  - Hypovolemia – fluid resuscitation, may require whole blood transfusion, fresh frozen plasma, platelets concentrate and cryoprecipitate transfusion.
  - Indication for blood product transfusion: Hemoglobin (Hb) < 7gm/dl (maintain Hb 7-9gm/dl) Platelets: counts < 50,000 /microL (or reducing in trend), Cryoprecipitate : low fibrinogen level
  - Others, case to case in life-threatening bleeding: recombinant factor VIIa, antifibrinolytic agent)
  - Vasoactive drugs may be needed
  - Vitamin K replacement (intravenous or subcutaneous)
  - Nil by mouth and maintenance intravenous drip (saline with dextrose)
  - Nasogastric tube placement (to insert with caution!) – to quantify the blood loss and lavage to remove blood from the stomach, which could precipitate encephalopathy (Do not insert if the bleed has stopped as this may precipitate further bleed!)
  - Acid suppression - Proton pump inhibitors or histamine 2 receptor antagonists
  - Intravenous broad-spectrum antibiotics should be considered.
  - Once stable - Gastroscopy and sclerotherapy or endoscopic variceal ligation.
  - In the event of continuous bleeding - balloon tamponade with Foley cather or Sengstaken – Blakemore tube (Patient should be intubated and mechanically ventilated for airway protection)
  - Transjugular intrahepatic portosystemic shunt (TIPSS)
  - Prophylactic therapy for variceal bleed: non-selective beta-blockers (propranolol and carvedilol)

Drug	Dosage
Octreotide	Initial bolus: 1-2 µg/kg (maximum 100 µg) followed by 1-5µg/kg/h intravenous infusion (max – 50 µg/h) (dose titrated to the response); +/- titrated 24 hours after bleeding stops or 2-4µg/kg/dose 8h (subcutaneous)
Terlipressin	8-20µg/kg q4-8h (use under guidance by paediatric gastroenterologist)

Table 7

- **Hepatorenal syndrome (HRS)**
  - HRS Type 1 – rapid progression, declining urine output, and increasing creatinine < 2 weeks duration
  - HRS Type 2 – moderate renal failure, a more steady and slower progression.
  - Management of HRS - Liver transplantation
  - Avoidance of precipitating factors – hypovolemia, nephrotoxic agents.

- **Porto-pulmonary hypertension (PoPH)**
  - Mean pulmonary artery pressure (MPAP) > 25mmHg (with high pulmonary vascular resistance), normal capillary wedge pressure (PCWP) <15mmHg in the presence of PHT.
  - Dyspnoea, chest pain, fatigue, and hemoptysis. Systolic murmur with loud P2.
  - Diagnosis: Echocardiography
  - Management – prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase inhibitors.
  - Severe PoPH is a relative contraindication of OLT.

- **Hepatopulmonary syndrome**
  - PaO2 < 70mmHg or alveolar-arterial oxygen gradient > 15mmHg and intrapulmonary vascular dilatation in patients with CLD
  - Dyspnea (low saturation, ventilation-perfusion mismatch - orthodeoxia), clubbing, cyanosis, spider naevi
  - Diagnosis: Contrast-enhanced echocardiography (microbubbles in the right side of the heart)
  - Supportive management - supplementation of oxygenation (<PaO2 <60mmHg)
  - Very severe HPS – High mortality post-liver transplantation

- **Cirrhotic cardiomyopathy**
  - Associated with increased cardiac output, systolic and /or diastolic dysfunction, long QT interval, hardly overt left ventricular failure
  - Standard medical therapy for the management of heart failure and should consider for liver transplantation

- **Orthotopic Liver Transplantation (OLT)**
  - Definitive treatment of CLD and ESLD.

- **Indications for OLT assessment**
  - Liver decompensation (prolonged INR, low albumin, ascites)
  - Disordered metabolism (jaundice, loss of muscle mass, osteoporosis)
  - Portal hypertension
  - Encephalopathy
  - Spontaneous bacterial peritonitis, HPS, HRS,
  - Recurrent cholangitis, intractable pruritus
  - Tumors
  - Quality of life (failure to thrive, poor academic performance, lethargy)

The severity of liver dysfunction score

Pediatric end-stage liver disease (PELD) score < 12 years of age (mathematical formula; INR, total bilirubin, albumin, age and presence of growth failure)

Model for end-stage liver disease (MELD) score > 12 years of age (mathematical formula; renal dialysis, creatinine, total bilirubin, INR, and sodium)

PELD > 17, MELD > 15 – OLT confers a significant survival benefit, consider referral to liver transplant centre for OLT assessment

Chapter 86:
Approach to Gastrointestinal Bleeding

Determine type of Gastrointestinal (GI) Bleeding

Upper GI bleed

- Haemetemesis - vomiting out blood whether fresh or stale.
- Melaena - passing out tarry black stools per rectum.

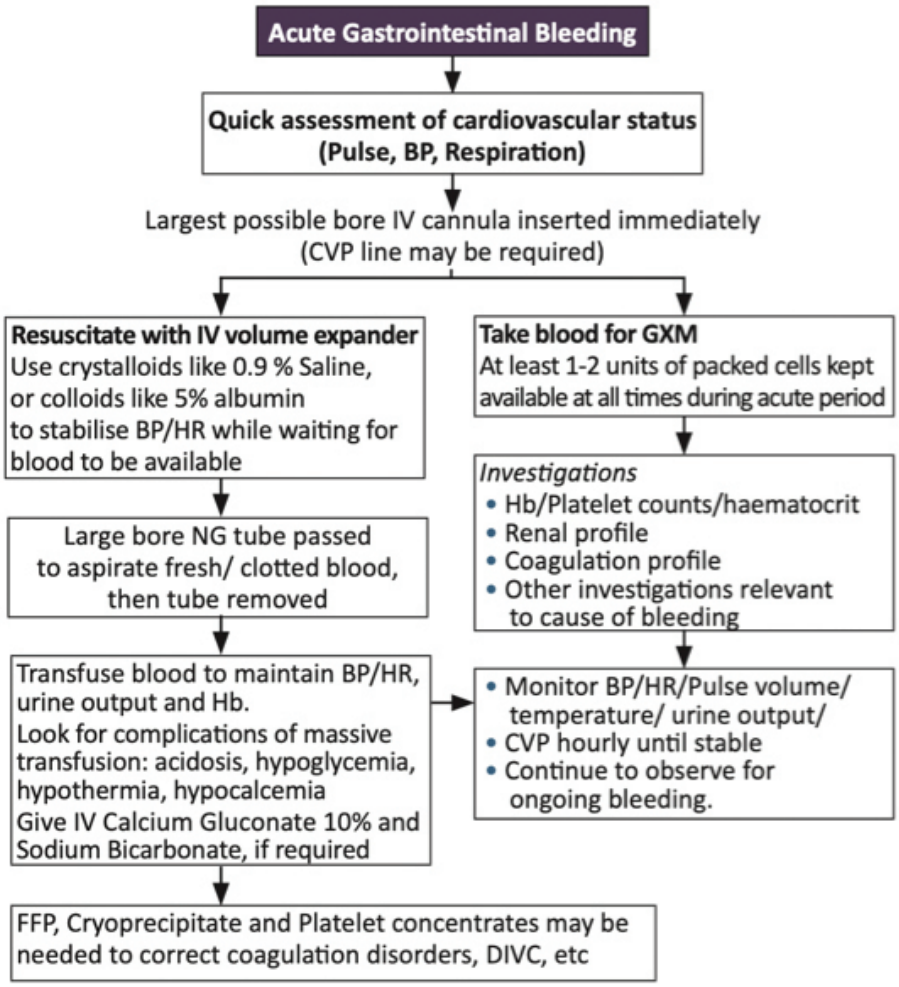
Lower GI bleed

- Haematochezia – passing out bright red blood per rectum. Sometimes, these are medical emergencies that carry significant mortality.

Salient features

- Duration and severity of haemetemesis, maelaena and/or haematochezia.
- Evidence of hypovolaemic shock.
- Rule out bleeding diathesis.
- Look out for non GI mimics of GI blood loss. such as epistaxis, maternal blood, dental issues, haemoptysis and medications such as iron that can mimic melaena.

ACUTE RESUSCITATION IN A CHILD WITH GASTROINTESTINAL BLEEDING



One of the most helpful factors in narrowing the cause of GI bleeding is the patient's age:

Differential Diagnosis of Gastrointestinal Bleeding		
	Upper GI Bleeding	**Lower GI bleeding**
Infant	*Mucosal* Oesophagitis, e.g. reflux, allergic Gastritis Mallory-Weiss tear Gastric heterotopia *Structural* Gastric or intestinal duplication *Other* Haemorrhagic disease of the newborn Vascular anomalies Swallowed maternal blood DIVC	*Mucosal* Necrotizing enterocolitis Infectious colitis Eosinophilic/allergic colitis Hirschsprung's enterocolitis *Structural* Intestinal duplication Meckel's diverticulum Intussusception Other DIVC
Child	*Mucosal* Oesophagitis Gastritis Peptic ulcer disease Mallory-Weiss tear *Other* Oesophageal varices Hereditary telangiectasia Vascular anomalies Foreign body DIVC	*Mucosal* Anal fissure Peptic ulcer disease Infectious colitis Ulcerative colitis/Crohn's disease Juvenile polyp Solitary rectal ulcer Hemorrhoid Lymphonodular hyperplasia *Structural* Intestinal duplication Meckel's diverticulum Intussusception Volvulus Visceral artery aneurysm *Other* Hemolytic-uremic syndrome DIVC Henoch-Schönlein purpura Dieulafoy's malformation Munchausen syndrome by proxy Arteriovenous malformation
Adapted from Pediatric Gastroenterology: The requisites in Pediatrics; Eds Chris Liacouras, David Piccoli		

Decision making after acute resuscitation

Reassessment of patients

When patient's condition is stable and resuscitative measures have been instituted,
Assess patient for cause of bleeding and the need for surgery/endoscopy.
History is reviewed.
Ask for history of chronic liver disease, dyspepsia/abdominal pain, chronic or intermittent gastrointestinal bleeding (e.g. polyps), drug ingestion (anticoagulants, aspirin), or acute fever (dengue haemorrhagic fever), easy bleeding tendencies, diarrhoea, constipation, haematological disorders, antibiotics treatment (pseudomembranous colitis).
Physical examination should be directed towards looking for signs of chronic liver disease (spider angiomata, palmar erythema, portal hypertension or splenomegaly) or telengiectasia / angiomata / purpura / pigmentation in mouth, trunk and extremities, etc.
perianal exam – fissures, fistula etc.

Diagnostic measures to localise source of bleeding

- Oesophagogastro-duodenoscopy (OGDS) or colonoscopy can be
- performed when patient's condition is stable.
- Double contrast barium study less useful than endoscopy but may be indicated in patients when endoscopy cannot precisely locate the source of bleeding (e.g. in intussusception).
- Ultrasound abdomen should be requested if there is evidence of liver disease, splenomegaly or intussusception is suspected.
- Nuclear scintigraphy eg Meckel's scan can be useful in detecting Meckel's diverticulum
- Visceral angiography can precisely locate the source of bleeding. But is only reserved for patients with a difficult bleeding problem.

Definitive measures to management of gastrointestinal bleeding

Medical Cause

Bleeding peptic ulcer

- Start H2 receptor antagonist (e.g. cimetidine).
- Proton pump inhibitor (eg: omeprazole) can be considered as it has higher acid suppressant activity.
- If biopsy shows presence of Helicobacter pylori infection, treat accordingly.
- Stop all incriminating drugs e.g. aspirin, steroids and anticoagulant drugs if possible.

Bleeding oesophageal varices or ulcer

- Do not transfuse blood too rapidly as this will lead to increase in Central Venous Pressure (CVP) and a rapid increase in portal pressure may precipitate further bleeding.
- Aim to maintain Hb around 9 g/dL.
- Refer Paediatric Surgeon and Paediatric Gastroenterologist to consider use of octreotide.
- If bleeding continues and the patient is not responsive to all of the above management, consider placing a Sengstaken-Blackmore Tube. This however is RARELY needed, and it is performed under emergency circumstances. Patient must be intubated and transferred to intensive care setting prior to Sengstaken Blackmore insertion.
- Sengstaken Blackmore tube size depends on the child's weight
  10-30 kg paediatric size 14F
  > 30 kg paediatric size 16F
- For infants < 10kg in whom use of a Sengstaken tube is not possible because of size, a Foley catheter inserted orally may be effective.

Pseudomembranous colitis

- Stop all antibiotics – usually this measure will heal most mild pseudomembranous colitis.
- Consider oral metronidazole or oral vancomycin in moderate to severe pseudomembranous colitis

Bleeding in neonates

- Rule out swallowed maternal blood esp at birth
- Consider to give IV vitamin K 0.3mg/kg even coagulation results are pending.

Bleeding in a child with suspected liver disease

- Consider to give IV vitamin K 0.3mg/kg (max 10mg)
- Think of variceal bleed if there are signs of portal hypertension

Surgical Cause

When surgical cause is suspected, early referral to the surgeon is important so that a team approach to the problem can be adopted.

- Intussusception requires immediate surgical referral and intervention may be attempted by the radiologist and proceed with surgical intervention if failed radiological reduction.
- Meckel's diverticulum (painless PR bleed)
- Malrotation with volvulus (urgent referral to avoid further ischaemia to bowel)

Section 14

INFECTIOUS DISEASE

Chapter 87:
Paediatric HIV

Screening of children for HIV status

- Babies of HIV positive mothers.
- Abandoned babies / street children.
- Babies of mothers with high risk behaviour (e.g. drug addicts, commercial sex workers, multiple sex partners / single-teenage or underage).
- Sexually abused children and children with sexually transmitted disease.
- Children receiving regular blood transfusions or blood products
  e.g. Thalassaemics.

Deliveries and infant nursing

- Standard precautions must be observed at all times. It is vital to use protective barriers such as gloves, mask, goggles and gown with waterproof sleeves. Boots are to be used for institutional deliveries.
- All equipment, including resuscitation equipment should be cleaned and sterilised.
- For home deliveries, battery operated suction device should be used.
- Standard precautions are to be observed in caring for the babies.
- For parents or relatives, gloves are given for use when handling the placenta after discharge, or during burial of stillbirth or dead babies at home.
  The placenta from HIV positive mothers should be soaked in formalin solution before disposal. Alternatively, the placenta can be sealed in a plastic bag or other leak-proof container with clear instructions to parents not to remove it from the container.

Immunisation

- Vaccines protect HIV-infected children from getting severe vaccine-preventable diseases, and are generally well tolerated.
- All routine vaccinations can be given according to schedule, with special precautions for live vaccines i.e. BCG and MMR:
  - BCG : safe if child is asymptomatic and not immunosuppressed (e.g. at birth); omit if symptomatic or immunosuppressed.
  - MMR : safe, omit in children with severe immunosuppression (CD4<15%)
- Other recommended vaccines:
  - Pneumococcal conjugate vaccine.
  - Varicella-zoster vaccine, where available. 2 doses with 2 months interval. Omit in those with severe immunosuppression (CD4 < 15%).

Despite vaccination, remember that long term protection may not be achieved in severe immune suppression i.e. they may still be at risk of acquiring the infections!

Interventions to limit perinatal transmission

- Vertical transmission of HIV may occur while in utero, during the birth process or through breast-feeding. The rates vary from 25 - 30%.
- Breastfeeding confers an additional 14% risk of transmission, and is therefore generally contraindicated.
- Blood and blood products should be used judiciously even though the risk of transmission of HIV infection from blood transfusion is very small.

Several interventions have proven effective in reducing vertical transmission:

- Total substitution of breastfeeding with infant formula.
- Elective Caesarean section.
- Antiretroviral (ARV) prophylaxis.

Factors associated with higher transmission rate
Maternal • Low CD 4 counts • High viral load • Advanced disease • Seroconversion during pregnancy *Foetal* • Premature delivery of the baby • Delivery and procedures • Invasive procedures such as episiotomy • Foetal scalp electrodes • Foetal blood sampling and amniocentesis • Vaginal delivery • Rupture of membranes > 4 hours • Chorioamnionitis **Transmission rate not increased if maternal viral load fully suppressed*

Management of Babies Born to HIV Infected Mothers

Children born to HIV positive mothers are usually asymptomatic at birth. However, all will have acquired maternal antibodies. In uninfected children, antibody testing becomes negative by 10-18 months of age.

During pregnancy
Counsel mother regarding:

- Transmission rate (without intervention) : 25 to 30%.
- ARV prophylaxis +/- elective LSCS reduces transmission to < 2%
- Feeding baby with infant formula as breast feeding doubles the risk of transmission. In situation where a mother insists to breastfeed, refer to specialist and take risk-reduction measures to reduce the risk of HIV transmission.
- Difficulty in making early diagnosis because of presence of maternal antibody in babies. Stress importance of regular blood tests and follow-up.

Neonatal Period

- Admit to ward or early review by paediatric team (if not admitted).
- Examine baby for:
  - Evidence of other congenital infections.
  - Symptoms of drug withdrawal (reviewing maternal history is helpful).
- Most babies are asymptomatic and only require routine perinatal care.
- Start on prophylaxis ARV as soon as possible.
- Sample blood for:
  - HIV DNA/RNA PCR (done in IMR, do not use cord blood; sensitivity 90% by 1 month age).
  - FBC
  - Other tests as indicated: LFT, RFT, HbsAg, Hepatitis C, CMV, syphilis serology.

MANAGEMENT OF HIV IN CHILDREN

Clinical Features

Common presenting features are:

- Persistent lymphadenopathy
- Hepatosplenomegaly
- Failure to thrive
- Recurrent infections (respiratory, skin, gastrointestinal)
- Developmental delay, regression

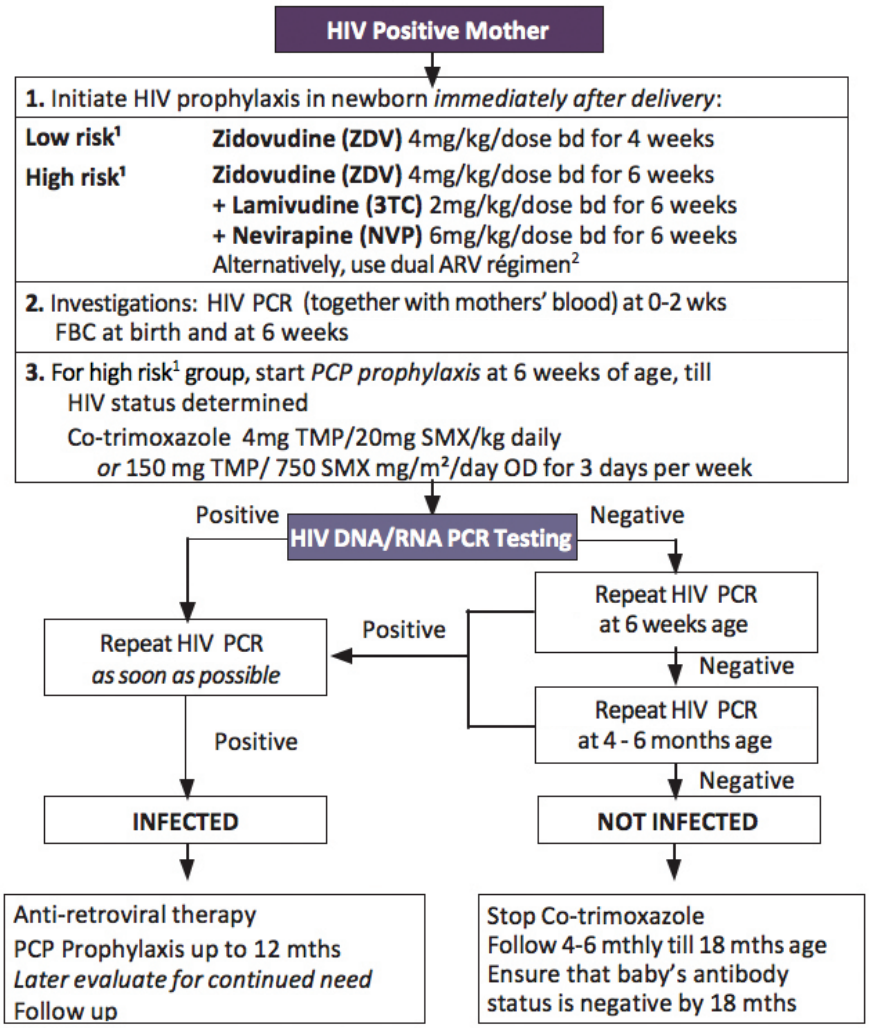
Diagnosis of HIV infection

- In children > 18 months age: 2 consecutive positive HIV antibody tests.
- In children < 18 months age: 2 positive HIV DNA/RNA PCR tests.

Monitoring

- Monitor disease progression through clinical, immunological ($CD4^+$ count or %) and viral load status.
- CD4+ count and viral load assay are done at diagnosis, 2-3 months after initiation or change of combination antiretroviral therapy (ART) and every 3-4 months thereafter (more frequently if change of therapy is made or progression of disease occurs).

MANAGEMENT OF HIV EXPOSED INFANTS



Footnote:

1. Low risk - Infant of HIV–infected pregnant mother who is on ART and has sustained viral suppression
   High risk - Infant at higher risk of HIV acquisition e.g. infant born to HIV-infected mother who:
   - Has not received intrapartum/antepartum ARV
   - Has received only intrapartum ARV
   - Has received antepartum ARV but does not have viral suppression near delivery
2. Dual ARV regimen (Zidovudine + Nevirapine) may be considered in circumstances where mum has low viraemia (VL <400 copies/ml)
3. ARV should be served as soon as possible (preferably within 6-12 hours of life) and certainly no later than 48 hours.
4. Dose of Sy ZDV for premature baby
   < 30 weeks: 2mg/kg 12 hourly from birth to 4 weeks, then 3mg/kg 12hourly age 4-6 weeks
   >30 weeks: 2mg/kg 12hourly from birth to 2 wks, then 3mg/kg 12hourly age 2-6 wks.
5. If oral feeding is contraindicated, then use IV ZDV at 1.5mg/kg/dose.

Antiretroviral Therapy

Clinical outcome following the introduction of ART in children is excellent, with reduced mortality and morbidity reported from various cohorts. However, this needs to be balanced with: the failure of current drugs to eradicate infection, long-term medication side effects and compliance-adherence issues.

When to start?

- ART is now recommended to be started in all children and adolescents living with HIV. Early initiation of ART reduces mortality, improves neurodevelopmental, growth and pubertal outcomes, improves immune reconstitution and reduces inflammation.
- Rapid ART initiation (within 7 days) should be offered following HIV diagnosis and clinical assessment and when parents and child are ready to start.
- Provide adherence support and assessment before starting ART and at all subsequent visits. Stress that non-adherence to medications allows continuous viral replication and encourages the emergence of drug resistance and subsequent treatment failure.
- Please consult a specialist/consultant before starting treatment.

WHO Clinical Staging Of HIV for Infants and Children With Established HIV infection (Adapted from WHO 2007)

Classification of HIV-associated Immunodeficiency	Age related CD4 values			
	< 11 mths (CD4 %)	12-35 mths (CD4 %)	36-59 mths (CD4 %)	≥5 years (cells/ mm^3 or CD4 %)
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 or <15%

Clinical categories

There are 2 widely used clinical classification systems i.e CDC's 1994 Revised Paediatric Classification and the more recently updated WHO Clinical Classification system. Both classification systems are quite similar with only minor differences.

WHO Clinical Staging Of HIV for Infants and Children With Established HIV infection (Adapted from WHO 2007)
Clinical stage 1 (Asymptomatic)
• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2 (Mild) *
• Unexplained persistent hepatosplenomegaly • Papular pruritic eruptions • Extensive wart virus infection • Extensive molluscum contagiosum • Recurrent oral ulcerations • Unexplained persistent parotid enlargement • Lineal gingival erythema • Herpes zoster • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis) • Fungal nail infections
(*) Unexplained refers to where the condition is not explained by other causes.

WHO Clinical Classification system (continued)
Clinical stage 3 (Advanced) *
• Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5 ºC, intermittent or constant, for longer than one month) • Persistent oral candidiasis (after first 6 weeks of life) • Oral hairy leukoplakia • Acute necrotizing ulcerative gingivitis/periodontitis • Lymph node TB • Pulmonary TB • Severe recurrent bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease including bronchiectasis • Unexplained anaemia (<8.0 g/dl), neutropenia (<0.5 x 10^9/L) or chronic thrombocytopenia (<50 x 10^9/ L)

Clinical stage 4 (Severe) *
• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • Pneumocystis pneumonia • Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia) • Chronic herpes simplex infection; (orolabial or cutaneous of more than one month'sduration, or visceral at any site) • Extrapulmonary TB • Kaposi sarcoma • Oesophageal candidiasis (or Candida of trachea, bronchi or lungs) • Central nervous system toxoplasmosis (after the neonatal period) • HIV encephalopathy • Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age over 1 month • Extrapulmonary cryptococcosis (including meningitis) • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis) • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis • Disseminated non-tuberculous mycobacteria infection • Cerebral or B cell non-Hodgkin lymphoma • Progressive multifocal leukoencephalopathy • HIV-associated cardiomyopathy or nephropathy
(*) Unexplained refers to where the condition is not explained by other causes.

Which drugs to use?

For all first-line regimens, always use a combination of at least 3 drugs – 2 NRTIs plus a drug from a different class (see Table below)

Age group	Preferred first-line regimen	Alternative first-line regimen
Neonate	ZDV + 3TC + NVP	ZDV + 3TC + LPV/r* ZDV + 3TC + RAL**
Children	ABC + 3TC + DTG ZDV + 3TC + DTG	ABC + 3TC + EFZ (or NVP) ABC + 3TC + LPV/r ZDV + 3TC + EFZ (or NVP) ZDV + 3TC + LPV/r
Adolescents	TDF + FTC (or 3TC) + DTG	TDF + FTC (or 3TC) + EFV

- *Kaletra (LPV/r) is only approved for use in infants > 14 days.
- **Raltegravir (RAL) film-coated tablet is not recommended to be cut/crushed. Use chewable tablet or oral suspension, if available.
- Mono or dual therapy are not recommended except when used for mother-to-child transmission prophylaxis during neonatal period.

When to change?

- Treatment failure based on clinical, virologic and immunological parameters
  e.g. deterioration of condition, unsuppressed / rebound viral load or dropping of CD4 count/%.
  - Assess and review adherence.
  - Perform genotypic resistant testing to help choose appropriate ARV.
  - If genotypic resistant testing not available, preferable to change all ARV (or at least 2) to drugs that the patient had not been exposed to before
  - Choices are very limited! Do not add a drug to a failing regime.
  - Consider potential drug interactions with other medications.
  - In a patient with advanced disease, the patient's quality of life must be considered.
- Toxicity or intolerance of the current regimen
  - Choose drugs with toxicity profiles different from the current regimen.
  - Changing a single drug is permissible.
  - Avoid reducing dose below lower end of therapeutic range for that drug.
- Treatment simplification/optimization
  - In virologically suppressed children, may consider simplifying drug regimen to once daily low pill burden regimens with optimal toxicity profiles and efficacy data.
- Consult infectious diseases specialist before switching.

Follow up

- The aim of ART is to achieve an undetectable VL (< 50copies/ml) and CD4 reconstitution.
- Follow up usually every 3 – 4 months. However, if just commencing/ switching ART, then every 2-4 weeks.
- Ask about medication:
  - Adherence (who, what, how and when of taking medications)
  - Side effects e.g. vomiting, abdominal pain, jaundice.
- Examine: Growth, head circumference, pallor, jaundice, oral thrush, lipodystrophy syndrome (especially if on PI).
- FBC, CD4 count, viral load 3-4 monthly, RFT, LFT, Ca/PO4 every 6 months; fasting lipid profiles, blood sugar and urinalysis yearly.
- CD4 count can be monitored less frequently (every 6–12 months) in children who are clinically stable, have good adherence, virologically suppressed and CD4 count values that are well above the threshold for opportunistic infection risk.
- Explore social, psychological and financial issues e.g. school, home environment etc. Many children are orphans, live with relatives, adopted or under NGO's care. Referral to social welfare often required. Compliance- adherence to therapy strongly linked to these issues.

Other issues

- HIV / AIDS is a notifiable disease. Notify health office within 1 week of diagnosis.
- Screen other family members for HIV.
- Refer parents to Physician Clinic if they have HIV and are not on follow up.
- Disclosure of diagnosis to the child (would-be teenager, issues on sexual rights)
- Be aware of Immune Reconstitution Inflammatory Syndrome (IRIS)
  - In this condition there is a paradoxical worsening of a known condition (e.g. pulmonary TB or lymphadenitis) or the appearance of a new condition after initiating ARV.
  - This is due to restored immunity to specific infectious or non-infectious antigens.
- Address adolescent's issues
  - Common issues include peer pressure, sexual health, pregnancy, substance use/abuse.
  - Plan a transition program to adult care services.

Categories of antiretroviral drugs*					
Nucleoside / Nucleotide reverse transcriptase inhibitors (NRTI)	**Non nucleoside re-verse transcriptase inhibitor (NNRTI)**	**Protease inhibitors (PI)**	**Integrase inhibitors**	**CCR5 antagonists**	**Fusion inhibitors**
Abacavir (ABC) Zidovudine (ZDV) Lamivudine (3TC) Tenofovir (TDF/TAF) Emtricitabine (FTC)	Nevirapine (NVP) Efavirenz (EFZ) Etravirine (ETV) Rilpivirine (RPV)	Ritonavir (RTV) Lopinavir/ Ritonavir (LPV/r, Kaletra) Atazanavir (ATV) Darunavir (DRV)	Dolutegravir (DTG) Raltegravir (RAL) Elvitegravir (EVG) Bictegravir (BIC)**	Maraviroc (MVC)**	Enfurvitide (T-20)**
Fixed-dose combination tablets (FDC) ZDV + 3TC combined tablet (Combivir / Zovilam) TDF + FTC combined tablet (Truvada / Tenof-EM) ABC + 3TC combined tablet (Kivexa) ABC + 3TC + ZDV combined tablet (Trizivir) TDF + 3TC + DTG combined tablet (Teldy) EVG + COBI*** + FTC + TAF (Genvoya) Footnote: * Not all ARVs are suitable for use in children ** Bictegravir, Maraviroc and Enfuvirtide are not registered in Malaysia *** Cobicistat (COBI) is a pharmacokinetic enhancer (boosting agents) for certain PIs and Integrase inhibitors					

Antiretroviral drugs dosages and common side effects			
Drug	**Dosage**	**Side effects**	**Comments**
Abacavir (ABC)	> 3 months: 8 mg/kg/dose bd or 16mg/kg/dose od (maximum dose 300mg bd)	Diarrhoea, nausea, rash, headache; Hypersensitivity, Steven-Johnson (rare)	NEVER restart ABC after hypersensitivity reaction (may cause death) occur in HLA B*5701 positive
Lamivudine (3TC)	< 4 weeks: 2mg/kg/dose bd > 4 weeks: 4mg/kg/dose bd > 3 months: 5mg/kg/dose, bd (maximum dose 150mg bd)	Diarrhoea, abdo pain; pancreatitis (rare)	Well tolerated Use oral solution within 1 month of opening
Zidovudine (ZDV)	< 4 weeks: 4mg/kg bd > 4 weeks: 180-240mg/m^2/dose, bd (maximum dose 300mg bd)	Anaemia, neutropenia, headache	Large volume of syrup not well tolerated in older children
Tenofovir (TDF)	≥ 2 year: 8mg/kg/dose, od (maximum dose 300mg od) TDF + FTC combo > 35kg: 1 tab od	Renal insufficiency, decreased bone density (especially in young children)	Should be taken with food. Tablet can be crushed and added to liquid
Emtricitabine (FTC)	< 3 month: 3mg/kg/dose, od > 3 month: 6mg/kg/dose, od (maximum dose 200mg od)	Headache, insomnia, diarrhea, skin discoloration	Only available in combination with Tenofovir
Efavirenz (EFZ)	> 3 year: 367mg/m^2/day, od 10-15kg 200mg 15-20kg 250mg 20-25kg 300mg 25-32kg 350mg 33 –40kg 400mg > 40kg 600mg	Rash, headache, insomnia	Inducer of CYP3A4 hepatic enzyme; so has many drug interactions
Nevirapine (NVP)	< 4 weeks: 6mg/kg/dose, bd > 4 weeks: 150-200mg/m^2/day od for 14 days, then increase to 300-400mg/m^2/day, bd (maximum dose 200mg bd)	Severe skin rash, headache, diarrhea, nausea	Few data on use with PI. Practice is to increase PI dose by about 30%

Antiretroviral drugs dosages and common side effects			
Drug	**Dosage**	**Side effects**	**Comments**
Ritonavir (RTV)	For boosting other PIs. See specific drug. Not recommended as a single PI.	Vomiting, nausea, headache, diarrhoea; hepatitis (rare)	Take with food to increase absorption and reduce GI side effects. Solution contains 43% alcohol and is very bitter!
Kaletra (Lopinavir/ ritonavir)	≥ 2 weeks: 300/75mg/m^2/ dose, bd	Diarrhea, asthenia	Low volume, but a bitter taste. Higher dose used with NNRTI Do not cut/crush tablet
Darunavir (DRV)	≥ 3 year: 15-30kg: 375mg bd+50mg RTV bd, 30-40kg: 450mg bd+RTV 60mg bd, ≥40kg: 600mg bd+100mg RTV bd	Skin rash, hepatotoxicity	Contains sulphonamide moiety – check allergies especially Co-trimoxazole.
Atazanavir (ATV)	≥6 year: 15-34kg: 200mg od + RTV 100mg od (≥35kg): 300mg od + RTV 100mg od	Nausea, headaches, rash, jaundice	Take with food
Dolutegravir (DTG)	14-19kg: 40mg od > 20kg: 50mg od Integrase inhibitor resistance: 50mg BD	Insomnia, mood changes, headache, hepatitis, rash, weight gain	Tablet can be cut or crushed. Film-coated tablet and dispersible tablet are not bioequivalent
Raltegravir (RAL)	< 25kg: 6mg/kg/dose, bd > 25kg: 400mg bd	Nausea, head- ache, dizziness, skin rash	Not recommended to cut/ crush film-coated tablet.

Horizontal Transmission Within Families

- Despite sharing of household utensils, linen, clothes, personal hygiene products; and daily interactions e.g. biting, kissing and other close contact, repeated studies have failed to show transmission through contact with saliva, sweat, tears and urine (except with exposure to well defined body fluids i.e. blood, semen, vaginal fluids).
- It is important to stress that the following has not transmitted infection:
  - Casual contact with an infected person
  - Swimming pools
  - Droplets coughed or sneezed into the air
  - Toilet seats
  - Sharing of utensils such as cups and plates
  - Insects

Note: It is difficult to isolate the virus from urine and saliva of seropositive children. So, day care settings are not a risk. However, due to a theoretical risk of direct inoculation by biting, aggressive children should not be sent to day care. Teachers should be taught to handle cuts/grazes with care.

Guidelines for post exposure prophylaxis

- Goal is to prevent HIV infection among those sustaining exposure, and provide information and support during the follow up interval until infection is diagnosed or excluded with certainty.
- Risk for occupational transmission of HIV to Health Care Workers (HCW).
- Risk for HIV transmission after a percutaneous exposure to HIV infected blood is 0.3%; risk after mucous membrane exposure is 0.1%.
- Risk is dependent on:
  - Type, volume of body fluid involved
  - Type of exposure that has occurred
  - Viral load of the source patient
  - Disease stage

Treatment of an Exposure Site

- Wash wounds, skin exposure sites with soap, water; flush mucous membranes with water.
- Notify supervisor; refer HCW to designated doctor as in hospital sharp injury protocol.

Chapter 88:
Malaria

Uncomplicated malaria:

- Symptoms of malaria infection and a positive parasitological test (microscopy or Rapid Diagnostic Test) but with no features of severe malaria (clinical or laboratory).

Treatment

A. Uncomplicated *Plasmodium falciparum*

First-line treatment:

PREFERRED ACT (Artemisinin-based Combination Therapy)

ACT: Artemether / lumefantrine (**Riamet**)
Tablet FDC (20mg artemether and 120mg lumefantrine)

Weight (Kg)	Dose (given twice daily for 3 days)
5 to <15	DI: 1 tab stat then 1 tab again after 8 hours D2-3: 1 tab BD
15 to 24	D1: 2 tabs stat then 2 tabs again after 8 hours D2-3: 2 tablets BD
25 to 35	D1: 3 tabs stat then 3 tabs again after 8 hours D2-3: 3 tablets BD
≥35	D1: 4 tabs stat then again 4 tabs after 8 hours D2-3: 4 tabs BD

ALTERNATIVE ACT

ACT: Artesunate / mefloquine FDC
Available as FDC tablet 25/55mg and 100/220mg

Weight (kg)	Dose (given daily for 3 days)
5 to <9	25/55 mg PO q24h for 3d
9 to <18	50/110 mg POq24h for 3d
18 to <30	100/220 mg PO q24h for 3d
≥30	200/440 mg PO q24h for 3d

- Treat infants weighing < 5 kg with uncomplicated P. falciparum malaria with ACT as for children weighing 5 kg.
- Add primaquine 0.25mg base/kg single dose OD to all patients on D1. G6PD testing is not required prior to administration with this dose.
- Riamet should be administered with high fat diet preferable to be taken with milk to enhance absorption.

Recurrent P. falciparum

- Recurrence of P. falciparum malaria can result from re-infection or recrudescence (treatment failure).
- Treatment failure may result from drug resistance or inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an individual, or substandard medicines

Failure within 28 days

- An alternative ACT is used (if Riamet was used in the first regimen, use Artesunate/mefloquine for treatment failure and vice-versa).
- Artesunate 4mg/kg OD plus clindamycin 10mg/kg bd for a total of 7 days
- Quinine 10mg salt/kg 8 hourly plus clindamycin 10mg/kg bd for a total of 7 days.

Failure after 28 days

- Treat as new infection with preferred ACT

Treatment for Plasmodium vivax, *knowlesi or malariae.*

Preferred treatment for *Plasmodium vivax, Plasmodium knowlesi*, or malariae**
Use ACT such as Riamet or artesunate/mefloquine as in Plasmodium falciparum *PLUS* Primaquine 0.5mg base/kg for 14 days or 1mg base/kg for 7 days# for Plasmodium vivax (maximum 30 mg base)
• * P. malariae and P. knowlesi do not form hypnozoites, hence do not require radical cure with primaquine. • # A shorter regimen (7 days) can lead to better adherence compared to the standard 14-day regimen and thus to fewer relapses. • G6PD testing is required prior to administration of 0.5mg base/kg primaquine. • For G6PD deficiency, intermittent primaquine regimen of 0.75mg base/kg weekly for 8 weeks can be given.

Severe *P.falciparum* malaria

- All Plasmodium species can potentially cause severe malaria, the commonest being P. falciparum
- Young children especially those aged below 5 years old are more prone to develop severe or complicated malaria.

Clinical features:	**Laboratory findings:**
- impaired consciousness - prostration (generalised weakness and unable to stand, sit or walk unaided) - failure to feed - multiple convulsions (more than two episodes in 24 hour) - deep breathing, respiratory distress - circulatory collapse or shock - clinical jaundice plus evidence of other vital organ dysfunction - haemoglobinuria - significant bleeding (nose, gum or venepuncture sites etc) - pulmonary oedema with saturation <92%	- hypoglycaemia (blood glucose < 2.2 mmol/l or < 40 mg/dl) - metabolic acidosis (plasma bicarbonate < 15 mmol/l) - severe anaemia (Hb < 5 g/dl, packed cell volume < 15%) - hyperlactataemia (lactate > 5 mmol/l) - renal impairment (blood urea>20 mmol/L or creatinine > 265 umol/L) - hyperparasitaemia P falciparum > 10% - Severe knowlesi malaria defined as: hyperparasitaemia density of >100000/µl and Jaundice and parasite density > 20 000/µl

1. First-line Treatment

IV Artesunate

Weight	Dose (mg/kg)	Loading	Maintenance
20kg and above	2.4	3 doses at: Time:0 Time: 12 hour Time: 24 hour	Following by Once daily
Less than 20kg	3		

Parenteral artesunate should be given for a minimum of 24h (3 doses) or until patient is able to tolerate orally and thereafter to complete treatment with a complete course of oral ACT (3 days of Artesunate/ mefloquine or Riamet).

Avoid using Artesunate + mefloquine if patient presented initially with impaired consciousness as increased incidence of neuropsychiatric complications associated with mefloquine following cerebral malaria have been reported.

Do not use IV artesunate as monotherapy. If IV artesunate needs to be continued indefinitely, clindamycin (10 mg/kg/dose bd) or doxycycline (>8years) must be added to the regimen to complete total 7 days treatment.

IM artesunate (same dose as IV) can be used in patients with difficult intravenous access.
Children with severe malaria should be started on broad-spectrum antibiotic treatment immediately at the same time as antimalarial treatment.

Patient on treatment for severe malaria should have blood smear performed 1 day after completion of treatment and continue daily (till D7 preferably) until smears are negative.

Second-line Treatment

IV Quinine

Weight	Loading dose	Days 1-2 (Time 8 hr)	Maintenance
All patients	Time 0 hour 20mg/kg (max 1.4 gram)	Starting at Time 8 hour: 10mg/kg (Maximum 700mg) Every 8 hours for 48 hour	For IV >48 hour: 10mg/kg (Maximum 700mg) Every 12 hours

Rapid intravenous administration of quinine is dangerous. Each dose of parenteral quinine must be administered as a slow, rate-controlled infusion (usually diluted in 5% dextrose and infused over 4 h). The infusion rate should not exceed 5 mg salt/kg bw per hour.

Reduce IV quinine dose by one third of total dose (10mg/kg tds to 10mg/kg bd) if unable to change to Oral quinine after 48 hours or has renal failure or liver impairment.

Add Doxycycline (>8years) (2.2 mg/kg up to 100mg) BD OR Clindamycin (10 mg/kg/dose bd) given for 7 days once patient can take orally

2. Mixed Malaria infections

Mixed malaria infections are not uncommon. ACTs are effective against all malaria species and are the treatment of choice. Treatment with primaquine should be given to patients with confirmed *P.vivax* infection.

3. Follow-up

Patients should be followed up weekly for a month. Thereafter, follow up for those infected with P. vivax infection should be followed up monthly for one year.

4. Malaria Chemoprophylaxis

Prophylaxis	Duration of prophylaxis	Pediatric Dosage
Atovaquone/proguanil (Malarone)	Start 1-2 days before, continue daily during exposure and for 7 days thereafter	**Pediatric tablet** of 62.5 mg atovaquone and 25 mg proguanil: 5-8 kg: 1/2 tablet daily >8-10 kg: 3/4 tablet daily >10-20 kg: 1 tablet daily >20-30 kg: 2 tablets daily >30-40 kg: 3 tablets daily **>40 kg: 1 adult tablet daily**
Mefloquine (Tablet with 250mg base, 274mg salt)	Start 2-3 weeks before, continue weekly during exposure and for 4 weeks thereafter	<15 kg: 5mg of salt/kg; 15-19 kg: ¼ tab/week; 20-30 kg: ½ tab/week; 31-45 kg: ¾ tab/week; >45 kg: 1 tab/week
Doxycycline (tab 100mg)	Start 1-2 days before, continue daily during exposure and for 4 weeks thereafter	1.5mg base/kg once daily (maximum 100 mg) **<25kg or <8 yr: Do Not Use** 25-35kg or 8-10 year: 50mg 36-50kg or 11-13 year: 75mg >50kg or >14 year: 100mg

Chapter 89:
Tuberculosis

Definition

- Disease with the symptoms, signs and /or radiographic findings caused by MTB complex (including *M. tuberculosis* and *M. bovis*) infection.
- The disease may be pulmonary or extrapulmonary, (i.e., central nervous system (CNS), lymph nodes (LN), bone & joint etc) or disseminated (i.e., miliary or both pulmonary and extrapulmonary).

Clinical features

- Constitutional symptoms such as difficult feeding, anorexia, difficult/ poor weight gain, weight loss, lethargy/ less playful and fever should be present though non-specific
- Other symptoms are based on organs involved:
- *Pulmonary:* chronic cough/ respiratory symptoms, wheezing in young infant, haemoptysis and pleuritic chest pain are more common in older child/ adolescent
- *Lymph node:* gradually increase in size, matted and not responding to antibiotic, cold abscess, discharging sinus
- *CNS:* irritability, lethargy, encephalopathy, seizure
- *Spine/ Bone:* bone swelling +/- sinus, pathological fracture

Diagnosis of TB disease

Diagnosis in children is challenging as they have paucibacillary disease (smear negative) and symptoms mimic common childhood illnesses.

- *Recent contact* with a person (usually adult) with active TB is a very useful tool in assisting the TB diagnosis in children
- *Symptoms and signs suggestive of TB* are as listed above. Infants are more likely to have nonspecific symptoms like low-grade fever, cough, weight loss, failure to thrive, and signs like wheezing, reduced breath sounds, tachypnoea and respiratory distress.
- *Positive TST test* (≥10 mm induration at 72 hours; tuberculin strength of 10 IU PPD).
- Suggestive *chest X-ray* changes:
  - Enlarged hilar lymph nodes +/- localised obstructive emphysema Persistent segmental collapse consolidation not responding to conventional antibiotics.
  - Calcification in lymph nodes - usually develops > 6 months after infection.
  - CXR changes in young infant/ children can be non-specific
- *Laboratory tests:* Presence of AFB on smears of clinical specimens and positive histopathology or cytopathology on tissue specimens are highly suggestive of TB. Isolation of M. tuberculosis by culture from appropriate specimens is confirmatory.

The tests to consider include but are not limited to the following:

Pulmonary TB:
- Chest radiograph
- Early morning gastric aspirates/nasopharyngeal aspirate[1]
- Sputum[1] (if > 12 years or younger but able to expectorate sputum)
- Pleural fluid[1] or biopsy[1]

Central Nervous System (CNS) TB
- Cerebrospinal fluid (CSF) for FEME, acid fast bacilli (AFB) smear, TB culture and molecular testing.
- Computed tomography scan (CT) head with contrast/MRI

TB Lymph node
- Excisional biopsy or fine needle aspirate[1]

Abdominal TB
- CT abdomen with contrast/ultrasound abdomen
- Biopsy of mass/mesenteric lymph node[1]

TB osteomyelitis
- CT/MRI of affected limb
- Biopsy of affected site

Miliary/Disseminated TB
- As for pulmonary TB
- Early morning urine and CSF[1]

[1]Note: All these specimens should be sent for AFB smear and TB culture and susceptibility testing. Molecular testing e.g., UltraXpert should be send if smear negative. Adenosine Deaminase (ADA) for pleural fluid and Cytopathology/histopathology should be carried out on appropriate specimens. All children evaluated require a chest x-ray to rule out pulmonary TB.

Diagnostic Work-up

- Every effort should be made to collect clinical specimens to assure confirmation of diagnosis and drug susceptibility.
- If the index case is known, its culture and susceptibility results can be used to guide the therapy.
- The diagnostic work-up for TB disease is tailored to the organ system most likely affected as summarised in the table above.

Treatment of TB disease

- Antimicrobial therapy for TB disease requires a multidrug treatment regimen. Drug selection is dependent on drug susceptibility in the area the TB is acquired (especially refugee patients), disease burden and exposure to previous TB medications and HIV prevalence. If needed, treatment regimen can be adjusted once drug susceptibility is available.
- Directly observed therapy is recommended for treatment of active TB.
- Drug resistant TB can be considered if the source has drug resistant TB or confirmed if investigations (XpertUltra and sensitivity) indicate resistance.
- Infants with TB, severe TB, disseminated TB and HIV with TB should be managed in consultation with Paediatric ID.

Treatment of TB disease

- Duration of treatment depends on the type of organs involved, extend of disease and HIV status. Short course 6-month regimen with 2 months intensive and followed by 4 months continuation phase is suitable for Pulmonary TB and non-severe extrapulmonary tuberculosis e.g., TB Lymph node.
- In consultation with paediatric ID, longer course of prolonged TB treatmen up to 9 to 12 months is needed for severe pulmonary TB, disseminated TB, TB CNS and other severe extra-pulmonary TB like TB spine.
- Treatment regimens have 2 phases, an initial intensive phase followed by continuation phase:
- ***Intensive Phase*** (2 months): consists of daily Isoniazid, Rifampicin and Pyrazinamide. A 4th drug (Ethambutol) is usually added especially when initial drug resistance may be present or for extensive disease e.g. miliary TB or where prevalence of HIV is high.
- ***Maintenance Phase*** (4 months): Isoniazid and rifampicin for the remaining 4 months daily

Anti-TB dosage in children

- Children tolerates TB drug better with less side effect than adult. TB dosage calculated as per kg of body weight is higher for children compared to adult. Dose adjustment needed if significant weight gain. Dispersible fixed dose combination (FDC) for children is available.

Recommended dose of anti-TB drugs in children		
Drug	**Dose (range) in mg/kg body weight**	**Maximum dose (mg)**
Isoniazid	10 (7 – 15)[a]	300
Rifampicin	15 (10 – 20)	600
Pyrazinamide	35 (30 – 40)	2000 (2 g)
Ethambutol	20 (15 – 25)	1000 (1 g)

[a]The higher end of the range for INH dose applies to younger children. As the children grow older the lower end of the dosing range becomes more appropriate. (**Source:** *World Health Organization. Guidance for National Tuberculosis Programmes on The Management of Tuberculosis in Children (2nd Edition). Geneva: WHO;2014*)
**Pyridoxine 5 - 10 mg daily needs to be added if INH is prescribed.

WHO recommended dose for FDC in children		
Weight band (kg)	**Number of tablets daily**	
	Intensive phase RHZ 75/50/150*	**Continuation phase RH 75/50**
4- 7	1	1
8 - 11	2	2
12 - 15	3	3
16 - 24	4	4
≥25	*Adult FDC doses recommended*	

- *Ethambutol should be added in the intensive phase for children with extensive disease. (**Source:** F*ixed-dose combinations for the treatment of TB in children. World Health Organization, 2018. Available from: https://www.who.int/tb/FDC_Factsheet.pdf*)

Corticosteroids

- Indicated for children with TB meningitis.
- May be considered for children with pleural and pericardial effusion (to hasten reabsorption of fluid), severe miliary disease (if hypoxic) and endobronchial disease.
- Steroids should be given only when accompanied by appropriate anti- TB therapy.
- Dosage: prednisolone 1-2mg/kg per day (max. 40 mg daily) for first 3-4 week, then taper over 3-4 weeks.

Monitoring of Drug Toxicity

Indications for baseline and routine monitoring of serum transaminases and bilirubin are recommended for:

- Severe TB disease.
- Clinical symptoms of hepatotoxicity.
- Underlying hepatic disease.
- Use of other hepatotoxic drugs (especially anticonvulsants).
- HIV infection.
- Routine testing of serum transaminases in healthy children with none of the above risk factors is not necessary.
- Children on Ethambutol should be monitored for visual acuity and colour discrimination.

Breast-feeding and the mother with Pulmonary TB

- TB treatment in lactating mothers is safe as the amount of drug ingested by the baby is minimal. Hence if the mother is already on treatment and is non-infective, the baby can be breastfed.
- Women who are receiving isoniazid and are breastfeeding should receive pyridoxine.
- If the mother is diagnosed to have active pulmonary TB and is still infective:
  1. The newborn should be separated from the mother for at least one week while the mother is being treated.
  2. Mother should wear a surgical mask subsequently while breast feeding until she is asymptomatic and her sputum is AFB-smear negative.
  3. Breast feeding is best avoided during this period, however, expressed breast milk can be given.
  4. The infant should be evaluated for congenital TB. If this is excluded, BCG is deferred and the baby should receive isoniazid for 3 months and then tuberculin tested.
  5. If tuberculin negative and mother has been adherent to treatment and non-infectious, isoniazid can be discontinued and BCG given.
  6. If tuberculin positive, the infant should be reassessed for TB disease and if disease is not present, isoniazid is continued for total of 6 months and BCG given at the end of treatment.
  7. Other close household contacts should be evaluated for TB.
- Congenital TB is rare but should be suspected if the infant born to a tuberculous mother fails to thrive or is symptomatic.

Latent TB Infection (LTBI)

- Children < 5 years especially those below 2 years old with LTBI have the highest risk of progression to active TB including disseminated and CNS TB.
- Active TB usually develops within two years of infection but can occurred within weeks in infants.
- Early investigation and treatment for LTBI are necessary to prevent active TB.
  LTBI in children is a diagnosis established by:
  1. Demonstrating prior TB infection using a LTBI test either TST or IGRA.
  2. Excluding active TB disease with symptoms screening and chest-X-ray.
- Evaluation for active TB must be pursued in all children with a positive TST or IGRA. Children with LTBI should be totally asymptomatic and their chest-X-ray are usually normal.
  *** In immunocompromised children, both IGRAs and TST should be interpreted with caution.*

  The following are children with high-risk of progression to active TB:
  - Household contacts* of bacteriologically confirmed PTB
  - Infant and children living with HIV
  - Other risk group including those immunocompromised children having anti-TNF treatment, ESRF on dialysis, diabetes and organ or haematological transplant recipients

  * Definition of household contact: refer *"CPG Management of TB (Fourth edition) MOH,2021."*

Recommended dosage for LTBI treatment in children Dose				
Drugs	**Duration**	**Interval**	**Dose**	
Isoniazid (6H)	6 months	Daily	1. Age 10 years and older: 5 mg/kg/day 2. Age <10 years: 10mg/kg/day (Range 7-15 mg/kg) Maximum dose: 300 mg	
Rifampicin (4R)	4 months	Daily	1. Age 10 years and older: 10 mg/kg/day 2. Age <10 years: 15mg/kg/day (Range 10-20 mg/kg) Maximum dose: 600 mg	
Isoniazid + rifampicin (3HR)	3 months	Daily	Dose of INH and RIF same as above	
Rifapentine# + isoniazid (3HP)	3 months (Given in total of 12 doses)	Weekly	*Isoniazid:* 10 - 15 kg: *300 mg* 16 - 23 kg: *500 mg* 24 - 30 kg: *600 mg* >31 kg: *700 mg* (For children age 2-14 years old)	*Rifapentine:* 10 - 15 kg: *300 mg* 16 - 23 kg: *450 mg* 24 - 30 kg: *600 mg* >31 kg: *750 mg* (For children age 2-14 years old)

Rifapentine is currently not available in Malaysia
Pyridoxine 5 - 10 mg/day should be given to patients on Isoniazid.

LTBI treatment regimen

Current regimens used to treat LTBI in children include:

a. Rifampicin daily for four months (4R).
b. Isoniazid and rifapentine weekly for three months (12 doses) (3HP).
c. Isoniazid and Rifampicin daily for three months (3HR).
d. Isoniazid daily for six or nine months (6H/9H).

- The preferred regimens for LTBI treatment are:
  1. 4R for all children >28 days of age or 3HP for children aged >2 years.
  2. 6H for all newborns aged 28 days and below.
- Alternative regimens include 3HR, 6H or 9H.
- In HIV-infected children with LTBI, 6H is the preferred regimen for:
  1. Children <2 years of age.
  2. Children ≥2 years of age on antiretroviral treatment with Rifamycin drug interaction

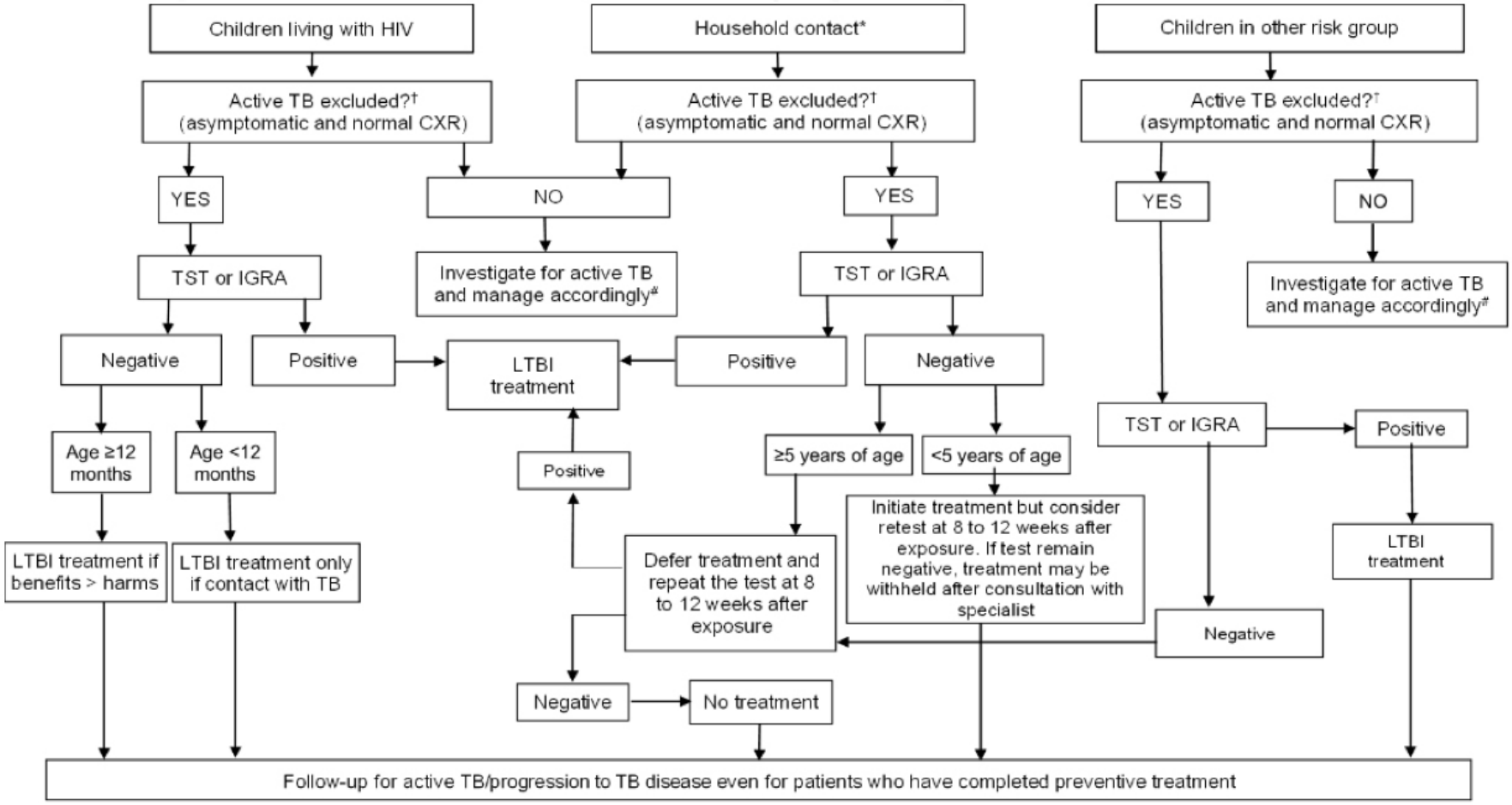
Monitoring and follow-up of LTBI

The objectives of follow-up during and after LTBI treatment in children:

- Monitor progression to active TB.
- Identify possible ADR.
- Monitor and ensure adherence.
- Adjust treatment dose according to the latest body weight.
- In general, clinical monitoring every four to six weeks for the first three months is appropriate, followed by every two to three months thereafter, regardless of regimen used.
- The duration of follow-up is at least two years from initiation of treatment.

Routine LFT monitoring is not needed in children receiving LTBI treatment but is warranted for children who develop clinical symptoms of liver injury. If the LFT is deranged the patient should be managed in consultation with expert. Counselling and support of patients and families on the importance of LTBI treatment will improve treatment acceptance and adherence. As LTBI treatment is given to a child who is otherwise well and healthy, development of any unexpected ADR may affect the adherence and parents may default subsequent follow-up. Therefore, it is important to educate the patient and family about potential ADRs. They should understand the need to stop treatment and seek medical advice immediately if signs or symptoms of drug toxicity are suspected.

LTBI TESTING AND TREATMENT IN CHILDREN AT RISK OF PROGRESSING TO ACTIVE TB



*/† :Refer to notes on diagnosis of LTBI. #If active TB is confirmed, to treat accordingly. If no active TB detected after investigations, follow the pathway as active TB excluded. **Adapted** from *World Health Organization. WHO Consolidated Guidelines on Tuberculosis: Tuberculosis Preventive Treatment: Module 1: Prevention. Geneva: World Health Organization; 2020*

Chapter 90:
BCG Lymphadenitis

In Malaysia, BCG is given intradermally at birth to prevent disseminated TB including TB meningitis.

- Regional lymphadenopathy is one of the more common complications of BCG vaccination and arises as a result of enlargement of ipsilateral lymph nodes, principally involving the axillary node.
- Differential diagnoses to consider are:
  - Pyogenic lymphadenitis.
  - Tuberculous lymphadenitis.
  - Non-tuberculous lymphadenitis.
- The following are features suggestive of BCG lymphadenitis
  - History of BCG vaccination on the ipsilateral arm.
  - Onset usually 2 to 4 months after BCG vaccination, although it may range from 2 weeks to 6 months. Almost all cases occur within 24 months.
- There is absence of fever or other constitutional symptoms.
- Absent or minimal local tenderness over the lesion(s).
- >95% of cases involve ipsilateral axillary lymph nodes, but supraclavicular or cervical glands may be involved in isolation or in association with axillary lymphadenopathy.
- Only 1 to 2 discrete lymph nodes are enlarged (clinically palpable) in the majority of cases. Involved lymph nodes are rarely matted together.
- Two forms of lymphadenitis can be recognized:
  a. **non-suppurative or simple** which may resolve spontaneously within a few weeks – this is a normal reaction and may go unnoticed.
  b. **suppurative** - involves an enlarging lymph node with fluctuant appearances, oedema and erythema of the overlying skin and increased pigmentation. Happens in 30-80% of cases of lymphadenitis.
- Once suppuration has occurred, the subsequent course is usually one of spontaneous perforation, discharge and sinus formation. Healing eventually takes place through cicatrization and closure of the sinus, the process taking several months with possible scarring.

Correct Technique to give BCG Vaccination
Needle Short (10mm) 26-27 gauge needle with a short bevel using a BCG or insulin syringe *Site* Left arm at Deltoid insertion Dose • 0.05 mls for infants (< 1 year of age) • 0.1 ml for children > 1 year. *Route* Intradermal
Do not give BCG at other sites where the lymphatic drainage makes subsequent lymphadenitis difficult to diagnose and dangerous (especially on buttock where lymphatic drains to inguinal and deep aortic nodes).

MANAGEMENT

Assessment

Careful history and examination are important to diagnose BCG adenitis

- BCG lymphadenitis without suppuration (no fluctuation)
  - Most non suppurative BCG lymph nodes will regress without intervention in 4 – 6 months and can be managed conservatively
  - Drugs are not required.
  - Reassurance and follow-up is advised.
  - Several controlled trials and a recent meta analysis (Cochrane database) have suggested that drugs such as antibiotics (e.g. erythromycin) or antituberculous drugs neither hasten resolution nor prevent its progression into suppuration.
- BCG lymphadenitis with suppuration (fluctuation)
  - Needle aspiration is recommended. Usually one aspiration is effective, but repeated aspirations may be needed for some patients.
  - Surgical excision may be needed when needle aspiration has failed (as in the case of matted and multiloculated nodes) or when suppurative nodes have already drained with sinus formation.

Needle aspiration

A systemic review of five RCTs showed that fine needle aspiration shortens the resolution of BCG abscess at 6 months, prevents spontaneous perforation and associated complications and shortens the duration of healing and is safe.

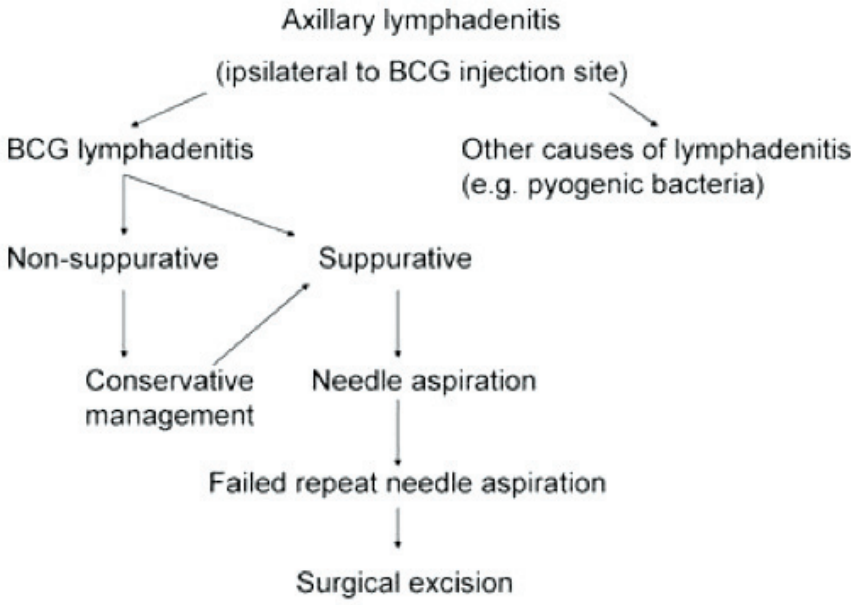
Persistent Lymphadenitis/ disseminated disease

The following findings may indicate disseminated BCG infection:

- Systemic manifestations: fever, anemia, loss or poor weight gain.
- Distant lymph node(s) enlargement, beyond the ipsilateral lymph node(s) such as right axillary or inguinal.
- Cutaneous lesions or abscesses beyond the region of vaccination
- Hepatosplenomegaly.
- Bone tenderness or swelling reflecting underlying osteomyelitis.
- Signs of meningeal involvement, such as seizures.

Investigations for disseminated BCG infection

The investigations should be obtained with guidance of pediatric immunology and infectious diseases specialists. These may include identification of the *M. bovis* from the patient's organs by culture and/or standard PCR, as well as typical histopathological changes with granulomatous inflammation, in addition to identifying the specific underlying immunodeficiency status. Radiological investigations such as bone scan and abdominal Computed Tomography (CT) scan may be beneficial in evaluating the site(s) and extent of dissemination. Thus all infants presenting with BCG lymphadenitis should be followed up till resolution.

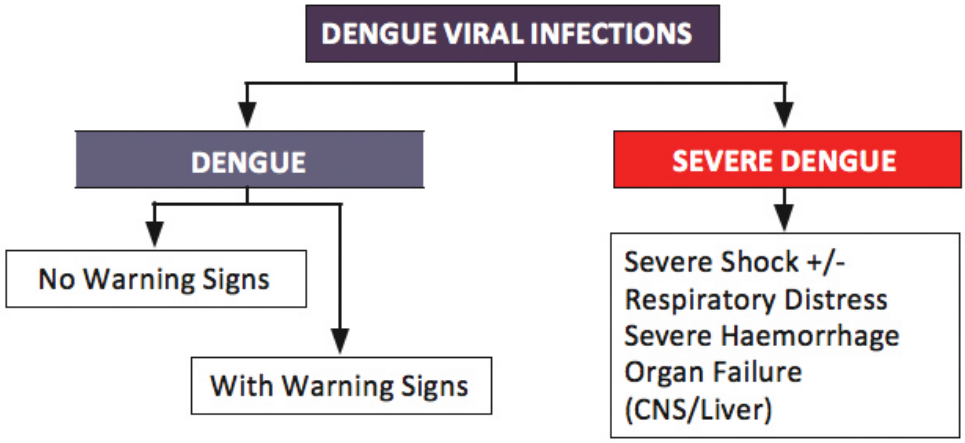

Axillary lymphadenitis
(ipsilateral to BCG injection site)
BCG lymphadenitis
Other causes of lymphadenitis
(e.g. pyogenic bacteria)
Non-suppurative
Suppurative
Conservative management
Needle aspiration
Failed repeat needle aspiration
Surgical excision

Chapter 91:
Dengue Viral Infections

Introduction

- Dengue virus infections affect all age groups and produce a spectrum of illness that ranges from asymptomatic to a mild or nonspecific viral illness to severe and occasionally fatal disease.
- The traditional 1997 World Health Organization (WHO) classification of dengue was changed to the 2009 WHO classifications that encompass various categories of dengue since dengue exists in continuum.
- The term DHF used in previous classification put too much emphasis on hemorrhage; However, ***the hallmark of severe dengue (and the manifestation that should be addressed early) IS NOT HEMORRHAGE but increased vascular permeability that would lead to shock.***

CLASSIFICATION OF DENGUE VIRAL INFECTIONS, WHO 2009



This system divides dengue into TWO major categories of severity:
- Dengue: with or without warning signs, and
- Severe dengue.

Criteria for dengue with or without warning signs (adapted from WHO 2009 dengue classification and severity)	
Probable Dengue *Live in and travel to dengue endemic area *Fever and any 2 of the following: 1. Nausea, vomiting 2. Rash 3. Aches and pain 4. Leucopenia 5. Any warning signs **Laboratory confirmed dengue** (important when no sign of plasma leakage)	**Warning Signs** Clinical: • Continuous abdominal pain (not intermittent) or tenderness • Persistent vomiting (≥2 episodes of vomiting that amounts to fatigue or requires intravenous fluids) • Clinical fluid accumulation • Mucosal bleed • Lethargy, restlessness • Liver enlargement > 2cm

Dengue can be diagnosed through: • Detection of dengue virus protein by non-structural protein 1 antigen (NS1 Ag): rapid test/ELISA • Antibody detection of IgM/IgG(serology) • Combination of NS1 Ag with IgM/IgG (combo test) • OR • Genome detection by RT-PCR or virus isolation (reference laboratory)	*Laboratory:* Increased in haematocrit (HCT) with concurrent rapid decrease in platelet count

Criteria for Severe Dengue
1. Severe plasma leakage leading to: • Shock (Dengue Shock Syndrome) • Fluid accumulation (pleural effusion, ascites) with respiratory distress 2. Severe bleeding As evaluated by paediatrician 3. Severe organ involvement: • Liver: elevated transaminases (AST or ALT ≥ 1000) • CNS: impaired consciousness, seizures • Heart and other organ involvement

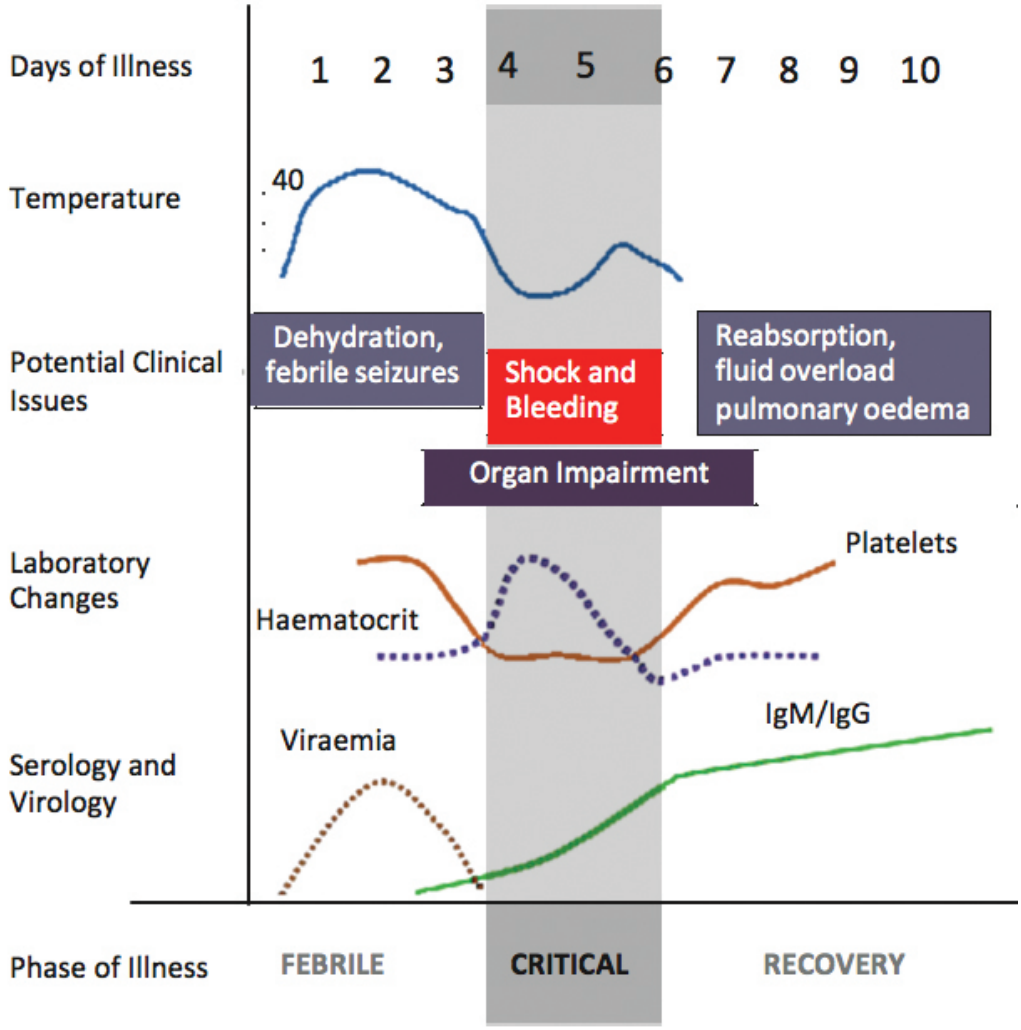
Management of children with Dengue

- Dengue is a complex and unpredictable disease but success can be achieved with mortality rates of 1% when care is given in timely manner.
- The best part is, the care is simple and inexpensive since ALL that is needed is clinical acumen, knowing different phases of dengue and what to expect during these phases.
- There is currently no specific anti-viral for dengue hence therapy is targeted to those individuals with capillary leakage needing fluid therapy, reversing shock when it happens and stopping fluid when the individual enters recovery phase.
- The timing of intervention starts at frontline healthcare personnel whether they are in A&E or OPD or even health clinics. This involve early recognition that the child that presents to you do indeed have dengue.
- The healthcare personnel involved in managing dengue cases day to day need to familiarize themselves with the THREE main well demarcated phases of dengue: febrile, critical; and recovery (see next page)
- Since dengue is endemic in Malaysia; all children that presents to us with persistent fever without any obvious source need to have dengue as a differential.
- PROBABLE CASE DEFINITION OF DENGUE can be used to suspect whether a child with fever has dengue or not.

  Example: a 5-year-old child with 2 days of persistent fever without any obvious source, who also has body aches and abdominal pain fulfills the case definition of probable dengue.
- In early phase of disease, it is difficult to differentiate dengue with other childhood illness; therefore, using probable case definition and performing FBC at first encounter would be useful to differentiate dengue from other illness.
- Temporal relationship of fever cessation (defervescence) is important as, in DENGUE (unlike other viral illness) manifest its severity (leakage/ shock) when temperature seems to have declined.

- Relation of rash with onset of fever also helps to differentiate Dengue Fever with other childhood viral illness. For example, a child who presents with fever and cough, coryza and conjunctivitis (3C's) with rash at Day 4 of illness could be having measles.
- The other febrile illness (OFI) that a child might present with during initial stages among others are: influenza, chikungunya, Infectious mononucleosis, scarlet fever, COVID-19, drug reactions etc.

PHASES OF DENGUE IN RELATION TO SYMPTOMS AND LABORATORY CHANGES



Adapted from World Health Organization: Dengue Hemorrhagic Fever: Diagnosis, Treatment, Prevention and Control. Third Edition. Geneva, WHO/TDR, 2009.

Note: During viraemic phase of dengue, viral study of PCR/culture (in reference laboratory) or NS1 Ag test will be positive.

Priorities during first encounter are:

1. Establish whether patient has dengue or not
2. Determine phase of illness
3. Recognize warning signs and/or the presence of severe dengue if present.
4. Does the child have co-morbidities that put the child at high risk of having severe dengue?
5. Does the child need admission, or can the child be managed as out-patient?

- Most patients with Dengue Fever can be managed without hospitalization provided they are generally well with no warning signs or evidence of abnormal bleeding, oral intake and urine output are satisfactory, and the caregiver is educated regarding fever control and avoidance of non-steroidal anti-inflammatory agents (NSAIDS).
- They should also be familiar with the course of illness (natural history) and be educated on when to bring the child back to healthcare facilities. (refer Appendix 4, CPG Dengue in Children 2nd edition)
- Home Care Advice for Children with Dengue card/leaflet that emphasizes on danger/warning signs is also important. This should be given to parents/guardian for all children who are managed as outpatient.
- These children need daily clinical and/or laboratory assessment by trained doctors or nurses until the danger period has passed and they had recovered from dengue.
- Monitor these children using Dengue Monitoring Record (Appendix 5, CPG Dengue in children, 2nd edition)

If dengue is suspected or confirmed, disease notification is mandatory.

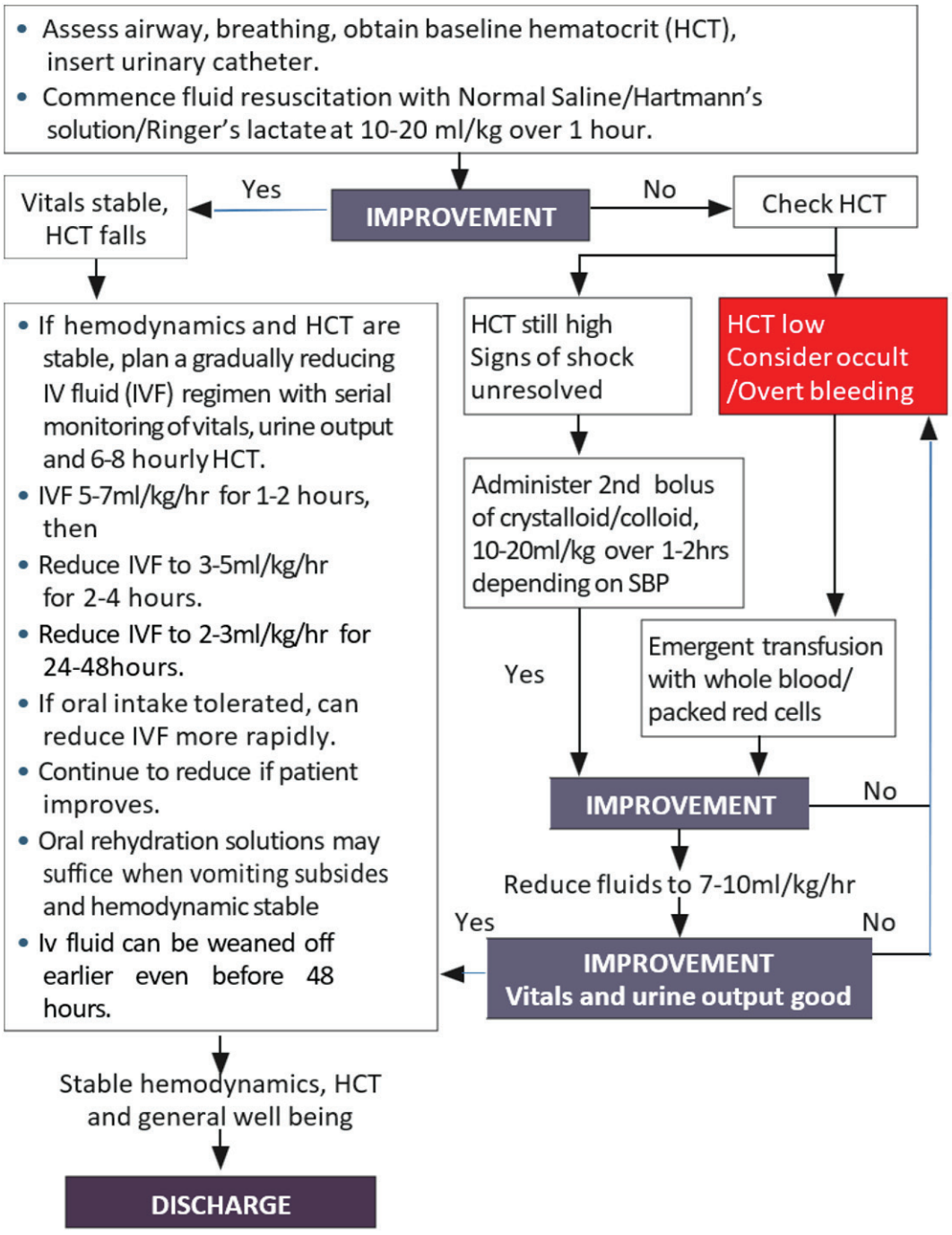
Indication for Hospitalisation are:

- Presence of warning signs.
- Features of severe dengue
- Infants.
- Children with co-morbid factors (e.g. diabetes, renal failure, immune compromised state, hemoglobinopathies and obesity).
- Social factors - living far from health facilities, transport issues.

The THREE major priorities of managing hospitalized patient with dengue in the critical phase are:
A - Replacement of plasma losses.
B - Early recognition and treatment of hemorrhage.
C - Prevention of fluid overload.

- Fluid therapy in a patient with dengue shock has two parts: initial, rapid fluid boluses to reverse shock followed by titrated fluid volumes to match ongoing losses.
- However, for a patient who has warning signs of plasma leakage but is not yet in shock, the initial fluid boluses may not be necessary.
- Fluids in dengue MUST be managed in way that it is given ONLY when it is needed and off when patient enter convalescent/recovery phase.
- Haemodynamic state should be used as MAIN driver of IVF therapy. HCT as guide. Not the other way around.
- Limit fluid in febrile phase. If IVF is needed to correct hydration, USE only isotonic solutions (example NS).
- During the febrile phase of dengue, one of the complications that can occur is dehydration. Please look for the severity of this and correct and support the child 's fluid need with combination of ORS, IVF and encourage the child's normal dietary intake.

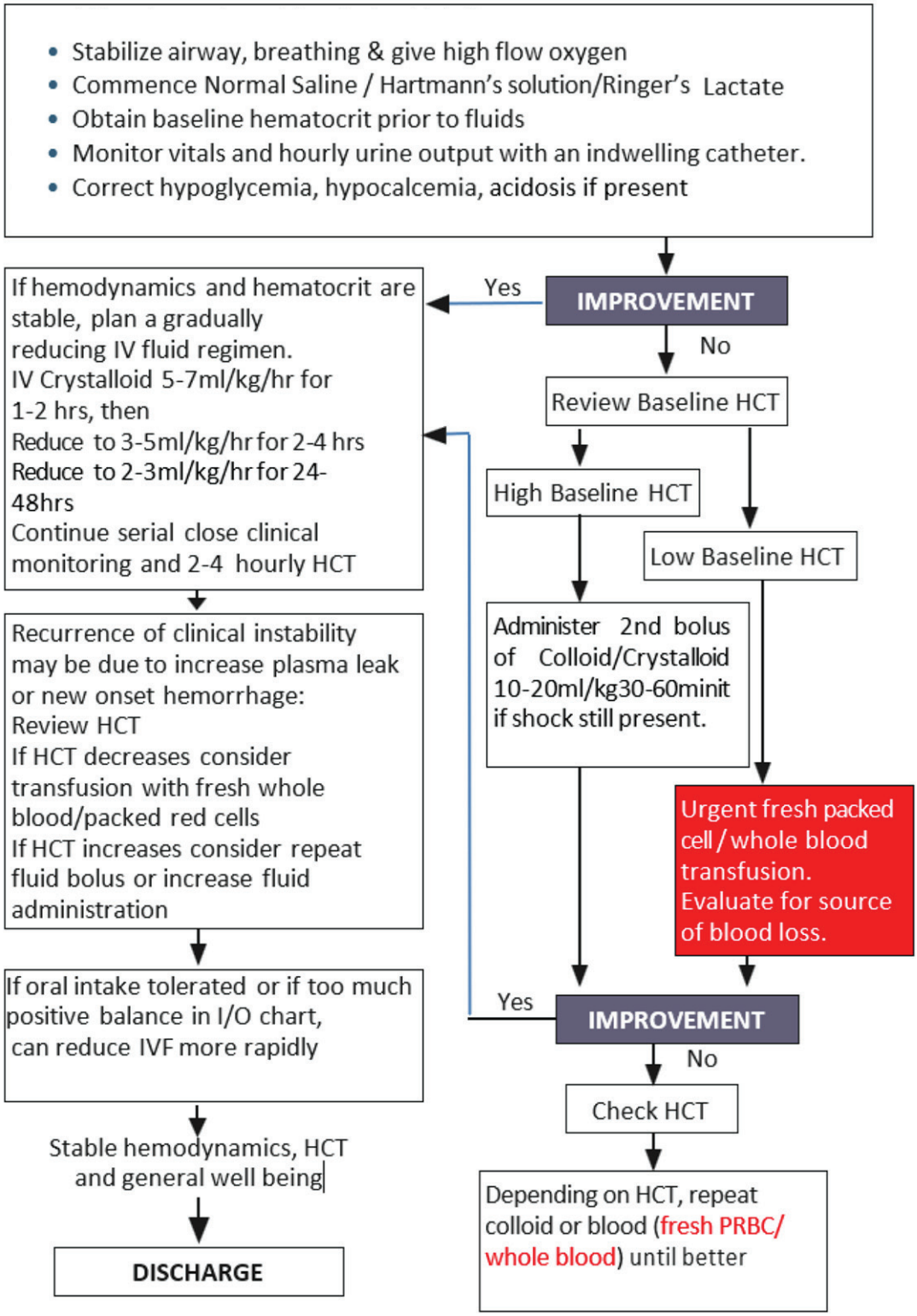
VOLUME REPLACEMENT FLOWCHART FOR PATIENTS WITH SEVERE DENGUE AND COMPENSATED SHOCK



Note:

- Recurrence of clinical instability may be due to increased plasma leak or new onset hemorrhage.
- Review HCT before and after fluid therapy.

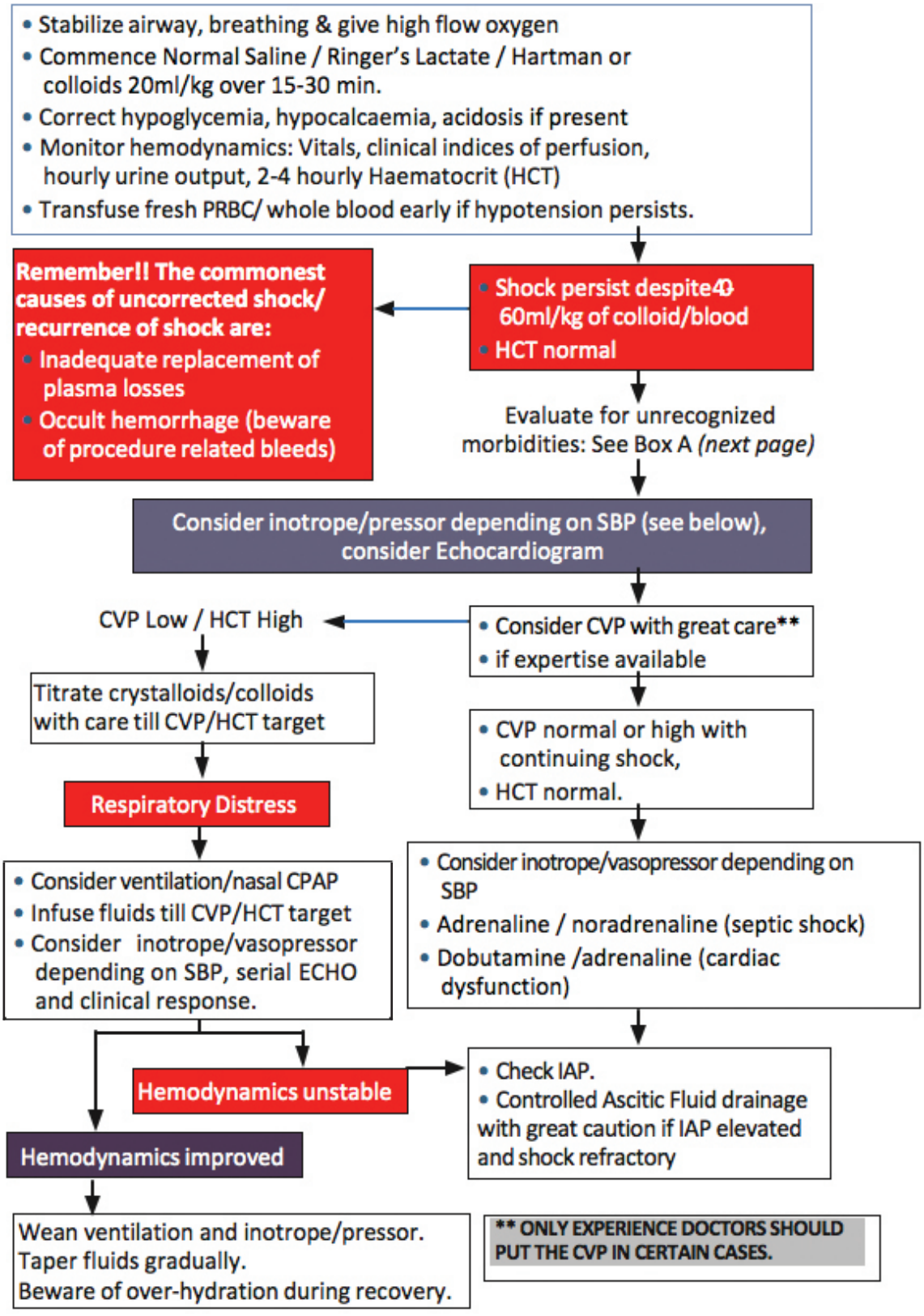
APPROACH TO CHILD WITH SEVERE DENGUE AND HYPOTENSION



Remember!

- The commonest causes of uncorrected shock/recurrence of shock are:
  - Inadequate replacement of plasma losses
  - Occult hemorrhage (beware of procedure related bleeds)
- Be aware of side effects of colloids like allergic reaction/coagulopathy

APPROACH TO CHILD WITH SEVERE DENGUE AND REFRACTORY SHOCK (LATE PRESENTER)



SBP: Systolic blood pressure, PRBC: Packed red blood cell, CVP: Central venous pressure, ECHO: Echocardiogram, IAP: Intra-abdominal pressure

BOX A: Unrecognized morbidities that may contribute to refractory dengue shock.

1. ***Occult bleeds***
   Rx: Whole blood/PRBC transfusion
2. ***Co-Existing bacterial septic shock/Malaria/Leptospira, etc.***
   Rx: antibiotics/antimalarials, cardiovascular support, blood transfusion. Do not start antibiotic for pleural effusion since it's part and parcel of plasma leakage in dengue or to correct persistent acidosis/high lactate (usually due to prolonged/refractory shock).
   Use of large amount of NS also can give rise to hyperchloremic acidosis.
3. ***Myocardial Dysfunction (systolic or diastolic)***
   Rx: Cardiovascular support, evaluate with ECHO if available
4. ***Positive pressure ventilation contributing to poor cardiac output***
   Rx: Titrated fluid and cardiovascular support
5. ***Elevated intra-abdominal pressure (IAP)***
   Rx: Cautious drainage
6. **Wide-Spread Hypoxic-ischemic injury with terminal vasoplegic shock**
   No treatment effective

ECHO: Echocardiogram; IAP: Intra-abdominal pressure; Rx: Treatment

BOX B: Criteria for pediatric intensive care unit/high dependency unit referral

Dengue patients should be referred to pediatric intensive care units/high dependency unit in the event of life-threatening situation characterized by one or a combination of the following:

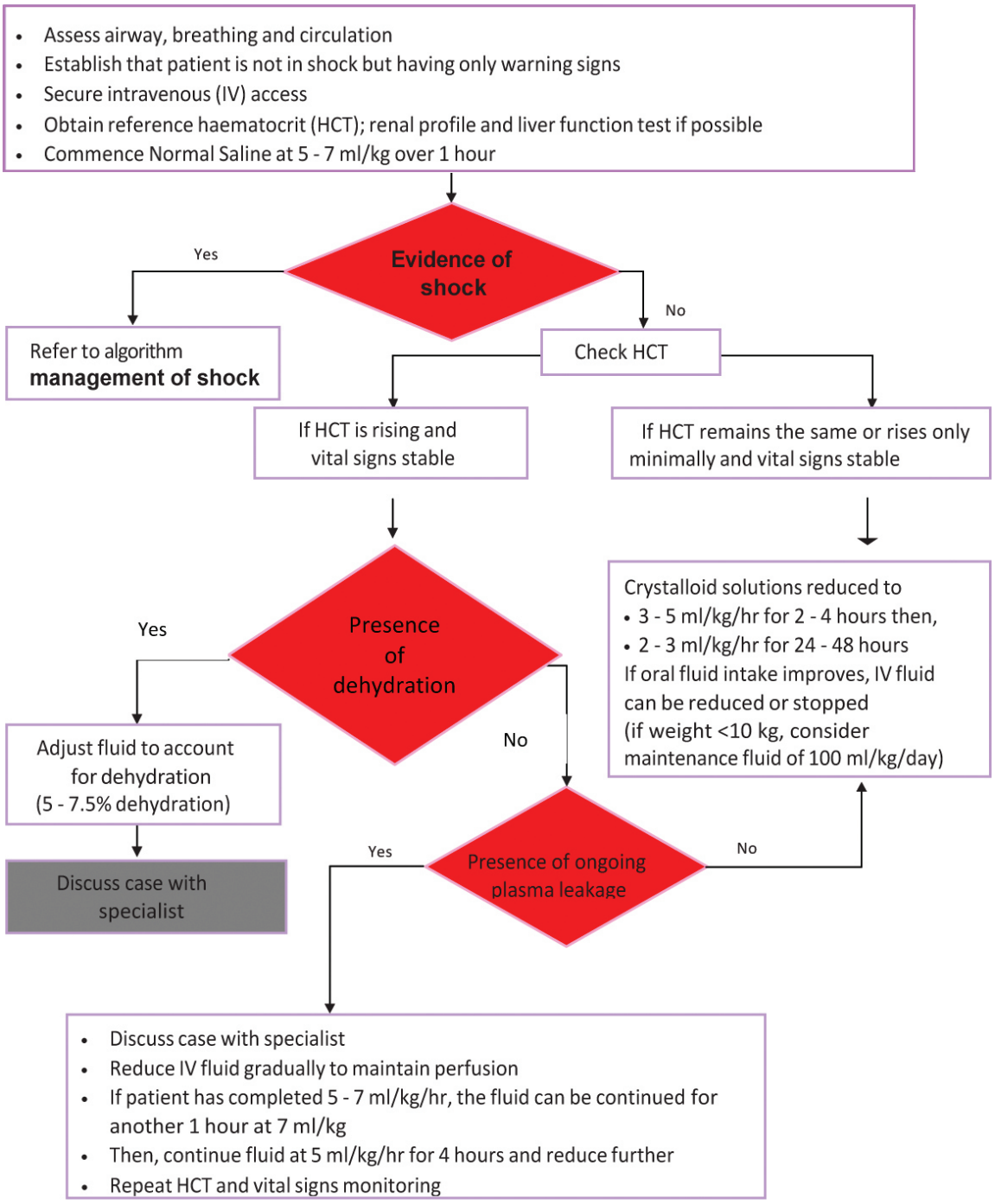
- Prolonged and/or decompensated shock
- Severe bleeding with severe disseminated intravascular Coagulopathy
- Fluid overload
- Respiratory distress and failure
- Severe organ impairment (hepatic damage, renal impairment, cardiomyopathy, encephalopathy or encephalitis

Volume replacement flowchart for patient with dengue with "warning signs"

- Judicious volume replacement with IV fluid therapy from this early stage may modify the course and severity of the disease (algorithm)
- Assess airway and breathing and obtain baseline HCT level.
- Commence fluid resuscitation with normal saline/Ringers' lactate at 5-7ml/kg over 1-2 hours.
- If hemodynamic and HCT are stable, plan a gradually reducing IVF regime.
- Titrate fluid on the basis of vital signs, clinical examination, urine output (aim for 0.5ml-1ml/kg/hr), and serial HCT level.
- IVF:5-7ml/kg/hour for 1-2 hours, then:
- Reduce IVFs to 3-5ml/kg/hour for 2-4 hours;
- Reduce IVFs to 2-3ml/kg/hour for 24-48 hours;
- Continue serial close monitoring and every 6-8 hourly HCT level.
- Oral rehydration solutions may suffice when vomiting subsides and hemodynamic stabilize.
- A monitored fluid regimen may be required for 24-48 hours until danger period subsides

HCT-hematocrit; IVF, intravenous fluid

Fluid Management of Children with Dengue with Warning Signs



Guidelines for reversing dengue shock while minimizing fluid overload

Severe dengue with compensated shock:

- Stabilize airway and breathing, obtain baseline Hct level, initiate fluid resuscitation with NS/RL at 10-20 mL/kg over 1 hr, and insert urine catheter for objective measurement of urine output.

Severe dengue with hypotension:

- Should be managed more vigorously.
- Secure IV access as soon as possible (within 5 minutes) and obtain baseline HCT. At the same time stabilize airway and breathing
- Initiate fluid resuscitation with 1-2 boluses of 20 mL/kg NS/RL or
- synthetic colloid over 15-30 mins until pulse is palpable, slow down fluid rates when hemodynamics improves.
- Repeat second bolus of 10 mL/kg colloid if shock persists and Hct level is still high
- Synthetic colloids may limit the severity of fluid overload in severe shock.
- Hydroxyethyl starch (HES) is currently not recommended in DSS. Use colloid that you are familiar with.

End points/goals for rapid fluid boluses:

- Improve circulation as evidenced by decreasing tachycardia, improving BP and pulse volume, warm and pink extremities and CRT <2 seconds (Table 1 : Hemodynamic assessment)
- Improve end-organ perfusion as evidenced by improving consciousness level and urine output.
- Achieve appropriate decrease in HCT
  - If baseline Hct level is low or "normal" in presence of shock, hemorrhage likely to have worsened shock, transfuse fresh WB or fresh PRBCs early.
- After rapid fluid boluses, continue isotonic fluid titration to match ongoing plasma leakage for 24–48 hrs; if patient not vomiting and is alert after shock, correction with oral rehydration fluids may suffice to match ongoing losses.
- Check Hct level 2-4 hourly for first 6 hrs and decrease frequency as patient improves.

Goals for ongoing fluid titration:

- Stable vital signs, serial Hct measurement showing gradual normalization (if not bleeding), and low normal hourly urine output are the most objective goals indicating adequate circulating volume; adjust fluid rate downward when this is achieved.
- Plasma leakage is intermittent even during the first 24 hrs after the onset of shock; hence, fluid requirements are dynamic.
- Targeting a minimally acceptable hourly urine output (0.5-1 mL/kg/hr) is an effective and inexpensive monitoring modality that can signal shock correction and minimize fluid overload.
- A urine output of 1.5–2 mL/kg/hr should prompt reduction in fluid infusion rates, provided hyperglycemia has been ruled out.
- Separate maintenance fluids are not usually required; glucose and potassium may be administered separately only if low.
- Hypotonic fluids can cause fluid overload; also, avoid glucose- containing fluids, such as 1/2Glucose Normal Saline (GNS or I/2 GNS): the resultant hyperglycemia can cause osmotic diuresis and delay correction of hypovolemia. Tight glucose monitoring is recommended to avoid hyper/hypoglycemia.
- Commence early enteral feeds when vital signs are stable, usually 4–8 hrs after admission.
- All invasive procedures (intubation, central lines, and arterial cannulation) must be avoided; if essential, they must be performed by the most experienced person. Orogastric tubes are preferred to nasogastric tubes. Avoid repeated veno-puncture.
- Significant hemorrhage mandates early fresh WB or fresh PRBC transfusion; minimize/avoid transfusions of other blood products, such as platelets and fresh-frozen plasma unless bleeding is uncontrolled despite 2–3 aliquots of fresh WB or PRBCs.

NS/RL, normal saline/Ringer's lactate; Hct, hematocrit; BP, blood pressure; WB, whole blood; PRBC - Packed Red Blood Cells; HCT-hematocrit; IVF, intravenous fluid GNS-glucose/normal saline

*** It is recommended that baseline hematocrit is obtained for all cases and repeat hematocrit done following each fluid resuscitation to look at child 's response and to plan subsequent fluid administration. In PICU/HDW settings, ABG machine can be used to look at HCT and in general wards, either, SPIN PCV or FBC (sent to lab).*

Interpretation of hematocrit (HCT)

- Baseline HCT on the first three days of illness is a useful reference point.
- The rise of HCT level beyond 20% of the baseline during critical phase indicates significant plasma leakage and the need for IV fluid therapy.
- HCT alone is not the driver for fluid therapy.
- The interpretation of HCT will be most meaningful if the corresponding hemodynamic state and response to fluid therapy are known at the time of blood sampling
  - A rising or persistently high HCT with unstable vital signs indicates active plasma leakage and the need for a further bolus of fluid resuscitation.
  - A rising or persistently high HCT in patients with stable vital signs and adequate urine output does not require extra IV fluid. Continue to monitor closely and usually the HCT will start to fall within the next 24 - 48 hours as plasma leakage stops.
  - A decrease in HCT with signs of shock may indicate major occult haemorrhage and urgent transfusion with fresh packed red cells/ fresh whole blood is needed. Occult bleeding may take several hours to become apparent and the patient's HCT will continue to decrease without achieving haemodynamic stability.
  - A decrease in HCT with stable vital signs and adequate urine output, indicates haemodilution or reabsorption of extravasated fluids. This signifies the start of recovery phase and IV fluids must be discontinued immediately to avoid pulmonary oedema

The following table shows the normal range of HCT in different age groups.

Age	HCT (%)
Cord blood	45-65
2 weeks	42-66
3 months	31-41
6 month – 6 years	33-42
7 years -12 years	34-40
Adult male	42-52
Adult female	37-47

Table 1: Haemodynamic Assessment: Continuum of Haemodynamic Changes

Parameters	Normal Circulation	Compensated shock*	Decompensated / Hypotensive shock
Consciousness level	Clear and alert	Clear and alert	Change of mental state (Restless, drowsy)
Extremities	Warm and pink extremities	Cold extremities	Cold, clammy extremities
Capillary refill time (CRT)	Brisk (<2 sec)	Prolonged (>2 sec)	Very prolonged, mottled skin
Peripheral pulse volume	Good volume peripheral pulses	Weak & thready peripheral pulses	Feeble or absent peripheral pulses
Heart rate	Normal heart rate for age	Tachycardia	Severe tachycardia with bradycardia in late shock
BP	Normal BP for age	Normal systolic pressure with raised diastolic pressure Postural hypotension	Hypotension/ unrecordable BP
Pulse pressure	Normal pulse pressure for age	Narrowed pulse pressure (≤20 mmHg)	Unrecordable
Respiratory rate	Normal respiratory rate for age	Tachypnoea	Metabolic acidosis/ Tachypnoea
Urine output	Normal	Reducing trend	Oliguria/anuria

*Unless the child is touched, parameters of shock will be missed e.g., cold extremities, weak peripheral pulses, prolonged CRT

Modified: World Health Organization. Handbook for Clinical Management of Dengue. Geneva: WHO; 2012

Discharge of Children with Dengue

- Patients who have been monitored for dengue may be discharged if they fulfil all the clinical and laboratory criteria stated below.

Clinical criteria	• Afebrile for 24-48 hours without antipyretics. • Improvement in clinical status (general well-being, return of appetite, normal hemodynamic status & urine output) • At least 48 hours since recovery from shock. • No respiratory distress.
Laboratory criteria	• Increasing trend of platelet count • Stable HCT without IVF

HOME CARE ADVICE FOR CHILDREN WITH DENGUE

(Please take this card to your health facility for each visit)

What should be done?

- Adequate bed rest.
- Adequate fluid intake:
  - >5 glasses for average-sized adults or accordingly in children.
  - For children encourage fluid intake about 6-8 drinks a day. Generally, children need about:
    - Age < 5 years: 100-120 ml per drink
    - Age 5-10 years:160-180 ml per drink
    - Age > 10 years:200-220 ml per drink.
  - Milk, fruit juice (caution with diabetes patient) and isotonic electrolyte solution (ORS) and barley/rice water or coconut water.
  - Plain water alone may cause electrolyte imbalance.
- Take Paracetamol 10mg/kg/dose NOT MORE than 3-4 times in 24 hours in children.
- Tepid sponging.
- Look for mosquito breeding places in and around the home and eliminate them.

What should be avoided?

- Do not take acetylsalicylic acid (Aspirin), mefenamic acid (Ponstan), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs), or steroids.
- *If you are already taking these medications please consult your doctor.*
  Antibiotics are not necessary.

If any of following is observed, take the patient immediately to the nearest hospital. These are warning signs for danger:

- Bleeding:
  - Red spots or patches on the skin; bleeding from nose or gum, vomiting blood; black-colored stools; heavy menstruation/vaginal bleeding.
- Frequent vomiting.
- Severe/persistent abdominal pain.
- Drowsiness, mental confusion or seizures.
- Pale, cold or clammy hands and feet.
- Difficulty in breathing.
- Lethargy or poor feeding

Dengue monitoring record (example)

Patient's name:
Identification Card No. / Passport No:
Address:
Date of onset of fever:
Result of Dengue Combo Test: (Date:)
Date of notification:

Date	Day of fever	Vital BP/PR/Temp	Hb (g/dl)	HCT (%)	TWC	Platelet	Clinic	Next appt.

Chapter 92:
Diphtheria

Introduction

- Diphtheria is a clinical syndrome caused by Corynebacterium diphtheria.
- Diphtheria can be classified based on site of disease: nasal diphtheria, pharyngeal and tonsillar diphtheria, laryngeal or laryngotracheal diphtheria, and cutaneous diphtheria.
- Diphtheria may cause systemic complication such as myocarditis (mortality 50%), neuritis presenting as paralysis of soft palate and rarely non-oliguric acute kidney injury.

Management of an Acute Case

- All suspected and confirmed patients must be placed under strict isolation until bacteriological clearance has been demonstrated after completing treatment. Strict droplet precautions and hand hygiene must be observed by healthcare workers.
- Obtain specimens for culture from nose, throat, or any mucosal membrane (tissue). Obtain specimen before the commencement of antibiotic and specimen must be transported to the laboratory promptly.
- Notify laboratory personnel as special tellurite enriched culture media (Lofler's or Tindale's) are needed.

Diphtheria Antitoxin (derived from horse serum)

- Definitive treatment:
  - Early, single dose of IV infusion (over 60 minutes) diphtheria antitoxin should be administered on the basis of clinical diagnosis, even before culture results are available.
- Tests for hypersensitivity is recommended for IV administration.

Form of diphtheria	Dose (units)	Route
Pharyngeal/Laryngeal disease of 48 hours or less	20,000 to 40,000	IM OR IV
Nasopharyngeal lesions	40,000 to 60,000	IM OR IV
Extensive disease of 3 or more days durations or diffuse swelling of the neck (bull-neck diphtheria)	80,000 to 120,000	IM OR IV
Cutaneous lesions (not routinely given)	20,000 to 40,000	IM

Begin antibiotic therapy

Antibiotic is indicated to stop toxin production, treat localised infection, and to prevent transmission of the organism to contacts. It is not a substitute for antitoxin treatment.

REGIME

Penicillin

- IV aqueous crystalline Penicillin 100,000 to 150,000 U/kg/day in 4 divided doses, maximum 1.2 million U. Or IM procaine Penicillin 25,000 to 50,000 U/kg/day (maximum 1.2million U) in 2 divided doses.
- Change to oral Penicillin V 125-250mg QID once patient can take orally.
- Total antibiotic duration for 14 days.

OR

Erythromycin

- IV OR Oral 40-50 mg/kg/day, maximum 2g/day.
- Total antibiotic duration for 14 days.

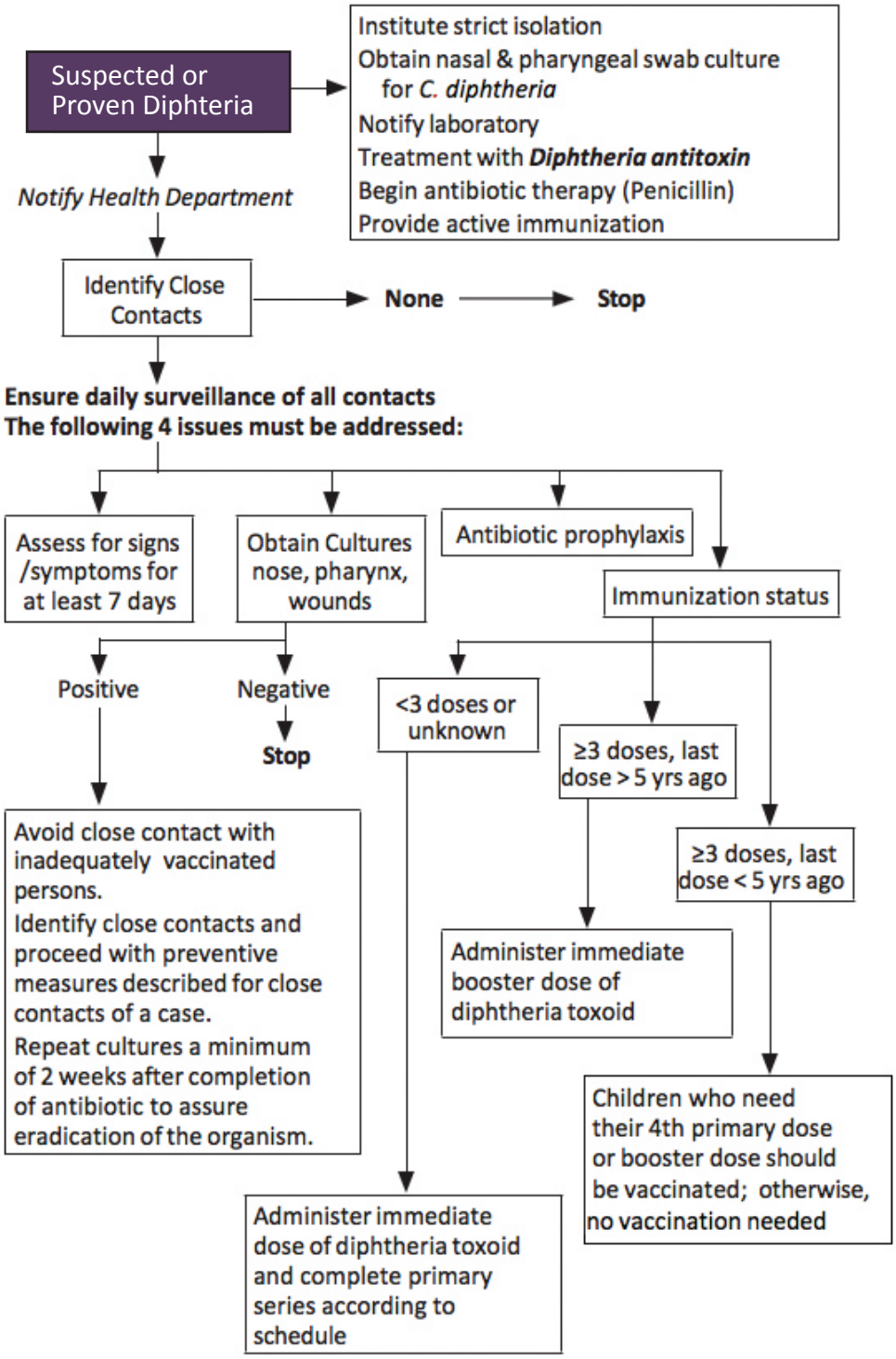
Immunization

- Before discharge, to catch up diphtheria toxoid immunization.
- Diphtheria infection does not necessary confer immunity.

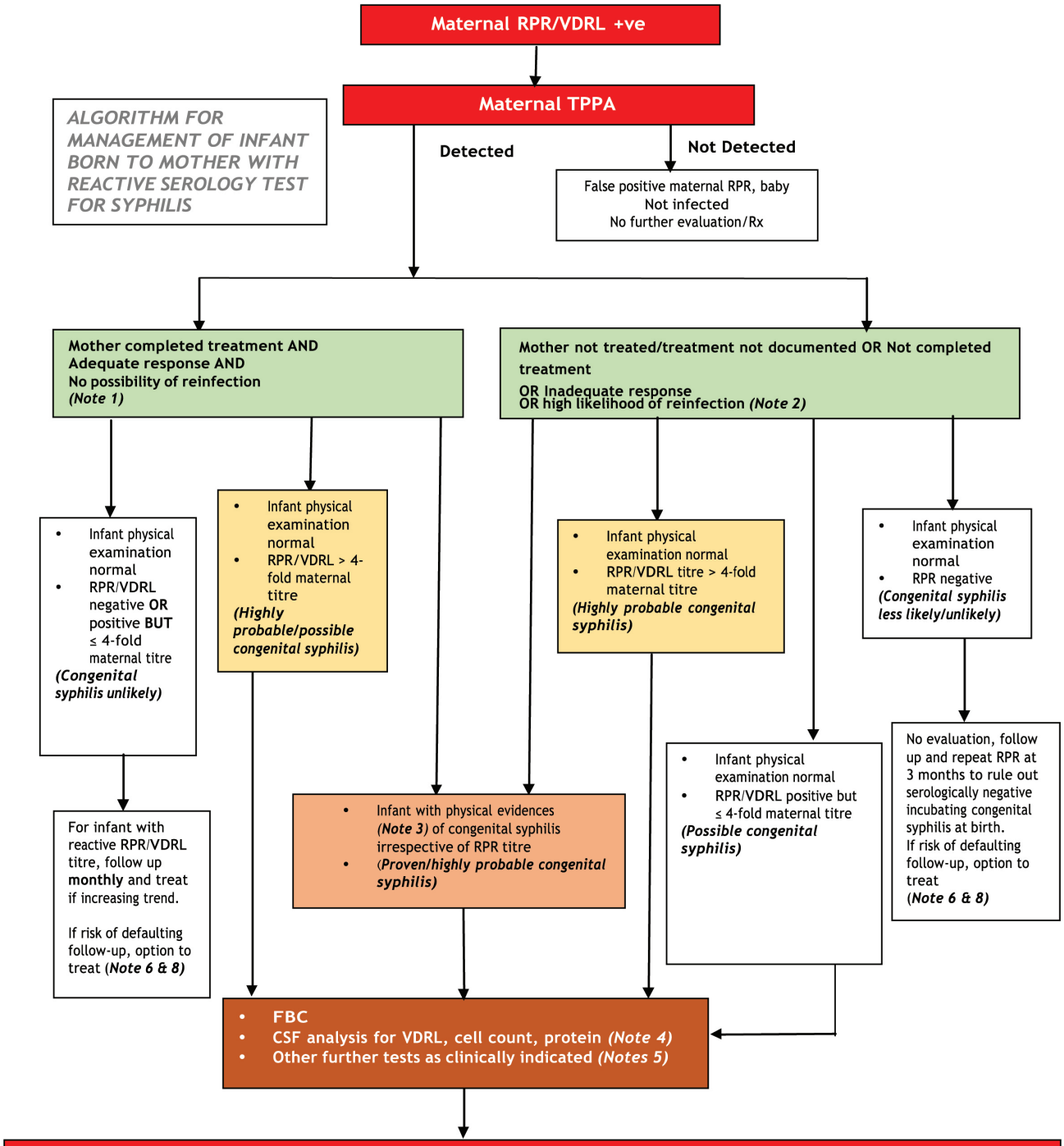
Management of close contacts and asymptomatic carriers

- Refer to diphtheria protocol
- Antibiotic prophylaxis for close contact to complete 7 days if throat swab is Negative. Either penicillin or erythromycin can be used for prophylaxis.

FLOW CHART FOR THE CASE MANAGEMENT AND INVESTIGATION OF CLOSE CONTACTS IN DIPHTHERIA



Chapter 93:
Congenital Syphilis



Treatment: IV Penicillin G 50,000u/kg/dose every 12 hours for first 7 day of life, then every 8 hours after 7th day of life, for a total duration of 10 days if CSF normal OR 14 days if CSF abnormal.
Alternative regimen: IM Procaine Penicillin G 50,000u/kg/dose daily for 10-14 days
(Note: If > 1 day of treatment is missed, the entire course of treatment should be restarted)
Notification and refer parents to STD Clinic/FMS at local health clinic (**Note 7**).
Follow up: Repeat VDRL/RPR every 3 months, until test non-reactive or titre has decreased 4-fold ***(Note 8)***. If titre persistent or increase by 6-12 months, infant should be revaluated (including CSF examination). Persistent RPR and CSF abnormality should be managed in consultation with ID. If CSF VDRL is positive/abnormal indices noted that cannot be explained by other illness, re-treatment for possible neurosyphilis is required.

NOTES TO ALGORITHM ON PREVIOUS PAGE:

1. **Mother completed treatment is defined as**
   - Had received adequate penicillin regime as per national/local treatment guideline. (Mother with late latent syphilis/unknown stage of disease requires 3 dose of IM benzathine Penicillin given 1 week apart) **AND**
   - Treatment completed more than 30 days prior to delivery with ***NO possibility*** or reinfection (i.e., single sexual partner/husband who are fully treated/not infected/***NOT*** recently diagnosed with syphilis/NO Risk of reinfection) **AND**
   - Documented 4-fold decrease in RPR/VDRL titre OR remained low and stable (i.e., serofast) before and during pregnancy and at delivery (e.g., VDRL< 1:2/RPR< 1:4).

   **If mother status unsure for any reasons, cases may be discussed with attending FMS/dermatologist to ascertain their treatment status
2. **Mother is considered as "not completed treatment"** if any of the criteria in ***note 1*** above is ***NOT met***
3. **Clinical features of congenital syphilis:** non-immune hydrops, IUGR, jaundice (direct/conjugated hyperbilirubinemia), hepatosplenomegaly, rhinitis, skin rash, pseudoparalysis of extremity.
4. **CSF analysis** (nontraumatic tap): Normal value differed by gestational age and higher in preterm infants. *Newborn* ≤16-19 WBCs/mm3 or protein level of ≤115-118 mg/dL. *2nd month of life* ≤9-11 WBCs/mm3 or protein level ≤89-91 mg/dL. *Older infant* 5 WBCs/mm3 and protein level of 40 mg/dL considered as upper limit of normal. For infant with abnormal initial CSF at birth, LP should be repeated if RPR remained positive after 6-12 months.
5. **Other tests, as clinically indicated:** long-bone x-ray, CXR, LFT, cranial ultra-sound, ophthalmologic examination and auditory brainstem response.
6. **For infant with a reactive RPR but not treated AND follow up cannot be ensured**, option to give single dose of IM Benzathine Penicillin G 50,000 units/kg. ***However, infants born to mother with untreated early syphilis at time of delivery are at increased risk of congenital syphilis, full course of treatment should be considered even if the infant RPR is nonreactive.***
7. **Notification:** ALL cases of suspected/probable/proven congenital syphilis MUST be notified to local health department irrespective of treatment was given or not.
8. **Follow up:** All sero-reactive infants/infant born to sero-reactive mother should receive careful follow up examination and serologic testing as mentioned above. VDRL/RPR titre s***hould decline by age of 3 month*** and ***should be non-reactive by age of 6 month*** if the infants were not infected or were infected but adequately treated.

Additional Notes:

* RPR indicates rapid plasma reagin test; and VDRL, Veneral Disease Research Laboratory slide test. RPR is currently the preferred ***nontreponemal test*** for syphilis in all MOH facilities. Nontreponemal test may be falsely negative/nonreactive in ***early primary syphilis, latent acquired syphilis of long duration***, and ***late congenital syphilis***. Occasionally, RPR/VDRL test performed on serum sample containing high concentration of T pallidum antibody will be weakly reactive or falsely negative (known as prozone phenomenon); diluting the serum will result in a positive test.

* RPR titre are generally higher than VDRL, therefore when RPR/VDRL are used to monitor treatment response, same test must be used throughout the follow up period, preferably performed in the same laboratory, to ensure comparability of result.

* In order to compare infant RPR titre with maternal titre at birth, ensure mother blood taken at or immediately after delivery, and test performed in the same laboratory. Infant RPR test on umbilical cord sampling is not recommended as umbilical cord may be contaminated with maternal blood and could yield a false-positive result. Wharton's jelly within the umbilical cord also can yield a false negative result.

Chapter 94:
Paediatric COVID-19

Introduction

- The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in a pandemic of coronavirus disease 2019 (COVID-19), which continues to cause infections worldwide.
- COVID-19 is primarily transmitted through respiratory droplets but may also spread by airborne transmission or contact with surfaces.
- Children with the following conditions may be at increased risk for severe disease:
  - Medical comorbidities (congenital heart disease, chronic lung disease, cerebral palsy, diabetes)
  - Immunosuppression
  - Obesity
  - Young infants

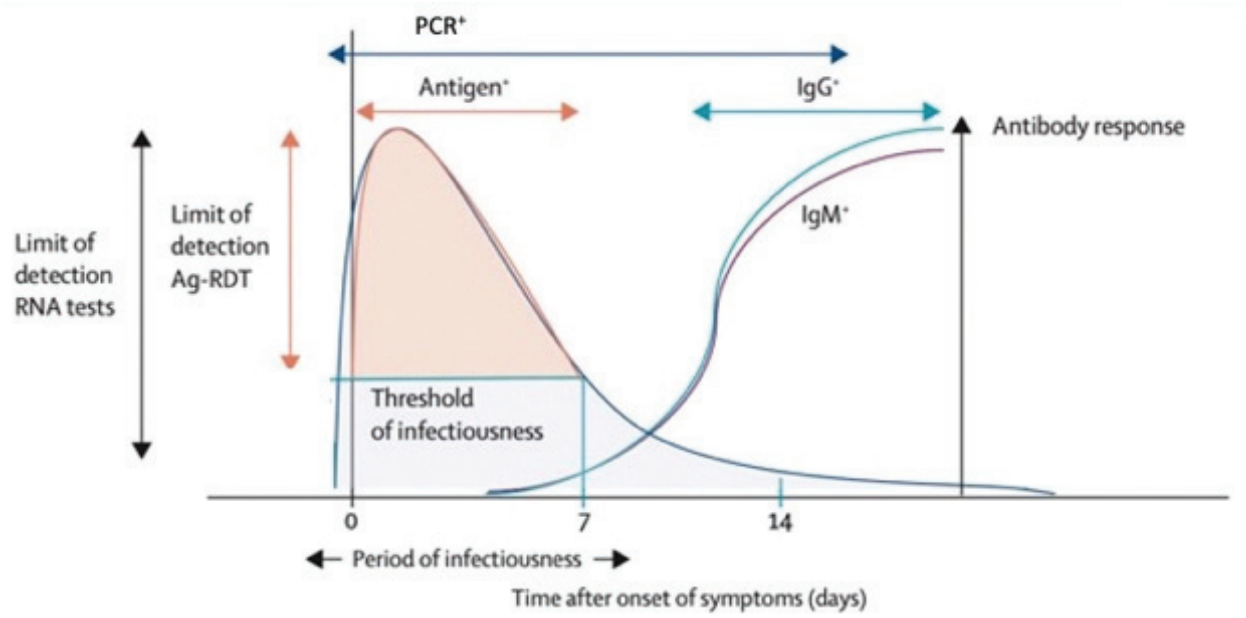
Clinical manifestations

- The incubation period of SARS-CoV-2 ranges from 2-14 days with an average of 3 days.
- Pediatric COVID-19 manifests in a wide clinical spectrum, ranging from asymptomatic infection to symptomatic disease which overlaps with common clinical syndromes such as upper respiratory tract infection, bronchiolitis, pneumonia, viral croup, asthma, febrile seizures and acute gastroenteritis.
- Clinicians should have a low threshold for suspicion since the symptoms and clinical manifestations of COVID-19 are non-specific, especially when there are high rates of community transmission, or if the child is in close contact with someone with confirmed or suspected infection.

Diagnosis

- The diagnosis of acute SARS-CoV-2 infection can be made either through a reverse transcription polymerase chain reaction (RT-PCR) assay or antigen detection test.
- RT-PCR has higher sensitivity, but antigen detection tests are more accessible and convenient. Antigen tests are also less costly and have a shorter turnaround time.
- Upper respiratory samples (via a nasopharyngeal swab, nasopharyngeal aspirate or combined nasal/oropharyngeal swab) are the primary specimens for SARS-CoV-2 viral tests.
  - Samples from the endotracheal aspirate may be used for ventilated patients.
  - Saliva samples can be a convenient point-of-care test, but results should be interpreted with caution, especially if the test was conducted without clinical supervision. Clinicians should also be mindful of potential reliability issues with the wide variety of brands available in the market.
- Clinical pointers:
  - Clinicians who use RT-PCR testing should be aware that the RT-PCR may remain positive for a considerable period even after the child has recovered from the infection and may incorrectly attribute an unrelated current infection to COVID-19.
  - Clinicians who use antigen testing should be aware of the lower sensitivity compared to RT-PCR, and negative antigen tests performed may warrant confirmation with additional testing if the clinical suspicion remains high.
  - Potential false-negative results could occur caused by low viral loads, improper sampling timing (too early or too late), poor technique, or sample degradation during sample transport.
  - Testing for other respiratory viruses (eg influenza and RSV) may be warranted depending on the clinical presentation as coinfection of SARS-CoV-2 with other respiratory pathogens can occur.

- Serology testing have limited utility for diagnosis in the acute setting since antibodies towards SARS-CoV-2 generally take several weeks to develop.
  - Serology tests have the highest sensitivity three to four weeks after the onset of symptoms.
  - Therefore, serology testing would be useful for assessing patients with suspected MIS-C, for determining past or recent infection, and for sero-surveillance studies.
  - If a serologic test was performed on an individual who has received a spike protein COVID-19 vaccine, it is best to perform a test that detects antibodies to antigens other than the spike protein, such as the nucleocapsid protein.
- Full blood count findings in children with COVID-19 are non-specific, but may include mild abnormalities in white blood cell count (either increased or decreased lymphocyte counts).
- Inflammatory markers such as C-reactive protein (CRP) might not be raised even in children with severe COVID-19 pneumonia.
- Radiologic findings in children with COVID-19 include unilateral or bilateral infiltrates on chest radiograph, which can be indistinguishable from pneumonia due to other respiratory viral pathogens.



Timeline for optimal use of different diagnostic tests for COVID-19 detection and host response. (RW Peeling et al. Lancet 2022).

Classification of severity

- COVID-19 was largely described as a respiratory illness early in the pandemic. However, the awareness of its clinical manifestations has evolved as the pandemic progressed.
- Previous classifications of disease severity largely focused on the respiratory system, with limited consideration for the severe manifestations of other organ systems. An international consensus for severe disease in children is lacking.
- The following definition was revised from the WHO Clinical Progression scale to reflect the patient trajectory and resource use over the course of the clinical illness and has been used in a large-scale study among Malaysian children.

Asymptomatic
- No symptoms
- Positive SARS-CoV-2 test by antigen detection or RT-PCR assay

Mild disease
- Presence of symptoms
- No clinical signs of pneumonia or dehydration
- If hospitalized, no medical intervention is required apart from clinical surveillance

Moderate disease
- Presence of symptoms
- Clinical signs of pneumonia or dehydration present
- Patients who require medical intervention during hospitalization, including nasal oxygen support, IV hydration therapy, steroids, blood investigation monitoring, and empirical antibiotic therapy.
- No manifestations related to severe disease

Severe disease
- Mild or moderate clinical features, plus any manifestations that suggest disease progression:
  - Respiratory distress with need for high flow nasal cannula oxygen, non-invasive ventilation, or mechanical ventilation
  - Compensated or decompensated shock
  - Severe organ involvement such as myocarditis, acute kidney injury, encephalitis, severe hepatitis, coagulopathy

Management

- COVID-19 generally runs a mild clinical course in most children. A study among Malaysian children revealed that severe pneumonia presents early in the course of illness, with a median of 3 days of illness before hospitalization.
- The decision for hospital admission should be guided by clinical evaluation, underlying comorbidities, social and geographical factors, and phase of illness.
- Patients should be isolated in the highest level of isolation available in the ward. Airborne precautions would be required if the child receives nebulized medications, high-flow oxygen, non-invasive or mechanical ventilation.
- The management of pediatric COVID-19 is largely symptomatic with consideration of the presenting clinical syndrome such as upper respiratory tract infection, bronchiolitis, pneumonia, exacerbation of asthma, croup, gastroenteritis, or febrile seizures.
- Corticosteroids:
  - May be beneficial in patients with severe respiratory disease on mechanical ventilation.
  - Dose of Dexamethasone (IV or oral): 0.15mg/kg/day (max dose 6mg) for a total of 7-10 days.
- Other medications:
  - Venous thromboembolism prophylaxis may be required in patients who are obese and mechanically ventilated.
  - Intravenous immunoglobulin (IVIG) would be beneficial in patients who meet the criteria for MIS-C.
  - Antivirals such as Remdesivir may be considered for high-risk patients who present in the early viremic phase after consultation with the pediatric infectious disease specialist.
  - Paxlovid (nirmatrelvir/ritonavir) has not been licensed for children under 12 years of age at time of writing.
  - Other immunomodulatory agents (eg anti IL-1, anti IL-6) may be considered for patients with severe disease after consultation with the pediatric infectious disease specialist.
- Immunization:
  - Pediatric vaccination for COVID-19 is discussed separately (refer to National pediatric COVID-19 vaccination guidelines).

Multisystem Inflammatory Syndrome in Children (MIS-C)

- MIS-C is an uncommon but serious complication associated with COVID-19.
- The clinical features of MIS-C may mimic Kawasaki disease, toxic shock syndrome or viral myocarditis. These include persistent fever, rash, hypotension, gastrointestinal symptoms, myocarditis and raised Empiric antibiotics may be initiated for patients with MIS-C, with the choice of antibiotics depending on the local institution practices.
- A baseline echocardiogram should be performed for all cases of MIS-C. The echocardiogram can be repeated 6 weeks later if the initial results were normal but would need to be repeated earlier if the initial results were abnormal or if there is evidence of clinical deterioration.

Treatment of MIS-C

- Intravenous immunoglobulin:
  - Dose: 2g/kg infused over 8-12 hours.
  - For children who are obese, the dose should be based on the ideal body weight (max dose 100g/day).
  - For patients with significant cardiac dysfunction, IVIG may be infused in divided doses over two days to reduce the risk of fluid overload.
  - Blood samples for SARS-CoV-2 antibodies should be collected prior to administration of IVIG.
  - Treatment with IVIG alone may be reasonable in patients with mild disease without evidence of cardiovascular compromise.
  - Repeated doses of IVIG are generally not recommended due to the risk of volume overload and hemolytic anemia.

- Steroids:
  - Glucocorticoids can be used in combination with IVIG for patients with moderate to severe manifestations, or as second line therapy in mild cases when there is inadequate response to IVIG (eg persistent fever, rising inflammatory markers), or as monotherapy in mild cases when IVIG is unavailable.
  - Glucocorticoid therapy can be initiated with IV Methylprednisolone 1-2mg/kg/day in two divided doses (max daily dose 60-80mg).
  - This can be converted to an equivalent oral dose of Prednisolone once the patient improves clinically and tapered off over two to three weeks.
  - In life-threatening or refractory cases, pulsed IV Methylprednisolone 10-30 mg/kg/day (max daily dose 1g) for one to three days may be used.

- Aspirin for most patients:
  - Dose: 3-5mg/kg/day, max 81mg/day
  - Duration: 4-6 weeks or until normalization of inflammatory markers and LV function.
  - Consult pediatric cardiologist for recommended dose and duration of aspirin if coronary artery aneurysm present.
  - Contraindications: patients with platelet counts < 80,000, active bleeding, or having intercurrent viral infection (eg varicella).

- VTE prophylaxis:
  - Recommended in patients with severe disease who at high risk for venous thromboembolism (eg obesity, malignancy, family history of thrombophilia, severe cardiac dysfunction, central venous catheters, immobility)
  - In young children, the decision is made on a case-to-case basis.
  - When VTE is used, LMWH is the preferred agent. Dose:
    - <60kg: SC Enoxaparin 0.5mg/kg bd
    - >60kg: SC Enoxaparin 30mg bd

- Contraindications:
  - Impaired renal function with creatinine clearance <30
  - Active bleeding or known bleeding disorder
  - Significant coagulopathy (INR >2, PTT > 40)
  - Severe thrombocytopenia (Platelet <25k)
  - Lumbar puncture in the last 6 hours
  - Epidural or paraspinal hematoma
  - Recent surgery in the last 72 hours
- Non-pharmacologic strategies (eg pneumatic compression devices, early mobilization) may be used if pharmacologic thromboprophylaxis is contraindicated.

- GI prophylaxis:
  - Omeprazole can be given until the completion of steroid therapy.

- Refractory or rapidly progressive disease
  - Consult the pediatric infectious disease, pediatric rheumatology or pediatric intensive care specialist for other treatment options with biologics (IL-1, IL-6 or TNF inhibitors)

Section 15

DERMATOLOGY

Chapter 95:
Atopic Dermatitis

Introduction

- A chronic inflammatory itchy skin condition that usually develops in early childhood and follows a remitting and relapsing course. It often has a genetic component.
- Leads to the breakdown of the skin barrier making the skin susceptible to trigger factors, including irritants and allergens, which can make the eczema worse.
- Although not often thought of as a serious medical condition, it can have a significant impact on quality of life.

Diagnostic criteria
Major features (must have 3) Hanifin and Rajka criteria
Pruritus
Typical morphology and distribution • Facial and extensor involvement in infancy, early childhood • Flexural lichenification and linearity by adolescence
Chronic or chronically relapsing dermatitis
Personal or family history of atopy (asthma, allergic rhinoconjuctivitis, atopic dermatitis)
Minor / less specific features
Xerosis
Preauricular fissures
Icthyosis / palmar hyperlinearity / keratosis pilaris
Ig E reactivity
Hand/foot dermatitis
Cheilitis
Scalp dermatitis (cradle cap)
Susceptibility to cutaneous infection (e.g. Staph. aureus and Herpes simplex virus)
Perifollicular accentuation (especially in pigmented races)

Triggering factors

- Infection: Bacterial, viral or fungal
- Emotional stress
- Sweating and itching
- Irritants: Hand washing soap, detergents
- Extremes of weathers
- Allergens
- Food: egg, peanuts, milk, fish, soy, wheat.
- Aeroallergens: house dust mite, pollen, animal dander and molds.

Management

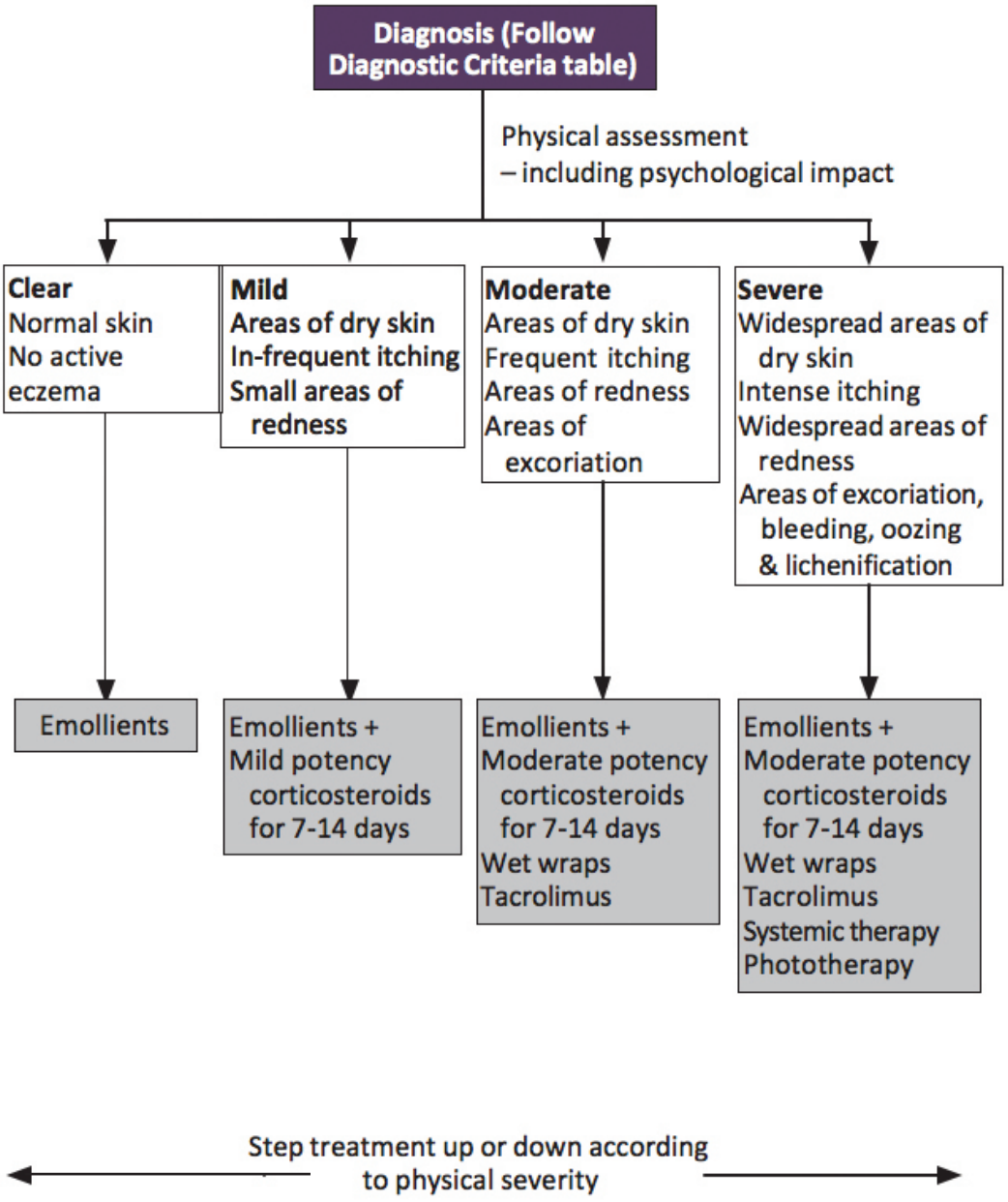
- Tailor the treatment of atopic dermatitis individually depending on
  - The severity.
  - Patient's understanding and expectation of the disease and the treatment process.
  - Patient's social circumstances.
- Comprehensive patient education is paramount, and a good doctor-patient relationship is essential for long-term successful management.
- In an acute flare-up of atopic dermatitis, evaluate for the following factors:
  - Poor patient compliance
  - Secondary infection: bacterial (e.g. Staphylococcus aureus), viral
  - (e.g. herpes simplex virus)
  - Persistent contact irritant/allergen.
  - Physical trauma, scratching, friction, sweating and adverse environmental factors.

Bath & Emollients

- Baths soothe itching and removes crusting. They should be lukewarm and limited to 10 minutes duration. Avoid soaps. Use soap substitute
  e.g. aqueous cream or emulsifying ointment.
- Moisturizers work to reduce dryness in the skin by trapping moisture.
- Apply to normal and abnormal skin at least twice a day and more frequently in severe cases.
- Emollients are best applied after bath. Offer a choice of unperfumed emollients and suitable to the child's needs and preferences,
  e.g. Aqueous cream, Ung. Emulsificans, and vaseline.

N.B. Different classes of moisturizer are based on their mechanism of action, including occlusives, humectants, emollients and protein rejuvenators. In acute exudation form KMNO4 1:10,000 solutions or normal saline daps or soaks are useful – as mild disinfectant and desiccant.

USE STEPPED CARE PLAN APPROACH FOR TREATMENT MEASURES



Topical Corticosteroids

- Topical corticosteroid is an anti-inflammatory agent and the mainstay of treatment for atopic eczema.
- Topical steroid are often prescribed intermittently for short term reactive treatment of acute flares and supplemented by emollients.
- Choice depends on a balance between efficacy and side-effects.
- The more potent the steroid, the more the side-effect.
- Apply steroid cream once or twice daily.
- Avoid sudden discontinuation to prevent rebound phenomenon.
- Use milder steroids for face, flexures and scalp.
- Amount of topical steroid to be used – the finger tip (FTU) is convenient way of indicating to patients how much of a topical steroid should be applied to skin at any one site. 1 FTU is the amount of steroid expressed from the tube to cover the length of the flexor aspect of the terminal phalanx of the patient's index finger.
- Number of FTU required for the different body areas.
  - 1 hand/foot/face 1 FTU
  - 1 arm 3 FTU
  - 1 leg 6 FTU
  - Front and back of trunk 14 FTU
- Adverse effect results from prolonged use of potent topical steroids.
- Local effects include skin atrophy, telangiectasia, purpura, striae, acne, hirsutism and secondary infections. Systemic effects are adrenal axis suppression, Cushing syndrome.

Steroid Potency	
Potency of topical steroid	**Topical steroid**
Mild	Hydrocortisone cream/ointment 1%
Moderate	Bethametasone 0.025% (1:4dilution) Eumovate (clobetasone butyrate)
Potent	Bethametasona 0.050% Elomet (mometasone furoate)
Super potent	Dermovate (clobetasone propionate)

Systemic Therapy

Consist of:

- Relief of pruritus
- Treatment of secondary infection, and
- Treatment of refractory cases

Relief of Pruritus

- Do not routinely use oral antihistamines.
- Offer a 1-month trial of a non-sedating antihistamine to:
  - Children with severe atopic eczema
  - Children with mild or moderate atopic eczema where there is severe itching or urticaria.
- If successful, treatment can be continued while symptoms persist.
- Review every 3 months.
- Offer a 7–14 day trial of a sedating antihistamine to children over 6 months during acute flares if sleep disturbance has a significant impact. This can be repeated for subsequent flares if successful.

Treatment of secondary infection

- Secondary bacterial skin infection is common and may cause acute exacerbation of eczema. Systemic antibiotics are necessary when there is evidence of extensive infection.
- Commonly Staphyloccus aureus.
- Useful in exudation form where *superinfection occurs*.
- Choice:
  - Oral cloxacillin 15mg/kg/day 6 hourly for 7-14 days, or
  - Oral Erythromycin / cephalosporin
- Secondary infection can arise from Herpes simplex virus causing *Eczema Herpeticum*. Treatment using antiviral e.g. Acyclovir may be necessary.

Refractory cases

- Refractory cases do not response to conventional topical therapy and have extensive eczema. Refer to a Dermatologist (who may use systemic steroids, interferon, Cyclosporine A, Azathioprine, Dupilumab, JAK inhibitors or/and phototherapy).

Other Measures

- Avoid woolen toys, clothes, bedding.
- Reduce use of detergent (esp. biological).
- BCG contraindicated till skin improves.
- Swimming is useful (MUST apply moisturizer immediately upon exiting pool).
- Avoid Aggravating Factors.

For Relapse

- Check compliance.
- Suspect secondary infection – send for skin swab; start antibiotics.
- Exclude scabies.
- For severe eczema, emollient and topical steroid can be applied under occlusion with 'wet wrap'. This involves the use of a layer of wet, followed by a layer of dry Tubifast to the affected areas i.e. limbs and trunk. The benefits are probably due to cooling by evaporation, relieving pruritus, enhanced absorption of the topical steroid and physical protection of the excoriation.

Prognosis

- Tendency towards improvement throughout childhood.
- Two third will clear by adolescence.

Chapter 96:
Common Cutaneous Infections

- This Chapter will include 4 common cutaneous infections
  - Viral - Molluscum Contangiosum, Viral Wart
  - Bacterial - Impetigo
  - Fungal - Tinea Capitis

Introduction

1. Molluscum Contangiosum
   - Common and benign viral skin infection caused by a member of the pox virus, called molluscum contangiosum virus (MCV).
   - Transmitted via autoinoculation, physical contact with infected person, contaminated fomite or sexual contact.
   - Incubation period: 2 weeks to 6 months
   - Clinical features:
     - Solitary or multiple, grouped, pearly white, or flesh-coloured, dome-shaped papules with central umbilication
     - Lesions vary in size from 1mm-10mm; giant lesions are primarily seen in HIV patients.
     - commonly found in areas with friction with clothing such as trunk and abdomen.
     - Can persist from weeks to months.
     - BOTE (Beginning of the end) sign refers to skin redness and swelling of a molluscum lesion when the lesion starts to regress. This phenomenon is likely due to a host immune response towards the infection and could be mistaken as bacterial superinfection.
   - Diagnosis is generally straightforward based on clinical features. Expression of a white cheesy material by lateral pressure on a lesion is classic.
   - Treatment options:
     1. **Wait and see approach** -in mild infections (not bothersome to the child or very few lesions) as spontaneous resolution may occur.
        - Resolution usually takes 6-9 months but can persist for a few years.
     2. **Topical medications- could be offered as first line therapy and may take weeks to months to work:**
        i. Keratolytic agent: Salicylic acid 10% -20% cream OD
        ii. Irritating agent: Benzoyl peroxide 10% cream, Retinoid cream e.g. tretinoin 0.05% OD
        iii. Alkaline compound which dissolves keratin: Hydrogen peroxide 1-10% OD
        iv. Vesicant agent: Cantharidin cream (blistering agent)- once in every 3-4 weeks
        v. Immunomodulator: Imiquimod 5% 3 times a week

2. Viral Warts (Verrucae)
   - Common and benign viral infection of the skin and mucosae in children.
   - Caused by non-malignant strains of human papillomavirus (HPV), except for sexually transmitted ones (type 16 and 18) which are associated with cervical, vulval and penile cancer.
   - Transmitted via autoinoculation, physical contact with infected person, contaminated personal belongings, vertical transmission, or sexual contact.
   - Incubation period: 1 to 6 months
   - Clinical features:
     - Vary based on location (palmoplantar, periungual, respiratory, oral, anogenital etc.) and subtypes.
     - Subtypes of viral warts are as follows:
       - Common warts, also known as verruca vulgaris (HPV types 2 and 4)- present as hyperkeratotic papules with rough, irregular surface and can occur in almost any part of the body
       - Filiform/digitate warts- usually seen on the face, eyelids, lips, nares and neck. They are long and thin lesion protruding from the skin surface.
       - Flat warts, also known as verrucae planae or plane warts (HPV types 3 and 10)- present as smooth, flesh-coloured or hyperpigmented papules, mainly distributed over sun-exposed areas such as the face, the dorsum of hands.
       - Deep plantar warts/myrmecia (HPV types 1,4,7 and 10)- present as small papules and progress to deep lesion with a rough keratotic surface. It is usually surrounded by a well-demarcated rim of compressed keratin.
       - Cystic warts (HPV 60,63 and 65)- appear as a nodule on the weightbearing surface of the sole. The surface is usually smooth but may become hyperkeratotic.
       - Mosaic warts (HPV 1,4,7 and 10)- formed by smaller plantar warts which tend to coalesce over the palms or soles.
       - Condyloma acuminata also known as anogenital warts-present as multiple flesh-coloured, soft, verrucous papules which often are “mirror image” on each side of the anus. Other areas of involvement include the penile glans, shaft, scrotum, and vulva.
     - Although self-limiting in immunocompetent individuals, lesions can persist from months to years.
     - Can be painful.
   - Diagnosis is generally evident based on clinical features.
   - In a child diagnosed with condyloma acuminata, a thorough history taking, and physical examinations are important to look for evidence of sexual abuse.
   - Treatment options:
     1. **Wait and see approach** -most lesions are reported to have spontaneous resolution within 2 years.
     2. **Manual filing and pairing**- using a scalpel.
     3. **Topical medications** -could be offered as first line therapy and may take weeks to months to work:
        i. Keratolytic agents: Salicylic acid 10% -20% cream OD or applied nightly under occlusion using a tape, duct tape or plaster.
        ii. Irritating agents: Retinoid cream e.g. tretinoin 0.05% OD -might be more useful in flat warts.
        iii. Cytotoxic chemotherapy: 5-flurouracil OD -suitable for facial flat warts, Podophyllotoxin 0.5% cream OD
        iv. Immunomodulator: Imiquimod 5% 3 times a week for anogenital warts.

4. **Physical destructive methods:**
   i. Cryotherapy
   ii. Curettage
   iii. Laser therapy
   iv. Electrocautery
   v. Surgery
5. **Oral medication-** reserved for patients with extensive lesions not responding to first line treatment and other destructive methods:
   i. Cimetidine 30-40mg/kg/day in 3 divided doses-advised to discuss with a dermatologist.
6. **Intralesional immunotherapy-** suitable for periungal and subungal lesions:
   i. Candida – intralesional injection of compound derived from purified extract of Candida albicans
   i. Bleomycin

- Refer to a paediatric dermatologist in the following circumstances:
  - Lesions persist more than 1 year or become more widespread despite multiple courses of treatment.
  - Lesions in immunocompromised patients.
  - Anogenital distributed lesions

Bacterial infection:

1. Impetigo
   - contagious superficial skin infection found most commonly in children aged between 2 to 5 years of age
   - 2 classic forms: bullous and nonbullous impetigo
   - Transmitted via autoinoculation through fingers, towels or clothing.

	NonBullous impetigo (70% of cases)	Bullous impetigo(30% of cases)
Age group	• More common in Infants and children	• More common in neonates and infants
Causative organism	• group A β-hemolytic streptococci(GAS)– majority of cases • *Staphylococcus. Aureus* • *Or both*	• *Staphylococcus Aureus- majority of cases*
Distribution	• Exposed areas e.g. face, neck and extremities	• Intertriginous areas e.g. axillae, perineal and neck folds • Convex surfaces e.g. thigh, buttock, lower abdomen although can spread rapidly to other parts of body
Clinical features	• begins with erythematous papule or pustule that soon develops into thin-roofed vesicle surrounded by a narrow rim of erythema. • The vesicle ruptures easily with release of a thin, cloudy, yellow fluid that subsequently dries, forming a honey-coloured crust, the hallmark of nonbullous impetigo	• Presents as flaccid, thin-walled bullae or tender, shallow skin erosion surrounded by a remnant of the blister roof. • Localised form of Staphylococcal Scalded Skin syndrome (SSSS).
Clinical features	• Topical antibiotic(with both Staph. Aureus and GAS coverage) for localized disease without systemic symptoms: 1. Fusidic acid 2% cream- apply to affected skin 3 times a day for 7 -14 days 2. Mupirocin cream or ointment- apply to affected skin 3 times a day for 7-14 days *Tips: Remove the crust using warm water before applying topical antibiotic.* • Oral antibiotic reserved for extensive disease: 1. Oral cephalexin 25mg/kg/dose BD or 12.5mg/kg/dose QID 2. Oral cefuroxime 15 mg/kg /dose BID 3. Oral amoxicillin & clavulanate 25mg/kg/ dose (based on Amoxicillin dose) divided dose 4. Oral cloxacillin 25-50mg/kg/dose QID 5. Oral clindamycin 6. 3-6mg/kg/dose QID (If methicillin-resistant S. aureus is suspected or proven) • Total duration of antibiotic of 7 days is sufficient and can extend to 14 days if needed.	• Topical antibiotic not recommended. • Should treat using systemic antibiotics with good coverage for Staph. Aureus and GAS) as per non-bullous impetigo. **Reminder: In view of the relative prevalence of staphylococcal impetigo, non-β-lactamase penicillins such as amoxicillin and penicillin V are less desirable treatment choices unless the impetigo is proven to be exclusively due to GAS.*

Fungal Infection:

1. Tinea Capitis
   - Commonest superficial fungal(dermatophytes) infection of the skin and hair of the scalp.
   - Primarily affect prepubertal children.
   - Dermatophytes are keratinophilic fungi which belong to 3 genera: T*richophyton, Microsporum, and Epidermophyton.*
   - Trichophyton Tonsurans is currently the most common cause of tinea capitis worldwide but *Microsporum Canis* is the commonest in Asian countries.
   - Ways of transmission:
     - Anthropophilic- human
     - Zoophilic - animal
     - Geophilic -soil
     - Indirectly through sharing fomites: hats, hairbrushes, etc
   - Different clinical presentation may arise depending on the causative organism, the type of hair invasion, and the specific host inflammatory response.
   - Types of hair invasion:
     1. endothrix- the fungus grows completely within the hair shaft and the hyphae are converted to arthroconidia (spores) within the hair while the cuticle surface of the hair remains intact.
     2. ectothrix - the hyphae of the fungus destroy the hair cuticle and grow around the exterior of the hair shaft.
     3. favus -The production of hyphae are parallel to the long axis of the hair shaft. When the hyphae degenerate, long tunnels are left within the hair shaft.
   - Clinical presentations:
     - Various clinical manifestations found depending on the causative dermatophyte, the type of hair invasion, as well as the host inflammatory response.

Clinical features	Remarks
Alopecia	One or multiple patches on the scalp
Scaling	*Scales around the hair follicles*
Erythema	Localized or widespread
Pustules	Scattered and multiple
“black dots”	Alopecia with hair shafts broken off at surface of skin, resulting in multiple black dots on the scalp
Kerion	Boggy, tender plaque with pustules and purulent discharge; represents a vigorous host immune response
Scarring	Rarely seen when untreated; usually follows kerion
Favus	Yellow, cup-shaped crusts around the hair
Cervical lymphadenopathy	Multiple, usually occipital
Dermatophyid (Id) reaction	Widespread, papular or papulovesicular eruption; extremity-predominant; usually seen after initiation of therapy; must be recognized as distinct from true drug reaction

- Investigations:
  1. Direct microscopic examination of skin scrapings and hair- strands of hairs including the roots and skin scrapings are mounted in 10%–20% potassium hydroxide (KOH) solution onto a glass slide. The slide is gently heated and microscopically examined for hyphae and spores.
  2. Fungal culture of hair and skin scrapings - Plucked hair fragments and skin scrapings are placed directly on a culture medium.
  3. Wood's lamp examination- When ectothrix dermatophytes e.g. Microsporum species are examined under a Wood's lamp the scalp hair and skin show a bright yellow-green fluorescence.
- Treatment options:
  - Advise against sharing personal belonging and maintain good hand hygiene.
  - Systemic antifungal treatment are the choice of treatment because topical antifungal agents do not penetrate down to the hair follicle root.
  - Adjunctive therapy: ketoconazole 2%, selenium sulphide 1% or ciclopirox 1% shampoo 3 times per week.
  - Dosing for pediatric regimens for the treatment of tinea capitis:

Antifungal agent	Dosage	Duration of treatment
Griseofulvin		6–12 weeks or longer until fungal cultures are negative. First line treatment especially for Microsporum sp.
Microsize	20–25 mg/kg/day OD	
Ultramicrosize	10–15 mg/kg/day OD	
Terbinafine	10–20 kg: 62.5 mg/day OD 20–40 kg: 125 mg/day OD >40 kg: 250 mg/day OD	Trichophyton spp.: 4 weeks Microsporum spp.: 8–12 weeks
Itraconazole	3- 5 mg/kg/day OD	Daily dosing: 2–6 weeks Pulse regimen (1 week on with 3 weeks off): 2–3 pulses (range: 1–5)
Fluconazole	5–6 mg/kg/day	3–6 weeks

- Kerion:
  - an inflammatory fungal infection of the hair follicle of the scalp, characterized by boggy swelling, purulent discharge, alopecia, and lymphadenopathy.
  - May result in residual scarring alopecia.
  - Could be mistaken as a bacterial infection.
  - Treatment option:
    - As per Tinea Capitis and may need to be extended.
    - Antibiotic therapy is not recommended unless there is evidence of secondary bacterial infection due to trauma.
    - No role of surgical incision and drainage.
    - Use of oral steroids remains controversial and is not generally recommended as a routine care.
- Follow up:
  - Repeat culture of skin scraping and plucked hair after 4 weeks
  - Continue treatment for another 2 weeks if follow-up culture result is positive.
  - Treatment could be discontinued once the culture result is negative.
  - For patients who demonstrated no clinical improvement (lesion expanding in size, no regrowth of hair and presence of new lesion), consider increasing the dose of current agent or to extend duration of therapy, or to switch to another antifungal agent.

Chapter 97:
Infantile Haemangiomas (IH)

- IH are the most common benign vascular tumour of infancy.
- Clinical course is marked by rapid growth during early infancy followed by slower growth, then gradual involution. (80% of IH size was reached during the early proliferative stage at a mean age of 3 months and 80% of IH completed the early proliferative growth phase by 5 months old).[1]
- A minority cause functional impairment and even more cause psychosocial distress.
- Despite involution, some are left with residual skin changes (eg. thinned skin, scar, fibrofatty tissue and telangiectasias).
- Diagnosis can be made clinically.
    - Imaging of IHs is not indicated for diagnostic purposes unless the lesion has an atypical appearance or behaviour.
    - Imaging is indicated if there are ≥5 cutaneous IHs,(abdominal ultrasonography) or associated anatomic abnormalities are suspected (ultrasound or MRI of relevant structures).[2]

Clinical subtypes of haemangiomas:

- IH can usually be classified as localized, segmental, indeterminate, and multifocal.
- Clinical appearance of IH depends on the level(s) of the skin affected.
- Superficial haemangiomas involve the superficial dermis and appear as bright red “strawberry” lesions, whereas deep haemangiomas involve the deep dermis and subcutis resulting in a tumor with a bluish colour.
- Mixed haemangiomas, involve the dermis and subcutis and demonstrate clinical features of both types.[3]

Management

Consult early (by 1 month of age) for lesions that are potentially high risk because of the following associations:

- potential for disfigurement (the most common reason treatment is needed);
- life-threatening complications;
- functional impairment;
- ulceration; and
- underlying abnormalities

Table 1: High-Risk IH[2]

IH Clinical Findings	IH Risk
1. Life-threatening	Obstructive airway haemangiomas
a. "Beard-area" IH	Liver haemangiomas, cardiac failure, hypothyroidism
b. ≥5 cutaneous IHs	
2. Functional impairment	
a. Periocular IH (>1 cm)	Astigmatism, anisometropia, proptosis, amblyopia
b. IH involving lip or oral cavity	Feeding impairment
3. Ulceration	
a. Segmental IH: IH of any size involving any of the following sites: lips, columella, superior helix of ear, gluteal cleft and/ or perineum, perianal skin, and other intertriginous areas (eg, neck, axillae, inguinal region)	Increased risk of ulceration PHACE syndrome LUMBAR syndrome
4. Associated structural anomalies	High risk of scarring and/or permanent disfigurement
a. Segmental IH of face or scalp	Risk of disfigurement via distortion of anatomic landmarks and/or scarring and/or permanent skin changes
b. Segmental IH of lumbosacral and/or perineal area	
5. Disfigurement	
a. Segmental IH, especially of face and scalp	Permanent alopecia (especially if the haemangioma becomes thick or bulky); profuse bleeding if ulceration develops (typically more bleeding than at other anatomic sites)
b. Facial IH (measurements refer to size during infancy): nasal tip or lip (any size) or any facial location ≥2 cm (>1 cm if ≤3 mo of age)	Greater risk of leaving permanent scarring and/or permanent skin changes depending on anatomic location
c. Scalp IH >2 cm	
d. Neck, trunk, or extremity IH >2 cm, especially in growth phase or if abrupt transition from normal to affected skin (ie, ledge effect); thick superficial IH (eg, ≥2 mm thickness)	Permanent changes in breast development (e.g., breast asymmetry) or nipple contour
e. Breast IH (female infants)	

Treatment

- Most haemangiomas require no treatment.
- Active non-intervention is recommended in order to recognize those that may require treatment quickly.
- Treatment should be individualized depending on:
  - age of the patient,
  - size of the lesion(s),
  - location,
  - presence of complications and rate of growth or involution at the time of evaluation.
- The potential risk(s) of treatment is carefully weighed against the potential benefits.
- Educate caregivers of infants with an IH about the condition, including the expected natural history and its potential for causing complications or disfigurement.[2]

High risk haemangiomas (refer Table 1)

- High risk haemangiomas should be referred by primary care doctors for evaluation and treatment early (by 4 -6 weeks of life) and treatment should be started by paediatricians with experience in managing IH.

Oral propranolol is the first-line therapy

- Starting dose of 1 mg/kg per day in 2 or 3 divided doses.
- Increase to a target dose of 2 mg/kg per day (within 7 days) unless there are comorbidities (eg, PHACE syndrome) or adverse effects (eg,sleep disturbance, progressive IH ulceration) that necessitate a lower dose.
- Can increase further to 3mg/kg per day if response inadequate.
  *If PHACE syndrome patients who are at high risk of stroke require treatment with propranolol, use the lowest effective dose, slowly titrate the dose, and administer the drug 3 times daily. (to minimize abrupt changes in blood pressure)2

  Duration: Propranolol should be continued until 9 to 12 months old. Rebound growth during tapering or after stopping the medication may occur in 10% to 25% of patients and can occur even after 6 months of therapy.

Patient education:
- Propranolol be administered with or after feeding and that doses be held at times of diminished oral intake or vomiting to reduce the risk of hypoglycemia.
- Evaluate patients for and educate caregivers about potential adverse effects of propranolol, including sleep disturbances, bronchial irritation, and clinically symptomatic bradycardia and hypotension.[2]

Monitoring
- Routine ECG is not required.
- ECG screening only in the following children
  1. in infants with a baseline heart rate below normal for age
  2. in infants with a family history of congenital heart conditions or arrhythmias or with a maternal history of connective tissue disease
  3. when there is a history of arrhythmia or one is auscultated during examination.[2]
- The majority of infants do not require any monitoring when starting propranolol. Patients younger then 4 weeks of adjusted gestational age, pre-term infants, and those with feeding difficulties or other additional disorders need measurement of heart rate and blood pressure for 2 hours in hospital after the first dose, and if the dose is doubled or trebled.[4]

Other systemic therapy:
- Prednisone and prednisolone are second-line agents that may be used if there are contraindications to or an inadequate response to propranolol.
- Topical timolol may be prescribed for thin and/or superficial IHs.
- Intralesional steroids, surgery and laser therapy may be beneficial in selected IHs.[2]

Surgery
- The benefits and risks of surgery must be weighed carefully, since the scar may be worse than the results of spontaneous regression.
- Surgery is especially good for small, pedunculated haemangiomas and occasionally, in cases where there may be functional impairment. It is usually used to repair residual cosmetic deformities.
- Generally, it is recommended that a re-evaluation be done when the child is 4 years old, in order to assess the potential benefit of excision.[6]

Chapter 98:
Scabies

Introduction

- Scabies is caused by the human itch mite Sarcoptes scabiei var. hominis.
- The lifecycle of the sarcoptes lasts for 4-6 weeks.
- Mites burrow into human skin and lay their eggs, which later hatch and grow into adults .
- Any part of the body may be affected, and its transmission is by skin to skin contact.

Clinical features

Symptoms

- Intense generalised pruritus that is usually worse at night
- The pruritus is due to a delayed type-IV hypersensitivity reaction to the mite, and mite products (faeces and eggs)
- The main symptom takes 2 - 6 weeks to develop after primary infestation.
- History of itching in family members or close contacts concurrently or in the recent past

Signs

- Characteristic burrow, which is a linear intra-epidermal tunnel produced by the moving mite. It appears as short wavy greyish/ white thread like elevations.
- Classic sites: interdigital folds, wrists, elbows, umbilical area, genital area and feet.
- In infants, burrows are common on the palms and soles, and sides of the feet. They can also be found on the heads of infants particularly post auricular folds.
- Nodular Scabies - papules or nodules seen at the site of mite infestation often affect the scrotum, axillae, back, or feet of children.
- Crusted or Norwegian Scabies - seen in young infants or immunosuppressed patients. Widespread mite infestation causes hyperkeratotic and/or crusted generalized rash.

Diagnosis

- Scrapings taken from burrows examined under light microscopy may reveal mites.
- A history of scabies in a family member or contact with scabies should be sought out specifically.
- Dermatoscopy and digital photography are non-invasive alternative methods for identifying the presence of scabies mites.

Treatment - General advice

- Topical treatment must be applied to the entire skin surface, from jawline downwards including all body folds, groin, navel and external genitalia, as well as the skin under the nails (especially crusted scabies).
- At any time during treatment, medications should be re-applied if it is washed off i.e. after hand washing.
- Patients with scabies and their close physical contacts, even without symptoms, should receive treatment at the same time. Prescriptions must be provided for all household members.
- After completion of treatment, patients should use fresh, clean bedding and clothing. If possible, potentially contaminated clothes and bedding should be washed at high temperature (>50°C) or kept in a plastic bag for up to 72 hours, because mites that are separated from the human host will die within this time period.
- Only allow the patient to go to school 24 hours after the start of treatment.

- The pruritus of scabies may be treated with diphenhydramine or other antipruritic medication if necessary. The pruritus can persist up to three weeks post treatment even if all the mites are dead, and therefore is not an indication to retreat unless live mites are identified.
- Any superimposed bacterial skin infection should be treated at the same time as the scabies treatment. Topical antibiotic is not indicated in patients who are already treated with systemic antibiotics

Treatment- drug therapy

Treatment	Regime	Contraindications/ caution	Side effects	Comments
Permethrin 5% Cream / lotion	Rinse off after 8 to 12 hrs & repeat 1 week later	Percutaneous absorption in animal tests shows 40 - 400 times lower than Lindane 1%	Itching & burning / stinging sensation on application.	First-line therapy by CDC. Effective, well tolerated and safe
Benzyl Benzoate 10 – 25% lotion	Rinse off after 24 hours then reapply. To be kept on the skin surface continuously for 24 hrs for 2-3 days (with baths taken between each application)	Pregnant and breast feeding women and infants < 2 years	Skin irritation and burning sensation May cause conjunctivitis if exposed to eyes. May worsen/cause post- scabetic eczematous reaction Affects compliance	Effective & inexpensive Compliance is an issue
Precipitated Sulphur 6 to 10% Petroleum base	Rinse off after 24 hours and then reapply every 24 hrs for next 3 days (with a bath taken between each application)	Low toxicity	Messy, malodourous, stain clothing, causes irritant contact dermatitis	Safe for infants, pregnant and breastfeeding women
Crotamiton 10% Ointment	Classical scabies Rinse off after 24 hours and reapply for 5-7 additional days Nodular scabies: Apply to nodules 3x/day for 7-14 days	Avoid massive and prolonged use in pregnant women and infants	Irritant contact dermatitis	Use for treatment of nodules in children Lack of efficacy and toxicity data
Ivermectin	Oral drug 200 µg/kg single dose and repeat after 2 weeks	Not for children < 5 years old or < 15kg. Avoid in pregnant and lactating women.	Use with other drugs which reinforces GABA activity can lead to augmented activity (valproate, barbiturates, benzodiazepines)	Suitable for patients unlikely to adhere to topical therapy. Useful for mass treatment or outbreaks. Effective if combined with Benzyl Benzoate in patients with AIDS

Treatment in specific considerations

Clinical condition	Recommended therapy	Alternative therapy	Additional measures	Comments
CLASSICAL SCABIES				
1. Infants < 2 months	Sulphur 6% in petroleum in ointment base for 3 days	-	Treat whole body including face (avoid eyes and mouth)	Treat all family members/ close contacts simultaneously
2. Children < 2 years	Two applications of Permethrin 5% for 8-12 hours at one week apart	Sulphur 6% in petroleum in ointment base for 3 days	Treat whole body including face (avoid eyes and mouth)	Crotamiton cream TDS for 5-7 days for nodular scabies
3. Children < 12 years	Two applications of Permethrin 5% for 8-12 hours at one week apart	Benzyl Benzoate 12.5% Whole body neck and below for 3 consecutive days	-	Crotamiton cream TDS for 7-14 days for nodular scabies
4. Adults	Two applications of Permethrin 5% for 8-12 hours at one week apart	Benzyl Benzoate 25% Whole body neck and below for 3 consecutive days	-	People in close physical contact, even without symptoms, should receive treatment at the same time
5.Pregnancy/ lactating women	Two applications of Permethrin 5% for 8-12 hours at one week apart	-	-	-
6. Crusted scabies	Permethrin and Ivermectin for Scabies	**Oral Ivermectin** alone or in combination with permethrin is very useful OR Several applications of **Benzyl Benzoate**	Apply keratolytic agents (salicylic acid ointment) to hyperkeratotic areas. Keep nails short and apply medication to subungual areas	Patients may need admission. Strict control to prevent spread of infection
7. Nodular scabies	Topical anti-inflammatory agents; e.g. topical corticosteroids of mid potent to potent for a short duration of 2 weeks.	Two applications of Permethrin 5% for 8-12 hrs at one week apart	-	-

TREATMENT FAILURE

Can be recognized in patients with

- New papules/vesicles or burrows appearing at any stage after completion of a course of scabicides.
- The itch still persists at least 6 weeks after the first course of treatment of scabicides (particularly, if it persists at the same intensity or is increasing in intensity).

Management of treatment failure

- Re-educate and re-counsel patient and family members
- Re-treat with topical scabicides using an alternative agent

INDICATIONS FOR REFERRAL TO SPECIALIST CARE:

- Diagnostic uncertainty / failure to respond to adequate treatment of the patient and contacts
- Crusted scabies
- Patients with complications such as severe infections

Chapter 99:
Stevens-Johnson Syndrome

Definitions

STEVENS-JOHNSON SYNDROME (SJS)

- Severe erosions of at least two mucosal surfaces with extensive necrosis of lips and mouth, and a purulent conjunctivitis.
- Epidermal detachment may occur in SJS, but less than 10% of the body surface area is involved.
- Morbidity with this disease is high, and can include photophobia, burning eyes, visual impairment and blindness.

TOXIC EPIDERMAL NECROLYSIS (TEN)

- Severe exfoliative disease associated with systemic reaction characterized by rapid onset of widespread erythema and epidermal necrolysis.
- Involves more than 30% loss of epidermis.

SJS/ TEN OVERLAP

- Involves 10-30% of body surface area.

MYCOPLASMA PNEUMONIAE-INDUCED RASH AND MUCOSITIS/ RESPIRATORY INFECTION-INDUCED RASH AND MUCOSITIS (MIRM/RIRM)

- A variant of SJS/TEN secondary to respiratory infection, clinically predominant mucositis with limited or absent skin involvement.
- Higher chance of recurrence

Risk factors for SJS

- HIV infection
- mmunodeficiency state: post-organ transplant, systemic lupus erythematosus and autoimmune diseases
- Malignancy (particularly blood cancer)
- rior history of SJS
- A family history of SJS, especially, if an immediate blood relative has had it
- Genetic factors: Having certain genetic variation like HLA-B*1502 puts one at increased risk. There is a role for HLA typing in South-east Asians (HLA B 1502) before use of Carbamazepine.

Salient features

- Acute prodromal flu-like symptoms, fever, conjunctivitis and malaise 1-3 days before rash develops.
- Skin tenderness, morbilliform to diffuse or macular erythema target lesions (particularly atypical targets), vesicles progressing to bullae. Blisters on the face, and upper trunk, then exfoliation with wrinkled skin which peels off by light stroking (Nikolksy' sign).
- Buccal mucosa involvement may precede skin lesion by up to 3 days in 30% of cases.
- Less commonly the genital areas, perianal area, nasal and conjunctival mucosa.
- In the gastrointestinal tract, esophageal sloughing is very common, and can cause bleeding and diarrhea.

- In the respiratory tract, tracheobronchial erosions can lead to hyperventilation, interstitial oedema, and acute respiratory distress syndrome.
- Skin biopsy of TEN - Extensive eosinophilic necrosis of epidermis with suprabasal cleavage plane.
- Renal profile – raised blood urea, hyperkalaemia and creatinine.
- Glucose - hypoglycaemia.

Aetiology in Steven Johnson Syndrome / TEN
Drugs Antibiotics: Sulphonamides, amoxycillin, ampicillin, ethambutol, isoniazid Anticonvulsants: Phenobarbitone, carbamazepine, phenytoin, lamotrigine Non-Steroidal Anti-Inflammatory Drugs: Phenylbutazone, salicylates *Detailed timeline is important. Patient may react to medication while using it or up to 2 weeks after discontinuation *Infection* Virus: herpes simplex, enteroviruses, adenoviruses, measles, mumps Bacteria: *Streptococcus, Salmonella typhi, Mycoplasma*

Aim of treatment: To remove the cause and prevent complications

Management

Supportive Care

- Admit to isolation room where possible.
- May need IV fluid resuscitation for shock.
- Good nursing care (Barrier Nursing and hand washing).
- Use of air fluidized bed, avoid bed sores.
- Adequate nutrition – nasogastric tubes, IV lines, parenteral nutrition if severe mucosal involvement.
- Adequate analgesia

Specific treatment

- Eliminate suspected offending drugs
- IV Immunoglobulins at a dose of 0.4 Gm/kg/per day for 5 days. IVIG is a safe and effective in treatment for SJS/TEN in children. It arrests the progression of the disease and helps complete re-epithelialization of lesions.
- Cyclosporin has been shown to reduce mortality.
- Systemic corticosteroid and tumour necrosis factor-alpha inhibitors have also been used.

Monitoring

- Maintenance of body temperature. Avoid excessive cooling or overheating.
- Careful monitoring of fluids and electrolytes – BP/PR.
- Intake / output charts, daily weighing and renal profile.

Prevent Complications

Skin care

- Handle skin carefully, reduce shearing forces to minimize extent of epidermal detachment.
- Cultures of skin, mucocutaneous erosions, tips of Foley's catheter.
- Treat infections with appropriate antibiotics.
- Topical antiseptic preparations: saline wash or $KMnO_4$ wash.
- Dressing of denuded areas with paraffin gauze / soffra-tulle.
- Surgery may be needed to remove necrotic epidermis.

Eye care

- Early and frequent eye assessment.
- Antibiotic or antiseptic eye drops 2 hourly.
- Synechiae should be disrupted.

Oral care

- Good oral hygiene aimed at early restoration of normal feeds.

Discharge

- Parents should be counselled about:
  - future avoidance of culprit drugs if likely
  - risk of recurrence
  - potential long term sequelae including skin pigmentation changes & scarring, nail, eye, oral, dental, respiratory (particularly bronchiolitis obliterans), urogenital problems & psychological complications.

Section 16

GENETIC AND METABOLIC

Chapter 100:
Diagnosis and Management of Inborn Errors of Metabolism

Introduction

- Inborn errors of metabolism (IEM) are biochemical genetic disorders that result from the deficiency of enzymes, membrane transporters, or other functional proteins.
- IEMs are individually rare but cumulatively common.
- Children may present with acute overwhelming sickness or a prolonged, smouldering illness. For the former, rapid diagnosis is vital to limit morbidity and mortality. For the latter, diagnosis is important for the initiation of appropriate clinical care.

"Red flags" that should prompt IEM investigations:

- Neonates with unexplained sepsis-like appearance, overwhelming or progressive diseases without evidence of infection, particularly after normal pregnancy and birth.
- Recurrent episodes of vomiting, ataxia, seizures, lethargy, altered consciousness, particularly when preceded by vomiting, fever, infections or fasting.
- Patients with unexplained symptoms and signs of metabolic acidosis, hyperammonaemia or hypoglycaemia.
- Severe hypotonia.
- Severe global developmental delay, especially with loss of skills.
- History of being severely symptomatic and needing longer to recover with benign illnesses (e.g., upper respiratory tract infection).
- Unusual dietary preferences (e.g., protein or carbohydrate aversion).
- Subtle neurological or psychiatric abnormalities in older children or adolescents.
- Epileptic encephalopathy.
- Movement disorder (e.g., dystonia).
- Hepatomegaly, cirrhosis, liver failure, cholestatic jaundice.
- Dysmorphic syndromes (e.g., coarse facial features).
- Hypertrophic cardiomyopathy.
- Skin signs: ichthyosis, light sensitivity.
- Eye abnormalities - cataract, corneal opacities, pigmentary retinopathy.
- Chronic muscle weakness with pain.
- Renal stone disease in children.
- Renal tubular disease in children.
- An unusual smell from skin or urine: sweaty feet, burnt maple syrup, etc.
- Neuro-imaging abnormalities.

Classification

While the most recent international classification of IEM encompasses >1400 disorders, from a clinical point of view, all IEM can be classified into 3 groups from a clinical diagnostic perspective and a pathophysiological approach.

1. Small molecule disorders
2. Disorders involving energy metabolism
3. Complex molecule disorder

GROUP 1: SMALL MOLECULE DISORDERS (2 subgroups)

1a: Accumulation of small (diffusible water-soluble) molecules

- Causes acute or progressive "intoxication".
- Symptoms and signs result primarily from accumulation of the "intoxicating" compound and can reverse as soon as it is removed.
- Do not interfere with foetal development.
- Presents after a symptom-free interval (days to weeks).
- "Metabolic crisis" induced by food and catabolism.
- Most disorders are treatable.
- Most disorders have metabolic marker(s) & are detectable by:
  - First line tests: blood glucose, blood ammonia, blood acid-base status, blood lactate, urine/ blood ketones.
  - Second line tests: analysis of plasma amino acids (AA), urine organic acids (OA) and dried blood spot (DBS) acylcarnitine ± plasma total homocysteine.
  - Almost all disorders can be diagnosed by molecular genetic testing. Bloods can be taken first with DNA extracted and stored with consent in the event of an ill patient who may succumb before diagnostic results are out.

Interpretation of initial first line investigations results

- Serves as a guide only: consult the metabolic team about abnormal results.
- Table below is most relevant for neonates and small infants.
- Must also take into account the clinical context, including the period of fasting prior, hydration status, stage of illness and administered fluids or other management.

IEM	Glucose	Lactate	Metabolic acidosis	Ammonia	Anion Gap#	Urine ketones
Maple Syrup Urine Disease	Low or Normal	Normal	Variably present	Normal	May be increased	Positive
Organic Acidurias	Low or Normal	May be high	Very acidotic	May be high	Usually increased	Positive
Fatty Acid Oxidation Disorders	Low or Normal	May be high	Variably present	May be high	May be increased	Negative or low
Urea Cycle Disorders	Normal	Normal	Early, respiratory alkalosis Late, metabolic acidosis May be normal	High	Normal	Negative

#Anion gap = $[Na^+]$ – $[Cl- +. HCO_3-]$ (Normal 7 – 16 mmol/L)

- Main disorders:

i. Urea cycle disorders (UCD)

- Most common cause of severe hyperammonaemia.
- **Clinical:** Severe neonatal onset form: rapidly progressive encephalopathy in the first days of life after a short symptom-free interval. Respiratory alkalosis is common early, but metabolic acidosis may mask it later if systemic shock develops. The initial presentation is often described as "sepsis-like" but unlike neonatal sepsis, blood pressure is usually in the (high) normal range or even increased in the early stages of hyperammonaemic encephalopathy. In some patients signs of acute liver failure, including coagulopathy, may be found. Late onset form: failure to thrive, feeding problems, vomiting, chronic/unexplained neurological symptoms, episodic encephalopathy with lethargy, ataxia, seizures, behavioural problems, protein aversion. Arginase deficiency differs from other UCD because patients rarely present in the neonatal period but manifests as progressive spastic paraplegia and developmental delay between 2 -4 years old, sometimes with episodic hyperammonaemia.
- **Diagnosis:** ↑↑ NH_4^+, Plasma amino acid – abnormal profile, ↑urine orotic acid (identifies OTC deficiency and differentiates from NAGS/CPS1 deficiency). Molecular genetic testing is recommended for definitive confirmation.

Blood NH4+ values	Neonates:	Healthy	<110 µmol/L
		Sick	Up to 180 µmol/L
		Suspect IEM	>200µmol/L
	After the neonatal period:	Healthy	<50 µmol/L
		Suspect IEM	>100 µmol/L

- **Acute treatment:**

Emergency management of acute hyperammonaemia: Rapid and efficient management is of utmost importance – short time-span from first symptoms to irreversible brain damage and death. The prognosis is considered very poor in patients with any of the following characteristics: 1. Coma >3 days; 2. significantly elevated intracranial pressure; 3. Blood NH_4^+ concentration in plasma >1000 µmol/L.

Step 1: Basic life support

- Ensure basic life functions (ventilator and circulatory support)

Step 2: Stop the offending precursor nutrients

- Stop protein intake (for a maximum 48 hours)

Step 3: Promotion of anabolism

- Give hypercaloric management.
- IV 10% (or higher) glucose with appropriate electrolytes (Na^+, K^+) at the rate according to patient's age, at least:
  - 10 mg/kg/min in a neonate
  - 8 mg/kg/min in infants
  - 6 mg/kg/min in all others
- Administration of lipids (1-2g/kg/d) or protein-free medical formula will provide additional energy and help promote anabolism.
- In a neonate, aim to achieve 120 – 140 kcal/kg/day. In older infants or children, aim to achieve 120 – 140% caloric requirement for age and sex.
- Adjust volume according to individual demands and hydration status. Check glucose; add insulin if necessary.
- Effective antiemetic (Granisetron or ondansetron) to control vomiting.

Step 4: Detoxification

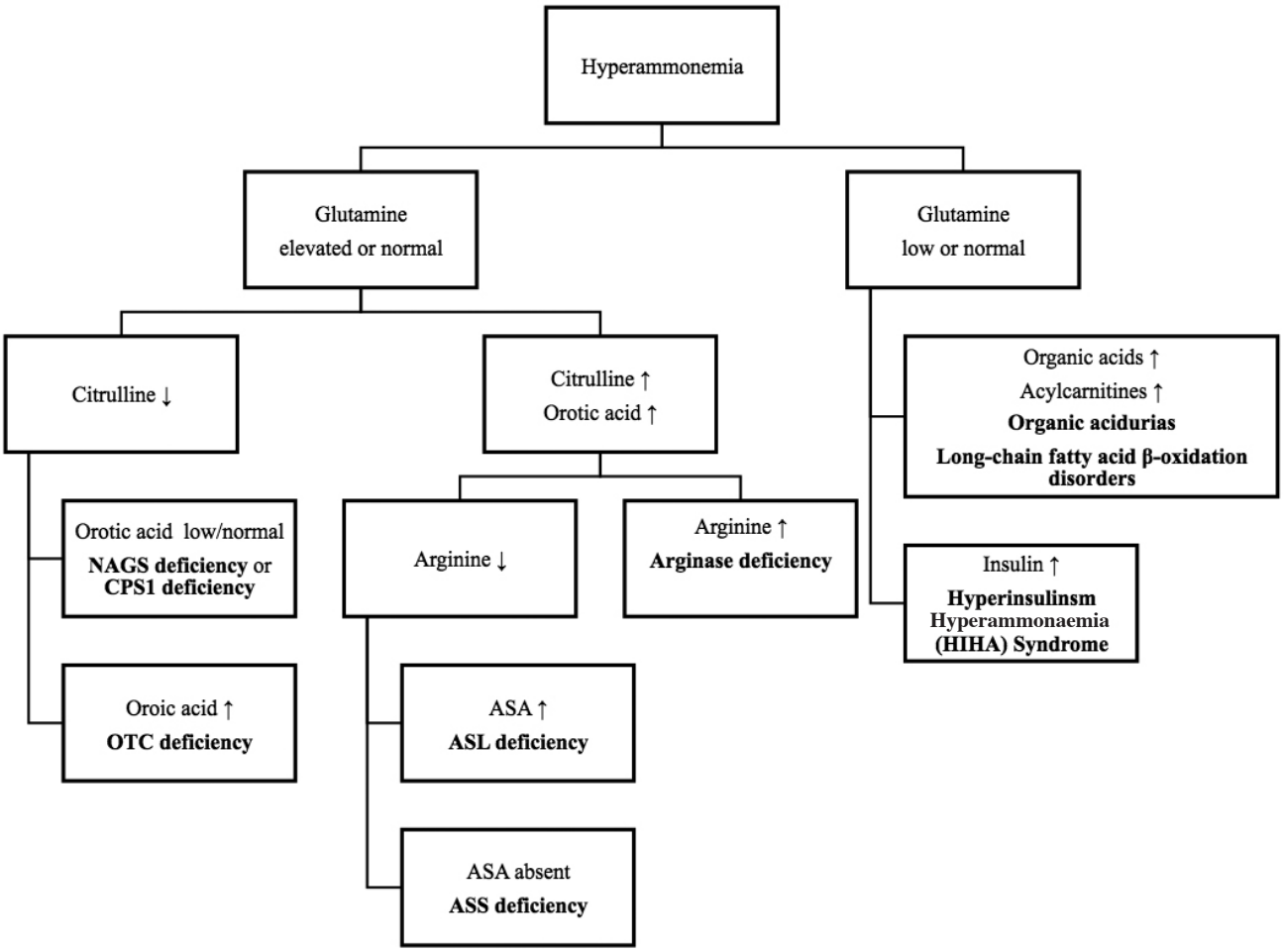
- Pharmacotherapy: Remove NH_4^+ using IV nitrogen scavengers (sodium benzoate and sodium phenylbutyrate) and replenish urea cycle intermediates (arginine, citrulline (CPS1 deficiency, OTC deficiency)).

Drug*	Loading dose over 1.5 – 2 hrs (bolus)	Followed by maintenance dose over 24 hrs
IV L-Arginine** IV Sodium benzoate IV Sodium phenylbutyrate	250 mg/kg 250 mg/kg 250 mg/kg	250 mg/kg 250 mg/kg 250 mg/kg
Should be diluted in glucose 5% to a total volume of 25mls and administered as a bypass to the regular infusion. **400 mg/kg in ASL deficiency. Avoid Arginine in arginase deficiency.		

- In undiagnosed patient in whom hyperammonaemia could be caused by either UCD (a.k.a Primary hyperammonaemia) or organic acidurias (a.k.a. secondary hyperammonaemia), consider to add carglumic acid (see section on organic acidurias).
- Check blood NH_4^+ after 2 hrs. Thereafter, it must be determined at least every 3 - 4 hours until the acute situation is successfully managed.
- Reintroduction of protein/essential amino acids (oral or parenteral) must not be delayed for more than 48 hours.
- If at any time during the crisis the blood NH_4^+ escalates to >500 µmol/L or if the patient is encephalopathic (seizures, severely reduced consciousness or coma), continuous renal replacement therapy should be started as soon as possible.
- The method will depend on the experience of the local hospital but haemodiafiltration or haemodialysis have been proven most efficient while peritoneal dialysis with currently used solutions may be considered only if a more effective dialytic technique cannot be applied or for bridging to this more effective technique. Do not perform exchange transfusion.
- Management to induce anabolism and infusion of nitrogen scavengers must be continued during and after completion of renal replacement therapy to prevent rebound hyperammonaemia.
- When blood NH_4^+ is persistently >1,000 µmol/L and prolonged coma evaluate whether to aim at all out treatment or to start palliative care.

Step 5: Other supportive treatment

- Introduce supporting therapies, such as:
  - Treating infections
  - Managing seizures
- **Long-term treatment:**
  - Low-protein diet (titrate according to individual protein tolerance/safe level) – combination of low but high biological value natural protein and medical formula containing essential amino acids (30-50% of the protein requirement).
  - Ensure sufficient intake of essential nutrients & calories to promote normal growth
  - May require nasogastric tube feeding or gastrostomy
  - Oral sodium benzoate 250 - 500 mg/kg/day
  - Oral sodium or glycerol phenylbutyrate 250 - 500 mg/kg/day
  - CPS1 or OTC deficiency: oral arginine or citrulline (preferred) 100-200 mg/kg/day. ASS or ASL deficiency: oral arginine 200 - 400 mg/kg/day
  - Carglumic acid in individuals with NAGS deficiency and partially responsive CPS1 deficiency.
  - Give vitamins and trace elements.
  - Consider lactulose
  - Consider early liver transplantation, particularly in individuals with severe neonatal onset OTC and CPS1 deficiency.
  - Monitor growth and laboratory values regularly (Target blood NH4+ <80 µmol/L, glutamine <1,000 µmol/L, glycine 100 - 150 µmol/L, arginine 80-150 µmol/L, essential amino acids should all be in the normal range)
  - Acute decompensation: dietary indiscretion causes NH_4^+ to increase but only rarely results in acute decompensation and encephalopathy. In contrast, infections and injuries trigger a large endogenous mobilization of muscle protein and can precipitate metabolic crisis and hospitalisation.
  - Treatment of intercurrent illness (with poor feeding, vomiting, diarrhea, fever): In order to prevent metabolic decompensation it is imperative to prepare & educate the parents/ caretakers to an individualized home-based sick day management plan. To interrupt the catabolism in its early stage:
    - Stop protein intake (not more than 48 hours)
    - Give sufficient fluid (water, juice, electrolyte solution) and extra calories (carbohydrates as glucose polymer)
    - If tolerated, special medical formula should be continued
    - Reintroduce protein after 48 hours and increase stepwise until the amount of maintenance treatment is reached. E.g. one day ½ of the normal amount of protein, next day ¾, then full amount. (Prolongation of inadequately low protein intake increases the risk of protein catabolism.)
    - Immediate hospital admission and check blood ammonia if the clinical condition deteriorates, oral intake is poor at home or the disease course is prolonged.
    - Administer caloric management that promotes anabolism even if blood ammonia is normal, until patient recovers.



NAGS: N-acetylglutamate synthase; CPS1: Carbamylphosphate synthase I; OTC: Ornithine transcarbamylase; nASS: Argininosuccinate synthase; ASL: Argininosuccinate lyase; ASA: Argininosuccinic acid

ii. Maple syrup urine disease (MSUD)

- **Clinical:** (1) Severe neonatal onset form: progressive encephalopathy starting on 3rd-5th days of life, no abnormalities in routine laboratory tests except ketonuria. Hypoglycemia is rare. Odor of urine may be highly characteristic (maple syrup-like). Acute cerebral oedema is a well-recognized complication (fully reversible if treated early), may progress to cerebral herniation. (2) Attenuated forms (intermittent, intermediate): developmental delay, fluctuating/progressive neurological disease, recurrent ataxia, spastic diplegia, chronic vomiting with failure to thrive.
- **Diagnosis:** Plasma AA: elevation of branched-chain amino acids (BCAAs) -↑↑↑Leucine (Leu, most neurotoxic), ↑Isoleucine (Ile), ↑Valine (Val). Presence of alloisoleucine is diagnostic. Urine OA: ↑ branched-chain oxo- and hydroxyacids, e. g. 2-OH-isovaleric acid, 2-oxoisocaproic acid. Molecular genetic test is recommended for definitive confirmation.

- **Treatment:**
- **Acute treatment:**

Step 1: Basic life support
- Ensure basic life functions (ventilator and circulatory support)

Step 2: Stop the offending precursor nutrients
- Stop BCAAs/natural protein intake (for 24 to 72 hours)

Step 3: Promotion of anabolism
- Step (i) – Hypercaloric/anabolic nutritional support that contains iv 10% (or higher) glucose infusion, BCAA-free formula (enteral feeding via tube feeding + perfusor) and IV lipid (1-2 g/kg/d) ± IV insulin (if persistent hyperglycemia or glucosuria) to enhance protein anabolism. Effective antiemetic (Granisetron or ondansetron) to control vomiting. Serial monitoring of blood BCAAs levels is essential. Step (ii) - Plasma concentrations of Val and Ile will normalize before Leu concentrations normalize. If Val and Ile fall below normal then it will become rate limiting for protein synthesis ➔ avoid secondary deficiency of Ile and Val by early oral supplementation (each 100-300 mg/day); Step (iii) – Reintroduce Leu to the diet when plasma Leu drops to ≤ 400 µmol/L by adding natural protein e.g. breastmilk or infant formula.

Step 4: Detoxification
- Promoting protein anabolism is key to reducing toxic levels of BCAAs. Reduction in leucine concentration at 750 µmol/L or more per 24 hrs is normally achievable with hypercaloric nutritional therapy.
- However, in patients with very high concentrations of BCAAs or if nutritional therapy is insufficient, consider continuous renal replacement therapy (to reduce risk of cerebral herniation).

Step 5: Other supportive treatment
- Introduce supporting therapies, such as:
  - Treating infections
  - Managing seizures
  - Managing cerebral edema
- Long-term treatment:
- Dietary restriction of BCAAs (especially leucine) by restricting natural protein (number of protein or Leu exchange is titrated to patient's Leu tolerance) and use of BCAA-free medical formulas and low protein foods, and careful supplementation of isoleucine and valine (regular monitoring of plasma BCAAs); sufficient intake of essential nutrients & calories to promote normal growth.

- Consider liver transplant in individuals with severe clinical phenotype (poor metabolic control, frequent metabolic decompensations).
- Early intervention of any intercurrent illness to prevent metabolic decompensation. Parents/ care taker should be educated to initiate sick day protocol upon the first signs of an illness: increasing BCAA-free medical formula intake to 120% of the usual intake, decreasing leucine intake by 50%–100%, and providing small but frequent feedings throughout a 24 hour period. Minor illnesses can be managed at home. Immediate hospital admission if poor oral intake, the clinical condition deteriorates or the disease course is prolonged or in serious cases.

iii. Classical organic acidurias: isovaleric acidemia (IVA), Propionic acidemia (PA), isolated Methylmalonic acidemia due to Methylmalonyl-CoA mutase or cblA or cblB deficiency (MMA)

- **Clinical:** Severe neonatal onset form: metabolic encephalopathy "intoxication type"- lethargy, feeding problems, vomiting, dehydration, truncal hypotonia/limb hypertonia, coma, multi-organ failure progressing to death, unusual odor in IVA. Late onset form: recurrent episodes of metabolic crisis (ketoacidotic coma, lethargy, ataxia, focal neurological signs); chronic progression of organ dysfunction (brain, heart, kidney, pancreas, optic nerve).
- **Laboratory/Diagnosis:** Ketonuria, persistent metabolic acidosis, ↑ anion gap, ↑lactate, ↑NH_4^+, hypoglycemia or hyperglycemia, neutropenia, thrombopenia, pancytopenia, ↑ AST/ALT. Urine OA: specific metabolite in IVA - ↑ 3-hydroxyisovaleric acid, isovaleryglycine; PA - ↑ propionic acid, propionylcarnitine, 3-hydroxypropionate and methylcitrate; MMA - ↑ methylmalonic acid. DBS acylcarnitines; IVA - ↑C5, PA & MMA: ↑C3. Plasma AA: ↑ Glycine. Molecular genetic test is recommended for definitive confirmation.

- **Treatment:**
- **Acute treatment:**

<u>Step 1: Basic life support</u>

- Ensure basic life functions (ventilator and circulatory support)

<u>Step 2: Stop the offending precursor nutrients</u>

- Transiently stop natural protein intake (24 – 48 hours)

<u>Step 3: Promotion of anabolism</u>

- Induce anabolism with IV 10% (or higher) glucose infusion and protein-free formula (enteral feeding via tube feeding + perfusor, IV lipids (1-2 g/kg/d) ± effective antiemetic (Granisetron or ondansetron)

Step 4: Detoxification & correction of metabolic acidosis

- Correct metabolic acidosis with IV sodium bicarbonate

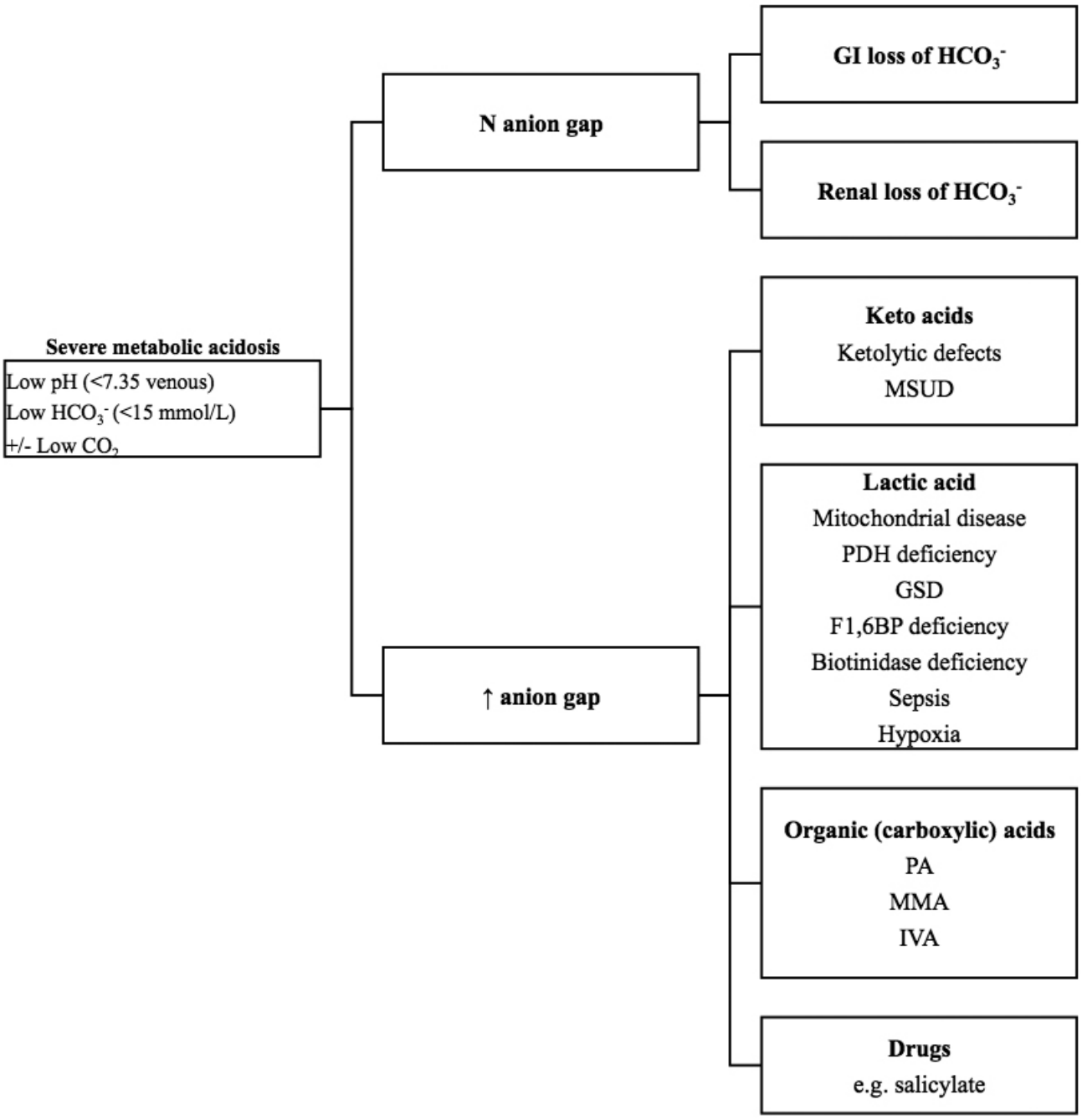
Using sodium bicarbonate to treat acidosis
HCO_3- deficit ΔHCO_3- = normal HCO_3- (24mmol/L) - actual HCO_3- HCO_3- deficit is correct for volume of distribution HCO_3- deficit = ΔHCO_3- x weight (Kg) x 0.4, or in infant use 0.5 for the correction factor Treatment: Replace ½ of the HCO3- deficit in the first 1 – 3 hours Replace ½ over the next 24 hours

- Stimulate NH_4^+detoxification by oral Carglumic acid (loading dose of 50–100 mg/kg followed by 200 mg/kg/day in 3 divided doses)
- Enhance removal of toxic metabolites and prevent carnitine depletion by IV/ oral L-carnitine (100–200 mg/kg/day).
- Consider continuous renal replacement therapy if metabolic acidosis and hyperammonaemia remain intractable

Step 5: Other supportive treatment

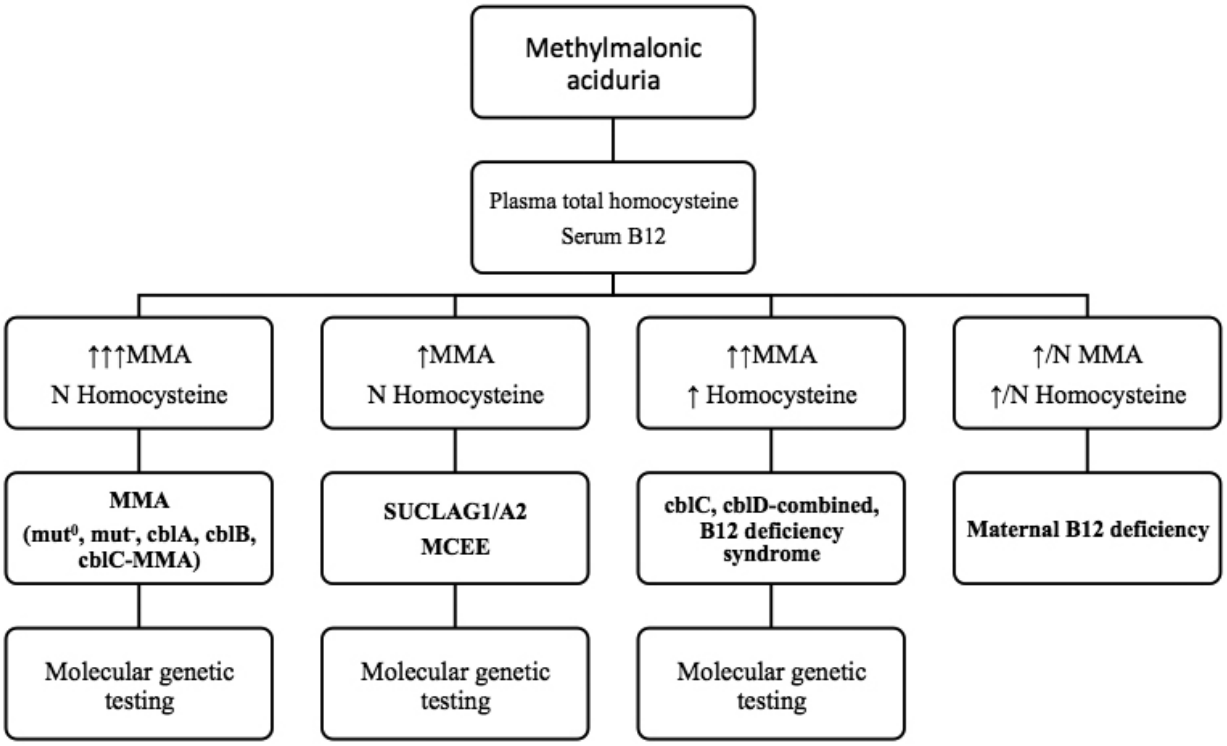
- Introduce supporting therapies, such as:
  - Treating infections
  - Managing seizures
- Long-term treatment:
- Diet - low protein diet (1–1.5 g/kg/day) aiming to reduce toxic precursor AAs while maintaining sufficient intake of essential nutrients & calories; supplementation of precursor-free special formula
- L-carnitine (50 – 100mg/kg/day)
- Intermittent oral metronidazole (PA, MMA, 10-20mg/kg/day for 10 consecutive days each month).
- Every patient with MMA should be tested for responsiveness to vitamin B12 (when in stable condition) – IM vitamin B12 for 5 days with serial urine MMA quantification. >50% reduction in urine mean MAA is indicative of responsiveness.
- Monitor complications: pancreatitis, basal ganglia infarct (PA, MMA), chronic kidney disease (MMA), cardiomyopathy and prolonged QTc (PA), optic atrophy (PA).
- Consider liver transplant in individuals with severe clinical phenotype.
- Early intervention of any intercurrent illness to prevent metabolic decompensation.

Algorithm to aid understanding of the aetiology of metabolic acidosis based on the anion gap



PDH: Pyruvate dehydrogenase; GSD: Glycogen storage disorders; F1,6BP: Fructose-1,6-bisphosphate

An algorithm of conditions to be considered in the differential diagnosis of elevated urine methylmalonic acid



B12 deficiency syndromes include intrinsic factor deficiency, Imerslund-Gräsbeck syndrome, and others causes of abnormal gastrointestinal B12 absorption. Cbl: cobalamin; MMA: methylmalonic acid; Mut: Methylmalonyl-CoA mutase Complete (mut^0 complete deficiency of the enzyme, mut– partial deficiency of the enzyme), MCEE: Methylmalonyl-coenzyme A epimerase.

iv. Cerebral organic aciduria: Glutaric aciduria type I (GA1)

- **Clinical:** Macrocephaly (early sign), temporal brain hypoplasia, acute or insidious onset of striatal damage at the age of 6-36 months, complex movement disorder with predominant dystonia and truncal hypotonia. Metabolic/lactic acidosis, hyperammonemia and hypoglycemia are inconsistent/ absent.
- **Diagnosis:** Urine OA: ↑ glutaric acid, 3-OH-glutaric acid (diagnostic); DBS acylcarnitines: ↑C5DC; molecular genetic testing is recommended for definitive confirmation, and also recommended in low-excreters where glutaric acids are not detected in the urine.
- **Treatment:**
- Low-lysine diet while maintaining sufficient intake of essential nutrients & calories, often combined with the use of lysine-free, tryptophan-reduced medical formula (Beware of Tryptophan deficiency)
- Carnitine supplementation (100 mg/kg/day)
- Emergency treatment during catabolic episodes to protect against encephalopathic crises/acute striatal injury. Vomiting and diarrhoea is particularly dangerous – even in the absence of fever.
- ↓ or omit natural protein for 24 -48 hrs
- Frequent high carbohydrate feeds (glucose polymer)
- If tolerated, special medical formula should be continued
- ↑ L-carnitine supplementation.
- If feeds are not tolerated, admit hospital for high-dose iv glucose infusion and give medical formula via tube feeding + perfusor ± effective antiemetic (Granisetron or ondansetron). IV lipid (1-2g/kg/ day) provide additional energy and help promote anabolism.
- With increasing age, and in particular after age 6 years, the risk of acute neurological insult appears to be much reduced

v. Tyrosinemia type 1

- **Clinical:** Acute: (neonate/infant): severe liver failure, vomiting, bleeding, septicemia, hypoglycemia, renal tubulopathy (Fanconi syndrome). Chronic: hepatomegaly, cirrhosis, growth retardation, rickets, renal tubulopathy, neuropathy, neurological crises (due to porphyrins).
- **Diagnosis:** Urine OA - ↑ succinylacetone (diagnostic); plasma AA - ↑ Tyr, ↑ Met, ↑ α-fetoprotein; urine porphyrins - ↑ δ-aminolevulinic acid. Molecular genetic test is recommended.
- **Treatment:** Nitisinone (NTBC) 1(-2) mg/kg/day (inhibitor of 4-OH-phenylpyruvate dioxygenase, blocks the accumulation of toxic metabolites; beware of ↑ Tyr); Phe- + Tyr-restricted diet
- **Prognosis:** With nitisinone good; liver transplant no longer needed in most patients.
- **Complications:** Hepatocellular carcinoma (watch AFP), renal failure.

vi. Other

DISORDER	CLINICAL	DIAGNOSIS	TREATMENT
Classical galactosemia	Progressive symptoms after the start of milk feeds, prolonged jaundice, liver dysfunction, Gram negative organisms' sepsis, bilateral cataract → death from hepatic and renal failure	↑ Galactose, ↑Galactose-1-Phosphate, ↓Galactose-1-phosphate uridyltransferase (GALT). Molecular genetic test.	Lactose-free, galactose-restricted diet
Citrin deficiency (a.k.a. Citrullinemia Type II)	Neonatal/infantile period: cholestatic jaundice, full cheeks, hepato(spleno)megaly, secondary galactossemia, cataract. Childhood period: craving for protein & fat-rich foods, aversion to CHO-rich foods, failure to thrive, fatty liver, dyslipidemia. Adult: liver cirrhosis, hyperammonaemia crises	Plasma AA: ↑citrulline, ↑Threonine, ↑Methionine, ↑Tyrosine (abnormalities are transient during neonatal/infantile period). Molecular genetic test recommended for patient and all asymptomatic siblings.	Neonatal/infantile: lactose/galactose-free formula (during cholestasis#), MCT oil, lipid soluble vitamins. Older ages: low CHO diet, MCT oil (monitor growth), protein and lipid rich diet. Avoid high-carbohydrate meals and alcohol.
Classical homocystinuria	Progressive myopia, lens dislocation, Marfan-like appearance, cerebral venous sinus thrombosis / other thromboembolism, epilepsy, intellectual disability	↑↑ Plasma total homocysteine (tHcy) (>150 µmol/L). Molecular genetic test.	Pyridoxine 50 -100mg/day for 4 weeks. If no response: methionine-restricted diet, betaine (to keep tHcy <50 µmol/L)
Phenylketonuria	Untreated: severe intellectual disability, epilepsy, hypopigmentation	Plasma AA: ↑↑ phenylalanine (Phe), ↓ tyrosine (DD: BH4 deficiency) Molecular genetic test.	BH4 responsiveness test. If no response: Phe-restricted diet (to keep Phe 120 – 360 µmol/L)

DISORDER	CLINICAL	DIAGNOSIS	TREATMENT
Glycine encephalopathy (a.k.a. nonketotic hyperglycinemia)	Neonatal intractable seizures, hypotonia, lethargy, hiccups, apnea, EEG: burst suppression (mimics hypoxic ischemic encephalopathy). Attenuated form: developmental delay, epilepsy	CSF: Plasma glycine ratio >0.08 (normal <0.02), molecular genetic test for confirmation.	Evaluate whether to aim at all out treatment or palliative care. To treat: Dextromethorphan 5 – 15 mg/kg/day, benzodiazepines, sodium benzoate (to keep plasma glycine <300 µmol/L)
Sulfite oxidase deficiency & Molybdenum cofactor deficiency (MoCoD)	Infantile epileptic encephalopathy, MRI brain – cystic encephalomalacia	Fresh urine sulphite test: positive; ↑ urine sulphocysteine, ↓serum uric acid in MoCoD. Molecular genetic test.	Substitution of cPMP in MoCoD type I. Symptomatic/ palliative care for others.
Cobalamin C defect	Neonatal/infantile feeding difficulties, lethargy, neurological deterioration, seizures, abnormal movement, pancytopenia. Attenuated form: developmental delay, behavioural issues, epilepsy	Plasma AA: ↓methionine, Urine OA: ↑MMA, Plasma tHcy ↑. Molecular genetic test.	IM hydroxocobalamin 1mg 3 – 5 times/ week, betaine, folate, methionine supplement
Biotinidase deficiency (BTD) & holocarboxylase synthase (HLCS) deficiency	Skin rashes, hair loss, progressive neurological symptoms, metabolic acidosis, immune deficiency	↑ lactate, urine OA: 3-OH-isovaleric acid, DBS acylcarnitines: ↑C5OH, DBS biotinidase enzyme activity: ↓in BTD, normal in HLCS deficiency. Molecular genetic test	Biotin 5-10mg/day (BTD), 10-20mg/day (HLCS deficiency)
Antiquitin deficiency (pyridoxine-responsive seizures)	Neonatal onset epileptic seizures	↑ Piperidine-6-carboxylate (P6C), ↑ pipecolic acid, ↑ α-aminoadipic semialdehyde (urine, CSF, plasma). Molecular genetic test	Pyridoxine 5-15mg/ kg/day. Consider folinic acid, diet lysine restriction and arginine supplement
Methylenetetra-hydrofolate reductase (MTFHR) deficiency	Progressive neurological deterioration, apnea	Plasma AA: ↓methionine, Plasma tHcy ↑. Molecular genetic test	i.m. hydroxocobalamin 1mg/day, betaine, folinic acid, methionine supplement

- # use normal infant formula once the cholestasis has resolved.

1b: Deficiency of Small Molecules

- Symptoms result primarily from the defective synthesis or transportation of an essential molecule (e.g. non-essential amino acids, neurotransmitters, cofactors, etc.)
- Defects often cause neurodevelopment disruption, with congenital presentation
- Share many characteristics with disorders in the complex molecules
- Most but not all are irreversible
- A few are or should be treatable by supplementing the missing product distal to the block
- Metabolic markers are not always present
- Main disorders:

DISORDER	CLINICAL	DIAGNOSIS	TREATMENT
AA synthesis defects - **Serine** - **Glutamine** - **Asparagine**	Early onset epileptic encephalopathy, brain malformations, microcephaly, severe intellectual disability	Plasma/CSF amino acids. Molecular genetic test	Not or poorly treatable except serine deficiency (serine supplement)
Neurotransmitters (NT) synthesis disorders - **Tyrosine hydroxylase (TH) deficiency** - **Aromatic L-amino acid decarboxylase (AADC) deficiency** - **BH4 deficiency (a.k.a. atypical phenylketonuria)**	TH deficiency: severe dopamine deficiency with two phenotypes: (1) a severe neonatal onset complex encephalopathy with oculogyric crises, (2) an infantile onset, progressive, hypokinetic-rigid syndrome with dystonia	CSF NT analysis Molecular genetic test	L-Dopa 1 -10 mg/kg/day (start at low dose, gradually titrate to optimal dose as patients often have hypersensitivity to L-Dopa)
	AADC deficiency: severe combine dopamine and serotonin deficiencies. Infantile onset, progressive hypokinesia, truncal muscular hypotonia, limb rigidity, oculogyric crises, feeding difficulties, insomnia, temperature instability	CSF NT analysis Molecular genetic test	Pyridoxal phosphate trial, dopamine agonists (response is often poor). Consider intracerebral gene therapy
	BH4 deficiency: severe combine dopamine and serotonin + ↑ plasma phenylalanine. Infantile onset, developmental delay, progressive hypokinesia, truncal muscular hypotonia, limb rigidity, oculogyric crises, feeding difficulties, insomnia, temperature instability	Plasma AA: ↑ Phe CSF NT analysis Molecular genetic test	BH4 5mg/kg/day, L-Dopa 1 -10 mg/kg/day, 5(OH)tryptophan 1 – 5 mg/kg/day

GROUP 2: DISORDERS INVOLVING ENERGY METABOLISM

- These consist of IEMs with symptoms due, at least in part to a deficiency in energy production or utilization within the liver, myocardium, muscle, brain, and other tissues.
- In general, cytoplasmic energy defects are generally less severe and more treatable than mitochondrial energy defects.
- Diagnosis can be orientated by functional tests measuring glucose, lactate, ketones and other energetic molecules (AA, organic acids, acylcarnitines) in blood, CSF and urines and confirmed by enzyme assays and/or molecular genetic testing.
- Main disorders:

i. Glycogen storage disorders (GSD)

- Three main clinical presentations:
  - Liver: hypoglycaemia, hepatomegaly, growth retardation (GSD Ia, Ib, VI. IX. Oa)
  - Muscle: exercise intolerance, muscle cramps, cardiomyopathy (GSD 0b, II, V, VII)
  - Mixed/generalized: cardiomyopathy, liver/muscle involvement (GSD III, IV, IX)
- Diagnosis is confirmed by molecular genetic test (preferred) or biopsy (histology) and enzyme studies (rarely done nowadays)
- <u>GSD Ia and GSD Ib</u>
  - Most severe type of hepatic GSD
  - Clinical: First manifestation usually at the age of 3-6 months: recurrent hypoglycemia 3-4 hours after meals, truncal obesity, hepatomegaly, doll face, failure to thrive, small stature. GSDIb variant: same as above, plus neutropenia, leukocyte dysfunction, bacterial infections, diarrhea, inflammatory bowel disease (IBD)
  - Diagnosis: ↓ Glucose, metabolic acidosis, ↑ lactate, severe lipemia, ↑ triglycerides, ↑ uric acid. Molecular genetic test
  - Treatment: Avoid hypoglycaemia through frequent carbohydrate intake: Frequent meals (every 2 - 3 hours in infants, 4-hourly from childhood); slowly resorbed carbohydrates (uncooked corn-starch), no sucrose, limited fructose and lactose/galactose (vegetables, fruits); soy-based milk replacement + calcium; multivitamins, vitamin D. Nights: continuous feeds (infants 12 hours, adults 8 - 10 hours) via nasogastric tube, start as soon as possible after last daytime meal; or 4-hourly uncooked corn-starch. GSDIb: If neutropenia/infections, add Filgrastim (G-CSF). Consider Empagliflozin (SGLT2 inhibitor).
  - Monitor: use noninvasive continual blood glucose monitoring device (keep preprandial blood glucose > 3.5 - 4.0 mmol/L); serum: normal creatinine, calcium, phosphate, uric acid, liver function tests; triglyceride concentration <6.0 mmol/l); body mass index between 0.0 and + 2.0 SDS; yearly ultrasound scan of the liver, regular renal function and blood pressure checks, 3-yearly echo from age 10 years.
  - Complications (2^{nd} – 4^{th} decade): liver adenomas/carcinomas, anemia, osteoporosis, renal failure.

ii. Disorders of gluconeogenesis

- The typical feature is recurrent hypoglycaemia with lactic acidosis ± ketosis ± fluctuating hepatomegaly

DISORDER	CLINICAL	DIAGNOSIS	TREATMENT
Fructose-1,6-bisphosphate deficiency	Acute crisis (often neonatal) with hypoglycaemia, hepatomegaly, metabolic acidosis, hyperventilation, ketosis, ↑lactate, coma, seizures, brain damage.	↑Lactate, ↑ketones, Urine OA): 2-oxoglutaric acid, glycerol, glycerol-3-phosphate. Molecular genetic test.	Usually responds rapidly to treatment with intravenous/ oral glucose ± sodium bicarbonate. Avoidance of fructose/ sucrose/ sorbitol. Nocturnal feeds/uncooked cornstarch. Frequent intake of glucose when unwell (sick day protocol). Table sugar is sucrose and therefore not suitable when unwell.
Glycerokinase (GK) deficiency	Isolated GK deficiency: Mostly male. (X-linked). Recurrent vomiting, ↑ ketones, hypoglycaemia. Complex GK deficiency (Contiguous gene syndrome due to Xp21 deletion) – congenital adrenal hypoplasia ± Duchenne muscular dystrophy, sometimes OTC deficiency	Urine OA: ↑ glycerol. Pseudo-Hypertriglyceridemia. Molecular genetic test.	Treatment of associated conditions; fat-restricted diet

iii. Disorders of fatty acid beta oxidation

- The typical feature is hypoketotic hypoglycaemic coma, which may be accompanied by signs of liver dysfunction. The first manifestation is frequently in late infancy, precipitated by fasting or infection with vomiting.
- Clinical: Severe deficiencies of the carnitine shuttle and long-chain fatty acid oxidation cause severe neonatal lactic acidosis, hyperammonaemia (esp. in Carnitine-acylcarnitine translocate (CACT) deficiency), hepatopathy, cardiac arrhythmias and cardiomyopathy, often lethal.
- Milder deficiency variants of long-chain fatty acid oxidation and the carnitine shuttle may manifest in adolescence or early adulthood as chronic muscle weakness, pain, or recurrent rhabdomyolysis (sometimes precipitated by exercise or infection) or cause acute or chronic cardiomyopathy.
- Other manifestations include retinopathy, often starting in infancy, and peripheral neuropathy.
- Diagnosis: DBS acylcarnitines analysis is usually diagnostic but may be normal when well. It is important to repeat when unwell. Urine organic acid and serum total/free carnitine may be helpful. Molecular genetic test for confirmation.
- Treatment: Avoid fasting, early intervention in intercurrent illness e.g. gastroenteritis, etc.
- Acute: high dose iv glucose (7 - 10 mg/kg/min). **Do not give iv lipids.**
- **In proven disorders of long-chain fatty acid oxidation and the carnitine shuttle:**
- Acute: dialysis (rarely needed); medium-chain triglyceride via NG-tube or G-tube as slow continuous drip as needed
- Long-term: restrict dietary long-chain fatty acids; Low-fat or medium-chain triglycerides rich medical formula; frequent meals, continuous nocturnal feeding; mixture of essential long-chain fatty acids (alpha-linoleic, linoleic); consider triheptanoin

Multiple acyl-CoA dehydrogenase deficiency (a.k.a. Glutaric aciduria type 2)

- Deficient electron transfer from the FAD-dependent dehydrogenases to the respiratory chain; does not only affect fatty acid oxidation but also dehydrogenases involved in the metabolism of amino acids (e.g. Val, Leu, Ile, Trp, Lys).
- Clinical: Severe form: neonatal acidosis, hypotonia, hypoglycaemia, hyperammonaemia, hepatomegaly; odor of sweaty feet; facial dysmorphism, congenital malformations (renal cysts, hypospadias, etc.); usually fatal in the first weeks of life.
- Attenuated forms: episodic hypoglycaemia, liver dysfunction; cardiomyopathy; progressive encephalopathy, epilepsy; myopathy. Sometimes riboflavin responsive
- Diagnosis: DBS acylcarnitines. Urine OA: ↑ lactic, ↑glutaric, ↑ethylmalonic, ↑ dicarboxylic acids. Molecular genetic test.
- Treatment: Avoidance of fasting; frequent meals, low-fat diet; trial of riboflavin 100 - 150 mg/day.

iv. Disorders of ketone body metabolism

DISORDER	CLINICAL	DIAGNOSIS	TREATMENT
HMG-CoA synthase deficiency#	Acute hypoketotic hypoglycaemia, relative short fasting tolerance	Urine OA: dicarboxylic aciduria without ketosis, ↑ 4-hydroxy-6-methyl-2-pyrone (only in acute sample). Molecular genetic test	Avoidance of fasting
HMG-CoA lyase deficiency#*	Acute hypoketotic hypoglycaemia, metabolic acidosis, liver disease, often fatal with Reye-like crisis	Urine OA: ↑ 3-hydroxy-3-methylglutaric acid, ↑3-methyglutaconic acid. Molecular genetic test	Acute: as for organic aciduria – high dose IV glucose, carnitine. Do not use iv lipids. Long term: low fat diet (25% of daily energy requirement), protein restriction, carnitine.
Succinyl-CoA:3-oxoacxid-CoA transferase (SCOT) deficiency##	Recurrent severe ketoacidosis, hyperketotic hypoglycaemia	Fed state: persistent ketonuria; Fasting state: excessive ketonuria. Molecular genetic test for confirmation.	Acute: high dose IV glucose (7 - 10 mg/kg/min). Long term: avoidance of fasting, adequate caloric intake
Methylacetoacetyl-CoA thiolase deficiency (a.k.a. β-ketothiolase deficiency) ##	Recurrent severe ketoacidosis, hyperketotic hypoglycaemia ± ↑ NH_4^+ ± ↑ lactate	Urine OA: specific metabolites (e.g. ↑2-methyl-3-hydroxybutyrate, ↑tiglylglycine, ↑2-methylacetoacetate). Molecular genetic test	

#Ketogenesis disorders; ##Ketolytic disorders; *also affects Leucine catabolism

v. Pyruvate dehydrogenase complex deficiency

- Clinical: Neonatal encephalopathy, lactic acidosis, brain malformations (e.g. corpus callosum agenesis), dysmorphism; progressive encephalopathy in infancy (incl. Leigh or Leigh-like syndrome, focal brainstem lesions), apnea, episodic weakness, seizures; intermittent acute peripheral neuropathy, dystonia: childhood-onset intermittent episodes of weakness and ataxia. Most frequent PDHA1 variant (X-linked) – males are more severely affected than females.
- Diagnosis: ↑Lactate, pyruvate, alanine in body fluids, n- ↓lactate/pyruvate ratio; molecular genetic test.
- Treatment: trial of thiamine (150 - 1000 mg/day), ketogenic diet
- Prognosis: often poor in early onset patients

vi. Disorders of creatine biosynthesis or transport

- Clinical: intellectual disability, speech impairment and epilepsy due to cerebral creatine deficiency.
- Diagnosis: Low creatine concentrations in the brain can be recognized by MR spectroscopy; abnormal concentrations of creatine/creatinine and its precursor guanidinoacetate are usually found in serum and urine. Molecular genetic test for confirmation.
- Treatment: Creatine 400 mg/kg/day

vii. Glucose transporter protein deficiency (GLUT1 deficiency)

- Clinical: Severe forms: epileptic encephalopathy of infancy or early childhood, (secondary) microcephaly, psychomotor retardation. Milder variants: (exercise induced) fluctuating movement disorders (ataxia, spasticity, dystonia, chorea), childhood/juvenile/adult-onset absence epilepsy
- Diagnosis: CSF analysis (following a 4 - 6 hours fast): ↓ Glc < 2.7 mmol/l, CSF/blood Glc ratio <0.45 (normal 0.65 ± 0.1), n-↓ lactate/alanine; molecular genetic test (SLC2A1 gene)
- Treatment: Ketogenic diet; avoidance of drugs that inhibit GLUT1 (e.g. barbiturates, chloral hydrate, diazepam, tricyclic antidepressants, ethanol, methylxanthines/green tea)
- Prognosis: Satisfactory with early treatment

viii. Primary mitochondrial disorders (PMDs)

- A heterogeneous group of inborn errors of oxidative phosphorylation/ mitochondrial energy production caused by pathogenic variants in several hundred different nuclear and mitochondrial DNA genes.
- Mutations in nuclear genes coding for respiratory enzyme complexes structural subunits and assembly factors or proteins needed for mitochondrial DNA (mtDNA) maintenance & replication or gene expression predominate in younger age group.
- MtDNA mutations, often inherited in variable heteroplasmy (a situation where mutant and wild-type mtDNA coexist within the same cell) levels from mother, are more frequently associated with specific clinical syndrome and may present at any age.
- Heteroplasmy level may vary between cells, tissues, organs or different individuals carrying the same mtDNA mutation.
- A higher heteroplasmy (60% -80%) may lead to clinical symptoms while a low level of heteroplasmy may be clinically silent. E.g. For m.8993T>G and m.8993T>C pathogenic variants:

Heteroplasmy level	Clinical features
≤ 60%	Asymptomatic
~70% - 90%	NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa) syndrome
≥ 90%	Leigh syndrome

- The range of possible symptoms/signs in PMDs are very diverse; could arise from isolated organ (e.g. LHON), or multiple organs (more often)
  - **Central Nervous system:** Seizures, acute encephalopathy, developmental delay, neuroregression, migraine, ataxia, stroke (-like) episodes, malformations
  - **Peripheral nervous system:** Neuropathy
  - **Eye:** Optic neuropathy, retinopathy, ophthalmoplegia, ptosis
  - **Ear:** Sensorineural hearing loss
  - **Heart:** Cardiomyopathy, arrhythmia
  - **Muscle:** Fatigue, exercise intolerance, myopathy
  - **Gastrointestinal system:** Pseudoobstruction, delayed gastric emptying
  - **Liver:** Hepatopathy.
  - **Endocrine system:** Diabetes, hypothyroidism, hypoparathyroidism, hypogonadism.
  - **Kidney:** Renal tubulopathy, glomerulopathy
  - **Blood:** Sideroblastic anemia, pancytopenia, neutropenia
- It may manifest at any age: antenatal, neonatal, infancy, childhood, or adulthood
- Intra-uterine development may be affected, resulting in IUGR and brain malformations.
- Young children frequently present with encephalomyopathic disease while myopathies predominate in older children.
- Variable disease course: progressive, relatively static for long periods of time, or fluctuate with acute illness

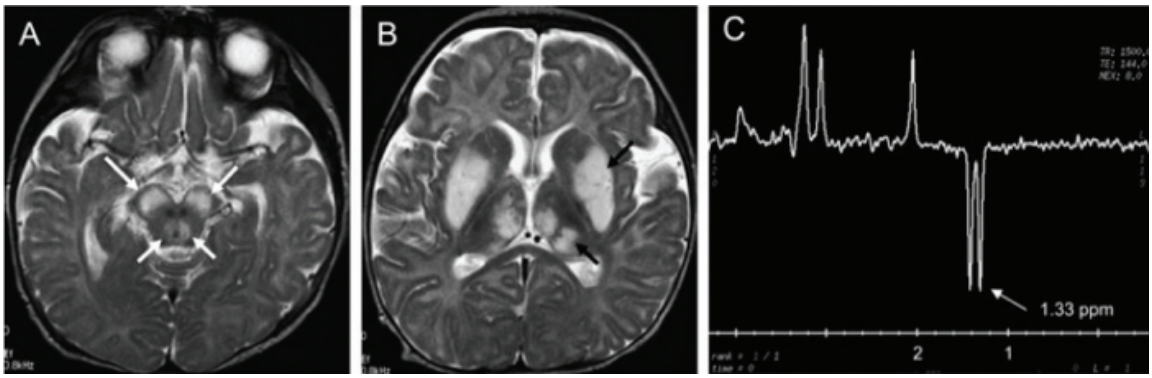
Biochemical Screening Tests in Suspected Mitochondrial Disease	
Test	**Remarks**
Blood lactate	Measure on several occasions, elevated levels are a helpful clue, but normal levels do not exclude mitochondrial disease. Beware of artefactual elevation (struggling child, excessive squeezing); lactate may also be elevated in hypoxia, after seizure, and with certain drugs.
CSF lactate	May be elevated, particularly when there is CNS involvement, but normal levels do not exclude mitochondrial disease.
Plasma amino acids	Elevated alanine may suggest a chronic/persistent elevation in blood lactate (May be the only clue in some patients with normal blood lactate)
Urine organic acids	Urine organic acid analysis may show Kreb's cycle intermediates such as fumarate. In addition, it can show elevated lactic acid, ethylmalonic acid, 3-methylglutaconic acid, MMA.

- Congenital lactate acidosis in newborns

Typical Characteristics of Elevated Lactate by Cause in newborns

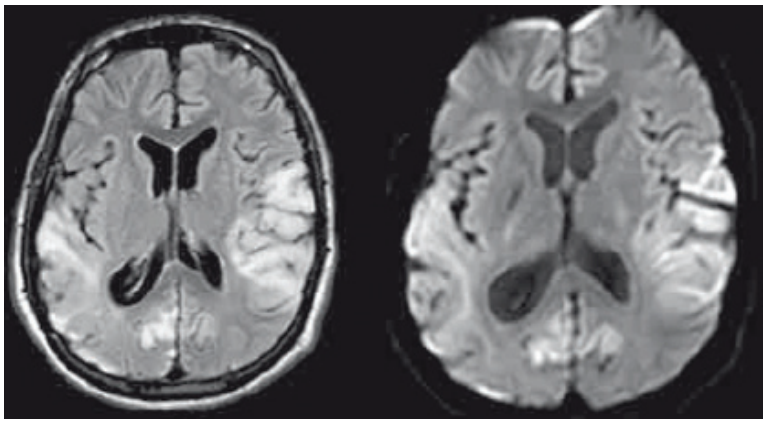
	Clinical Characteristics	Lactate	Lactate/ Pyruvate Ratio	Other biochemical Features
Spurious	Well appearing; phlebotomy difficult; delayed processing of sample	<4 mmol/L	High	None
Secondary to hypoxia	Hypotension, poor tissue perfusion; history of hypoxia or tissue injury	<5 mmol/L in most cases	High	None
Secondary to organic acidurias or Fatty acids oxidation defects	Sudden decompensation at 2-3 days after birth in previously well patient	5–10 mmol/L in most cases	High	May have accompanying hyperammonemia. Urine OA: specific metabolites suggestive of organic aciduria, ketonuria (organic acidurias), or dicarboxylic aciduria (fatty acid oxidation defect). Acylcarnitine profile: Fatty acid oxidation defect.
Primary due to pyruvate metabolic defect	Illness apparent around 24 hours after birth; structural brain anomalies; fetal alcohol-like facial features	10–20 mmol/L	Normal	Plasma amino acids: Very high alanine; citrulline is high in pyruvate carboxylase deficiency
Primary due PMDs (a.k.a Primary lactic acidosis) – generally poor prognosis	Hypertrophic cardiomyopathy; structural anomalies; lens clouding or cataracts; intrauterine growth restriction	10–20 mmol/L	High	Plasma amino acids: high alanine, proline, and often glutamine. Urine organic acids: variable elevations of 3-methylglutaconic acid, fumarate, ethylmalonic acid, dicarboxylic aciduria

- Neuroradiological studies
  - There are certain neuroradiological findings that are sensitive and quite suggestive in diagnosis of mitochondrial disease. MR spectroscopy may reveal lactate accumulation. CT brain may reveal symmetrical calcification, e.g. in basal ganglia. Four recognized MRI brain patterns are as follow:
    - Leigh syndrome pattern



Characteristic brain MRI pattern of Leigh syndrome. (A) Axial T2 weighted images show important bilateral hyperintensities in the brainstem (white arrows). (B) Axial T2 weighted images show hyperintensities in the basal ganglia and thalami (black arrows). (C) Magnetic resonance spectroscopy shows a lactate peak at 1.33 parts per million (ppm) (white arrow).

- Stroke-like pattern



Fluid-attenuated inversion recovery (left) and diffusion-weighted (right) MR brain images of a patient with MELAS showing the patchy abnormalities in multiple regions of the cortical tissue (not confined to a vascular territory). Acute changes may fluctuate, migrate, or even disappear completely during the acute to subacute phase.

- Leukodystrophy (frequently diffuse, patchy, or cystic/cavitating white matter lesions)
- Cerebral or cerebellar atrophy (non-specific) or pontocerebellar hypoplasia (e.g. PCH6)

- The molecular genetic test has rapidly evolved to become the confirmatory test of choice for the definitive diagnosis of mitochondrial disease.

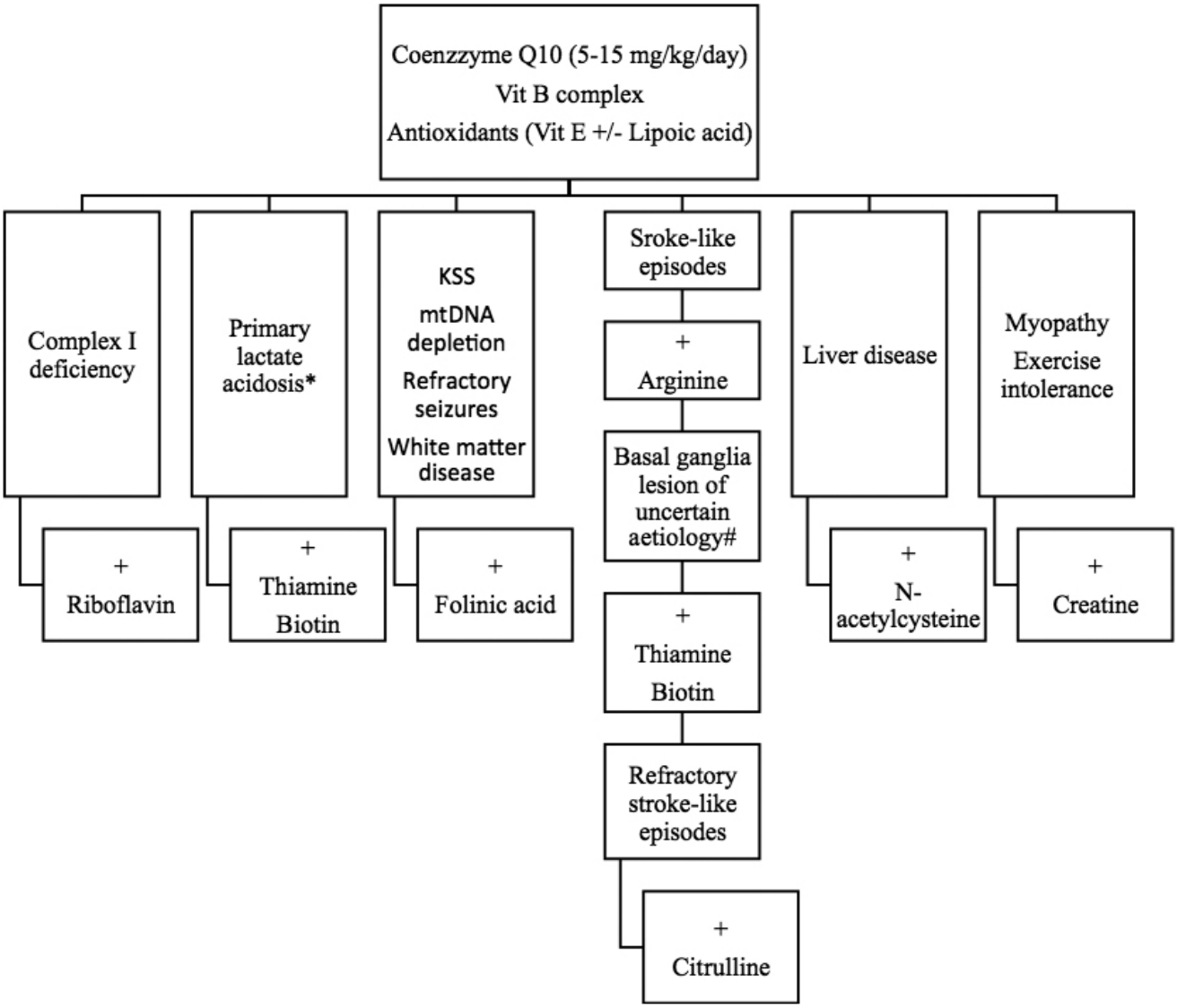
Molecular Genetic Diagnostic Approaches for Mitochondrial Disease	
Molecular Genetic Test	**Remarks**
Targeted mtDNA genetic testing for point mutation and/or single large-scale deletion	When the clinical presentation is typical, targeted genetic test allows confirmation of a clinical diagnosis. For example, testing for common mtDNA mutations for MELAS; single large scale deletion test for Kearns-Sayre syndrome. A negative blood result does not rule out the diagnosis because of tissue-dependent and age-dependent variation in heteroplasmy level (blood heteroplasmy level decreases significantly over time). It should be repeated on other tissues (that are clinically more severely affected and/or heteroplasmy level shows very little age-dependent variation) e.g. uroepithelial cells (urine sample), muscle, buccal mucosa cells, etc.
Targeted nuclear gene sequencing	Example: Sequencing of POLG1 when clinical presentation (childhood onset progressive encephalopathy, seizures, liver failure) is typical.
Targeted nuclear gene panel	When there are findings indicating a particular condition that is genetically heterogeneous. For example, mtDNA depletion panel when mtDNA depletion syndrome is suspected.
Whole exome/genome sequencing that includes mitochondrial genome sequencing	This is the most comprehensive approach. It not only allows diagnosis of a mitochondrial disorder but also other disorders that are in the differential diagnosis. However, there is a likelihood of finding more variants of unknown significance.

- Treatment: A multidisciplinary team is required to provide supportive care.
- General measures:
  - Ensure adequate intake of calories, fluids and electrolytes; avoid fasting
  - Avoid/treat condition with high energy consumption:
    - Treat fever efficiently.
    - Treat seizures/epilepsy efficiently (avoid valproate)
- Metabolic acidosis is common in PMDs. Types of acidosis: ketoacidosis (due to impaired β-hydroxybutyrate oxidation), lactic acidosis and renal tubular acidosis. Symptoms, signs with acidosis: mental state changes, hyperpnea, bradycardia, hypotension, arrhythmia, anorexia, vomiting, failure to thrive, delayed myelination, etc.
  Acute treatment:
  - Corrects metabolic acidosis with iv Sodium Bicarbonate.
  - Monitor for hypernatremia and respiratory failure.
  - Minimize dextrose to maintain euglycemia (High dextrose can cause increased elevation in lactate).

  Long term treatment: Consider ketogenic diet.

- Contraindicated drugs:
  - Sodium valproate -Absolute contraindication in PMD caused by POLG mutations. In other PMDs, may be considered in exceptional circumstances.)
  - Aminoglycosides – For short term, emergency use – the benefits outweigh the risks. For long term elective use – must exclude mtDNA mutations (m.1555A>G, m.1494C>T in MT-RNA1) that are associated with aminoglycoside-induced sensorineural hearing loss.
  - Lactated Ringers (LR) - If Lactate < 5 mmol/L, LR is not contraindicated. If LR is deemed the most appropriate resuscitation fluid, benefit may outweigh risk for individual patients

- General anaesthesia and surgery
  - In general, most PMD patients tolerate anaesthetics well
  - Most risk attributable to the severity and extend of organ involvement such as cardiomyopathy, respiratory muscle weakness, bulbar dysfunction or severe lactic acidosis. Performs baseline comorbidities evaluation.
  - Fasting should be minimized and caloric and fluid intake maintained
  - small intravenous boluses of propofol (avoid prolonged use as the maintenance of anaesthesia), benzodiazepines, or ketamine
- Stroke-like episode (SLE)
  - A subacute, evolving brain syndrome
  - Diagnosis of a SLE requires the combination of clinical assessment, MRI and EEG (and other differential diagnoses excluded)
    - Clinical: headache, nausea and vomiting, complex visual symptoms including visual filed defects, encephalopathy, focal-onset seizures (with or without associated focal neurological deficits) including Epilepsia partialis continua, new-onset neuropsychiatric symptoms (excessive anxiety, aggressiveness, agitation or psychosis - SLE involve frontal, temporal or limbic lobe)
    - MRI brain: cortical and sub-cortical signal abnormalities not confined to vascular territories
    - EEG: focal epileptic discharges
  - Genetic aetiology: m.3243A>G (most common), POLG, other rarer mtDNA mutations
  - Possible pathophysiology mechanisms of SLE: i. mitochondrial angiopathy (impaired vasodilation due to reduced nitric oxide production); ii. mitochondrial cytopathy (causes cytotoxic edema due to ATP depletion, disrupted calcium homeostasis, etc →neuronal hyperexcitibility →driver of SLE is seizure activity →neuronal death if untreated)
  - Treatment: **To treat the seizures/cytotoxic edema** - IV levetiracetam is recommended, but phenytoin (with cardiac monitoring) or phenobarbitone (with respiratory monitoring) can be used. Avoid valproate. To treat **angiopathy** – IV arginine infusion 250 - 500 mg/kg over 60-90 minutes given within 3 hours of symptom onset is recommended. May be given daily for up to 5 days, May stop sooner if neurologic symptoms resolve.
- Although randomized, controlled trial data are lacking, supporting preclinical evidence and favourable benefit to-risk ratios justify empiric trial of vitamins and cofactors to support mitochondrial function in PMDs with further modification based on tolerability concerns or additional patient-specific genetic and/or clinical phenotypes.
- PMDs that are potentially treatable using specific therapies:
  - Disorders of Coenzyme Q10 biosynthesis – high dose of CoQ10 (30mg/kg/day)
  - LHON – idebenone 900mg/day (within 6 months, ideally as soon as possible from onset, maintains for at least 1 year or until a plateau in term of improvement is reached)



Dose: Vitamin E 1-2 IU/day, Lipoic acid 50-600mg/day, Biotin 10-20mg/day, Riboflavin 50-400mg/day, Thiamine 50-300mg/day,
Arginine 150-300mg/kg/day, Citrulline 150-300mg/kg/day, Folinic acid 1.5-5 mg/kg/day, N-acetylcysteine 10mg/kg/day, Creatine 100mg/kg/day
#While investigating for SLC19A3-related Biotin-thiamine-responsive basal ganglia disease;
*While investigating for biotinidase deficiency & PDH deficiency

Disease (onset)	Diagnostic criteria	Symptoms of Acute Decompensation	Common (Chronic) Symptoms	Genetic
Leigh Syndrome (infancy or early childhood)	Both A and B: A. Neurodevelopmental regression or delay B. Bilateral lesions of the basal ganglia, midline brainstem or both by brain CT, brain MRI (T2/ FLAIR hyperintense lesions)	• Rapid progression to respiratory failure • Dysphagia/drooling • Profound (lactic) acidosis • Cardiomyopathy • Metabolic stroke: • Increased weakness, seizures • Hepatopathy • Neuroregression	• Global Developmental Delay • Hypotonia/hypertonia • Movement disorder • Dysconjugate gaze • Elevated lactate in blood and CSF • Abnormal MRI brain • Bilateral basal ganglia and/or brainstem lesions • Eating & swallowing difficulties • FTT • Metabolic acidosis on bicarbonate supplementation	mtDNA point mutations: m.8993T>G/C, other mtDNA muttaions (maternally inherited); Nuclear gene mutations: SURF1, etc. (>100 genes, mostly autosomal recessive, some are X-linked)
MELAS Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like Episodes (4 – 60 yrs, mean at 14 yrs for paediatric cases)	All of A – C: A. Stroke-like episodes (sudden-onset focal neurological deficit with brain MRI or CT showing a cerebral lesion that does not conform to a large vessel territory and typically affects cortex and adjacent white matter) B. Encephalomyopathy C. Lactate acidosis	• Stroke-like episodes: o Focal neurological deficits o Abnormal MRI brain with acute DWI+ o Medically actionable with IV arginine • Seizures: o EPC (epilepsia partialis continua) or o Status epilepticus	• Migraine • Vision loss • Hemiplegia • Seizures • Short stature, FTT • Deafness • Diabetes • Hyperglycaemia, hypoglycaemia • Avoid over treating • DM results from insulin deficiency and resistance • Elevated lactate w/wo metabolic acidosis	mtDNA point mutations: 80% m.3243A>G, 20% other mtDNA mutations (maternally inherited)
Myoclonic Epilepsy with Ragged-Red Fibers (MERRF) (5 – 15 yrs)	All of A – C: A. Myoclonic seizures or myoclonus plus seizures B. Ataxia C. Mitochondrial myopathy (RRF, raised CK)	• Encephalomyopathy • Myoclonic epilepsy	• Ataxia • Neuropathy • Progressive dementia	mtDNA point mutations: 80% m.8344A>G, 20% other mtDNA mutations (maternally inherited)

Common classical mitochondrial syndrome

Disease (onset)	Diagnostic criteria	Symptoms of Acute Decompensation	Common (Chronic) Symptoms	Genetic
Alpers Syndrome (infancy or early childhood)	All of A – C: A. Psychomotor regression B. Intractable seizures (confirmed by EEG and lack of response to at least two anti-seizure medications) C. Hepatopathy (Liver disease/dysfunction)	• Seizures: o Refractory status epilepticus o Epilepsia partialis continua (EPC) o Continuous focal seizure or myoclonus • Fulminant liver failure: o Triggered by sodium valproate o Provoked by ffever, infection	• Developmental regression • Fluctuating LFTs • Elevated CSF protein • Cerebral folate deficiency • Brain MRI may show global atrophy or stroke like lesions	Nuclear genes: mostly *POLG* mutations (autosomal recessive)
Hepatocerebral syndrome (most common phenotype of Mitochondria DNA depletion syndrome in paediatric ages) (infancy or early childhood)	All of A-C A. Progressive or persistent liver dysfunction B. Encephalopathy C. Any one of i. Cognitive impairment ii. Increased skeletal muscle tone (spasticity) iii. Hyperactive reflexes iv. Diffuse, patchy, or cystic white matter lesions evident on brain MRI	• Neonatal hypoglycaemia • Liver dysfunction/failure (may mimic neonatal hemochromatosis) • Encephalopathy • Infection-associated deterioration	• Global developmental delay • Epilepsy • Myoclonus	Nuclear genes including *DGUOK, TWNK,* etc.

Disease (onset)	Diagnostic criteria	Symptoms of Acute Decompensation	Common (Chronic) Symptoms	Genetic
Kearns-Sayre Syndrome (KSS) due a single large scale mtDNA deletion (< 20 yrs)	All of A – D: A. Ptosis, Progressive External Ophthalmoplegia (PEO) or both B. Pigmentary retinopathy C. Cardiac conduction block D. Skeletal muscle involvement	• Hypocalcemia/hypoparathyroidism: • Tetany, seizures, rickets • Diabetes mellitus • Pancreatitis/pancreatic insufficiency • Stroke-like episodes	• CPEO (chronic progressive external ophthalmoplegia) • SNHL (sensorineural hearing loss) • Elevated CSF protein • Cerebral folate deficiency • Ataxia • FTT, short stature • Renal failure • Hepatopathy • Brain MRI Leigh syndrome or white matter changes • Cardiac conduction defects (some have pacemaker)	Single large scale mtDNA deletion (sporadic)
Chronic progressive external opthalmoplegia (CPEO) (early adulthood, occasionally childhood)	A ± B A. Ptosis, Progressive External Ophthalmoplegia (PEO) B. Limb myopathy, exercise intolerance, and dysphagia		• ptosis (bilateral) • limited peripheral vision owing to restricted eye movement: • additional features may include proximal limb weakness, pharyngeal weakness, tremor, ataxia, depression, peripheral neuropathy, SNHL, Cataracts, endocrine dysfunction	50%: Single large scale mtDNA deletion; 50%: nuclear genes including *POLG*
Leber's hereditary optic neuropathy (LHON) (12 – 30 yrs)	Both A and B: A. Acute-onset central vision loss in one or both eyes B. Family history compatible with maternal inheritance and not autosomal dominant inheritance (e.g., no male-to-male transmission)	• visual loss	• subacute painless visual loss; sequentially affect both eyes • males > females 4:1	mtDNA mutations: m.11778G>A, m.3460G>A, m.14484T>C (usually homplasmic, maternal inherited, variable penetrance)

GROUP 3: COMPLEX MOLECULE DISORDERS (2 subgroups)

- This expanding group encompasses diseases that disturb the metabolism of complex molecules that are neither water-soluble nor diffusible: sphingolipids (SPL), triglycerides (TG) phospholipids (PL), complex long chain fatty acids (LCFA), cholesterol and bile acids, glycosaminoglycans (GAGs), oligosaccharides (OLS), glycoproteins, glycolipids and nucleic acids.
- Metabolism of complex molecules take place in organelles (mitochondria, lysosomes, peroxisomes, endoplasmic reticulum and Golgi apparatus) and most pathways involve several organelles and require transporters.
- Clinical symptoms are permanent, very often progressive, independent of intercurrent events, and unrelated to food intake. Most disorders do not present with acute crises.

IIIa: Accumulation of Complex Molecules

- Catabolism or transport defects lead typically to storage of a visible compound like in classical LSD.
- In general there is no antenatal manifestations although in some severe forms, this is possible such as hydrops or malformations.
- Neurological presentations display progressive disorders with neurodegeneration with or without obvious visceral storage signs.
- Diagnosis is mostly based on urine screening (mucopolysaccharides, oligosaccharides, etc.) and leukocytes enzyme analysis and/or molecular genetic testing.
- Main disorders

i. Disorders of glycosaminoglycan degradation/Mucopolysaccharidoses(MPS)

- Clinical: Affected children often appear normal at birth but subsequently develop chronic progressive disease symptoms and signs. Affected organ systems vary between diseases and include the skeletal system and connective tissue (dysostosis multiplex, growth failure, joints contractures, facial dysmorphism, hernias, etc.), the nervous system (progressive neurological abnormalities, developmental regression, etc.), sensory organs (corneal clouding, deafness), internal organs (hepatosplenomegaly, cardiomyopathy, etc.), and others. All MPS are autosomal recessive except Hunter disease (MPS II), which is X-linked.
- Diagnosis: Primarily by the analysis of glycosaminoglycans (GAG) in urine; confirmation by leukocytes enzyme analysis and molecular genetic test.
- Treatment: Enzyme replacement therapy (ERT) for non-cerebral manifestations in MPS I, II, IVA, VI, and VII. Hematopoietic stem cell transplant (HSCT) is treatment of choice for severe MPS I to prevent cognitive decline (need to be performed before 2 yrs old). It can be used in MPS VI, but risks compared to ERT should be balanced; and controversial results in other MPS II. Otherwise, treatment is largely symptomatic.

ii. Pompe disease

- Clinical: Infantile-onset: hypertrophic cardiomyopathy, skeletal myopathy, hypotonia, respiratory failure, large tongue, failure to thrive, typical ECG (P waves, massive QRS wave and shortened PR interval), fatal in the first year if untreated. Late-onset: slowly progressive muscle weakness (only skeletal muscle), respiratory insufficiency.
- Diagnosis: enzyme assay (α-glucosidase) in dried blood spots, molecular genetic test.
- Treatment: ERT, multi-disciplinary supportive care including physiotherapy

iii. Disorders of sphingolipid degradation/sphingolipidoses

- Clinical: Sphingolipids are of special importance in the nervous tissue and reticuloendothelial system. Most sphingolipidoses present with prominent neurological symptoms: developmental delay/regression, epilepsy, ataxia, spasticity. Hepatosplenomegaly and cherry-red macula spot are not uncommon. Dysmorphism (e.g. coarse facies) ± skeletal deformities (dysostosis multiplex) present in GM1 gangliosidosis). Skin angiokeratoma (Fabry disease). Radiologically distinct leukodystrophies are metachromatic leukodystrophy and Krabbe disease. Foam cells in the bone marrow or vacuolated lymphocytes. Due to overlapping clinical features, it is challenging to diagnose specific disease on clinical ground alone.
- Diagnosis: ↑plasma chitotriosidase (in some), enzyme analyses in leukocytes or dried blood spots, and molecular genetic test
- Treatment: Specific therapies are available for some conditions, e.g. ERT for non-neuropathic type of Gaucher disease.

iv. Oligosaccharidoses (deficiency breakdown of sugar side chains of glycoproteins) e.g.fucosidosis, Sialidosis, alpha-mannosidosis, etc.

- Clinical: progressive neurological symptoms, epilepsy, developmental regression, Coarse facies, dysostosis multiplex (mild), angiokeratoma.
- Diagnosis: urine oligosaccharides analysis, enzyme analyses in leukocytes or dried blood spots, and molecular genetic test
- Treatment: symptomatic

v. Mucolipidoses (ML)

- Clinical: combined clinical features of MPS and sphingolipidoses.
- ML-II (a.k.a. i-cell disease) – Hurler-like but earlier, neonatal onset coarse facies, severe dysostosis multiplex
- ML-III – childhood onset, mild-to-moderate dysostosis multiplex, joint stiffness, coarse facies, etc.
- Diagnosis: ↑GAG, ↑multiple lysosomal enzymes in the plasma (due to failure in the transport of soluble lysosomal enzymes from the Golgi apparatus into the lysosome), molecular genetic test.
- Treatment: symptomatic

vi. Neuronal Ceroid lipoidfuscinoses (CLN)

- Clinical: epilepsy, cognitive and developmental regression, and loss of vision (retinal disease), specific EEG changes with photostimulation (CLN1)
- Diagnosis: DBS enzyme assays are available for CLN 1 and CLN2. Molecular genetic test for other types.
- Treatment: ERT for CLN2. Otherwise symptomatic.

IIIb: Deficiency of Complex Molecules

- Defects of synthesis, recycling, intracellular transportation/trafficking of complex molecules.
- No storage material.
- May interfere with fetal development.
- Most are irreversible disorders.
- Many have multisystemic presentation. Almost all present as chronic or progressive diseases independent of food and intercurrent event. Most involve nervous system.
- Only few have metabolic markers (peroxisome and cholesterol disorders)
- For all others the diagnosis is mostly based molecular genetic testing
- In general, there are no specific treatment with rare exception.
- Main disorders:

i. Congenital disorders of glycosylation (CDG)

- It is a large group of rare genetic disorders (~ 160 disorders) that affect the addition of sugar building blocks, called glycans, to proteins in cells throughout the body.
- Clinical: It should be considered in any unexplained clinical condition particularly in multiorgan disease with neurological involvement but also in non-specific developmental disability. Many CDG interfere with neurodevelopment in the foetal life.
- Diagnosis: Serum transferrin isoeletric focusing can be used for the screening of N-linked glycosylation defects. No biomarker for other types of CDG in which diagnosis is relies on molecular genetic test.
- The most common CDG is **Phosphomannomutase deficiency (PMM2-CDG)**:
  - Clinical: infancy: hypotonia, failure to thrive, dysmorphism: inverted nipples & unusual fat pads; multi-system disease (pericardial effusion, liver disease. coagulation defect, endocrine), severe cases fatal in infancy.
  - Late infancy - childhood: global developmental delay, severe cerebellar atrophy, ataxia, seizures, stroke-like episodes, retinitis, skeletal deformities, endocrine abnormalities (e.g. hypothyroidism, hypogonadism)
  - Diagnosis: Serum transferrin isoelectric focusing -Type I pattern. Enzyme assay and molecular genetic test.
  - Treatment: symptomatic

ii. Peroxisomal disorders

- A group of IEM affecting either the peroxisome biogenesis or a specific single enzyme involving the catabolism of very long chain, and branched chain fatty acids (phytanic acid), or complex molecule synthesis like bile acids or plasmalogens.
- Clinical: Many present at birth with a polymalformative syndrome, like Zellweger syndrome. Others present later between the 1st and 2nd decade of life with neurodegenerative disorders (Refsum disease, X-linked adrenoleukodystrophy, etc.)
- Diagnosis: ↑plasmaVLCFA found in majority of peroxisomal disorders. Many other biomarkers. Molecular genetic testing for definitive confirmation.
- Treatment: mostly symptomatic.

Zellweger syndrome: neonatal presentation with severe hypotonia, seizures, liver dysfunction (severe jaundice, cholestasis), dysmorphic and skeletal abnormalities, sensorineural deafness, retinopathy, cataracts, failure to thrive; X-ray: stippling of the epiphyses; MRI: pachypolymicrogyria; fatal within a few months.

X-linked adrenoleukodystrophy(ALD): Most common peroxisomal disorder.
Clinical: Childhood cerebral form: behavioural changes (e.g. ADHD), visual/hearing impairment, intellectual regression, ataxia, adrenal insufficiency, MRI brain -leukodystrophy predominantly involving the occipital lobe. Decerebration within 2 - 4 yrs. Adrenomyeloneuropathy (adolescent/young adult): progressive spastic paraparesis, sphincter problems, adrenal insufficiency. Addison disease only (childhood-adult): very rare.
Diagnosis: ↑plasma VLCFA. Molecular genetic test.
Treatment: Early hematopoietic stem cell transplantation. "Lorenzo's oil" is not effective.

iii. Others

- Phospholipids (PL), glycosphingolipids (GSL) and Fatty acids (FA) (long, very long, ultra long chain FA) synthesis and remodelling defects: a variety of progressive neurodegenerative symptoms, myopathy and cardiomyopathy (e.g. Barth syndrome), orthopedic signs (bone and chondrodysplasia, malformation), syndromic ichthyosis, and retinal dystrophy.
- Cholesterol and bile acid synthesis defects present either with polymalformative syndromes such as in Smith-Lemli-Opitz (SLO) syndrome, neonatal cholestasis, or with late-onset neurodegenerative disorders such as cerebrotendinous xanthomatosis (treatable by chenodeoxycholic acid).
- Glycosaminoglycans (GAG) synthesis disorders should be suspected in patients with a combination of characteristic clinical features in more than one connective tissue: bone and cartilages (short long bones with or without scoliosis), ligaments (joint laxity/dislocations) and the subepithelium (skin, sclerae). Some produce distinct clinical syndromes with bone dysplasias.

Chapter 101:
Common Genetic Syndromes in Paediatrics

DOWN SYNDROME (DS)

- Caused by the presence of a supernumerary chromosome 21, hence Trisomy 21.
- The most common chromosomal cause of intellectual disability, with a distinct collection of symptoms and clinical manifestations affecting multiple body systems.
- Originally described by John Langdon Down in 1866 though the chromosomal cause was only delineated in 1959.

Chromosomal Basis of Down syndrome	
Meiotic nondisjunction	95%
Translocation	3-4%
Mosaicism	1-2%
Partial trisomy	Rare; <1%
Recurrence Risk by Karyotype	
Nondisjunction Trisomy	
47(XX or XY) + 21	1% or maternal age related risk, whichever is higher
Translocation	
Both parents normal	Low; <1%
Carrier Mother	10-15%
Carrier Father	2-5%
Either parent t(21q;21q)	100%
Mosaics	< 1%
Incidence of Down syndrome	
Overall Incidence: 1 in 800-1000 newborns	
Odds of DS Live Birth by Maternal Age*	
Maternal Age (years)	**Counselling odds***
20	1 in 1450
30	1 in 950
35	1 in 350
40	1 in 85
41	1 in 70
42	1 in 55
43	1 in 45
44	1 in 40
45	1 in 35
47	1 in 30
*Adapted from Morris et al. 2002 table: Observed and predicted odds of Down syndrome live births by maternal age, with suggested counselling odds for use in clinic.	

Medical Problems Common in Down Syndrome	
Newborn	• Congenital heart defects (50%): AVSD [most common], VSD, ASD, TOF, PDA. • Gastrointestinal (12%): duodenal atresia [most common], pyloric stenosis, anorectal malformation, tracheo-oesophageal fistula, and Hirschsprung disease. • Vision: congenital cataracts (3%), glaucoma. • Hypotonia and joint laxity. • Feeding problems: usually resolves after a few weeks. • Transient abnormal myelopoiesis (≤ 10%): usually resolves spontaneously but is associated with a 20-30% risk of AML. • Pulmonary hypertension (1-5%). • Congenital hypothyroidism (1-2%). • Congenital dislocation of the hips. • Craniofacial features: upslanting palpebral fissures, epicanthal folds, flat nasal bridge, protruding tongue, small low-set ears, nuchal folds, flat occiput.
Infancy and Childhood	• Developmental delay. • Intellectual disability- mild to severe (IQ 30-70), language disorders. • Autistic spectrum disorder. • Behavioural problems: inattention, hyperactivity, maladaptive behaviour such as using social distraction to avoid a given task and stubbornness. • Seizure disorder (6-8%). • Recurrent respiratory infections (30-40%). • Hearing loss (>70%): conductive [commonest due to otitis media with effusion], sensorineural, or mixed. • Visual problems (60-80%): strabismus (50%), cataract (3%), nystagmus (35%), glaucoma, refractive errors (70%), nasolacrimal duct occlusion. • Obstructive sleep apnoea is common (30-60%): often multifactorial. • Leukaemia (2-3%; relative risk: 15 to 20 times) • Atlantoaxial instability (15%) – may result in spinal cord compression in 1-2% of cases. Symptoms of myelopathy/spinal cord compression include neck pain, changes in gait, unusual posturing of the head and neck (torticollis), loss of upper body strength, abnormal tendon reflexes, and changes in bowel/bladder functioning. • Hypothyroidism (10%). Prevalence increases with age. • Short stature – usually multifactorial: congenital heart disease, sleep related upper airway obstruction, coeliac disease, nutritional inadequacy due to feeding problems and thyroid problems. Hormone deficiency may contribute to this. • Over/underweight. About half of all DS are overweight by early childhood (3-8 years-old) due to low resting metabolic rates. • Dermatologic problems: seborrhoeic dermatitis, psoriasis. • Moyamoya disease: an uncommon vascular abnormality with an increased incidence among patients with DS.
Adolescence and Adulthood	• Puberty: timing and stages of puberty comparable to other healthy girls and boys. • In females, most ovulate and at least 50-70% are fertile. • Males are usually infertile due to partial gondal dysfunction and impaired spermatogenesis. • May have internalizing symptoms such as anxiety, social withdrawal and depression. • Thyroid disease by adulthood (50%) • Autoimmune conditions: Hashimoto thyroiditis, Graves' disease, Coeliac disease, type 1 diabetes, alopecia areata. • Increased risk of dementia /Alzheimer's disease in adult life. • Shorter life expectancy especially in those with congenital heart disease.

Management

- Communicating the diagnosis and counselling is preferably provided in private by a senior medical officer or specialist who is familiar with the natural history, genetic aspect and management of Down syndrome.
- Careful examination to look for associated complications.
- Initial investigations:
  - Pre or postnatal chromosomal analysis for confirmation of diagnosis.
  - Full blood count (FBC) and differentials
  - T4 /TSH at birth or by 1-2 weeks of life.
  - Echocardiogram by 2 weeks (if clinical examination or ECG were abnormal) or by 6 weeks old.
- Early intervention programs should begin at diagnosis if health condition permits.
- Assess understanding, strength & needs of family. Contact with local parent support groups should be provided. Some useful web resources are:
  - The Down Syndrome Medical Interest Group (UK and Ireland) www.dsmig.org.uk
  - The Down Syndrome Medical Interest Group-USA https://dsmig-usa.org/
  - Down Syndrome: Health Issues www.ds-health.com
  - Growth charts for children with Down Syndrome www.growthcharts.com
  - Educational issues www.downsed.org
  - Kiwanis Down Syndrome Foundation http://www.kdsf.org.my/
  - Persatuan Sindrom Down Malaysia http://downsyndromemalaysia.com/
  - Jabatan Pendidikan Khas http://www.moe.gov.my/index.php/my/pendidikan-khas
  - Jabatan Kebajikan Malaysia. http://www.jkm.gov.my/
  - Educational & support centre. http://www.malaysiancare.org/pwd_list

- Health surveillance & monitoring: refer to table below

Recommendations for Medical Surveillance for Children and Adolescents with Down Syndrome

	Birth - 6 weeks	4 - 6 months	12 months	18 months - 2½ years	3 - 3½ years	4 - 4½ years
Thyroid function tests[1]	T4, TSH	T4, TSH	T4, TSH	Annual T4, TSH surveillance		
Other Blood tests	FBC		FBC	FBC annually		
Growth monitoring[2]	Length, weight and head circumference checked regularly and plotted on Down syndrome specific growth charts.			Length and weight should be checked at least annually and plotted on Down syndrome specific growth charts.		
Eye examination	Visual behaviour. Check for congenital cataract and other eye anomalies	Visual behaviour. Check for congenital cataract and other eye anomalies	Visual behaviour. Check for congenital cataract and other eye anomalies	Formal Orthoptic, refraction, fundoscopic examination[3]		Visual behaviour. Check for congenital cataract and other eye anomalies
Hearing check	Neonatal screening	Full audiological review (hearing, auditory thresholds, impedance testing, otoscopy) by 6-10 months, then 6 monthly till 2 years-old, and then annually throughout school-age years.				

	Birth - 6 weeks	4 - 6 months	12 months	18 months - 2½ years	3 - 3½ years	4 - 4½ years
Cardiology Other advice	ECG within 2 weeks Echocardiogram 0-6 weeks		Screen for sleep disorders from 6-12 months old	Dental assessment		

Age 5 to 19 years	
Paediatric review	Annually Auscultation of the heart as part of routine monitoring
Hearing	Annually throughout school-age years, then 2 yearly audiological review throughout adult life
Vision/ Orthoptic check	2 yearly throughout life
Thyroid function tests Blood Tests	Annual T4, TSH surveillance life-long Annual FBC (Hb)
School performance	Check school performance and placement
Sexuality and employment	To discuss when appropriate, in adolescence Pubertal growth
Transition	Discuss transition to adulthood and transition to adult health care from adolescence

Note: The above table are suggested ages. Check at any other time if parental or other concerns. Perform developmental assessment during each visit.

Anticipatory Guidance:

1. Vaccinations: encouraged to follow National schedule; may offer influenza vaccine
2. For atlanto-axial /craniovertebral instability: Small risk for major neurological damage but cervical spine X-rays in children have no proven predictive validity for subsequent acute dislocation/ subluxation at the atlantoaxial joint. Children with DS should not be barred from normal sporting activities, with a clinical screening protocol for specialised sports. Appropriate care of the neck while under general anaesthesia or after road traffic accident is advisable.
3. Importance of early commencement of interventional therapies.
4. Offer resources and support services.

Table Footnote:

1. Asymptomatic patients with mild elevation of TSH (<10mU/l) but normal fT4 may not need treatment but recommended to test more frequently for uncompensated hypothyroidism. Offer thyroid peroxidase (TPO) antibodies testing if clinical suspicion of thyroid dysfunction at any stage.
2. Down syndrome centile charts at www. growthcharts. com. Consider weight for length charts of typically developing children for weight assessment. If BMI > 98th centile or underweight, refer for nutritional assessment and guidance. Re-check thyroid function if accelerated weight gain.
3. Performed by an ophthalmologist/ optometrist.

Adapted from Down Syndrome Medical Interest Group (DSMIG UK and Ireland) Guidelines/ Health Supervision for Children with Down Syndrome, American Academy of Pediatrics (2022)

TURNER SYNDROME (TS)

Introduction

- Synonymous: Ovarian hypoplasia syndrome/ Monosomy X/ XO syndrome
- First described by Henri Turner in 1938.
- It is the most common sex chromosomal abnormality found in females
- TS results from a deletion or the non-functioning of one X chromosome in females. 50% of TS have monosomy X (45,XO) and the other 50% of the population has a mosaic chromosomal component (45,X with mosaicism).

Epidemiology

Incidence: 1 in 2000 to 1 in 2500 live female births, prevalence unknown because of underdiagnosis

Presentation

Antenatally	**Infancy**	**Childhood**	**Adolescents**
Fetal hydrops Cystic hygroma Cardiac defects	Oedema of hands & feet	Poor growth /short stature Webbed neck Wide carrying angle	Delayed puberty/ amenorrhea Short stature Webbed neck

Diagnosis

The first step is a karyotype analysis with peripheral blood mononuclear cells. If TS is clinically suspected and the karyotype is negative, more cells should be analyzed on karyotype to exclude mosaic Turner.

Short Stature

- Girls with TS have short stature, and requires close monitoring of growth parameters. TS does not cause growth hormone deficiency but respond well to growth hormone therapy. Growth hormone treatment should be started once their height falls below 5% for age. Growth hormone therapy should continue until the patients reach their adult height and no longer have any growth potential.

Cardiac

- Coarctation of aorta (CoA) and bicuspid aortic valve are associated with TS. The other common cardiac problem is prolonged QT intervals. An echocardiography, ECG and assessment by cardiologist is required at time of diagnosis. If CoA is present, it may require corrective surgery. Throughout life, patients' need to be monitored annually for re-coarctation of aorta and aortic dilation.
- Blood pressure should be measured in the upper and lower extremities, there may discrepancy of upper and lower limb BP if CoA is present. Blood pressure should be maintained within the normal range to help decrease the risk of aortic dilation and dissection. Blood pressure should be controlled using beta-blockers as first-line, followed by ACE inhibitor.
- QT-prolonging drugs (antiarrhythmics, macrolide and fluoroquinolones, metronidazole, some antifungals, and antiretrovirals, psychiatric medications) should be avoided.

Cognitive function/learning disabilities

- Often have learning disabilities despite normal intelligence, may require special education and assessments at school.

Renal

- A renal ultrasound is necessary at the time of diagnosis. Common renal abnormalities encountered: collecting system malformations, positional/horseshoe kidney and malrotated kidneys

Ovarian Failure

- Estrogen therapy - Almost all girls with Turner syndrome need estrogen, even if they have spontaneous puberty. Estrogen therapy should be initiated at around 11 to 12 years of age if gonadotropins are elevated or there is no development of secondary sexual characteristics. Later, cyclic progestins are added to the regimen to induce cyclic uterine bleeding and prevent endometrial hyperplasia.

Osteoporosis/Bone Health

- Patients have an increased fractures because of low mineral density and osteoporosis. Their risk becomes lowered with estrogen therapy and supplemental vitamin D and calcium. TS also have risk for developing scoliosis, and need to be screened annually. Patients on growth hormone therapy may need more frequent screening for scoliosis. Monitor Vit D levels.

Screening for other comorbidities

- Celiac disease – Tissue transglutaminase immunoglobulin A antibodies should be measured if there are symptoms.
- Metabolic syndrome –there is risk for developing central obesity, type 2 diabetes mellitus and dyslipidemia. HbA1c and lipid profile should be measured annually, beginning at ten years of age.
- Gonadoblastoma – Patients with TS with marker chromosome elements on karyotype or patients who develop virilization, should be screened for the Y chromosome. If the Y chromosome is present, gonads should be removed, to prevent gonadoblastoma.

PRADER-WILLI SYNDROME (PWS)

- PWS is an imprinting disorder where the Prader-Willi Critical Region on chromosome 15q11.2-q13 demonstrates maternal-only imprinting (loss of paternal-only expressed genes).
- Hallmark features include severe hypotonia and feeding difficulties in infancy, followed by easy weight gain, then excessive eating and morbid obesity in early childhood unless externally controlled.
- Consensus diagnostic criteria for PWS have been developed by Holm et al. (PMID: 8424017)

Genetic mechanisms and testing strategies

Genetic mechanism	Proportion of PWS	Testing method*	Recurrence risk*
Paternal deletion	65%-75%	MS-MLPA FISH for SNRPN Chromosome microarray	<1%
Maternal uniparental disomy (UPD)	20%-30%	MS-MLPA SNP array	<1%
Imprinting defect (ID): -Imprinting center (IC) deletion -Epimutations	<0.5% 2%	MS-MLPA	Up to 50% if father also has an IC deletion <1%

*All patients tested positive via MS-MLPA, FISH, and microarray require a conventional karyotyping to detect chromosomal rearrangements that has implications for further parental testing and potential increased recurrence risk.

DNA methylation studies and MS-MLPA detect up to 99% of PWS.

Suggested testing strategy is MS-MLPA followed by microsatellite studies (for the non-deletion type) to distinguish between maternal UPD and imprinting defect.

Genetic counselling is recommended to detect occasional families with high recurrence risk and to investigate for PWS-like conditions following a negative PWS test.

Treatment strategies

A multidisciplinary approach is recommended.

Endocrinopathies

Growth hormone deficiency

- Early treatment with growth hormone (GH) improves growth, development, body composition and cognition.
- There is evidence to support early treatment before the onset of obesity, including during infancy.
- Polysomnography should be performed prior to GH initiation and 6-12 monthly afterward.

Central hypothyroidism

- Annual thyroid function test, low threshold for treatment.

Central adrenal insufficiency

- Children with PWS may be unable to mount a stress response although baseline cortisol levels are normal.
- Consider checking early morning cortisol and prescribing stress dose steroids during significant illness, or before surgical procedures.
- Monitor for hypoglycemia particularly in infants.

Hypogonadism

- Consider a trial of HCG for undescended testes.
- If testes do not descend by 18 months old, surgery is recommended.
- Consider cautious titration of gonadal steroid replacement to initiate secondary sexual characteristics during adolescence.
- Males are usually infertile. Females may be potentially fertile and the recurrence risk needs to be explored.

Type II diabetes mellitus

- To screen annually especially in obese PWS patients and treat as necessary.

Osteoporosis

- Bone density can be monitored by age of puberty (~ 14 years old).
- Ensure adequate nutritional intake of calcium/vitamin D and physical activities.

Nutrition

Infantile hypotonia, feeding and swallowing difficulties

- May need special feeding techniques e.g. orogastric tube feeding.
- Avoid gastrostomy tubes (risk of gastric dilatation and necrosis).
- Early referral to the dietician, speech and occupational therapist is recommended.

Hyperphagia

- Close oversight of diet throughout life with a dietician familiar with PWS. (PWS clinic dieticians are contactable through HKL Dietetic Department)
- Monitor for food seeking and food stealing behaviours and suggest appropriate interventions

Recommendations for Energy Intake:

- PWS patients only need about 60% of recommended daily allowance for age.
- The RYG (Red, Yellow, Green) system is effective for weight management in PWS patients
- For weight reduction, the recommendation is 7-9 kcal/cm height.
- For weight maintenance, 10-11 kcal/cm height.
- For older children and adults, recommendation is 800-1100kcal/day.

Daily exercise is essential for calorie expenditure, physical and motor development, glycemic control and stress reduction. PWS patients are insensitive to thirst, water must be offered regularly. Use of non-nutritive sweeteners are discouraged as it will augment craving and preference for sweet things.

Sleep Apnea

- Children with PWS are prone to sleep disordered breathing – central sleep apnea in infancy and obstructive sleep apnea (OSAS) in older children.
- Symptoms should be monitored at each visit, with low threshold to refer for polysomnography.

Temperature Dysregulation

- Body temperature may not increase during infection and therefore antibiotic therapy should not be delayed if suspicion for infection is high.
- Advise appropriate clothing and additional fluid intake during outdoor activities/sports

Scoliosis

- Monitor from infancy. Do not sit children upright until they are able to pull to sit on their own.
- Not a contraindication for treatment with growth hormone.

Patient support groups such as the PWS association can support families with PWS children. Introduction to such groups is recommended following diagnosis.

MARFAN SYNDROME

Marfan syndrome (MFS) results from an autosomal dominant mutation of the gene fibrillin-1 (FBN1) which is the main component of microfibrils, resulting in numerous possible deformities and defects involving the connective tissue. 75% cases are inherited from either of the parents and hence the importance of examining parents and siblings if necessary.

Clinical features

Manifestations vary widely, but the principal structural defects involve the cardiovascular, musculoskeletal and ocular systems, causing a typical constellation of long limbs, aortic root dilation, and dislocated lenses.

Diagnosis

Diagnose using revised Ghent criteria (see appendix, also available at Marfan Foundation); genetic testing is recommended for confirmation of diagnosis. Echocardiogram should include measurement at the aortic root at the sinus of Valsalva and the z-score calculated according to age, gender and BSA (https://marfan.org/dx/zscore-children/).

Management

1. All patients should routinely be given beta-blockers (atenolol, propranolol) to help prevent cardiovascular complications. These drugs lower myocardial contractility and pulse pressure and reduce progression of aortic root dilatation and risk of dissection. Angiotensin II receptor blockers also may be given. Aortic dissection is the most dangerous complication.
2. Prophylactic surgery is offered if aortic diameter is > 5 cm (may be less in children).
3. Severe valve regurgitation is surgically repaired.
4. Bacterial endocarditis prophylaxis before invasive procedures is not indicated except in patients who have prosthetic valves or who previously had infective endocarditis.
5. Scoliosis is managed with bracing as long as possible, but surgical intervention is encouraged in patients with curves of 40 to 50°.
6. Cardiovascular, skeletal and ocular findings (including echocardiography) should be reevaluated annually.
7. Appropriate genetic counseling is indicated
8. **Prognosis**

Advancements in therapy and regular monitoring have improved quality of life and reduced mortality. Median life expectancy increased from 48 years in 1972 to near normal in people receiving appropriate medical care. However, life expectancy is still reduced for the average patient, primarily because of the cardiac and vascular complications.

Appendix: Revised Ghent criteria

1. Family history: Yes/No
2. Aortic dissection: Yes/No
3. Aortic diameter: Z score :
4. Systemic features score:

In the absence of family history:

Ao=/>2	*EL +ve*	*Systemic score=/>7*	*FBN mutation +ve*	*Diagnosis*
Yes	Yes	No	No	Marfan syndrome
Yes	No	No	Yes	Marfan syndrome
Yes	No	Yes	No	Marfan syndrome
No	Yes	No	Asso with Ao	Marfan syndrome
No	Yes	Yes/No	No/not asso with Ao	ELS
No	No	=/>5[at least 1 skeletal feature]	No	MASS
No but MVP	No	<5	No	MVPS

In the presence of family history:

Ao=/>2	*EL +ve*	*Systemic score=/>7*	*FBN mutation +ve*	*Diagnosis*
	Yes			Marfan syndrome
		Yes		Marfan syndrome
Yes [=/>3 below 20 years]				Marfan syndrome

*Caveat: without discriminating features of SGS,LDS or vEDS
*MASS, myopia, mitral valve prolapsed, borderline (Z<2) aortic root dilatation, striae, skeletal findings phenotype
Systemic score: Maximum total: 20 points; score =/>7 indicates systemic involvement;

Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)	
Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)	
Hindfoot deformity = 2 (plain pes planus = 1)	
Pneumothorax = 2	
Dural ectasia = 2	
Protrusio acetabuli = 2	
Reduced US/LS AND increased arm/height AND no severe scoliosis = 1	
Scoliosis or thoracolumbar kyphosis = 1	
Reduced elbow extension = 1	
Facial features (3/5) = 1 (dolicocephaly, enopthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)	
Skin striae = 1	
Myopia > 3 diopters = 1	
Mitral valve prolapsed (all types) = 1	
Total	

US/LS ratio in children, abnormal ratios are US/LS < 1 (for age 0-5 years), US/LS < 0.95 (for 6-7 years), US/LS < 0.9 (8-9 years old) and < 0.85 (above age 10 years).

OTHER COMMON GENETIC SYNDROMES

Disorder	Clinical Features	Investigations	Management
22q11 deletion syndrome • Autosomal dominant contiguous gene deletion syndrome • De novo in 90% • Inherited from heterozygous parent in 10%	Congenital heart disease (64%) • Particularly conotruncal defects (VSD, TOF, interrupted aortic arch, truncus arteriosus) Palatal abnormalities (67%) • Velopharyngeal insufficiency • Submucosal cleft palate • Cleft palate, bifid uvula • Hypernasal speech Laryngotracheoesophageal abnormalities • Vascular ring • Laryngeal web • Laryngotracheomalacia • Subglottic stenosis Gastrointestinal abnormalities • Structural GI tract abnormalities • Constipation Immune deficiencies (77%) • Thymic hypoplasia • T cell and humoral abnormalities • Recurrent infections Genitourinary tract abnormalities (17%) Developmental delay and learning difficulties (70-90%) Craniofacial features • Hooded eyelids, ear anomalies, bulbous nasal tip, asymmetric crying facies, micrognathia Autoimmune disorders CNS abnormalities Hearing loss Eye abnormalities Skeletal abnormalities	Diagnostic options: • Targeted deletion analysis (95-100%) • FISH 22q11 Chromosome microarray (100%) Recommended surveillance: • Annual full blood count with differential • Antibody studies between 9-12 months • Serum ionized calcium (3-6 monthly during infancy then annually) • Annual thyroid function tests • Annual assessment for scoliosis	Multidisciplinary team management: • Geneticist • Cardiologist • Endocrinologist • Immunologist • Gastroenterologist • Nephrologist • ENT specialist • Ophthalmologist • Audiologist • Speech therapist, occupational therapist, physiotherapist • Dietician Immunologic assessment is recommended prior to administration of live vaccines

Disorder	Clinical Features	Investigations	Management
Williams Syndrome • Autosomal dominant contiguous gene deletion at 7q11.23 involving the ELN gene	Cardiovascular disease (Elastin arteriopathy) • Supravalvular aortic stenosis (75%) • Peripheral pulmonic stenosis Distinctive facies • Periorbital fullness • Stellate iris • Short nose with broad tip • Malar flattening • Thick lips, wide mouth • Small jaw • Large ear lobes Connective tissue abnormalities • Joint/skin laxity • Umbilical/inguinal hernias Intellectual disability Growth abnormalities Endocrine abnormalities • Idiopathic hypercalcemia (15-50%) • Hypercalciuria • Subclinical hypothyroidism (31%) • Early puberty (50%) • Impaired glucose tolerance (26% in adolescence, 63% in young adults) Specific behavioural traits • Overfriendliness, empathy • Generalized anxiety • Specific phobias • ADHD	Diagnostic options: Targeted deletion analysis: • FISH 7q11.23 (100%) Chromosome microarray (100%) Recommended surveillance: • Monitor serum calcium 6 monthly until age 2 years • Urine calcium/ creatinine ratio • Annual TFT until age 3 years • Annual blood pressure monitoring in both arms • Annual eye and hearing assessment • Annual cardiology assessment for the first 5 years, then 2-3 yearly for life	Cardiovascular disease • Surgical correction may be required • Anesthesia evaluation for surgical procedures and sedation due to risk of myocardial insufficiency and cardiac arrest for individuals with biventricular outflow tract obstruction Hypercalcemia • Dietician evaluation and reduction of dietary calcium • Avoid vitamin D supplements • Referral to endocrinologist / nephrologist for persistent hypercalcemia, hypercalciuria, nephrocalcinosis • Refractory hypercalcemia may be treated with oral steroids Hypothyroidism • Oral thyroxine

Disorder	Clinical Features	Investigations	Management
Noonan syndrome (RASopathy) Autosomal dominant inheritance: BRAF KRAS (5%) MAP2K1 MRAS NRAS PTPN11(50%) RAF1 (5%) RASA2 RIT1 (5%) RRAS2 SOS1 (10-13%) SOS2 (4%) Autosomal recessive inheritance: LZTR1 (8%) Inherited from an affected parent in 30-75% of cases	Characteristic facies: • Low set, posteriorly rotated ears with fleshy helices • Widely spaced and downslanted palpebral fissures • Epicanthal folds • Fullness or droopiness of upper eyelids (ptosis) Other features: • Broad or webbed neck • Superior pectus carinatum • Inferior pectus excavatum • Widely spaced nipples • Short stature (50-70%) • Cryptorchidism in males (60-80%) • Lymphatic dysplasia of lungs, intestines or lower extremities Congenital heart disease (50-80%) • Pulmonary stenosis • Atrial septal defects • Hypertrophic cardiomyopathy (10-29%) ECG abnormalities (90%) Joint hyperextensibility Hypotonia Developmental delay Intellectual disability (25%) Coagulation defects Hearing loss Renal abnormalities (11%)	Diagnostic options: Single gene testing for PTPN11 • Identifies 50% of Noonan syndrome Multigene panel testing Whole exome sequencing Recommended surveillance: • Coagulation defects • Coagulation screens: Platelet count, PT/APTT/INR • Specific coagulation defects: Platelet aggregation testing, von Willebrand factor, factor assays Endocrine • IGF-1 levels • TFT • Bone age Renal ultrasound	Short stature • GH therapy may be considered Cardiovascular disease: • Standard treatment as per cardiologist • Percutaneous balloon valvuloplasty for pulmonary stenosis • Hypertrophic cardiomyopathy is associated with significant early mortality Bleeding diastasis • Standard treatment as per hematologist Others: Ophthalmology evaluation Hearing assessment Skin examination Early intervention program (speech and occupational therapy)

Disorder	Clinical Features	Investigations	Management
CHARGE syndrome • Autosomal dominant disorder • Mostly de novo Heterozygous pathogenic variant in the CHD7 gene	Major criteria (4C's): • Coloboma • Choanal atresia or stenosis • Cranial nerve dysfunction (CN I, VII VIII, IX, X) • Characteristic ear abnormalities (CHARGE ear, middle ear and inner ear abnormalities, mixed hearing loss) Minor criteria: • Genital hypoplasia • Developmental delay • Cardiovascular malformations • Growth deficiency • Orofacial cleft • Tracheoesophageal fistula • Characteristic face (CHARGE face) • Typical CHARGE hand Definite CHARGE: 4 major, or 3 major and 3 minor criteria Possible CHARGE: 1 or 2 major and several minor criteria	Diagnostic options: Whole exome sequencing Multigene panel testing which includes **CHD7** gene Single gene testing for *CHD7* gene Recommended surveillance: • Eye assessment • ENT assessment • CT temporal bone/ mastoid • MRI brain • TFT • Calcium and vitamin D levels • Immunologic evaluation • ECG • Echocardiogram • Renal ultrasound • Blood pressure • Males with micropenis: consider HCG stimulation test • Delayed puberty: Evaluate for hypogonadotropic hypogonadism	Multidisciplinary team management: • ENT specialist • Geneticist • Cardiologist • Ophthalmologist • Endocrinologist • Immunologist • Audiologist • Speech, occupational, physiotherapist • Dietician Hearing rehabilitation should be started as early as possible, for optimal language development

Disorder	Clinical Features	Investigations	Management
Rett Syndrome • X-linked dominant inheritance • Heterozygous pathogenic variant in the MECP2 gene in females	Phases of disease: • Normal psychomotor development (first 6-18 months of life) • Short period of developmental stagnation • Rapid regression in motor and language skills (1-4 years) • Long term stability (> 5 years) During phase of neuroregression: • Repetitive, stereotyped hand movements replace purposeful hand use • Loss of previously acquired language skills • Episodic apnea / hyperpnoea • Bruxism • Impaired sleeping pattern • Inappropriate laughing/ screaming spells • Small, cold hands and feet • Diminished response to pain • Intense eye communication – 'eye pointing' • Abnormal muscle tone • Kyphosis/scoliosis • Acquired microcephaly • Seizures • Gait abnormalities	Diagnostic options: Single gene testing for the MECP2 gene Multigene panel which includes the MECP2 gene Whole exome sequencing Recommended surveillance: • Consider EEG and brain MRI if seizures present • Consider polysomnography for sleep disorder • ECG for prolonged QTc • Audiometry • Eye assessment • Bone densitometry for osteopenia • Nutritional status	Individualized treatment based on patient needs Multidisciplinary approach recommended Avoid drugs known to prolong QT interval, as individuals with Rett syndrome are at increased risk of arrhythmias associated with prolonged QTc Genetic counselling - MECP2 molecular testing should be offered to parents, and all first degree female relatives regardless of their clinical status. Apparently unaffected sisters of the proband may have no clinical manifestations due to skewed X-chromosome inactivation

Disorder	Clinical Features	Investigations	Management
Beckwith-Wiedemann syndrome (BWS) • Imprinting disorder caused by molecular defects within the imprinted 11p15.5 region	Cardinal features (2 points per feature) • Macroglossia • Hemihyperplasia • Omphalocele • Multifocal or bilateral Wilm's tumor or nephroblastomatosis • Hyperinsulinism (> 1 week and requiring escalated treatment) • Adrenal cortex cytomegaly, placental mesenchymal dysplasia Suggestive features (1 point per feature) • Birth weight >2SDS above the mean • Facial nevus simplex • Ear creases and/or pits • Transient hypoglycemia (<1 week) • Typical Beckwith-Wiedemann spectrum tumors • Nephromegaly or hepatomegaly • Umbilical hernia and/or diastasis recti >4: Clinical diagnosis of BWS >2 merits genetic testing for BWS	Diagnostic options: Methylation analysis of IC1 and IC2 • Loss of methylation of maternal IC2 (50%) • Paternal UPD for 11p15 (20%) • Gain of methylation on maternal IC1 (5%) *CDKN1C* gene analysis • If methylation analysis negative • Familial BWS • BWS with midline anomalies SNP array • Considered first in proband with intellectual disability Karyotype • Inversion or translocation involving 11p15.5 (<1%)	Hypoglycemia • Prompt treatment to reduce CNS complications Macroglossia • Anticipate difficult endotracheal intubation • Assess for potential sleep apnea • Specialized feeding techniques Assess for nephrocalcinosis in the presence of renal tract anomalies. Surveillance for embryonal tumors: • 3 monthly abdominal ultrasound until age 8 years • 3 monthly alfa-fetoprotein until age 4 years • Annual renal ultrasound between age 8 – 15 years for nephrocalcinosis and medullary sponge kidneys • Annual urinary calcium/ creatinine ratio

Disorder	Clinical Features	Investigations	Management
Silver-Russell syndrome	• Pre and postnatal growth failure • Feeding problems • Relative macrocephaly • Short stature • Triangular face • Frontal bossing • Clinodactyly • Body asymmetry *NH-CSS clinical criteria for Dx	• Hypomethylation of imprinting region 11p15.5 (45-50%) • Maternal UPD chromosome 7 (7-10%) • Deletion/ duplication/ translocation of imprinting region 11p15.5 (1%) • Another 40% meet NH-CSS clinical criteria but no molecular confirmation	Individualized treatment based on patient needs (Multidisciplinary approach) • Monitor for hypoglycemia at birth, increase risk because of IUGR • Treat feeding problem accordingly • Monitor growth and development • Monitor IGF1 levels, if low may benefit from growth hormone therapy • Lower limb discrepancy >2cm may need intervention

Disorder	Clinical Features	Investigations	Management
Tuberous sclerosis	**Neuro cognitive** • Cortical tubers • Subependymal nodules • Subependymal giant-cell astrocytoma(SEGA) • Seizure • TSC associated neuropsychiatry disorders (TAND): • ADHD, ASD, cognitive impairment OCDs, aggressive/ self-harming behavior **Cardiac** • Rhabdomyomas **Renal** • Renal cyst/renal angiolipoma **Dermatology** • Hypomelanotic macule • Ungal/subungal fibroma • Adenoma sebaceum • Forehead plaques • Shagreen patch **Ophthalmology** • Retinal hamartomas *Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference doi: 10.1016/j.pediatrneurol.2013.08.001	Gene mutation identification in • TSC1 gene (26%) • TSC2 gene (69%) • Unknown (5%) Autosomal dominant inheritance. Two thirds of affected individuals have TSC as the result of a de novo pathogenic variant.	Multidisciplinary approach: *Treatment of manifestations:* • SEGAs(large/ life threatening): mTOR inhibitor/ Neurosurgery • Seizures: AEDs especially vigabatrin in infantile spasms/ Epilepsy surgery. • Renal angiomyolipomas >4 cm/ growing rapidly: 1st line : mTOR inhibitors/ embolization/ renal sparing surgery • For facial angiofibromas: topical mTOR inhibitors. • For symptomatic cardiac rhabdomyomas: surgical intervention/mTOR inhibitor therapy • For TAND : psychologist/ psychiatrist Development and Education : early intervention programs / special needs education

Disorder	Clinical Features	Investigations	Management
Neurofibromatosis 1 (NF1)	Diagnostic criteria for NF 1 Clinical diagnosis based on presence of two of the following: 1. Six or more café-au-lait macules over 5 mm in diameter in prepubertal individuals and over 15mm in greatest diameter in postpubertal individuals. 2. Two or more neurofibromas of any type or one plexiform neurofibroma. 3. Freckling in the axillary or inguinal regions. 4. Two or more Lisch nodules (iris hamartomas). 5. Optic glioma. 6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis. 7. First-degree relative (parent, sibling, or offspring) with NF-1 by the above criteria. Arch Neurol 1988;45:575-578	Gene mutation identification in • NF1 gene By using the following: Single gene testing / Multigene panel / Whole exome sequencing Surveillance (Annually): • Neurological examination • Eye examination • Developmental assessment in children • Blood pressure monitoring MRI for identification and follow up of clinically suspected intracranial or other tumours Annual MRI breast/ mammography in women at age 30 years for breast cancer	Multidisciplinary team management: • Geneticist • Neurological • Neurosurgery • Spinal surgeon • Orthopaedic surgeon • Ophthalmologist • Developmental paediatrician • Education specialist Treatment of manifestations: • Surgical treatment of diffuse or large plexiform neurofibromas is possible. • Complete surgical excision of malignant peripheral nerve sheath tumors. • Dystrophic scoliosis need surgical management, no dystrophic scoliosis treated conservatively. • Individualized developmental and educational interventions +/-methylphenidate for ADHD

Disorder	Clinical Features	Investigations	Management

Cornelia de Lange (CdL) syndrome	Distinctive craniofacial features
	• Microcephaly
	• Synophrys with high arched and/or thick eyebrows
	• Long, thick eyelashes
	• Short nasal bridge
	• Upturned nasal tip with anteverted nares
	• Long /smooth philtrum
	• Thin vermilion of the upper lip
	• Down turned corners of the mouth
	• Highly arched palate with or without cleft palate
	• Micrognathia with or without mandibular spurs
	• Prenatal and postnatal growth failure
	• Developmental delay / intellectual disability
	• Limb abnormalities:
	  • Severe limb reduction defects
	  • Oligodactyly
	  • Micromelia
	  • Clinodactyly
	  • Short first metacarpal
	  • Hypertrichosis
		Autosomal dominant CdLS:
		• NIPBL(80%)
		• RAD21(<1%)
		• SMC3(1-2%)
		• BRD4(<1%)
		
		X-linked CdLS:
		• HDAC8(4%)
		• SMC1A (5%)
		
		Unknown (3-5%)
			Multidisciplinary team management. With special consideration on the following:
			• Aggressive management of GERD (medically and surgically)
			• Supplementary formulas
			• Gastrostomy
			• Early intervention: OT/ physiotherapy/ speech therapy
			• Standard treatment: Epilepsy
			• Vision issues Nasolacrimal duct
			• Hearing loss, Ceft palate
			• Cardiac defects, Cryptorchidism/ hypospadias

Coffin Siris syndrome (CSS)	Clinical features: • Fifth-digit nail / distal phalanx hypoplasia/aplasia • Developmental or cognitive delay of variable degree • Facial features: Coarse facial features, wide mouth with thick, everted upper and lower lips, broad nasal bridge, broad nasal tip, thick eyebrows, long eyelashes. • Central Hypotonia • Hirsutism/hypertrichosis • Sparse scalp hair particularly in the temporal regions	Gene panel testing / Whole exome sequencing to identify one of the following mutation: • ARID1B • ARID2 • SMARCB • SMARCE • SOX4 • SOX1 It is a autosomal dominant disorder and majority are De Novo mutations	Multidisciplinary team management: • Geneticist • Early intervention programs • Occupational therapy • Physiotherapy • Speech therapy • Dietitian • Ophthalmologist • Developmental paediatrician • Education specialist

Disorder	Clinical Features	Investigations	Management
Kabuki Syndrome	Typical facial dysmorphic features • Long palpebral fissures, eversion of lateral 1/3 of lower eyelid • Arched and broad eyebrows/ Sparse/notched lateral 1/3 eyebrows • Short columella • Depressed nasal tip • Large/prominent cupped ears • Skeletal anomalies • Spine: sagittal clefts, hemivertebrae, butterfly vertebrae, narrow intervertebral disc space, scoliosis • Others: Brachydactyly V, Brachymesophalangy, Clinodactyly of fifth digits • Persistence of fetal fingertip pads • Intellectual disability • Postnatal growth deficiency.	Gene mutation identification in • KMT2D 75% • KDM6A 3-5% By using the following: Single gene testing / Multigene panel / Whole exome sequencing	IMultidisciplinary team management: • Geneticist • Cardiologist • Ophthalmologist • Endocrinologist • Immunologist • Audiologist • Speech, occupational, physiotherapist • Dietician • Immunologist • Developmental paediatrician • Education specialist

Chapter 102:
Investigating Children Suspected Of Having A Condition With Genetic Basis

- Our understanding of the genetic aetiologies of many paediatric disorders has grown substantially in recent years
- Genetic diseases could be due to
  - **Chromosomal abnormalities** which include numerical abnormalities (aneuploidy) and structural abnormalities (deletion, duplication, insertion, inversion, and translocation). Numerical abnormalities and large structural abnormalities are detectable by conventional karyotyping. Detection of small structural abnormalities such as microdeletion and microduplication (a.k.a. **copy number variations (CNV)**) require molecular tools and techniques e.g. fluorescence in situ hybridization (FISH), Multiple Ligation-Dependent Probe Amplification (MLPA), Chromosomal Microarray Analysis (CMA, either single-nucleotide polymorphisms (SNP) array or array comparative genomic hybridization (aCGH)) or using software tools to infer CNV from data generated from Next generation sequencing (NGS)-based tests (targeted gene panels, whole exome sequencing (WES), and whole genome sequencing (WGS)).
  - **Pathogenic DNA sequence variants in single genes**, detectable by DNA sequencing.
  - **Nucleotide repeat expansion**, e.g. congenital central hypoventilation syndrome, myotonia dystrophy.
  - **Epigenetic changes (such as genomic imprinting)**, e.g. Angelman's syndrome, Prader-Willi syndrome.
  - **Mitochondrial genome abnormalities.**
- Choosing an appropriate genetic test is a multi-factorial consideration: clinical phenotype, availability of the tests, financial resource. etc. Consult the Clinical Genetics/Metabolic team if indicated.
- "Genetic first" approach with early genome-wide analyses such as whole exome sequencing (WES) or whole genome sequencing (WGS) may be easier, more cost-effective and potentially more rapid in arriving at a definitive diagnosis than a combination of several biochemistry screening tests that have a limited sensitivity and specificity.

General considerations in determining the appropriate genetic test

DD: developmental delay; ID: Intellectual disability, MCA: Multiple congenital anomalies

Table 1: Differential genetic diagnoses of some common paediatric conditions

Clinical phenotype	Differential diagnoses (First think of treatable disorders)	Investigations

Acute neurological deterioration "Intoxication" symptoms	• Urea cycle disorders
	• Maple syrup urine disease
	• Organic aciduria (Propionic acidemia, methylmalonic acidemia, Isovaleric acidemia, etc.)
	• Multiple carboxylase (biotin) deficiency
	• Carbonic anhydrase VA deficiency
		• First line tests:
		  • blood: glucose, NH4+, acid-base status, lactate
		  • Urine/blood ketones
		• Second line tests: plasma amino acids, urine organic acids and dried blood spot (DBS) acylcarnitines ± plasma total homocysteine

Epileptic encephalopathy	• Antiquitin deficiency (B-6 responsive seizures) • Early-onset vitamin B6-dependent epilepsy due to PLPBP deficiency • Pyridox(am)ine phosphate oxidase deficiency (Pyridoxal phosphate responsive) • Folinic acid responsive seizures • Multiple carboxylase (biotn) deficiency • GLUT1 deficiency • Serine deficiency • Creatine deficiency • Glycine encephalopathy • Sulfite oxidase deficiency • Molybdenum cofactor deficiency • Adenylosuccinate lyase deficiency • Congenital disorders of glycosylation • Several channelopathies (e.g. SCNA, KCNQ2, etc. mutations) • Synaptopathies • Brain malformations (e.g. lissencephaly, etc.)	• First line tests: Paired plasma and CSF amino acids, urine organic acids, DBS acylcarnitines, serum uric acid, fresh urine sulphite, urine sulphocysteine, urine purine & pyrimidine, urine/plasma/CSF Piperidine-6-carboxylate, urine pipecolic acid, urine α-aminoadipic semialdehyde, biotinidase assay, DBS/urine/plasma creatine & guanidinoacetate, serum transferrin isoelectric focusing, neuroimaging + MR spectroscopy • Second line tests: Consider molecular genetic test (epilepsy gene panel or whole exome sequencing)
Severe Hypotonia mimicking neuromuscular disorders	• Fatty acid oxidation disorders • Carnitine transport defect • Biogenic amine (neurotransmitters) de¬ciencies • Riboflavin transport defects • Primary CoQ10 defects • Mitochondrial myopathy • Peroxisome biogenesis defects • Congenital disorders of glycosylation (N-glycosylation defects/O glycosylation defects / IEM of the dolichols) • Prader-Willi syndrome	• First line tests: DBS acylcarnitines, plasma total & free carnitines, blood lactate, serum uric acid, serum CK, serum prolactin, CSF neurotransmitters, CSF/ urine pterins, urine organic acid (vanillactate), serum transferrin isoelectric focusing, PWS/AS MS-MLPA. • Second line tests: Consider molecular genetic test (neurometabolic gene panel or whole exome sequencing)

Clinical phenotype	Differential diagnoses (First think of treatable disorders)	Investigations
Liver failure/ dysfunction	• Galactosemia • Hereditary fructose intolerance • Tyrosinemia Type I • Urea cycle disorders • Bile acid synthesis defects • Long chain fatty acids β-oxidation disorders • Wilson disease • α-1 antitrypsin deficiency • Transaldolase deficiency • CDG1b • mtDNA depletion syndrome • GSD Type IV • Peroxisomal biogenesis disorders • Hereditary haemochromatosis	• First line tests: DBS Galactose-1-Phosphate & Galactose-1-phosphate uridyltransferase, plasma amino acids, urine organic acids, urine succinylacetone, urine bile acids analysis, dried blood spot acylcarnitines, plasma VLCFA, blood lactate, serum γ-GT, urine polyol, serum copper, serum caeruloplasmin, quantitation & phenotyping of α-1 antitrypsin • Second line tests: Consider molecular genetic test (liver disease gene panel or whole exome sequencing)
Cholestatic liver disease	High γ-GT: • Biliary atresia • Alagille's syndrome • Galactosemia • Hereditary fructose intolerance • Tyrosinemia Type I • Citrin deficiency • Progressive familial intrahepatic cholestasis Type III • α-1 antitrypsin deficiency • mtDNA depletion syndrome • Peroxisomal biogenesis disorders • Niemann Pick Type C • HFN1B defect Low/normal γ-GT: • Progressive familial intrahepatic cholestasis Type I and II • Bile acid synthesis defects • Smith-Lemli Opitz syndrome • TJP2 defect • Arthrogryposis Renal dysfunction and Cholestasis • MYO5B defect	• First line tests: DBS Galactose-1-Phosphate & Galactose-1-phosphate uridyltransferase, plasma amino acids, urine organic acids, urine succinylacetone, urine bile acids analysis, plasma VLCFA, blood lactate, • Second line tests: Consider molecular genetic test (JAG1 gene ± NOTCH2 gene analysis for Alagille's syndrome, SLC25A13 gene analysis for Citrin deficiency, liver disease/jaundice gene panel or whole exome sequencing)
Cardiomyopathy	• Primary carnitine deficiency • Fatty acid oxidation disorders • Infantile-onset Pompe disease • Primary mitochondrial disorders • Barth syndrome • Rasopathies	• First line tests: DBS acylcarnitines, blood lactate, urine organic acids, plasma total & free carnitines, DBS α-glucosidase. • Second line tests: Consider molecular genetic test (cardiomyopathy gene panel or whole exome sequencing)

Clinical phenotype	Differential diagnoses (First think of treatable disorders)	Investigations
Persistent/recurrent hypoglycemia	• Glycogenosis defects • Gluconeogenesis defects • Congenital hyperinsulinism • Fatty acid oxidation disorders • Carbonic anhydrase VA deficiency	• First line tests: Blood lactate, blood NH_4^+, lipid profile, serum uric acid, serum CK, DBS acylcarnitines, urine organic acid, serum insulin. • Second line tests: Consider molecular genetic test (hypoglycaemia gene panel or whole exome sequencing)
Predominant dysmorphia Malformations	• Peroxisomal defects • Cholesterol defects • Congenital disorders of glycosylation (N- glycosylation defects/O glycosylation defects/GPI anchor synthesis defects) • Chromosomal abnormalities (Copy number variations (CNV)) • Genetic syndromes	• First line tests: Detailed dysmophology analysis, Plasma VLCFA, total cholesterol, serum transferrin isoelectric focusing, karyotype. • Second line tests: Consider molecular genetic test (chromosomal microarray or whole exome sequencing which include CNV detection or WGS)
Unexplained global developmental delay/intellectual disabilities	• Chromosomal abnormalities (Copy number variations (CNV)) • Syndromic single gene (e.g., fragile X, Rubinstein-Taybi) • Nonsyndromic single gene • Metabolic (e.g., phenylketonuria, Smith-Lemli-Opitz syndrome) • Acquired/non-genetic causes	<u>Conventional approach:</u> • 1st line: Detailed dysmophology analysis, neuroimaging, audiology, ophthalmology assessement, karyotype, Fragile X gene test, T4/TSH, Creatine kinase, blood NH_4^+, blood lactate, plasma amino acids, DBS acylcarnitine, plasma total homocysteine, urine organic acid, DBS/urine/plasma creatine & guanidinoacetate, serum transferrin isoelectric focusing, Urine glycoaminoglycans, urine purine & pyrimidine, serum copper & ceruloplasmin, biotinidase assay • 2nd line: Chromosomal microarray, WES <u>Alternative approach:</u> • WES + CNV analysis (or WGS) + mtDNA genome sequencing as the 1st line test. Perform reverse phenotyping as indicated.

Post-mortem investigations

- If a child dies of an unknown, possible genetic disease, it is essential to collect representative post-mortem samples and discuss their analysis with Clinical Genetics/Metabolic team. Without diagnosis, genetic counselling of the parents and reliable risk assessment for future children is not possible.
- Samples/investigations:
- Mandatory
  - Save a blood sample for potential genetic testing
  - Option 1: Save 5 mls whole blood in EDTA bottle (pink top). Send it immediately (at room temperature) to genetic laboratory for DNA extraction and storage. If the transport is not immediately available, keep the blood in a refrigerator (4°C, maximum storage duration: not more than 4 weeks). For longer storage (months to years), blood sample should be stored in a freezer at -20°C to -80°C and remain there until they can be shipped to the laboratory
  - Option 2: Keep and store a dried blood spots specimen (spotted onto an appropriate filter paper card)
  - Basic IEM tests: plasma amino acid, urine organic acid, DBS acylcarnitines. (If possible, collect the blood and urine samples prior to expected death. Autolysis during the process of dying causes intracellular fluid to mix with extracellular fluid. This may lead to misleading changes of metabolites concentration).
- Consider
  - CSF (freeze immediately, if possible at -80°C)
  - Bile (spot on filter paper for acylcarnitines analysis)
  - Skin biopsy (store at ambient temperature in culture medium, send for fibroblast culture. DO NOT FREEZE)
  - Fine needle biopsy of muscle, heart, liver.

Management of an asymptomatic newborn but at risk of having potentially treatable IEM

- High risk scenario includes:
  - A previous child in the family has had an IEM.
  - Multiple unexplained early neonatal death.
  - Mother has HELLP/fatty liver disease during pregnancy
    (HELLP – Haemolytic Anaemia, Elevated Liver Enzymes, Low Platelets).
- Consider to transfer the expected newborn in utero or soon after delivery to a centre with facilities to diagnose and manage IEM.
- If potential/index patient diagnosis is known: screens for the specific condition, e.g. urea cycle disorders – monitor ammonia and plasma amino acid, MSUD – monitor plasma leucine (amino acids).
- If potential/index patient diagnosis is unknown: Collect dried blood spots for acylcarnitine profile, plasma amino acid and urine organic acid on 2nd or 3rd day after feeding, send it immediately and get result as soon as possible.
- Other essential laboratory monitoring may include: blood NH4+, VBG, blood glucose. Please discuss with metabolic team.
- To prevent decompensation before the disease status of the newborn is known:
  - provide enough calories (oral/IV)
  - dietary protein restriction may be necessary especially if index case presented very early (before 1 week). Protein-free formula should be given initially and small amount of natural protein (e.g. breast milk) can be introduced gradually after 48 hours depending on baby's clinical status.
- If the index patient presented after the first week, the newborn should be given the minimum safe level of protein intake from birth (approximately 1.5 g/kg/day). Breast feeding should be allowed under these circumstances with top-up feeds of a low protein formula to minimise catabolism.
- Get the metabolic tests result as soon as possible to decide whether the baby is affected or not.

Section 17

PAEDIATRIC SURGERY

Chapter 103:
Appendicitis

- Appendicitis is the most common surgical condition of the abdomen in children over the age of 4 years and yet can be a challenge to diagnose and manage.
- Although diagnosis and treatment have improved over the years, it continues to cause considerable morbidity and even mortality in Malaysia.
- The mortalities appear to be due to delay in diagnosis, causing consequences of inadequate perioperative fluid resuscitation, and replacement, delay in IV antibiotics commencement for sepsis.

Clinical Features

- Abdominal pain – Lower abdominal pain is an early and almost invariable feature.
- Usually the pain starts in the epigastrium or periumbilical region before localising to the lower abdomen or the right iliac fossa(migratory pain).
- However the younger child may not be able to localise the pain.
- If there is collection in perforated appendicitis, the abdominal pain is generalised.
- Nausea and vomiting occurs in about 90% of children and is an early symptom.
- Most children have a loss of appetite. A hungry child rarely has appendicitis.
- Diarrhoea is more common in the younger age group causing confusion with gastroenteritis.
- It can also be due to pelvic appendicitis or collection of pus within the pelvis.
- Dysuria and frequency are also commonly present in the child with pelvic appendicitis or perforated appendicitis.
- Fever is usually low grade for acute appendicitis, but becomes > 38^0C when the appendix has perforated.

Physical Findings

- General – the child is usually lethargic and may be dehydrated.
- Dehydration must be actively sought for especially in the obese child and the child with perforated appendicitis.
- Clinical assessment for dehydration e.g.; tachycardia, delayed capillary refill time, poor urine output, feeble pulse.
- Tenderness on palpation is essential for the diagnosis. It may be localised to the right iliac fossa or be generalised. The tenderness may also be mild initially and difficult to elicit in the obese child or if the appendix is at retrocaecal region.
- Eliciting rebound tenderness is usually not required to make the diagnosis and can cause unnecessary discomfort.
- Guarding signifies peritonitis but may be subtle especially if the child is toxic, obese and very dehydrated.
- Rectal examination is only required if other diagnoses are suspected e.g. ovarian or adnexal pathology in female patient.

Investigations

- Full blood count – The total white blood cell count may be elevated but a normal count does not exclude appendicitis.
- Blood Urea and Serum Electrolytes – Raised urea level with normal creatinine. Electrolytes imbalance.
- Serum Amylase – If pancreatitis cannot be ruled out as the cause of the abdominal pain.
- Ultrasound is commonly performed. It increases accuracy of diagnosis and can rule out other causes of pain but is dependent on the operator, patient habitus and cooperation.
- CT scan with IV contrast is considered in selective cases only when dilemma in diagnosis is encountered. It carries a high degree of diagnostic accuracy but is associated with high radiation risks and costs. It should only be done after adequate fluid resuscitation to avoid nephropathy.
- Therefore, the recommendation is that the child is assessed by a surgeon or a paediatrician preoperatively before imaging.
- If the diagnosis cannot be made with certainty, especially in preschool age, or the child is very ill and there are no facilities or personnel for intensive care, the child must be referred to the nearest paediatric surgical unit with commencement of fluid resuscitation, stabilisation and IV antibiotics prior to transfer.

Complications

- Perforation can occur within 36 hours of the onset of symptoms.
- Perforation rate increases with the duration of symptoms and delayed presentation is an important factor in determining perforation rate.
- Perforation rate: Adolescent age group - 30-40%
- In younger child - up to about 70%.
- If unsure of the diagnosis, active observation with adequate fluid resuscitation can be done.
- Antibiotics are to be started once the diagnosis is made. This has not been shown to increase the morbidity or mortality.
- Delaying surgery till daytime, while resuscitating and giving antibiotics also does not significantly affect the perforation rate, complications or operating time.
- Appendicular abscess or mass may be treated with IV antibiotics to settle the inflammatory and infectious process.
- If the child settles, this can then be followed by an interval appendicectomy, done within 6 weeks of the original disease.
- A repeated ultrasound is recommended prior to surgery to reassess the lesion.

Management

- Children with appendicitis (suspected or confirmed) should be reviewed by a specialist.
- Dehydration should be actively looked for.
- The heart rate, blood pressure, perfusion and the urine output should be closely monitored.
- The blood pressure is usually maintained in the children until they have decompensated.
- Rehydration must be aggressive, using 20 mls/kg aliquots of normal saline or Hartmann's solution (Ringer's lactate) given fast over ½ - 2 hours.
- The child should be reviewed after each bolus and the rehydration continued until the child's heart rate, perfusion, urine output and electrolytes are within normal limits.
- Using normal or half saline + 5% D/W as maintenance fluid, to add KCl in drip once acute renal failure is ruled out.
- Antibiotics should be started soon after the diagnosis is made.
- Non-operative management of UNCOMPLICATED appendicitis can be considered in centres with paediatric surgical expertise with selective criteria, such as confirmation of diagnosis by ultrasound with absent of appendicolith, patient is reasonably well and responding to antibiotics.
- Frequent assessment is mandatory. Surgery should be considered when symptoms persist 24-48 hours later after commencement of IV antibiotics.
- Presence of appendicolith is not recommended for non-operative management as it carries a high recurrent rate, up to 75%.
- However, operation is recommended in the child with perforated appendicitis.
- Inotropes may need to be started early if the child is in severe sepsis.
- Operation - There is no rush to take the child to the operating theatre. Fluid resuscitation is crucial. It is recommended that appendicectomies not be performed late at night (after 10pm), especially in the sick child. However, the time should be utilised to continue the resuscitation and antibiotics with close monitoring of the child.
- Surgery can be laparoscopic or open appendicectomy.
- At surgery, a peritoneal swab C+S is usually sent for child at extreme age, i.e. below 4 years old, in the presence of pus in peritoneal cavity.
- Pus must be fully evacuated before closing the abdomen.
- No drain is required and the skin can be closed with a subcuticular suture.

Chapter 104:
Vomiting in the Neonate and Child

- Vomiting in the child is NOT normal.
- Bilious vomiting is ALWAYS significant until otherwise proven.
- When is the vomiting significant?
  - Vomiting at Day 1 of life.
  - Vomit contains blood (red/black).
  - Bilious vomiting: green, not yellow. Bowel obstruction must be ruled out.
  - Faeculent vomiting.
  - Projectile vomiting.
  - Child is unwell - dehydrated/septic.
  - Associated failure to thrive.
  - Associated diarrhoea/constipation.
  - Associated abdominal distension.

CAUSES OF PERSISTENT VOMITING

Neonates

General
- Sepsis
- Meningitis
- Hydrocephalus/ neurological disorder
- Urinary tract infection
- Motility disorder
- Inborn errors of metabolism
- Congenital adrenal hyperplasia
- Poor feeding techniques

Oesophagus
- Atresia
- Webs
- Swallowing disorders
  - Oesophageal dysmotility
  - Duplication cyst

Stomach
- Gastro-oesophageal reflux
- Duodenal atresia/ stenosis

Small intestine
- Malrotation with midgut volvulus
- Stenosis/ atresia
- Adhesions/ Bands
- Meconium peritonitis/ ileus
- Necrotising enterocolitis
- Incarcerated hernia

Colon/ rectum
- Stenosis/ atresia
- Hirschprung's disease
- Anorectal malformation
- Meconium disease

Infants

General
- Sepsis
- Meningitis
- Hydrocephalus/ neurological disorder
- Urinary tract infection
- Tumours e.g. neuroblastoma
- Metabolic disorders

Oesophagus
- Oesophageal stricture due to corrosive ingestion
  - Congenital oesophageal stenosis
  - Oesophageal dysmotility

Stomach
- Gastro-oesophageal reflux
- Hypertrophic Pyloric stenosis

Small intestine
- Malrotation/ volvulus
- Adhesions
- Meckel's diverticulum
- Incarcerated hernias
- Appendix- rare

Colon/ rectum
- Intussusception
- Hirschprung's disease
- Enterocolitis/gastroenteritis

Older Child

General
- Sepsis
- Neurological disorder
- Tumours
- Metabolic disease

Stomach
- Gastro-oesophageal stricture/reflux
- Peptic ulcer disease
- Gastric volvulus
  - Intragastric tumor

Small intestine
- Malrotation/ volvulus
- Adhesions
- Meckel's diverticulum
- Appendicitis/ peritonitis

Large intestine/colon
- Intussusception
- Worm infestation
- Constipation: habitual with faecal impaction

GASTRO-OESOPHAGEAL REFLUX

- More common in infancy than generally recognized.
- Majority (>90%) resolve spontaneously within the first year of life.
- Small percentage develop complications.
- Please refer Chapter 81: on Gastroesophageal Reflux Disease (GERD)

PYLORIC STENOSIS

- Cause- unknown; Strong familial pattern.
- Usually first-born baby boy; usual presentation at 2nd to 8th week of life.

Clinical Features

- Vomiting -Frequent, forceful, non-bilious with/without haematemesis.
- The child is keen to feed but unable to keep the feed down.
- Failure to thrive.
- Dehydration.
- Constipation.
- Seizures.

Physical Examination

- Dehydrated
- A test feed can be given with the child in the mother's left arm and visible gastric peristalsis (left to right) observed for.
- The doctor's left hand then palpates beneath the liver feeling for an "olive sized pyloric tumour" palpable against the vertebra.

Investigations

- Investigation to confirm diagnosis are usually unnecessary.
  - Ultrasound - 100% accuracy. Pyloric muscle thickness > 3 mm, and length > 15mm.
  - Upper contrast study - string sign and shouldering of pyloric muscle
- However, pre-operative assessment is very important:
  - Metabolic alkalosis is the first abnormality
  - Hypochloraemia < 100 mmol/l
  - Hyponatraemia < 130 mmol/l
  - Hypokalaemia < 3.5 mmol/l
  - Hypocalcaemia < 2.0 mmol/l
  - Jaundice.
  - Hypoglycemia.
  - Paradoxical aciduria - a late sign.

Therapy

- Rehydration
  - Slow (rapid rehydration will cause cerebral oedema) unless the child is in shock
  - Fluid
    - 0.45% saline + 10%D/W (+ 5-10 mmol KCl/kg/day once the child has passed urine).
    - Rate (mls/hr) = [Maintenance (150 ml/kg body weight) + 5-10 % dehydration {% dehydration x body weight (kg) x 10}] /24 hours.
    - Replace gastric losses with normal saline.
    - Do NOT give Hartmann's solution (the lactate will be converted to bicarbonate which worsens the alkalosis)
  - Insert a nasogastric tube – free flow.
  - Comfort glucose feeds maybe given during the rehydration period but the nasogastric tube needs to be left on free drainage.
- Pyloromyotomy after the electrolytes have been corrected.

MALROTATION OF THE MIDGUT

A term that embraces a number of different types of abnormal rotation that takes place when the bowel returns into the intra-abdominal cavity in utero. This is important because of the propensity for volvulus of the midgut around the superior mesenteric artery causing vascular compromise of most of the small bowel.

Types of Clinical Presentation

Acute Volvulus

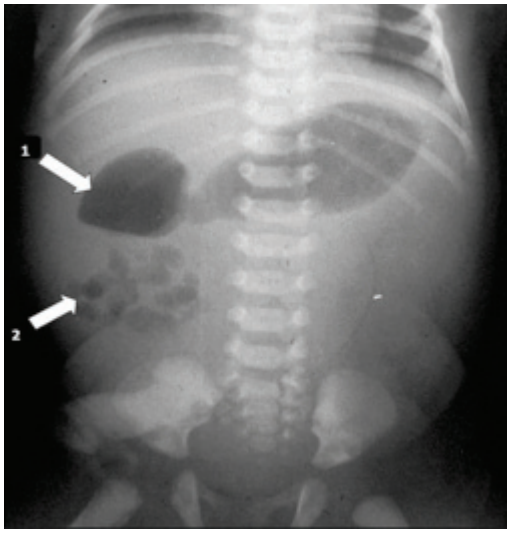
- Sudden onset of bilious/ non-bilious vomiting in a previously well child.
- Abdominal distention with/without a mass (late sign).
- Bleeding per rectum (late sign).
- Ill baby with distended, tender abdomen.

Chronic Volvulus

- Caused by intermittent or partial volvulus resulting in lymphatic and vascular obstruction.
- Recurrent colicky abdominal pain.
- Vomiting (usually bilious).
- Malabsorption.
- Failure to thrive.

Investigations

- Plain Abdominal X-ray
  - Dilated stomach +/- duodenum with rest of abdomen being gasless. And abnormal small bowel gas distribution. Figure below with the arrow 1 (prominent duodenal bulb) and 2 (abnormal small bowel gas distribution)



- Ultrasound - looks at the relationship of the Superior mesenteric artery and vein and a whirlpool sign to indicate volvulus
  - Upper Gastrointestinal contrast study with follow through
  - Duodeno-jejunal flexure to the right of the vertebra.
  - Duodenal obstruction, often with spiral or corkscrew appearance of barium flow.
  - Presence of small bowel mainly on the right side.

Treatment

Pre-operative Management

- Rapid rehydration and correction of electrolytes
- Fluids
  - Maintenance – 0.45% saline + 5% (or 10% if neonate) Dextrose Water with added KCl.
  - Rehydration – Normal saline or Hartmann's Solution (Ringer's Lactate)
- Orogastric or nasogastric tube with 4 hourly aspiration and free drainage.
- Antibiotics (+ inotropes) if septic.

Operative

- Emergency surgery is required if there is volvulus
- De-rotation of volvulus.
- ± Resection with an aim to preserve maximum bowel length (consider a second look operation if most of the bowel appears of doubtful viability).
- Division of Ladd's bands to widen the base of the mesentery to prevent further volvulus.
- Appendicectomy.
  - Arrange small bowel in left side while the colon on the right.

ATRESIAS

Duodenal Stenosis/ Atresia

- Antenatal diagnosis associated with polyhydramnios and double bubble sign.
- Usually at the second part of the duodenum.
- Presents with bilious/non-bilious vomiting.
- Can be associated with Down's Syndrome and gastro-oesophageal reflux.
- Abdominal X-Ray: double - bubble with or without gas distally.

Management

- Slow rehydration with correction of electrolytes and nutritional deficiencies.
- Decompression of the stomach with an orogastric tube
- Rule out associated anomalies
- Duodeno-duodenostomy/duodeno-jejunostomy as soon as stabilized.
- Postoperatively, the bowel motility may be slow to recover.

Ileal /Jejunal Atresia

- Atresia anywhere along the small bowel. Can be multiple.
- Presents usually with abdominal distension and vomiting within the first 48 hours of life (non-bilious initially and then bilious).
- Usually pass white or pale green stools, not normal meconium.
- Abdominal Xray - multiple dilated loops of bowel (triple bubble in proximal jejunum).
- Differential diagnoses – Long segment Hirschsprung's disease, Meconium ileus.
- Contrast enema - demonstrates a microcolon differentiating it from a Hirschsprung's disease and Meconium ileus

Management

- Evaluation for associated abnormalities.
- Insertion of an orogastric tube – 4 hourly aspiration and free drainage.
- Slow rehydration with correction of electrolyte abnormalities and nutrition.
- Laparotomy and resection of the dilated bowels with primary anastomosis, preserving as much bowel length as possible.
- Total parenteral nutrition as the motility of the bowel can be abnormal and takes a long time to recover.
- AXR – dilated loops of small bowel.
- Contrast enema – microcolon

Chapter 105:
Intussusception

- Intussusception is the invagination of one portion of intestine into another with 80% involving the ileocaecal junction.
- Early diagnosis and prompt fluid resuscitation reduces the morbidity rate and successful rate for non-surgical intervention.
- The incidence starts at 6 months of age, with the peak age group being 2 to 4 years.
- Majority of the children in this age group have no pathological lead point.
- Lymphoid hyperplasia has been linked.
- Children may also have a preceding viral illness.

Common lead points (usually in the age group outside the above):
- Structural – Meckel's diverticulum, duplication cysts.
- Neoplastic – Lymphoma, polyps, vascular malformations.
- Vascular – Henoch-Schonlein purpura, leukaemia.
- Miscellaneous – Foreign body.

Clinical Features

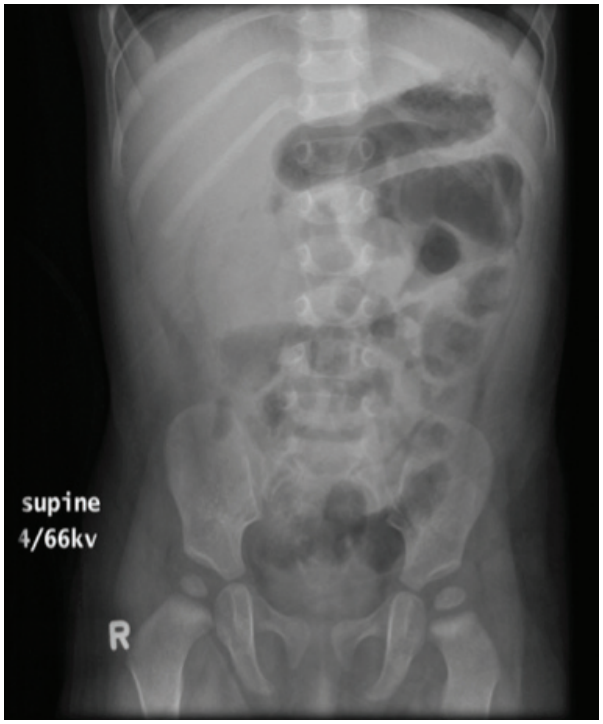
- Previously healthy or preceding viral illness.
- Pain - Sudden onset, severe intermittent cramping pain lasting seconds to minutes.
- During the time in-between attacks lasting between 5 to 30 minutes, the child may be well or quiet.
- Vomiting – Early reflex vomiting consists of undigested food but if the child presents late, the vomiting is bilious due to obstruction.
- Stools- Initially normal, then become dark red and mucoid ("red currant jelly").
- Note that small bowel intussusception may have an atypical presentation.

Physical Findings

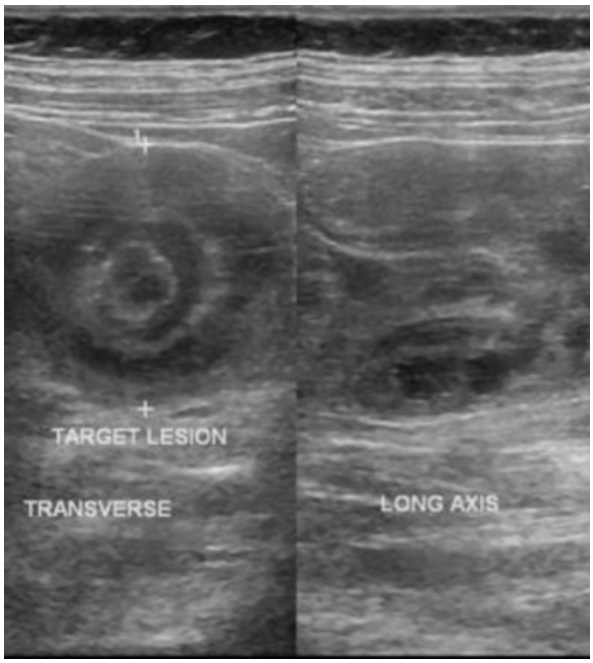
- Well- looking/drowsy/dehydrated/fitting (due to hyponatremia) depending on the stage of presentation.
- Abdominal mass (sausage shaped but may be difficult to palpate in a distended abdomen).
- Abdominal distension is a late sign.

Investigations

- Plain abdominal X-ray – paucity of bowel gas on the right side with loss of visualization of the lower border of the liver, dilated small bowel loops (see figure below).



- Ultrasound – Useful diagnostic tool. Target sign (see figure below) on axial section and pseudo-kidney sign on longitudinal section.



May also help to identify lead points if present.

Management
Resuscitation

- Aggressive rapid rehydration with boluses of 20 mls/kg of Normal saline/Hartmann's solution (Ringer's lactate).
- Clinical reassessment after each boluses is vital not to overload the child.
- Do NOT proceed to hydrostatic reduction or surgery till fully resuscitated.
- Close monitoring of vital signs and urine output.
- Antibiotics and inotropes may be required if the child is septic.

Non-operative reduction

- Should be attempted in most patients, if there are trained radiologists and surgeons available, successful reduction rate is about 80-90%.
- Types:
  - Hydrostatic reduction with saline under ultrasound guidance is now our preferred choice.
  - Pneumatic reduction.
- The younger child who has been sick for a longer duration of more than 36 hours and has complete bowel obstruction is at risk of colonic perforation during attempted enema reduction.
- Delayed repeat enemas done after 30 minutes or more after the initial unsuccessful reduction enema may improve the outcome of a select group of patients.
  - This select group of patients should be clinically stable and the initial attempt had reduced the intussusceptum till the ileocaecal valve.

Contraindications to enema reduction

- Peritonitis.
- Bowel Perforation.
- Severe Shock.
- Inadequate reduction

Indications for surgery

- Failed non-operative reduction.
- Bowel Perforation.
- Suspected secondary lead point.
- Small bowel intussusception.

Recurrence of intussusception

- Rate: 5-10% with lower rates after operative reduction.
- Success rate for non-operative reduction in recurrent intussusception is about 30-60%.

Successful management of intussusception depends on high index of suspicion, early diagnosis, adequate resuscitation and prompt reduction.

Chapter 106:
Inguinal hernias, Hydrocoele

- Both are due to a patent processus vaginalis peritoneum.
- The patent communication in the hydrocoele is smaller, so the sac contains only fluid.
- The hernia sac can contain bowel, omentum or ovaries.

INGUINAL HERNIA

- Incidence: 0.8%-4.4% in children, but 16-25% in premature babies.
- Boy: girl ratio = 6 : 1.
- Site: 60% right side but 10% may be bilateral.

Presentation

- Reducible bulge in groin – extends into scrotum when crying/straining.
- Lump in groin (girls) – sliding hernia containing ovary (rule out testicular
- feminization syndrome if bilateral).

Complications

- Incarceration/Irreducibility – Highest incidence (2/3) before age of 1 year
- Testicular atrophy.
- Torsion of ovary.

Management
Reducible hernia

- To operate (herniotomy) as soon as possible.
- Premature: before discharge (if possible at corrected age-44 - 60 weeks)
- Infant: as soon as possible.
- Older child: on waiting list.

Incarcerated hernia

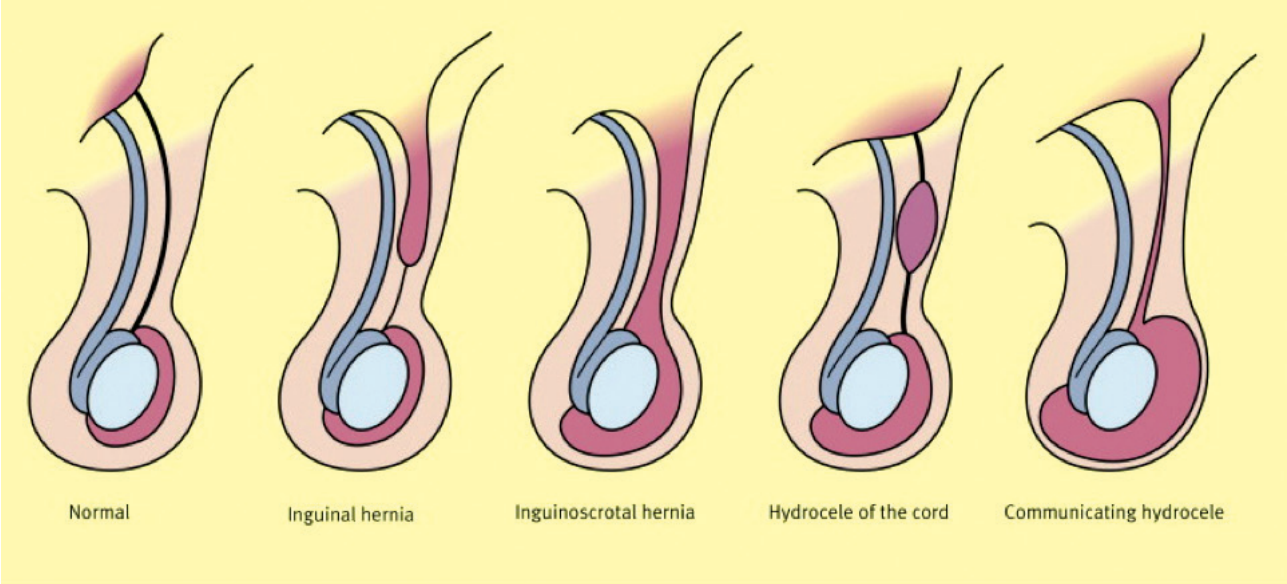
- Attempt manual reduction as soon as possible to relieve compression on the testicular vessels.
- The child is rehydrated and then given intravenous analgesic with sedation.
- Constant gentle manual pressure is applied in the direction of the inguinal canal to reduce the hernia.
- The sedated child can also be placed in a Trendelenburg position for an hour to see if the hernia will reduce spontaneously.
- If the manual reduction is successful, herniotomy is performed 24-48 hours later when the oedema subsides.
- If the reduction is not successful,the operation is performed immediately.

HYDROCOELE

- Usually present since birth.
- May be communicating or encysted.
- Is typically a soft bluish swelling which is not reducible but may fluctuate in size.

Management

- The patent processus vaginalis may close spontaneously within the first year of life
- If the hydrocoele does not resolve after the age of 2 years, herniotomy with drainage of hydrocoele is done.



Chapter 107:
Undescended Testis

- An empty scrotum may be due to the testis being undescended, ectopic, retractile or absent.
- Familial predisposition present in 15%. 10 - 25% are bilateral.

Incidence

- At birth: Full term 3.4%

Premature 30.3%

- At 1 year:Full term 0.8%

Premature 0.8%

- Adult 0.7-1%
- Spontaneous descent may occur within the 1st year of life after which descent is rare.

Complications

- Trauma (especially if in inguinal canal).
- Torsion - extravaginal type.
- Decreased spermatogenesis. Damage occurs in the first 6-12 months of life. 90% of patients with orchidopexy before 2 years have satisfactory spermatogenesis. If done after >15 years old, fertility is 15%. Fertility isalso affected by ductal anomalies.
- Testicular tumour: Risk is 22 times higher than the normal population (Intra-abdominal 6 times more than inguinal). Surgery makes the testis more accessible to palpation and thus an earlier diagnosis.
- Associated hernias (up to 65%), urinary tract anomaly (3%, e.g. duplex, horseshoe), anomalies of epididymis or vas deferens and intersex problems.
- Psychological problems.

Management

- Ask caretaker whether testis was ever felt in the scrotum, more easily felt during a warm bath and when squatting.
- Examine patient (older children can be asked to squat).
- A normal sized scrotum may suggest a retractile testis.
  - A retractile testis, once brought down to the scrotum, can stay in the scrotum transiently.
  - Surgery is usually not required for the retractile testis.
- The scrotum tends to be hypoplastic in true cryptorchidism.
- If bilateral need to rule out dysmorphic syndromes, hypopituitarism, and chromosomal abnormalities (e.g. Klinefelter). Exclude intersex disorders.
- Observe the child for the 1st year of life.
  - If the testis remains undescended after 1 year of life surgery is indicated.
- Surgery should be done between 6-18 months of age.
- Results of hormonal therapy (HCG,LH-RH) have not been good.
- However, the use of gonadotropin releasing hormone as an adjuvant to orchidopexy appears to possibly improve germ cell maturation in child with bilateral non palpable testes.
- A non-palpable testis may represent an inguinal testis that is difficult to palpate, an intra-abdominal testis, a vanishing testis or true tesiticular agenesis.
- For bilateral impalpable testis: Management of choice is Laparoscopy ± open surgery.
- Ultrasound, CT scan or MRI to locate the testes have not been shown to be useful.
- Check chromosomes and 17 OH progesterone levels if genitalia are ambiguous.

Chapter 108:
The Acute Scrotum

Causes of Acute Scrotum

- Acute testicular torsion.
- Torsion of epididymis and testicular appendages.
- Epididymo-orchitis.
- Incarcerated inguinal hernia.
- Idiopathic scrotal oedema.
- Acute hydrocele.
- Henoch-Schonlein purpura.
- Tumours.
- Trauma.
- Scrotal (Fournier's) gangrene.
- Symptomatic varicocele.

TORSION OF THE TESTIS

- Torsion of the testis is an emergency as failure to detort testis within 6 hours will lead to testicular necrosis.
- Undescended testis carries 10x risk of torsion.

Symptoms

- Sudden severe pain (scrotum and referred pain lower abdomen/inguinal for cryptoorchidism)
- Nausea and vomiting
- No fever or urinary tract infection symptoms until later

Physical Findings

Early

- Involved testis - high, tender, swollen. (depending on location - inguinal, abdomen for cryptoorchidism)
- Spermatic cord – swollen, shortened and tender.
- palpable testis - abnormal lie, usually transverse.
- Loss of cremasteric reflex

Late

- Less painful
- Hard in consistency
- same as early presentation

However, reactive hydrocele and scrotal oedema make it difficult to examine.

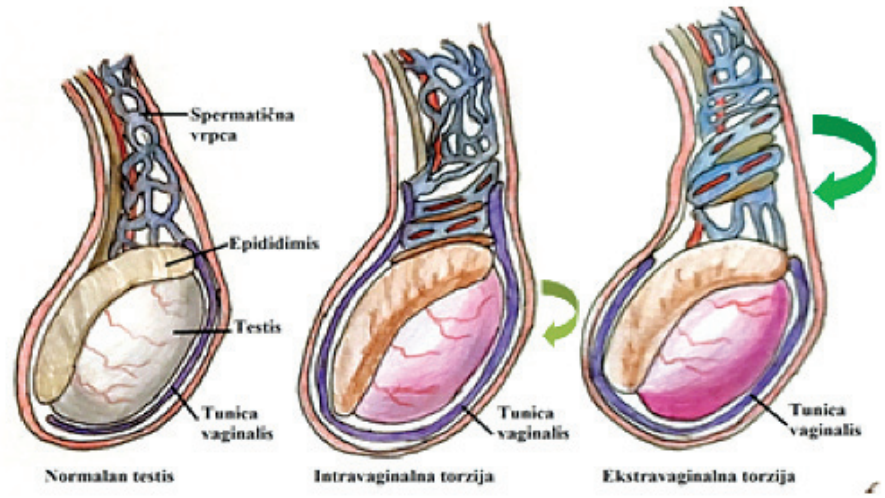
There are 2 types of torsion:

Extravaginal

- The torsion usually occurs in the perinatal period or during infancy and is thought to be probably due to an undescended testis.

Intravaginal

- This is due to a high investment of tunica vaginalis causing a "bell-clapper" deformity.
- It usually occurs in boys between 10-14 years old.
- The deformity is usually bilateral.



Investigation

- Urinalysis - normal
- Colour Doppler Ultrasonography - 85% sensitivity and 100% specificity looking for intratesticular arterial blood flow and spiral twisting of the spermatic cord.
- Highly operator dependent. However, edema may affect the findings.

Management

- High index of suspicious warrants a surgical exploration immediately without colour doppler ultrasonography.
- Exploration: salvage rate: 83% if explored within 5 hours; 20% if explored after 10 hours.
- If the testis is viable, bilateral orchidopexy after detorsion is done.
- If the testis is not viable, then an ipsilateral orchiectomy and a contralateral orchidopexy needs to be done.

TORSION OF APPENDAGES OF TESTIS AND EPIDIDYMIS

Appendages are Mullerian and mesonephric duct remnants.
Importance: May be confused with torsion of testis.

Symptoms
- Age – 8-10 years old.
- Sudden onset of pain, mild initially but gradually increases in intensity.

Physical Examination
Early
- Minimal redness of scrotum with a normal non-tender testis.
- Tender nodule "blue spot" (upper pole of testis) is pathognomonic.

Late
- Reactive hydrocele with scrotal oedema makes palpation of testis difficult.

Investigation
- Usually not needed.
- Colour Doppler Ultrasonography may show increased blood flow to the epididymis or testis leading to misdiagnosis of acute epididymitis or epididymoorchitis.

Treatment
- If sure of diagnosis of torsion appendages of testis, the child can be given the option of non-operative management with analgesia and bed rest.
- If unsure of diagnosis, explore and remove the twisted appendage (this ensures a faster recovery of pain too!).

EPIDIDYMO-ORCHITIS

Can occur at any age.
Route of infection
- Reflux of infected urine
- Blood borne secondary to other sites
- Mumps
- Sexually transmitted infection

Symptoms
- Gradual onset of pain with fever.
- May have a history of mumps.
- ± Dysuria/ frequency.
- post-pubertal - urethal discharge

Physical examination
- Testis may be normal with a reactive hydrocoele.
- Epididymal structures are tender and swollen.

Investigation
- Urinalysis and urine culture
- Colour doppler ultrasonography - TRO testicular torsion. Increased vascularity of the testis and epididymis.
- Investigate for underlying structural anomalies of the urinary tract and
- voiding dysfunction for recurrent episodes - USG KUB , MCUG
- Rule out sexual abuse

Treatment
- If unsure of diagnosis, explore.
- Treat infection with antibiotics.

IDIOPATHIC SCROTAL OEDEMA

The cause is unknown but has been postulated to be due to an allergy.

Symptoms

- Sudden acute oedema and redness of scrotum.
- Painless.
- Starts as erythema of perineum and extending to lower abdomen.
- Well child, no fever.
- Testes: normal.

Treatment

- This condition is self –limiting but the child may benefit from antibiotics and antihistamines.

Chapter 109:
Penile Conditions

Phimosis

- Definition - Inability to retract the foreskin either physiologic phimosis or pathological causes of tight preputial ring.
- In a normal child the foreskin is non-retractile (physiologic phimosis till age of 5 years)

Causes

- Congenital - rare
- Infection- balanoposthitis
- Recurrent forceful retraction of foreskin
- *Balanoxerotica obliterans (BXO)

Symptoms

- mostly asymptomatic
- Ballooning of foreskin on micturition.
- Recurrent balanoposthitis.
- Urinary retention.
- Urinary tract infection.

Management

- Treat infection if present with oral and topical antibiotics
- Sitz bath
- Application of topical steroid cream (0.05% betamethasone cream 2-3 times daily) should be trialled for 2-4 weeks
- Elective circumcision.

- *BXO:
- Chronic inflammation with fibrosis of foreskin and glans causing a whitish appearance with narrowing of prepuce and meatus.
- Treatment: careful circumcision ± meatotomy. (Will require long term follow-up to observe for meatal stenosis)

Balanoposthitis

(Balanitis - inflamed glans, Posthitis - inflamed foreskin)
Cause effect: phimosis with or without a urinary tract infection

Treatment

- Referral to paediatric surgeon / paediatric urologist
- Check urine cultures.
- Sitz bath.
- Analgesia.
- Antibiotics.
- Circumcision later if there is associated phimosis or recurrent infection.

Paraphimosis

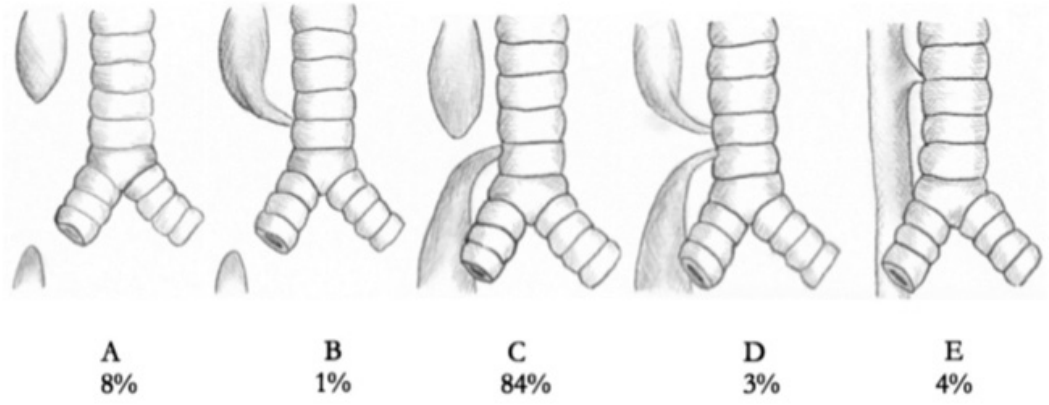
- Forceful retraction of the phimotic foreskin resulting in a constriction band causing oedema, pain and possible ischaemia of the glans and urine retention.
- Treatment
  - Immediate reduction of the foreskin under sedation/analgesia (Use an anaesthetic gel or a penile block, apply a warm compress to reduce oedema and then gentle constant traction on foreskin distally).
  - If reduction is still unsuccessful under a general anaesthetic then a dorsal slit is performed.
  - The child will usually need a circumcision later.

Chapter 110:
Neonatal Surgery

110.1 OESOPHAGEAL ATRESIA WITH OR WITHOUT A TRACHEO-OESOPHAGEAL FISTULA

Presentation

- Antenatal: polyhydramnios, absent gastric bubble, distension of upper oesophageal pouch during swallowing.
- "Mucousy" baby with copious amount of oral secretions.
- Unable to insert orogastric tube.
- Respiratory distress syndrome.
- Aspiration pneumonia and sepsis.
- The Figure showing types of configuration:



- Type C is the commonest, 84% oesophageal atresia with distal fistula.

Problems

- Oesophageal Atresia: Inability to swallow saliva with a risk of aspiration pneumonia.
- Tracheo-oesophageal fistula: Reflux of gastric contents, difficult to ventilate.
- Distal obstruction: If present and the baby is ventilated, prone for bowel perforation.
- Prematurity, and congenital heart disease: If present, associated with higher morbidity and mortality.

Management

- Evaluate the type of oesophageal atresia with/without fistula and associated anomalies e.g. penumonia, cardiac, chromosomal, duodenal and intestinal atresias, anorectal anomalies.
- Suction of the upper oesophageal pouch: A sump suction tube ("Replogle©") should be inserted and continuous low pressure suction done.
- Otherwise frequent intermittent (every 10-15 mins) suction of the oesophageal pouch and oropharnyx is done.
- This is continued even during transport of the baby, to prevent aspiration pneumonia.
- Maintain good oxygenation. Mechanical ventilation only if ABSOLUTELY NECESSARY.
- Fluids - Maintenance and resuscitation fluids as required.
- Position - Lie the baby horizontal and lateral or prone to minimise aspiration of saliva and gastric contents
- Monitoring – Pulse oximetry and cardiorespiratory monitoring.
- Keep baby warm.
- Refer to nearest centre with neonatal and paediatric surgical facilities.

110.2 CONGENITAL DIAPHRAGMATIC HERNIA

Types

- Bochdalek : Posterolateral, commonest, more common on left side.
- Eventration of the diaphragm.
- Morgagni – anterior, retrosternal.

Problems

- Associated pulmonary hypoplasia.
- Herniation of the abdominal viscera into thoracic cavity causing mechanical compression and mediastinal shift.
- Reduced and abnormal pulmonary arterial vasculature resulting in persistent pulmonary hypertension of the newborn (PPHN) and reversal to foetal circulation.
- High mortality rate (40-60%) associated with early presentation.

Presentation

Antenatal findings

- *Ultrasound: Absence of intra-abdominal stomach, presence of abdominal contents in the thorax
- Prognostic Antenatal Investigations:
- *Foetal MRI - location of liver, lung -head ratio and observed to expected ratio of lung volumes.
- *ECHO
- *Karyotyping

Presentation at birth

- Respiratory distress, absent breath sounds in chest.
- Scaphoid abdomen
- Chest X-Ray: bowel loops within the chest and minimal bowel in abdomen.

Late presentation

- Bowel obstruction
- Recurrent lower respiratory chest infections.
- Asymptomatic incidental chest x-ray finding.
- Mediastinal shift
- Bowel in left chest cavity

Differential Diagnoses

- Congenital cystic adenomatoid malformation.
- Pulmonary sequestration.
- Mediastinal cystic lesions e.g. teratoma, bronchogenic/duplication cysts.
- Eventration of diaphragm

Management

- Antenatal counselling: For delivery at hospital with neonatal intensive care facilities.
- Babies with sufficient respiratory effort may be monitored closely with minimal supplemental oxygen.
- Evaluation for associated anomalies and persistent pulmonary hypertension of the newborn (PPHN).
- Ventilation: Direct endotracheal intubation and ventilation without face mask- bag ventilation is required for those with significant respiratory distress at delivery and pre transport. Low ventilatory pressures are to be used to prevent pneumothorax. A contralateral pneumothorax or PPHN need to be considered if the child deteriorates. If the baby is unstable or high ventilatory settings are required, the baby should not be transported.
- Frequent consultation with a paediatrician or paediatric surgeon to decide when to transport the baby.
- Chest tube: If inserted, it should not be clamped during the journey.
- Orogastric Tube: Gastric decompression is essential here. A Size 8 Fr tube is inserted, aspirated 4 hourly and placed on free drainage.
- Fluids: Intravenous fluid management is critical and based on blood glucose and hydration state. Fluid overload must be avoided.
- May need inotropic support and other modalities to optimize outcome.
- Monitoring: Pre-ductal and post-ductal pulse oximetry to detect PPHN.
- Position: Lie baby lateral with the affected side down to optimise ventilation.
- Warmth.
- Consent: High risk.
- Air transport considerations.
- Referral to the paediatric surgeon for surgery when stabilised. Surgery may be performed on-site , or in OT.

110.3 ABDOMINAL WALL DEFECTS

- Exomphalos and Gastroschisis are the more common abdominal wall defects.
- Gastroschisis: Defect in the anterior abdominal wall of 2-3 cm diameter usually to the right of the umbilicus with loops of small and large bowel prolapsing freely without a covering membrane.
- Exomphalos: Defect of anterior abdominal wall of variable size (diameter of base). It has a membranous covering (Amnion, Wharton's jelly, peritoneum) and the umbilical cord is usually attached to the apex of the defect. The content of the large defect is usually liver and bowel but in the small defect the content may just be bowel loops.

Problems

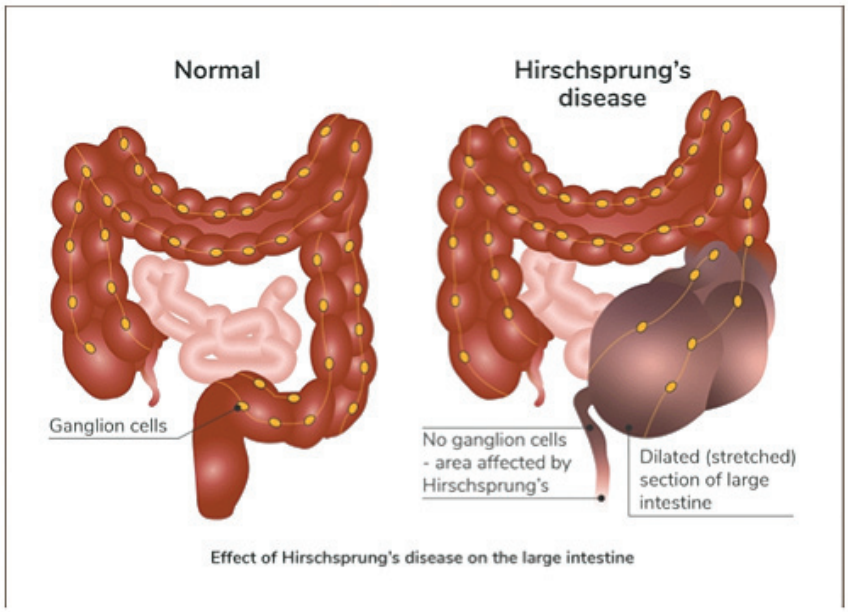
- Fluid loss: Significant in gastroschisis due to the exposed loops of bowel.
- Hypothermia: Due to the larger exposed surface area.
- High incidence of associated syndromes and anomalies especially in exomphalos.
- Hypoglycemia can occur in 50% of babies with Beckwith-Wiedermann's Syndrome (exomphalos, macroglossia, gigantism).

Management

- Evaluation: for hydration and associated syndromes and anomalies.
- Fluids: IV fluids are essential as losses are tremendous especially from the exposed bowel. Boluses (10-20 mls/kg) of normal saline, Sterofundin or colloids must be given frequently to keep up with the ongoing losses.
- A maintenance drip of ½ Saline + 10% D/W at 60 – 90 mls/kg (Day 1 of life) should also be given.
- Orogastric tube: Gastric decompression is essential here and a Size 8-10Fr tube is inserted, aspirated 4 hourly and placed on free drainage.
- Warmth: Pay particular attention to the temperature control. The increased exposed surface area and the fluid exudation will cause the baby to be wet and cold. Wrapping the baby's limbs with cotton and plastic will help.
- Care of the exposed membranes: The bowel/membranes should be wrapped with a clean non permeable sheath e.g; plastic film, without compressing, twisting and kinking the bowel. Please do **NOT** use "warm, saline soaked gauze" directly on the bowel as the gauze will get cold and stick to the bowel/membranes.
- Disposable diapers or cloth nappies changed frequently will help to keep the child dry.
- Monitoring: Heart rate, Capillary refill time, Urine output (the baby may need to be catheterised to monitor urine output or have the nappies weighed).
- Position: To position the bowel at the center of abdomen and supported by a 'doughnut' (cotton in a stockinette) after wrapping the bowel with non permeable sheath.
- Referral to the paediatric surgeon as soon as possible.

110.4 HIRSCHSPRUNG'S DISEASE

- Common cause of intestinal obstruction of the newborn.



Effect of Hirschsprung's disease on the large intestine

Aetiology

- Aganglionosis of variable length of the bowel, from distally, causing absent peristalsis and functional obstruction of the distal bowel.
- The primary aetiology has been thought to be due to cellular and molecular abnormalities during the development of the enteric nervous system and and a failure of migration of ganglion cells from the neural crest into the developing intestine, cranio-caudally fashion
- Genetic factors play a role with an increased incidence in siblings, Down Syndrome, congenital central hypoventilation syndrome and other syndromes.

Types

- Short segment , Rectosigmoid aganglionosis: commonest, more common in boys.
- Long segment aganglionosis, beyond rectosigmoid.
- Total colonic aganglionosis: extending into the ileum or jejunum, almost equal male: female ratio.

Clinical Presentation

May present as a neonate or later in life.

- Neonate (more than 90%)
- Delay in passage of meconium (94-98% of normal term babies pass meconium in the first 24 hours).
- Abdominal distension.
- Vomiting – bilious/non-bilious.
- Hirschsprung-associated enterocolitis (HAEC) – fever, foul smelling, explosive diarrhoea, abdominal distension, septic shock. Has a high risk of mortality and can occur even after the definitive procedure.

Older child.

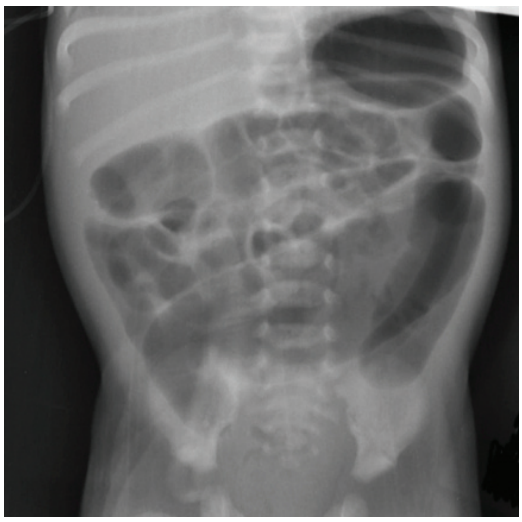
- History of constipation since infancy.
- Abdominal distension.
- Failure to thrive.
- Recurrent enterocolitis.

Other causes of delay in passage of meconium

- Prematurity.
- Sepsis, including urinary tract infection.
- Intestinal atresias.
- Meconium ileus.
- Hypothyroidism.

Investigation

- Plain Abdominal X-ray – dilated loops of bowel with absence of gas in the rectum, sometimes a megacolon is demonstrated. (Figure below)



- Contrast enema – presence of a transition zone with an abnormal rectosigmoid index.
- Rectal Biopsy: Gold standard investigation. Absence of ganglion cells and calretinin and presence of acetylcholinesterase positive hypertrophic nerve bundles (>40 micrometer) confirms the diagnosis.

Management

- Aggressive intravenous fluid resuscitation
- Intravenous broad spectrum antibiotics
- Gastric decompression
- Rectal washouts:
  - Using a large bore soft catheter inserted into the colon past the transition zone, the colon is washed out with copious volumes of warm normal saline until clear.
  - Rectal washout is discontinued if there is pain, bleeding or sign of peritonism, and sepsis.
- If the decompression is difficult with rectal washouts, an urgent ileostomy or colostomy is required. Stomas are also required for severe, recurrent enterocolitis, perforation of the bowel, malnutrition or a grossly dilated colon.
- Definitive surgery, with frozen section to confirm the level of aganglionosis, is planned once the diagnosis is confirmed.
- Postoperatively, the child needs close follow-up for bowel management and the development of enterocolitis.

110.5 INTESTINAL OBSTRUCTION

- Cause - May be functional e.g. Hirschsprung's disease or mechanical e.g. atresias, midgut malrotation with volvulus, anorectal malformations.

Problems

- Fluid loss due to the vomiting, bowel dilatation and third space losses.
- Dehydration.
- Sepsis.
- Diaphragmatic splinting.
- Aspiration secondary to the vomiting.
- Nutritional deficiencies.

Presentation

- Antenatal diagnosis – dilated fluid-filled bowels.
- Delay in passage of meconium (Hirschsprung's disease, atresias).
- Vomiting – bilious/non-bilious (Bilious vomiting is due to mechanical obstruction until proven otherwise).
- Abdominal distension (In malrotation with volvulus, abdominal distension is a late sign).
- Abdominal X-ray – dilated loops of bowel.

Management

- Evaluation – for onset of obstruction and associated anomalies (including anorectal anomalies).
- Fluids – Intravenous fluids are essential.
- Boluses - 10-20 mls/kg Normal saline, Sterofundin or colloids to correct dehydration and replace the measured orogastric losses.
- Maintenance - 0.45% Saline + 10% D/W + KCl as required.
- Orogastric tube – Gastric decompression is essential, a Size 8-10Fr tube is inserted, aspirated 4 hourly and placed on free drainage.
- If Hirschsprung's disease is suspected, a gentle rectal washout with warm normal saline can be performed after consultation with a paediatrician or a paediatric surgeon.
- Warmth.
- Monitoring – vital signs and urine output.
- Air transport considerations during transfer to the referral centre.

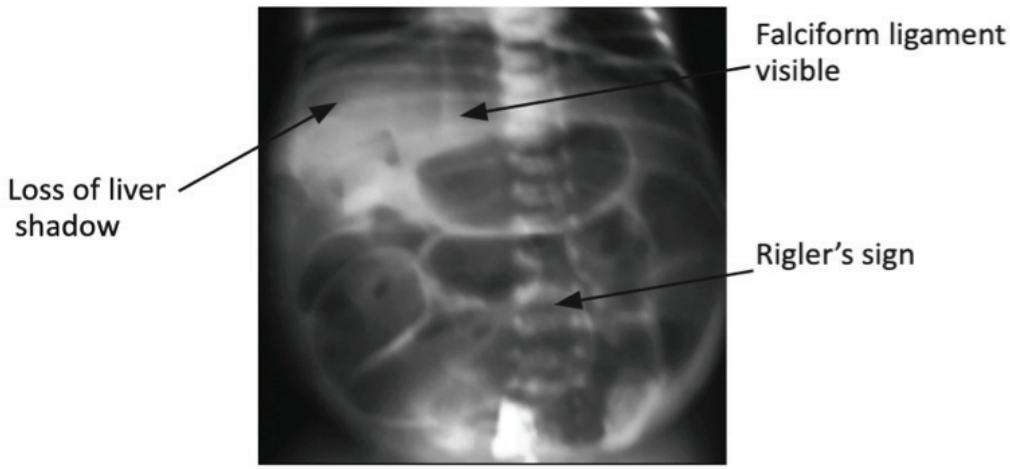
110.6 PERFORATED VISCUS

Causes

- Perforated stomach.
- Necrotising enterocolitis.
- Spontaneous intestinal perforations.
- Intestinal Atresias.
- Anorectal malformation.
- Hirschsprung's disease.

Management

- Evaluation: These babies are usually septic with severe metabolic acidosis, coagulopathy and thrombocytopenia.
- Diagnosis: A meticulous history of the antenatal, birth and postnatal details may elicit the cause of the perforation.
- Sudden onset of increased abdominal distension and deteriorating general condition suggests perforation.
- Supine abdominal x-ray showing free intraperitoneal gas. (Figure below)



- Ventilation: Most of the babies may require intubation and ventilation if they are acidotic and the diaphragm is splinted.
- Fluids: Aggressive correction of the dehydration, acidosis and coagulopathy should be done.
- Orogastric tube: It should be aspirated 4 hourly and left on free drainage.
- Urinary Catheter: Monitor hourly urine output
- Drugs: Will require antibiotics and possibly inotropic support
- Consultation with the paediatrician or paediatric surgeon of the regional referral centre before transfer of the baby.
- Peritoneal Drain: If there is a perforation of the bowel, insertion of a peritoneal drain (using a size 12-14 Fr chest tube or a peritoneal dialysis drain into the right iliac fossa) with/without lavage with normal saline or an isotonic peritoneal dialysate solution should be considered as a temporising measure while stabilising the baby prior to surgery. This can help to improve the ventilation as well as the acidosis.

110.7 ANORECTAL MALFORMATIONS

- Incidence – 1:4,000-5,000 live births
- Cause- unknown
- Antenatal diagnosis - rare
- Newborn Check – Important to clean off any meconium, part the cheeks of the buttocks and look for the anus. DO NOT insert a rectal thermometer as the incidence of perforation and false positives is high.

Krickenbeck Classification for Anorectal Malfomations (2005)	

Major Clinicla Groups
• Perineal(cutaneous) fistula
• Rectourethal fistula
  • Prostatic
  • Bulbar
• Rectovesical fistula
• Vestibular fistula
• Cloaca
• No fistula
• Anal stenosis
	Rare/Regional Variants
	• Pouch colon
	• Rectal atresia/stenosis
	• Rectovaginal fistula
	• H fistula
	• Others

Associated Anomalies

- Sacrum and Spine
  - Spinal dysraphism is common.
  - Good correlation between degree of sacral development and final prognosis. Absence of more than 3 sacrum: poor prognosis.
- Urogenital
  - Common anomalies – vesicoureteric reflux, renal agenesis.
  - Incidence – low in low types and high in cloaca (90%).
  - Vaginal anomalies – about 30%.
- Others
  - Cardiac anomalies.
  - Gastrointestinal anomalies e.g. duodenal atresia.
  - Syndromes e.g. Trisomy 21.

Investigations

- Chest and Abdominal X-ray.
- Echocardiogram.
- Renal and Sacral Ultrasound.
- Micturating cystourethrogram.
- Distal loopogram.

Management

- Observe for 12-24 hours.
- Keep nil by mouth.
- If abdomen is distended, to insert an orogastric tube for 4 hourly aspiration and free drainage.
- IV fluids – ½ saline with 10% Dextrose Water with KCl. May need rehydration fluid boluses if child has been referred late and dehydrated.
- Start IV antibiotics.
- Assess for urogenital, sacral and cardiac anomalies.

Boys

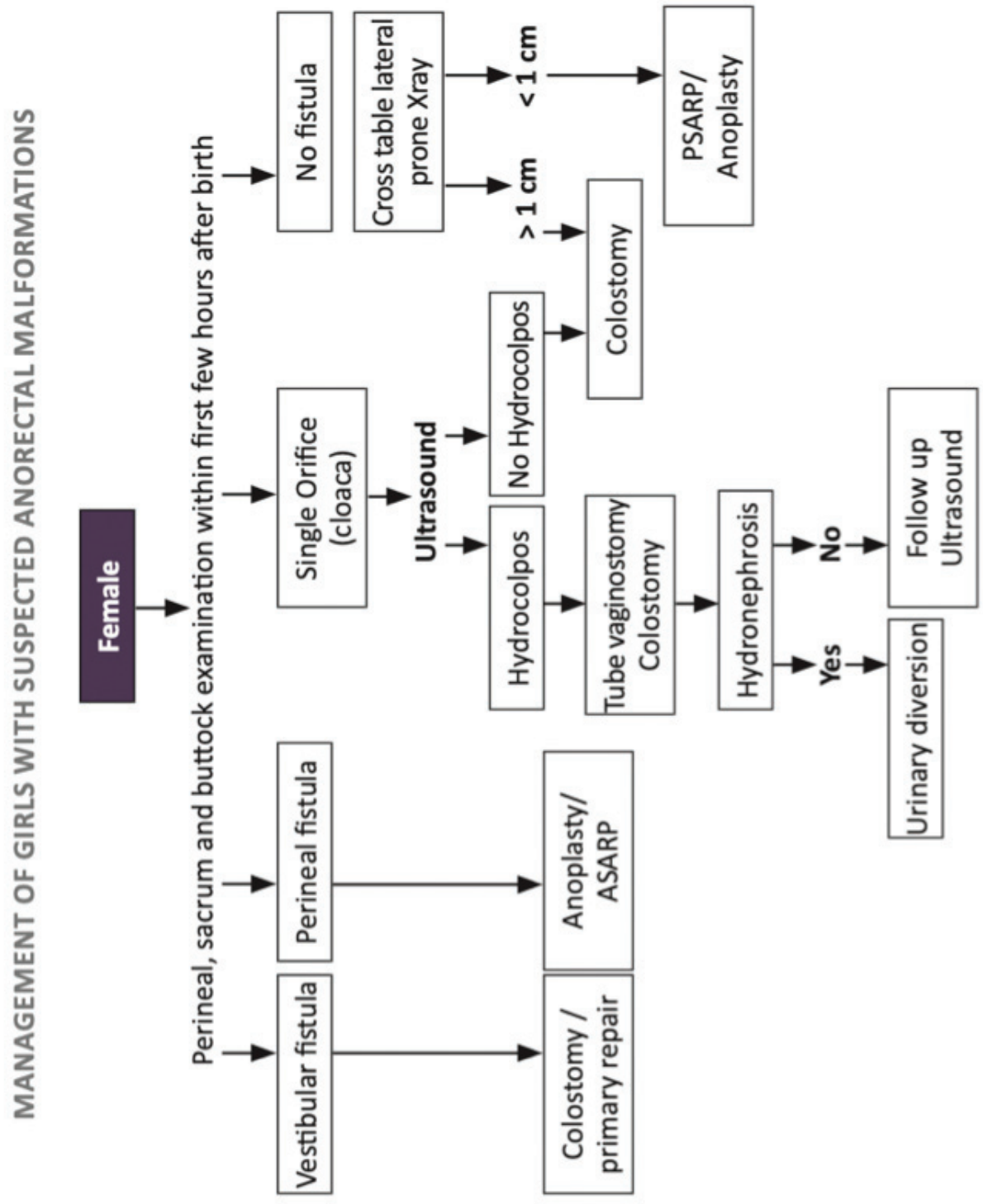
- Inspect the perineum and the urine – if there is clinical evidence of a low type, the child needs to be referred for an anoplasty. If there is evidence of meconium in the urine, the child requires a colostomy followed by the anorectoplasty a few months later.
- If there is no clinical evidence of perineal fistula, then to perform a colostomy

Girls

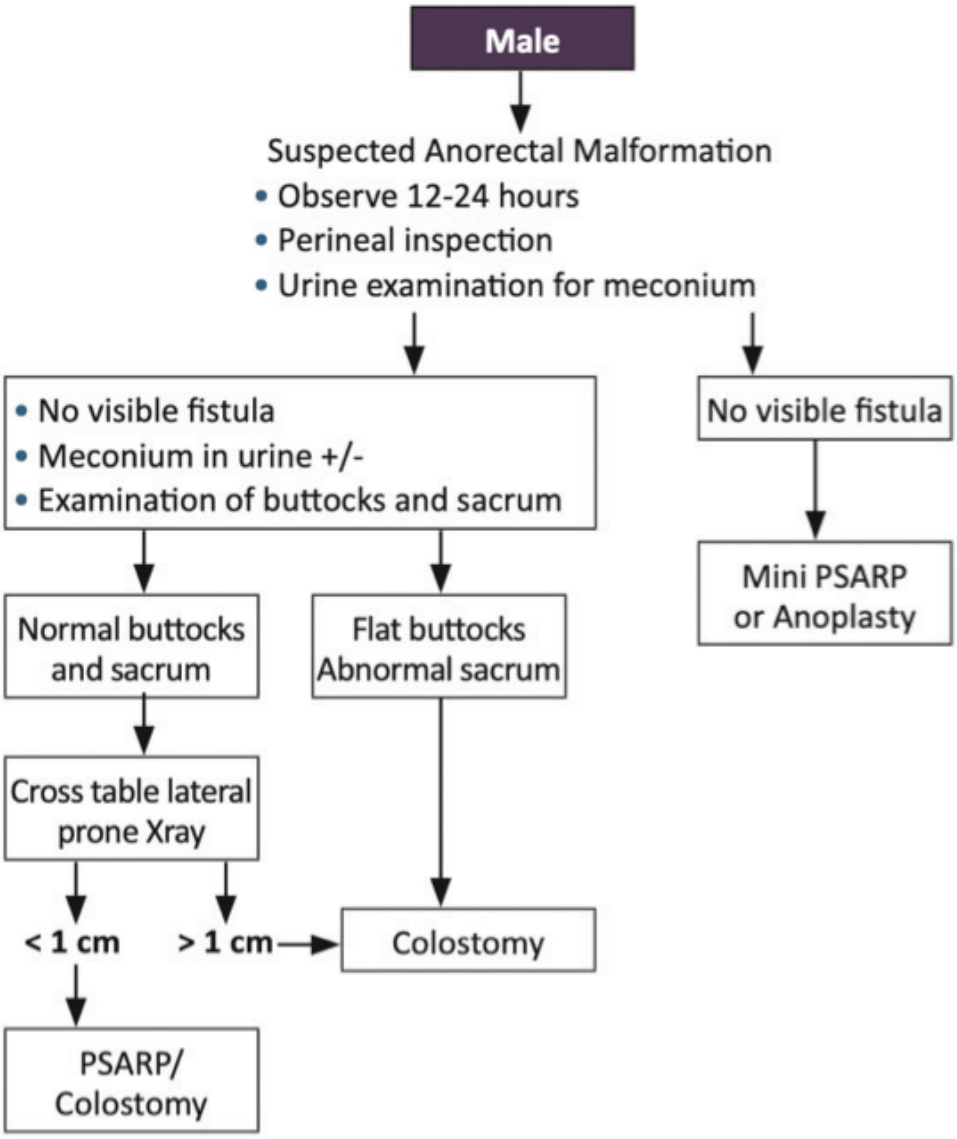
- Inspect the perineum.
- If there is a rectovestibular fistula or a cutaneous fistula, then a primary anoplasty or a colostomy is done.
- If it is a cloacal anomaly, the child needs to be investigated for associated genitourinary anomalies. The baby then requires a colostomy with drainage of the bladder and hydrocolpos if they are not draining well. The anorectovaginourethroplasty will be done many months later.
- If there is no clinical evidence of perineal fistula, then to perform a colostomy.

Definitive surgical procedures

- Perineal operation (Anoplasty)
- Anterior sagittal approach (ASARP)
- Sacroperineal approach
- Posterior sagittal anorectoplasty (PSARP)
- Posterior sagittal anorectovaginourethroplasty (PSARVUP)
- Abdominoperineal pull-through
- Laparoscopic assisted pull-through


MANAGEMENT OF GIRLS WITH SUSPECTED ANORECTAL MALFORMATIONS
Female
Perineal, sacrum and buttock examination within first few hours after birth
No fistula
Cross table lateral prone Xray
< 1 cm
PSARP/ Anoplasty
> 1 cm
Colostomy
Single Orifice (cloaca)
Ultrasound
No Hydrocolpos
Hydrocolpos
Tube vaginostomy Colostomy
Hydronephrosis
No
Follow up Ultrasound
Yes
Urinary diversion
Perineal fistula
Anoplasty/ ASARP
Vestibular fistula
Colostomy / primary repair

MANAGEMENT OF BOYS WITH SUSPECTED ANORECTAL MALFORMATIONS



Section 18

RHEUMATOLOGY

Chapter 111:
Juvenile Idiopathic Arthritis (JIA)

Definition

JIA is a heterogenous group of chronic arthritides in childhood. To diagnose JIA, one requires presence of definite arthritis of:

- Unknown aetiology
- Onset before the age of 16 years
- Persists for at least 6 weeks

Symptoms and Signs in JIA	
Articular Joint swelling Joint pain (may be absent) Joint stiffness / gelling after periods of inactivity Joint warmth Restricted joint movements Limping gait	**Extra-articular** *General* • Fever, pallor, anorexia, loss of weight • Growth disturbance • General: growth failure, delayed puberty • Local: limb length / size discrepancy, micrognathia *Skin* • Subcutaneous (rheumatoid) nodules • Rash – systemic, psoriasis, vasculitis • Nail pitting *Others* • Hepatomegaly, splenomegaly, lymphadenopathy, • Serositis, muscle atrophy / weakness • Uveitis: chronic (silent), acute in Enthesitis related arthritis (ERA) *Enthesitis**
** inflammation of the entheses (the sites of insertion of tendon, ligament or joint capsule into bone)*	

Helpful pointers in assessing articular symptoms			
	Inflammatory	**Mechanical**	**Psychosomatic**
Pain	+/-	+	+++
Stiffness	++	-	+
Swelling	+++	+/-	+/-
Instability	+/-	++	+/-
Sleep disturbance	+/-	-	++
Physical signs	++	+	+/-

Diagnosis and Differential diagnosis

- JIA is a diagnosis of exclusion.

Symptoms and Signs in JIA	
Monoarthritis *Acute* • Acute rheumatic fever • Reactive arthritis: Post viral/ post enteric /post streptococcal infection • Septic arthritis / osteomyelitis • Early JIA • Malignancy: leukaemia, neuroblastoma • Haemophilia • Trauma *Chronic* • JIA: oligoarthritis, ERA, psoriatic • Chronic infections: TB, fungal, brucellosis • Pigmented villonodular synovitis • Sarcoidosis • Synovial haemangioma • Bone malignancy	**Polyarthritis** • JIA – polyarthritis (RF positive or negative), ERA, psoriatic arthritis • Reactive arthritis • Lyme disease • Systemic Lupus Erythematosus • Other connective tissue diseases • Inflammatory bowel disease • Sarcoidosis • Familial hypertrophic synovitis syndromes • Immunodeficiency syndromes • Mucopolysaccharidoses

Helpful pointers in diagnosis

- Avoid diagnosing arthritis in peripheral joints if no observed joint swelling.
- Consider other causes, particularly if only one joint involved.
- Active arthritis can be present with the only signs being decreased range of movement and loss of function.
- In axial skeleton (including hips), swelling may not be seen. Diagnosis is dependent on inflammatory symptoms (morning stiffness, pain relieved by activity, pain on active and passive movement, limitation of movement). Investigations to exclude other diagnosis are important.
- In an ill child with fever, loss of weight or anorexia, consider infection, malignancy and other connective tissue diseases.
- In any child with severe pain (especially night pain), consider malignancy.

Investigations

- The diagnosis is essentially clinical; laboratory investigations are only supportive.
- No laboratory test or combination of tests can confirm the diagnosis of JIA.
- FBC and Peripheral blood film – exclude leukaemia. BMA may be required if there are any atypical symptoms/signs even if PBF is normal
- ESR or CRP – markers of inflammation.
- X-ray/s of affected joint/s: esp. if single joint involved to look for malignancy.
- Antinuclear antibody – a risk factor for uveitis
- Rheumatoid factor – assesses prognosis in polyarthritis and the need for more aggressive therapy.

**Antinuclear antibody and Rheumatoid factor are NOT required to make a diagnosis.*
** Other Ix done as neccesary : complement levels, ASOT, Ferritin, immunoglobulins (IgG, IgA and IgM), HLA B27, synovial fluid aspiration for microscopy and culture, echocardiography, MRI/CT scan of joint, bone scan.*

Management

Medical treatment

- Refer management algorithms based on number of joints affected (see following pages)

Dosages of drugs commonly used in JIA

Name	Dose	Frequency
Ibuprofen	5 - 10 mg/kg/dose (maximum 2.4 Gm/day)	3-4/day
Naproxen	5 - 10 mg/kg/dose (maximum 1 Gm/day)	2/day
Indomethacin	0.5 - 1 mg/kg/dose (maximum 150mg/day)	2-3/day
Diclofenac	0.5 - 1 mg/kg/dose	3/day
Methotrexate	10 - 15 mg/m^2/dose (maximum 25 mg/dose)	1/week
Folic acid	2.5 - 5.0 mg per dose	1/week
Sulphasalazine	15 - 25 mg/kg/dose (start 2.5 mg/kg/dose and double weekly; maximum 2 Gm/day	2/day
Hydroxychloroquine	5 mg/kg/dose	1/day
Methylprednisolone	30 mg/kg/dose (maximum 1 Gm / dose)	1/day x 3 days
Prednisolone	0.1 - 2 mg/kg/dose	1-3/day

Note: Patients on DMARDS (e.g. Methotrexate, Sulphasalazine) require blood (FBC, LFT, creatinine) monitoring for toxicity: 1 month after drug initiation,
1-2 months after increase in dosages, and every 2-3 months once on stable doses. Patients on long term NSAIDs require 3 monthly creatinine, ALT and UFEME.

Physiotherapy

- Avoid prolonged immobilization
- To improve and maintain range of joint motion, to strengthen muscles, to stretch deformities, to condition patient and improve endurance

Occupational Therapy

- Splinting when necessary to reduce pain and preserve joint alignment
- To adopt joint protection techniques
- To improve quality of life by adaptive aids and modification of environment

Ophthalmology referral

- All patients must have uveitis screening at initial diagnosis (uveitis can be asymptomatic but cause loss of vision) and have follow-up at regular intervals (frequency depending on risk) even if initial screening is normal.

Psychosocial support

- To improve self esteem
- Counselling and family support may be necessary

Nutritional support

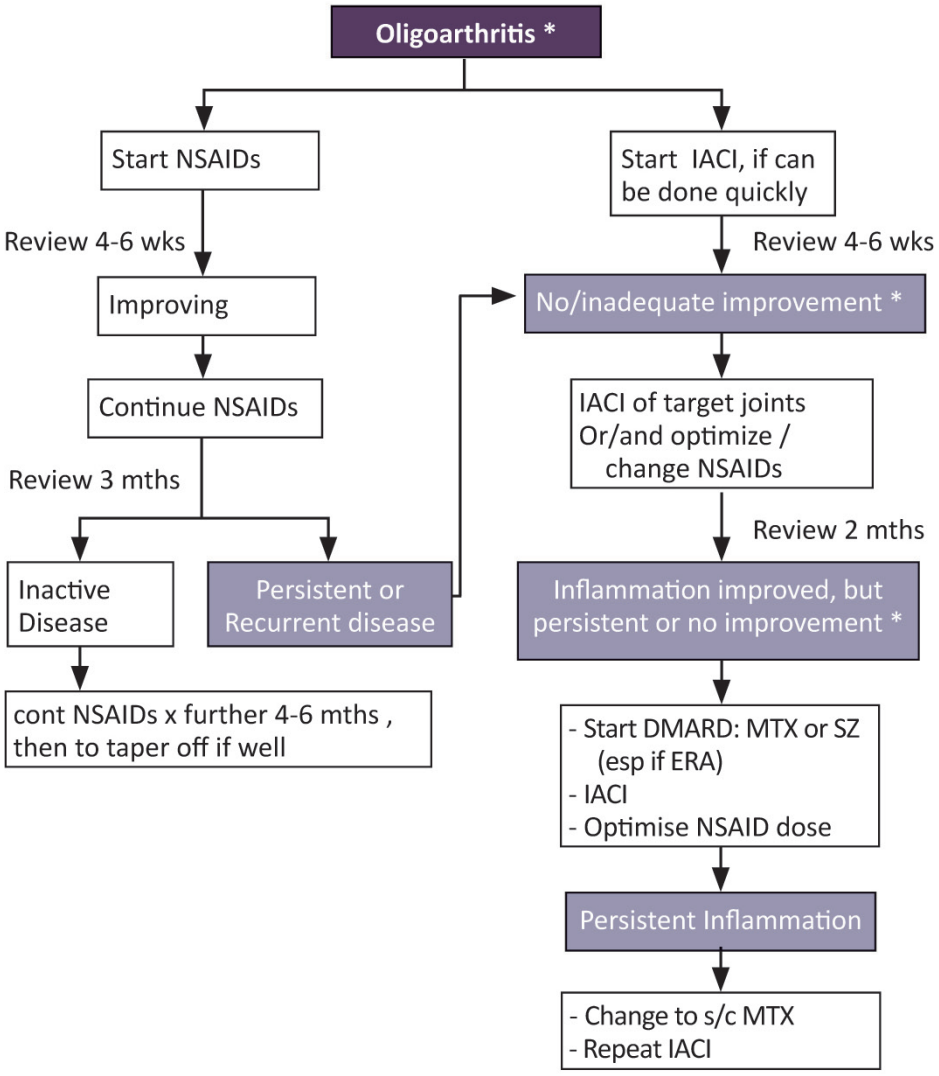
- Ensure a healthy well balanced healthy diet, with special emphasis on calcium intake (to promote bone health)

Others

- Disease education is important to promote acceptance and compliance
- Encourage regular exercise and participation in sports
- Encourage school attendance with adjustments to school life (classroom location, stairs etc.) and physical education classes
- Dental care is important
- Orthopedic referral when necessary (e.g. synovectomy, arthrotomy, arthrodesis, joint replacements)

TREATMENT FOR CHILDREN WITH CHRONIC ARTHRITIS

Oligoarthritis (1-4 joints)

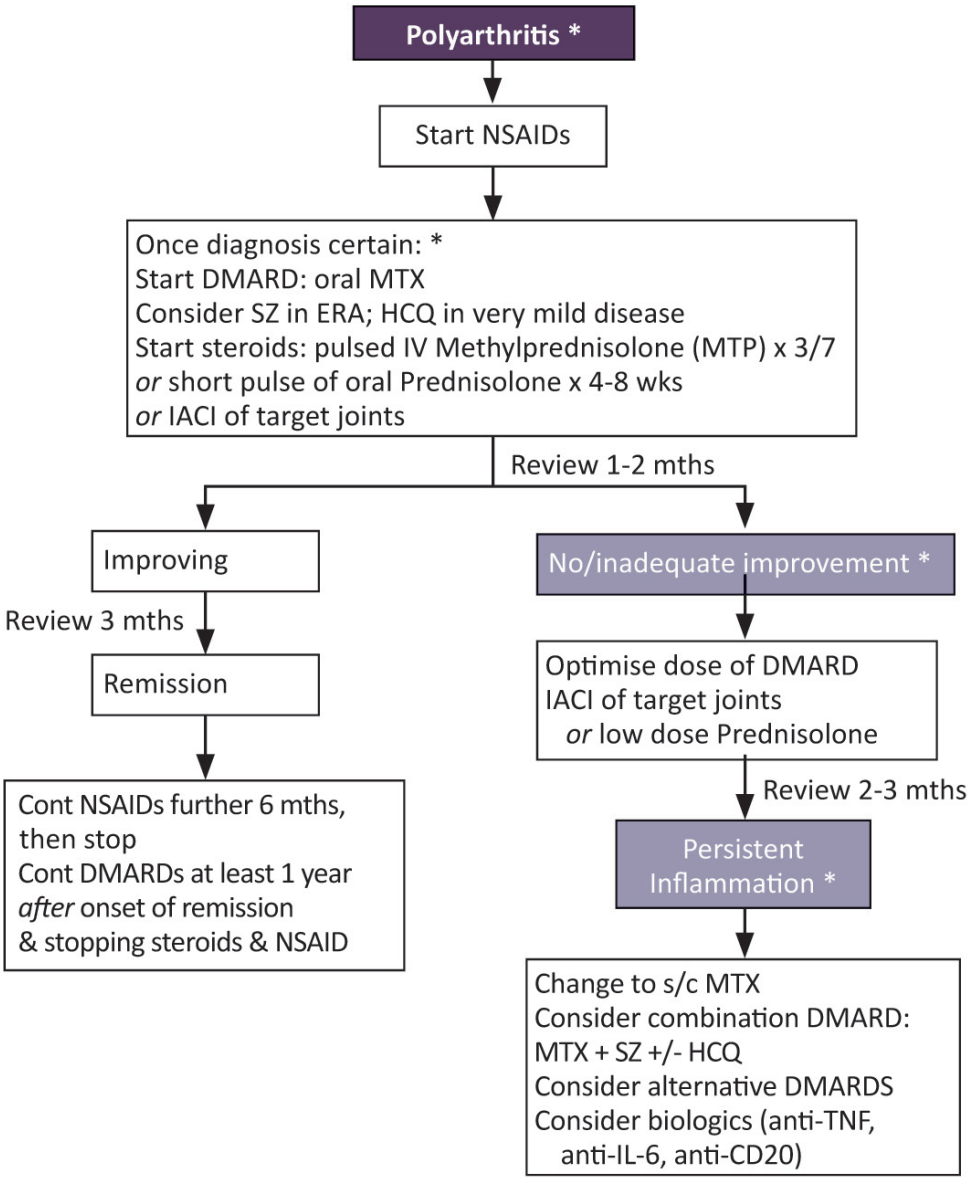


Note:
- Remember to screen for Uveitis
- All patients with persistent inflammation should be on DMARDs within 6 months of diagnosis even if only having oligoarthritis.

*, Consider referral to Paeds Rheumatologist / reconsider diagnosis;
Abbreviations:
IACI, Intra-articular corticosteroid injection; MTX , Methotrexate;
SZ, Sulphasalazine; DMARD, Disease modifying anti-rheumatic drugs.
s/c , subcutaneous

TREATMENT FOR CHILDREN WITH CHRONIC ARTHRITIS

Polyarthritis (> 5 joints)

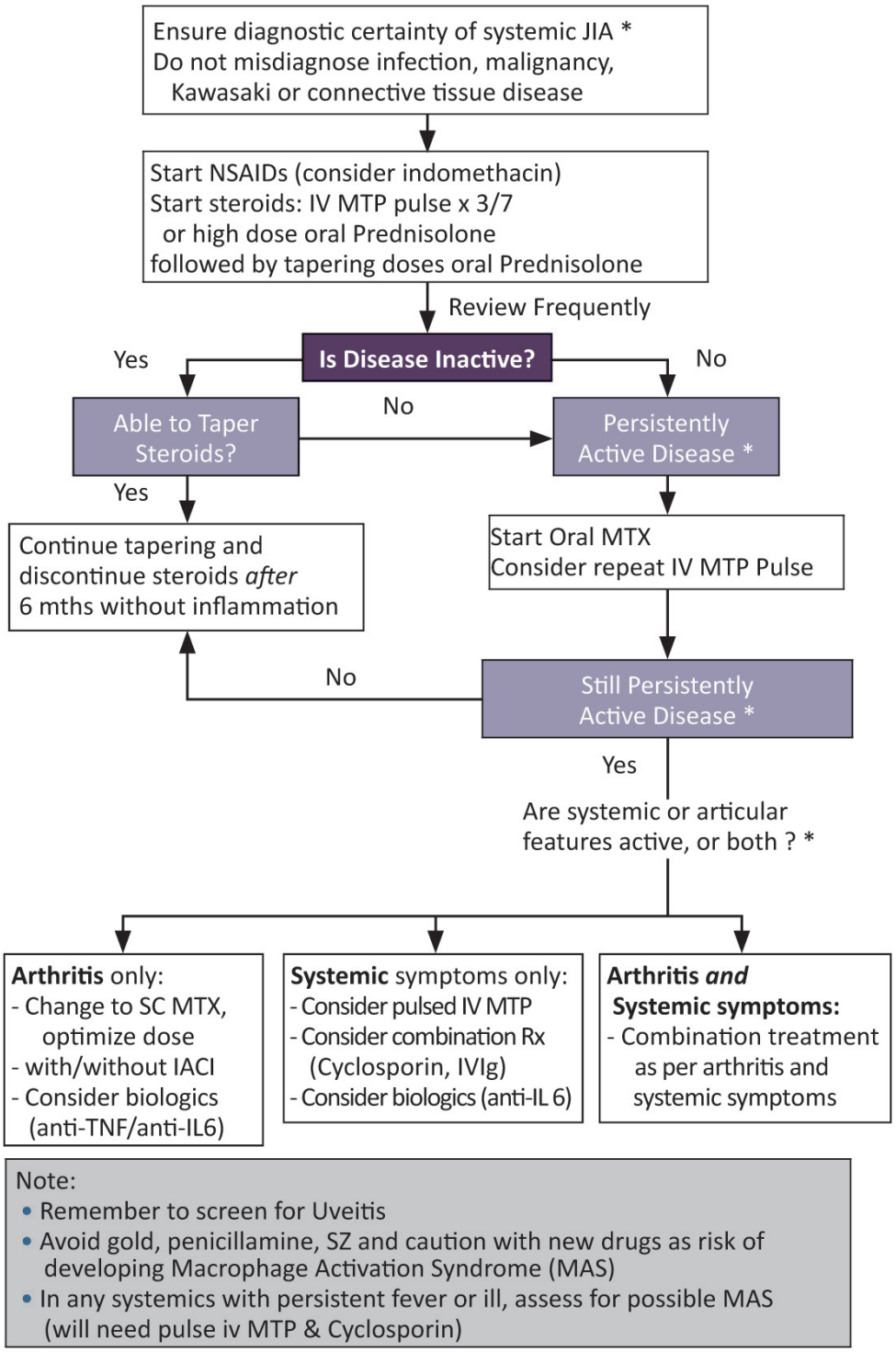


Note:
- Remember to screen for Uveitis
- Consider s/c route of MTX at diagnosis if polyarthritis severe
- Best opportunity to achieve remission in first two years of disease
- Avoid accepting low grade inflammation until all avenues explored

*, Consider referral to Paeds Rheumatologist / reconsider diagnosis;
Abbreviations:
IACI, Intra-articular corticosteroid injection; MTX , Methotrexate;
SZ, Sulphasalazine; HCQ, Hydroxychloroquine; ERA, enthesitis related arthritis;
DMARD, Disease modifying anti-rheumatic drugs.

TREATMENT FOR CHILDREN WITH CHRONIC ARTHRITIS

Systemic onset JIA



Note:
- Remember to screen for Uveitis
- Avoid gold, penicillamine, SZ and caution with new drugs as risk of developing Macrophage Activation Syndrome (MAS)
- In any systemics with persistent fever or ill, assess for possible MAS (will need pulse iv MTP & Cyclosporin)

*, Consider referral to Paeds Rheumatologist / reconsider diagnosis;
Abbreviations: as previous page; IVIG, IV immunoglobulins.

Chapter 112:
Systemic Lupus Erythematosus

Definition

- A chronic multisystem autoimmune condition with widespread inflammation of blood vessels and connective tissue, characterized by autoantibodies against self-antigens especially presence of Antinuclear antibody (ANA positive in 95% untreated SLE).
- Severity ranges from mild to life threatening and onset can be insidious or acute.
- Disease runs an unpredictable course, evolves over time and can result in significant long-term morbidity and mortality.

Epidemiology

- Only 15-20% of all SLE patients occur before the age of 18 years.
- Onset commonly around puberty (median age 10-12 years).
- Majority (85%) present > 8 years, rare under age 5 years.
- Female: male ratio = 4.5:1.

Clinical presentation

- Clinical manifestations of juvenile SLE (jSLE) are protean, variable and often involve multiple organ systems.
- If jSLE is suspected, a meticulous assessment of all organ systems needs to be performed.
- In general, jSLE is a more severe disease when compared to adult SLE, often presenting with severe renal, cerebral and haematological manifestations, and with higher overall disease activity, accruing more organ damage with time resulting in more long term morbidity and mortality.

Common presentations of JSLE (not exhaustive)
Constitutional Fever, loss of appetite, loss of weight, lethargy, lymphadenopathy ***Mucocutaneous*** Malar rash (60% jSLE), oral/nasal erythema and ulcers, maculopapular, vasculitic rash (petechiae, purpura, nodules, ulcers), photosensitivity, discoid rash (10%), diffuse alopecia, Raynaud's phenomenon, bullous, livedo reticularis. ***Cardiac*** Chest pain, pericarditis, pericardial effusion, myocarditis with heart failure, Libmann-Sacks endocarditis. ***Respiratory*** Shortness of breath, decrease effort tolerance, interstitial lung disease, pleuritis and pleural effusion, pulmonary haemorrhage. ***Gastrointenstinal tract*** Hepatosplenomegaly, hepatitis (25%), diffuse abdominal pain, serositis, diarrhoea, pancreatitis, gastrointenstinal tract vasculitis + bowel perforation. ***Renal*** Nephrotic syndrome, proteinuria, haematuria, hypertension, renal impairment, acute renal failure.

Common presentations of JSLE *(continued)*
Musculoskeletal Arthralgia, arthritis (usually non-erosive and non-deforming), myalgia, myositis, tenosynovitis ***Neuropsychiatric*** Headache, migraine, mood disorder, cognitive impairment, seizures (dif- ferential diagnosis - Posterior reversible encephalopathy syndrome (PRES)), stroke, psychosis (visual > auditory hallucinations), acute confusional state, cranial and peripheral neuropathies. ***Haematological*** Autoimmune hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia, Coombs positivity, Thrombotic thrombocytopenic purpura, antiphospholipid antibodies (40% jSLE, only half have thrombosis) ***Ocular*** Uveitis, optic neuritis, vaso-occlusive retinal vasculitis, retinopathy (cotton- wool spots), episcleritis

Diagnosis

- Diagnosis is based on the presence of clinical features supported by positive laboratory findings.
- Early diagnosis is crucial as a delay in treatment is associated with increased mortality and less likelihood of achieving remission.
- However, diagnosis can sometimes be challenging and thus early referral to a paediatric rheumatologist or paediatrician experienced in the care of jSLE is recommended.
- Differential diagnosis of SLE is broad and must include infection, malignancy and other inflammatory conditions.
- Various criteria have been developed for the classification of SLE
- (e.g. revised ACR criteria and SLICC criteria – see tables at the end of chapter) but these are primarily meant for research purposes.
- However, these criteria are often used to aid diagnosis. ACR criteria of fulfilling > 4 out of 11 criteria have high sensitivity (96%) and specificity (96%) for diagnosis of SLE.
- Caution: in some children with early SLE, these criteria may not be met yet and children can also present with isolated organ involvement (e.g. renal disease) which may not fulfill these criteria. Thus, criteria alone should not be a pre-requisite for diagnosis or instituting treatment.

Investigations For Initial assessment:

Investigation	Common results and interpretation
Full blood count & reticulocyte count (+ Peripheral Blood Film)	Low Hb: hemolytic, usually warm type /secondary to chronic disease/ iron deficiency; Low WCC, if high: consider infection, stress response, or due to steroids; Low lymphocytes: disease/ immunosuppression; Low neutrophils: rare; Low platelet: disease. (not to forget rarer causes of cytopenias - MAS or TTP)
Erythrocyte sedimentation rate	High, if paradoxically low ESR in an ill patient with pancytopenia; consider MAS
C-reactive protein	Normal, if high: consider infection, serositis, arthritis
Renal profile	Hyperkalemia, high creatinine in renal involvement, electrolyte imbalance
Liver function test	Raised ALT (AIH, active disease, fatty liver, adverse effect of drugs), low albumin, high bilirubin, high GGT
Cardiac enzymes	High (myositis, but note that myositis can be subclinical)
Urine FEME	Proteinuria, haematuria, urinary casts (especially red blood cell cast). If proteinuria present, quantify with urine protein: creatinine index or 24-hour urine protein.
ANA	Positive in 95% active untreated SLE. (Note: ANA is not diagnostic)
Anti-dsDNA Ab	Positive in 60% SLE (more specific than ANA), correlated with renal disease
ENA	Most common: anti-Ro, anti-La (both associated with neonatal lupus); anti Sm – correlated with renal disease
Complement 3 & 4	Low, complement levels correlate with disease activity. NB. Some patients have normal levels even if active disease, some may have congenital C4 deficiency
Thyroid function	Low or high (if abnormal to do thyroid autoantibodies)
Direct antibody test (direct Coombs)	Positive, but may not reflect ongoing active hemolysis
Coagulation profile	Prolonged aPTT suggests presence of lupus anticoagulant
Thrombophilia screen	Lupus anticoagulant and antiphospholipid antibodies (anticardiolipin and β2 glycoprotein 1 antibodies)
*MAS: Macrophage activation syndrome, TTP: Thrombotic thrombocytopenic purpura, AIH: Autoimmune hepatitis; ENA: Extractable Nuclear Antigen	

Other investigations (as indicated)

- IgG, IgA, IgM: usually high IgG (chronic inflammation). Immunoglobulins also to rule out underlying primary immunodeficiency
- Rheumatoid factor: positive in 10-30% jSLE, consider overlap if significant arthritis
- CXR
- Echocardiography, ECG
- Bone marrow aspiration
- Ophthalmology assessment
- Other organ assessment as indicated: Renal biopsy, Skin biopsy, MRI/MRV/MRA brain, EEG, Lumbar puncture, Abdominal ultrasound, OGDS and Colonoscopy, HRCT, Lung function test
- Fasting serum lipid, fasting blood sugar

MANAGEMENT

- Management of the child with SLE can be challenging and treatment must be individualized.
- Treatment options vary depending on organ involvement, disease activity and damage, access to medications as well as patient and institution preferences.
- The information below is a broad general guide based on common principles.

Aims

- Rapid reduction and control of disease activity to prevent long term organ damage.
- Maintain health and function, and aid patient and family to cope with disease and treatment.
- Minimise side effects of treatment

General

- Sun protection: sunblock SPF 50-60, avoid sun (hats, umbrellas and protective clothing) and avoid activities carried out under the sun (e.g. sports, school assembly)
- Adequate nutrition (especially dietary intake of calcium and vitamin D) and appropriate rest (but discourage inactivity)
- Treat any infections promptly and aggressively (60-80% infections due to bacteria, prone to encapsulated bacteria like pneumococcus, meningococcus, salmonella and haemophilus; virus like cytomegalovirus, herpes zoster and opportunistic organisms like pneumocystis jirovecii or cryptococcus)
- Immunisations: all routine immunisations recommended (especially pneumococcal and influenza). Live vaccinations contraindicated if on immunosuppressive agents.

SPECIFIC PHARMACOTHERAPY

Corticosteroids

- Usually required by all children even in the absence of major organ involvement.
- Is the mainstay of pharmacologic therapy but is associated with significant side effects. Need to balance the requirement versus side effects carefully aiming for lowest possible dose to maintain disease control with the least side effects.
- Can be given orally (Prednisolone) or intravenously (Methylprednisolone).
- Initial dose varies depending on severity of disease and extent of organs involved, Prednisolone: 0.5-2 mg/kg/day in at least 2 divided doses or IV Methylprednisolone 10-30mg/kg/day for 3-5 days, may be repeated up to weekly (maximum 1 gram, but generally not more than 500 mg/day as patients prone to infection/ sepsis)
- Tapering of steroid dose should occur once disease is controlled aiming for lowest possible dose. The rapidity of steroid taper depends on clinical response (resolution of symptoms and physical abnormalities), control of disease activity and towards normalization of laboratory findings (e.g. no cytopenias, improving or near normal complement levels, reducing proteinuria, improving urinalysis, lowering of antidsDNA levels)
- Generally, the higher the dose, the faster the taper. During active phase, will require divided doses. Once daily dose usually not recommended till 10 mg/day or less. Alternate day dosing may be inadequate to control ac- tive SLE despite lower risk of side effects.

Immunosuppressive agents

- Immunosuppressive agents are now started early soon after diagnosis for rapid control of disease with improved long-term outcome and as a steroid-sparing agent.
- The choice of immunosuppressive agents is largely dictated by the organ system/s involved and the severity of involvement.
- Azathioprine (1-2.5 mg/kg/day) is the most commonly used immunosuppressive agent, especially for haematological, dermatological, serositis, vasculitis and sometimes as maintenance therapy for lupus nephritis. Generally well tolerated, side effects include nausea, GI symptoms, hair loss, bone marrow suppression.
- Major organ involvement like renal, cerebral, cardiac and pulmonary or other life-threatening manifestations usually will warrant pulses of IV Cyclophosphamide together with generally a single pulse of IV Methylprednisolone at monthly intervals of minimum 6 months.
- Cyclophosphamide (500-1000mg/m^2/dose, max dose 1.2 g) is effective but associated with significant risks of infection (immunosuppression), haemorrhagic cystitis (prevented by Mesna), infertility and long term risk of cancer.
- Mycophenolate mofetil (600-1200mg/m^2/day): used for induction phase of lupus nephritis, but the cost precludes its use as first line. It is also used for various other significant manifestations including haematological, dermato- logical and myositis. Main side effect is GI upset which can be minimized by gradual introduction.
- Methotrexate (10-15 mg/m^2/week): arthritis, myositis and skin disease.
- Cyclosporin (3-5 mg/kg/day): nephritis especially membranous

Hydroxychloroquine

- An antimalarial recommended for all lupus patients as it can help reduce flares, reduce autoantibody production and cardio protective (lipid regulating, anti-platelet and anti-thrombotic, anti-hypertensive).
- Hydroxychloroquine (4-6mg/kg/day) is also useful for mild arthritis and skin disease.
- Needs yearly eye screening (for hydroxychloroquine induced retinopathy – present with subtle changes in colour vision and paracentral scotoma) and hearing assessment (ototoxicity)
- Caution in impaired renal function – consider stopping as increased risk of toxicity.

Others

- NSAIDs: myalgia, arthralgia, arthritis; and serositis
- Folic acid
- Bone health: Calcium, vitamin D
- Antihypertensive agents: as required in lupus nephritis. ACE inhibitors/ ARBs helpful to reduce proteinuria.
- Aspirin: low dose for those with significant titers of antiphospholipid antibodies, heparin (LMWH) followed by warfarin in the presence of thrombosis. (aim for INR 2.5-3.5)
- Intravenous immunoglobulin: sometimes used in ill children, in whom the possibility of severe infection cannot be excluded which precludes a pulse of iv Methylprednisolone.
- Plasmapheresis: occasionally used for severe refractory disease e.g. pulmonary haemorrhage, TTP.

Biological therapies – for resistant cases

- Newer therapies are showing promise with many more being researched.
- The currently used biological agents include Rituximab (anti-CD20 antibody) and Belimumab (anti-B lymphocyte stimulator antibody), first FDA approved drug for lupus.

Follow-up management

At every clinic visit, perform meticulous assessment looking for:

- Evidence of active disease
  - Detailed systematic assessment of all organ systems looking for symptoms of active disease & response to treatment.
  - Complete physical examination (CVS, Respiratory, Abdomen, Neurology including muscle power, Musculoskeletal, Skin including scalp and hair & mucosa, Fundus) including growth parameters, blood pressure, pubertal staging.
- Complications of disease (e.g. organ damage, atherosclerosis) or treatment (e.g. infections, immunosuppression, steroid toxicity - myopathy, AVN, cataract, glaucoma).
- Psychological issues – self-image & self-esteem, school issues, bullying, family support.
- Compliance to treatment regimen

Perform the following investigations to support assessment with the aim to adjust treatment:

- Full blood count
- ESR
- C-reactive protein
- Renal profile
- Liver function test
- Complement 3 & 4
- UFEME
- UPCI (Urine protein-to-creatinine index): if has proteinuria
- antidsDNA levels: if positive and able to measure titers, useful to monitor disease activity.
- Ca, PO4, VBG: for those with significant renal disease
- Muscle enzymes: if has myositis
- PT/INR: if on warfarin

Investigations to be done on a yearly basis to look for complications

- Fasting serum lipid
- Fasting blood sugar or HbA1c
- Thyroid function test

ACR Classification criteria for Systemic Lupus Erythematosus

(≥ 4 out of 11 criteria present simultaneously or serially over time)

Criteria	Definition
1. Malar rash	Flat or rash erythema over the malar eminences and spares the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scal- ing and follicular plugging; atrophic scarring may occur
3. Photosensitivity	Skin rash following sunlight exposure, by history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless
5. Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion
6. Serositis	Pleuritis – convincing history of pleuritic pain or rub on auscultation or evidence of pleural effusion or Pericarditis – documented by electrocardiogram, echocar- diogram or rub
7. Renal disorder	Persistent proteinuria greater than 0.5g/day or Cellular casts – may be red cell, hemoglobin, granular, tubular or mixed
8. Neurological disorder	Seizures in the absence of offending drugs or metabolic derangements, Or Psychosis in the absence of offending drugs or metabolic derangements
9. Haematological disorder	Hemolytic anemia with reticulocytosis or Leucopenia < 4000/ mm^3 on ≥ 2 occasions or Lymphopenia < 1500/ mm^3 on ≥ 2 occasions or Thrombocytopenia < 100,000/mm^3 on ≥ 2 occasions
10. Immunological disorder	Antibody to native DNA, or Antibody to Sm protein, or Antiphospholipid antibodies - either anticardiolipin anti- bodies, presence of lupus anticoagulant, or false positive serological test for syphilis
11. Antinuclear antibody	Presence of antinuclear antibody by immunofluorescence or an equivalent assay

Adapted from Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum 25:1271-1277, 1982; and Hochberg MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum 40: 1725, 1997.

SLICC classification criteria for Systemic Lupus Erythematosus
(At least 4 items of which one must be clinical and one immunologic, or biopsy proven nephritis with positive ANA and antidsDNA)

Clinical Criteria	
1.	Acute cutaneous lupus, including: • Lupus malar rash (do not count if malar rash discoid) • Bullous lupus • Toxic epidermal necrolysis variant of SLE • Maculopapular lupus rash • Photosensitive lupus rash • In the absence of dermatomyositis OR Subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with post inflammatory dyspigmentation or telangiectasia

2.	Chronic cutaneous lupus, including:
	• Classic discoid rash
	  • Localised (above the neck)
	  • Generalised (above and below the neck)
	• Hypertrophic (verrucous) lupus
	• Lupus panniculitis (profundus)
	• Mucosal lupus
	• Lupus erythematosus tumidus
	• Chilblains lupus
	• Discoid lupus/lichen planus overlap

3.	Oral ulcers *(In the absence of other causes, such as vasculitis, Behcet's disease, infections (herpesvirus), inflammatory bowel disease reactive arthritis and acidic foods)* • Palate, Buccal, Tongue OR Nasal ulcers
4.	Non scarring alopecia (diffuse thinning or hair fragility with visible broken hairs) *in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia*
5.	Synovitis involving 2 or more joints, characterized by swelling or effusion OR Tenderness in 2 or more joints and at least 30 minutes of morning stiffness

Clinical Criteria *(continued)*	
6.	Serositis *(In the absence of other causes, such as infection, uremia, and Dressler's pericarditis)* • Typical pleurisy for more than 1 day OR pleural effusion OR pleural rub • Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography
7.	Renal • Urine protein-to-creatinine ratio (or 24 hour urine protein) representing 500 mg protein/24 hours OR red blood cell casts
8.	Neurologic • Seizures • Psychosis • Mononeuritis multiplex (In the absence of other know causes such as primary vasculitis) • Myelitis • Peripheral or cranial neuropathy (In the absence of other known causes such as primary vasculitis, infection and diabetes mellitus) • Acute confusional state (In the absence of other causes, including toxic/ metabolic, uremia and drugs)
9.	Haemolytic anemia
10.	• Leucopenia (< 4000/mm^3 at least once) (In the absence of other known causes such as Felty's syndrome, drugs and portal hypertension) OR • Lymphopenia (<1000/mm^3 at least once) (In the absence of other known causes such as corticosteroids, drugs and infection.)
11.	Thrombocytopenia (<100,000/mm^3) at least once In the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura)

Immunologic criteria	
1.	ANA level above laboratory reference range
2.	Anti-ds DNA antibody level above laboratory reference range (or > 2-fold reference range if tested by ELISA)
3.	Anti-Sm: presence of antibody to Sm nuclear antigen
4.	Antiphospholipid antibody positivity as determined by any of the following: • Positive test result for lupus anticoagulant • False-positive test result for rapid plasma reagin • Medium – or high titer anticardiolipin antibody level (IgA, IgG, or IgM) • Positive test result for anti-β2 glycoprotein 1 (IgA, IgG or IgM)
5.	Low complement • Low C3 • Low C4 • Low CH50
6.	Direct Coombs' test *in the absence of hemolytic anemia*

Petri M, Orbai A, Alarcon G et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Ery- thematosus. Arthritis & Rheumatism, vol 64, No 8, Aug 2012, pp 2677-2686.

Section 19

POISON AND TOXINS

Chapter 113:
Snake Related Injuries & Envenomation

Introduction

- Different geographical regions and countries will have different snake species of medical importance.
- Snakes of medical importance in Malaysia are either equipped with venom or without venom. The venomous front-fanged snakes are from the family Elapidae (cobras, kraits, coral snakes and sea snakes) or Crotalinae (Pit vipers). Some non-front-fanged colubroids are also equipped with venom (cat snakes and keelbacks). Pythons may also pose a danger to humans.
- Snake venoms are made of a complex and diverse group of proteins, many with enzymatic activity. Envenomation syndromes are treated with timely administration of the appropriate antivenom in an adequate amount.
- The requirement for antivenom may differ from hospital to hospital based on the needs and presence of venomous snake species in the area.
- Early access to experts in the field (Clinical Toxicologist) will assist healthcare providers in snake species identification and optimal management for a favourable outcome.

Note: Assistance/query/consultation for identification and clinical management of snakebite can be obtained from the National Poison Centre Malaysia and the Remote Envenomation Consultation Services (RECS) Malaysia (http://mstoxinology.blogspot.com/p/recs.html).

Clinical features of common snakebite envenoming

- Local envenomation syndrome by cobra (Naja) species includes immediate pain, progressively worsening swelling, blistering and dermonecrosis. Systemic envenomation manifests as acute neurological and cardiac dysfunction including ptosis [an early sign], ophthalmoplegia, dysphagia [drooling of saliva], aphasia, dyspnea, muscle paralysis and dysrhythmia.
- Krait (Bungarus) species bites may cause minimal local effects and may go unnoticed. Systemic envenomation may be delayed and manifest as a sudden onset of rapidly progressive myalgia and muscle paralysis.
- Sea snake bites can be painless with minimal local effects. Systemic envenomation may present as generalised myalgia, stiffness, paresis, paralysis and myoglobinuria (dark coloured urine). Rhabdomyolysis may lead to acute renal failure.
- Pit viper bite envenomation may cause progressively worsening pain and swelling, haemorrhagic blisters, necrosis, hypovolaemic shock from third space fluid loss and bleeding due to coagulopathy.

Note: These clinical features are the manifestations of various toxins in the venom. Toxic venom components can vary even within the same snake species. The age, geographical distribution and prey specificity factors may influence the compositions of venom toxins.

MANAGEMENT

Prehospital & Primary Care

The objectives are to provide basic life support, to reduce the rate of venom absorption and to prevent further complications. Prehospital care interventions include:

- Calm the patient down and move to safety.
- Remove jewellery on the affected limb and loosen tight-fitting clothing.
- Immobilise the affected limb with a splint or sling and reduce movements. Pressure Bandaging and Immobilization (PBI) are to be applied only by a trained first-aider. Indications for PBI include:
  1) the snake is identified as krait, coral snake or sea snake
  2) if the snake is unidentified, the transport time to the hospital is prolonged (more than an hour).
- If venom enters the eye (venom ophthalmia), immediately irrigate with copious amounts of clean water.
- Transfer all patients to the nearest healthcare facility with emergency care.

Note: Document all symptoms and signs that may manifest before arrival at the hospital. Do not interfere with the bitten area by applying a tourniquet, making incisions, sucking, rubbing, vigorous cleaning, applying herbs/chemicals, massage, or electrical shocks. Take several good-quality pictures of the snake at a safe distance, e.g., using a mobile phone camera. Avoid wasting time searching for or killing the snake. If the snake was killed, bring it along in a secure container.

Emergency & Hospital Care

- Triage to the appropriate zone and perform rapid clinical assessment.
- Monitor vital signs and cardiac rhythm and resuscitate as indicated.
- Obtain detailed history of presenting complaint:
  1. time of incident
  2. location of the incident
  3. how exactly did the patient get bitten
  4. what happened to the snake
  5. part of the body bitten
  6. what was done after being bitten
  7. pain score progression (PSP) since incident
  8. current complaints
  9. allergy history (to horse or papaya) and other co-morbidities
- Perform close serial examination at fixed time intervals (every hour) for any changes over the bitten area (bite marks and surrounding skin), the rate of proximal progression of the oedema (RPP), PSP, palpable tender lymph nodes draining the area, and distal neurovascular status of the affected limb
  Take serial pictures of the affected area.
- Examine for neurological dysfunction (tailored according to child's age group), bleeding tendencies, and muscle tenderness and rigidity.
- Send initial laboratory investigations (full blood count, coagulation profile and Creatine Kinase) and repeat serially every 6 hours for the first 24 hours of the incident. Consider other tests as necessary (renal function tests, liver function test, fibrinogen level, D-dimer and urine examination). Review the trends.
- If laboratory blood test is not available or delayed and the diagnosis is unidentified snakebite or a pit viper bite, consider performing a serial bedside 20-min Whole Blood Clotting Test (20WBCT).
  Put 2mL of venous blood in a clean and dry glass test tube, leave it standing for 20 min, and then gently tip it once.

  Note: Unclotted blood suggests a pit viper bite with systemic envenomation.

- Review immunisation status: administer IM anti-tetanus injection if indicated. (Note: Arterial puncture and Intramuscular injections are contraindicated if the coagulation profile is abnormal)
- Administer analgesia (avoid NSAIDs in pit viper envenoming) and antivenom as indicated.
- Admit to medical ward for close serial observation of the progress and response to therapy (vitals, RPP, PSP, LN and blood tests). If there are no signs and symptoms of envenomation for at least 24hrs or if an expert confirms that the snake is a non-venomous species and the patient is asymptomatic, the patient may not require hospitalisation.

Antivenom

- Antivenom (AV) is the only proven antidote for envenomation.
- Not all snakebites, even by snakes equipped with venom, result in envenoming syndrome.
- Antivenoms carry a risk of adverse reactions. Therefore, the appropriate antivenom should be used only when it is indicated and administered as early as possible.
- Antivenoms appropriate for use in Malaysia are currently imported from Thailand and Australia.
- The dosage for children is the same as for adults (Table 1)
- Adrenaline, steroids, and antihistamines should not be given prophylactically unless indicated.
- Skin sensitivity test is not necessary as it poorly predicts anaphylactic reactions, may induce hypersensitivity and will cause unnecessary delay in antivenom therapy.

Indications for antivenom

Systemic envenomation

- Coagulopathy.
- Neurological abnormalities.
- Cardiovascular abnormalities.
- Generalised rhabdomyolysis / haemolysis.
- Acute kidney injury.
- Supporting laboratory results.

Local envenomation (with other considerations)

- Progressive significant oedema of the bitten area, especially if involving the fingers.
- Rapid speed of progression of oedema (trends of RPP) within a few hours.
- Palpable tender lymph node draining the affected limb.
- Rapidly expanding local necrosis.

Note: Helpful laboratory results suggesting envenomation include prolonged PT/APTT, raised INR, reduced fibrinogen level, thrombocytopenia, leucocytosis, anaemia, hyperkalaemia, hyponatraemia, myoglobinuria, and raised serum enzymes (e.g., Creatine kinase, aminotransferases).

Choice of antivenom

- If snake species is identified and AV is indicated, consider monovalent/ mono-specific antivenom.
- If snake species is unidentified and AV is indicated, consider Neuro Polyvalent or Hemato Polyvalent antivenom.

Preparation and administration

- Prepare adrenaline, hydrocortisone, antihistamines and resuscitative equipment prior to antivenom infusion.
- Reconstitute each vial of the freeze-dried antivenom with the solution supplied or 10ml WFI (water for injection). Gently swirl (never shake) to dissolve the freeze-dried powder. Further dilute the total reconstituted AV into 5-10ml/kg of crystalloid solution for children (maximum 500 mL).
- Infuse at a slow rate (1 to 2 ml/min) for 5-10 minutes and if there is no reaction, increase the rate to 5-10mls/min to complete the infusion in less than one hour.
- Closely observe the patient during and for at least 1 hour after completion of the intravenous antivenom infusion. Document pain score before, during, and after the antivenom infusion. Document vital signs and clinical progression (RPP, PSP, LN) every 10-15 min, then hourly.
- Repeat antivenom administration if deteriorating neurotoxic/cardiovascular signs or brisk bleeding 1 to 2 hours post AV, or persistent/recurrence of bleeding 6 hours post AV.

Antivenom reactions

- Early hypersensitivity reactions are mostly rate-dependent non-immune anaphylaxis. Symptoms range from itching, urticaria, nausea, vomiting, palpitation, bronchospasm, laryngeal oedema to circulatory shock.
- In the event of antivenom reaction:
  - Withhold antivenom infusion.
  - Give adrenaline IM 10 mcg/kg. 0.1 mL/kg of 1:10,000 (infant/young children) OR 0.01 mg/kg of 1:1,000 (older children), into the upper lateral thigh and repeat 5 to 10 minutes if not improved (max of 0.5 mg total dose). If IM injection is contraindicated, administer slow IV boluses of 0.1 mL/kg of 1:10,000 (0.1 mg/mL) solution every 3 to 5 minutes (maximum total dose of 0.3 mg).
  - If not improving, start IV infusion at 0.1 mcg/kg/min titrated to response.
  - Give boluses of IV 0.9% saline at 20 mL/kg as required.
  - Give slow IV antihistamine and steroid (e.g. chlorpheniramine maleate 0.2mg/kg), hydrocortisone 4mg/kg/dose).
  - Give nebulised adrenaline in the presence of stridor or partial obstruction.
  - Give nebulised salbutamol in the presence of bronchospasm or wheeze
  - Once the patient is hemodynamically stabilised and the signs and symptoms have subsided, the antivenom infusion should be restarted at a slower rate with close vigilance for further reactions.
- Pyrogenic reactions usually develop 1-2 hours after treatment and is believed due to pyrogenic contamination during the manufacturing process. Symptoms include fever, rigors, vomiting, tachycardia and hypotension.
- In the event of such a reaction, provide treatment as above and treat fever with paracetamol and tepid sponging.
- Late reactions (serum sickness) may occur between 1 to 12 days (mean 1 week) with symptoms of fever, arthralgia, lymphadenopathy, etc.

Treatment of serum sickness:

- Give chlorpheniramine maleate 0.25mg/kg/day in divided doses for 5 days.
- If fails to respond in 24hrs, give oral prednisolone (0.7mg/kg/day) for 5 days.

Anticholinesterases

- Should be considered in severe neurotoxic envenoming when antivenom is inadequate or unavailable.
- Give test dose of either IV Edrophonium chloride (Tensilon) 0.25mg/kg (max 10mg) or IV Neostigmine 0.05-0.07mg/kg (max 0.5-2.5mg), with IV Atropine sulphate 50µg/kg (max 0.6mg).
- If patient convincingly responds, maintain with IV Neostigmine methylsulphate (50-100µg/kg) and Atropine, 4 hourly by continuous infusion.

Supportive treatment

- Provide respiratory support/assisted ventilation in those with clinical signs of respiratory compromise/ paresis.
- Give analgesia to relieve pain (avoid aspirin/NSAIDs). In severe pain, IV tramadol may be given. Pain relief will generally be seen following optimal antivenom therapy.
- Give broad-spectrum antibiotics if the wound appears contaminated with devitalised tissues or necrosis has developed.
- Correction of coagulation abnormalities with fresh frozen plasma and platelets is strictly per case-by-case basis.
- Renal failure requires measurement of daily urine output, serum creatinine, urea and electrolytes. If urine output fails to increase after rehydration and diuretics (e.g. frusemide), start renal dose of dopamine (2.5µg/kg/minute IV infusion) and place on strict fluid balance. Dialysis may be required in severe cases of envenoming with renal complications.
- Clean and dress the wound. Debridement of necrotic tissues should be carefully carried out as needed and should not be mistaken with the debridement for necrotising fasciitis.
- Observe for the unlikely event of compartment syndrome (pain, swelling, cold distal limbs and muscle paresis). Orthopaedic opinion regarding surgical intervention must be supported with significantly raised (>40mmHg) intracompartmental measurements using Stryker or Wick catheters.
- Give an optimal amount of appropriate antivenom before any urgent surgical intervention.

Guide to dosages of appropriate antivenom for Malaysia		
Species the AV is raised from	**Manufacturer: Antivenom**	**First Dose ml/vial**
Monocle cobra, *Naja kaouthia*	QSMI Thai Red Cross: Cobra Antivenin	100mls/10 vials Subsequent dose 1-2 hr
King Cobra, *Ophiophagus hannah*	QSMI Thai Red Cross: King Cobra Antivenin	
Malayan krait, *Bungarus candidus*	QSMI Thai Red Cross: Malayan Krait Antivenin	50mls/5 vials Subsequent dose 1-2 hr
Banded krait, *Bungarus fasciatus*	QSMI Thai Red Cross: Banded Krait Antivenin	
Malayan pit viper, *Calloselasma Rhodostoma*	QSMI Thai Red Cross: Malayan Pit Viper	30mls/3 vials Subsequent dose 6 hr
Green pit viper, *Cryptelytrops Albolabris*	QSMI Thai Red Cross: Green Pit Viper Antivenin	
Malayan pit viper, *Calloselasma rhodostoma,* Green pit viper, *Cryptelytrops Albolabris,* Thai Russell's Viper, *Daboia siamensis*	QSMI Thai Red Cross: Hemato Polyvalent Snake Antivenom	30mls/3 vials Subsequent dose 6 hr
Monocled Cobra, *Naja kaouthia,* King Cobra *Ophiophagus hannah,* Banded Krait *Bungarus fasciatus,* Malayan Krait, *Bungarus candidus*.	QSMI Thai Red Cross: Neuro Polyvalent Snake Antivenom	50-100mls/ 5-10 vials Subsequent dose 1-2 hr
Beaked sea snake, *Hydrophis (Enhydrina) schistosus.*	Seqirus, Australia: Sea snake Polyvalent Antivenom	10-30mls/1-3 vials Subsequent dose 1-2 hr

Note:
- Subsequent doses are indicated according to the clinical signs and symptoms.
- The doses are based on animal studies and manufacturer's recommendations.
- Monocle cobra, *Naja kaouthia* antivenom has good cross-neutralisation with the Equatorial spitting cobra, *Naja sumatrana* venom.
- Green pit viper antivenom has good cross-neutralisation with venom from other green pit vipers belonging to the *Trimeresurus* complex group.
- Beaked sea snake, *Hydrophis* schistosus antivenom has good cross-neutralisation with many other sea snake venom.

Measuring Rate of Proximal Progression (RPP) of the oedema

1. A more informative parameter for reviewing progressive painful swelling
2. First: Determine the border of the micropore to be used to mark the proximal margin of the oedema, e.g. distal border to distal border of the micropore markers (Figure 1).
3. Second: Palpate for the most proximal margin of the swelling and apply a small strip thin micropore tape to the most proximal margin of the oedema.
4. Label the current time and date on the micropore tape.
5. Determine a fixed interval to review the progression, e.g., every hour for the first 24 hours.
6. Measure the distance between two micropore tape borders over the fixed time interval (Figure 2).
7. The RPP for that interval is documented in cm/hr.

Figure 1 (above).



Figure 2 (above).



Serial Clinical Progress Observation Chart at fixed regular time intervals

Date d/m	Time am/pm	GCS 3-15	PR bpm	BP mmHg	RR bpm	SpO2 %	PSP 0-10	RPP cm/hr	LN Yes/No

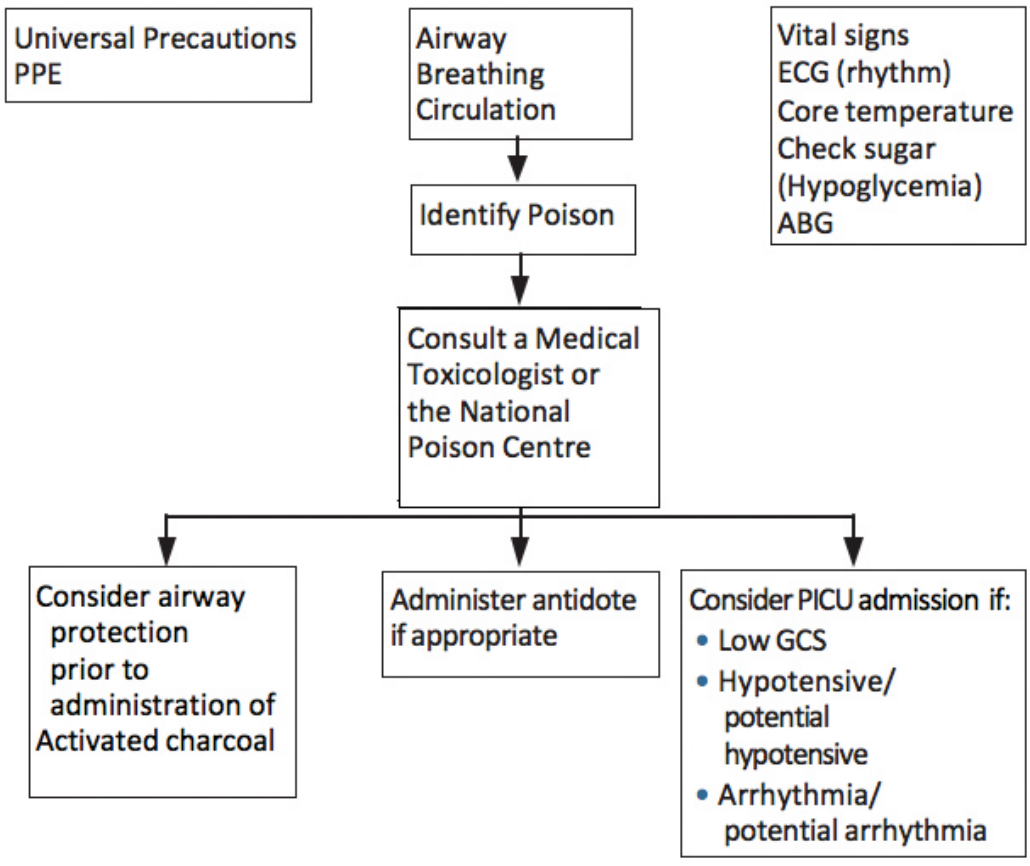
- PSP= pain score progression, RPP = rate of proximal progression, LN = enlarged tender lymph node

Serial Blood Results (every 4-6 hours for first 24 hours or after Antivenom administratrion)																
Date	Time	20WBCT	WBC	Hb	Platelets	PT	APTT	INR	CK							

Chapter 114:
Common Poisons

- Poisonings in paediatric patients are usually unintentional and the amount of toxin ingested is often minimal obviating the need for gastric lavage.
- However, in some situations related to dose per body weight even small amounts ingested can be fatal.
- A WHO report revealed that common poisoning agents among children in high income countries include pharmaceuticals, household products (e.g. bleach, cleaning agents), pesticides, poisonous plants, and bites from insects and animals, whereas, common poisoning agents in low-income and middle-income countries are fuels such as paraffin and kerosene, pharmaceuticals and household products.
- Ingestion remains the most common route of exposure for intentional or unintentional poisoning.
- The ingestion of anti-hypertensives, oral hypoglycemic agents, psychiatric drugs, toxic alcohols, salicylate oils and narcotics require special care and consideration.

PRINCIPLES OF THE APPROACH TO POISONING



Key points

- All poisoning cases should be investigated for any suspicion of neglect or abuse.
- Prehospital care personnel should be wary of contact or inhalation exposure causing poisoning.
- Gastric lavage in children has more risks than benefits and is very rarely performed. If performed, it should be limited to adolescent patients who have ingested large amounts of a potentially life-threatening toxin and the antidote is not available. The airway must be secured and the toxin must not be corrosive or contain hydrocarbon agents.
- Skin decontamination with water is usually sufficient for corrosives. Continue irrigation till skin pH tested with litmus paper is neutral to ensure proper decontamination. Soap and water will be required for hydrocarbons and organophosphates.
- Dermal exposure to toxic powders or solids should be brushed off prior to irrigation with copious amount of water.
- Neutralisation of acids with alkali or vice versa should never be attempted for fear of exothermic reactions resulting in dermal burns

- <u>ACTIVATED CHARCOAL (AC)</u>
  i. AC is a fine black powder prepared by pyrolysis (burning) of carbonaceous products. "Activation" increases the surface area of the particles.
  ii. Toxins adsorb to activated charcoal and thus the total surface area of the charcoal preparation is related to the amount of drug able to be adsorbed.
  iii. AC can be used in potentially toxic ingestions if the patient presents early (within 4 hours).
  iv. AC should not be given in patients who are unable to protect their airway and are at risk of aspiration
  v. Some toxins are not well adsorbed to activated charcoal. They include:
  C Corrosives/caustics
  H Heavy metals (Fe, lead, lithium)
  A Alcohol (ethanol, toxic alcohol)
  R Rapid onset
  C Chloride & Iodine
  O Other insoluble in water
  A Aliphatic hydrocarbon (Petroleum distillate)
  L Laxatives
  vi. Single dose activated charcoal (SDAC) is rarely needed to be given in pediatric poisoning cases.
  vii. The recommended dose for SDAC is 1g/kg body weight
  viii. Multiple-dose activated charcoal (MDAC) has proven efficacy in theophylline, phenobarbital, carbamazepine, dapsone, quinine toxicity, extended-release preparation and bezoar-forming medication.
  ix. The recommended dose for MDAC is 0.5g/kg body weight 4 – 6 hourly, but beware of contraindications that may include absence of gut mobility or perforation or loss of protective airway reflexes
  x. Complications of charcoal administration includes fatal aspiration, pneumonitis or small bowel obstruction.
  xi. For paediatric population, using opaque cups with a lid and straw may help facilitate/coax the patient into ingesting the AC and mixing with fruit juice or sweet drinks may be needed to make it more palatable.
- For some poisoning agents, haemodialysis or haemofiltration may be needed as a form of enhance elimination of the toxic agents.
- Administer antidotes if indicated. If antidote is not available at your centre, contact the hospital pharmacist on call to help and locate the source of the antidote.
- Ensure the patient is well hydrated with good urine output as this will facilitate renal excretion of most toxins.
- Toxinz®,Poisindex® and Uptodate® are a few resources currently available in most Malaysian hospitals. If the information you require is not available, you may consult a clinical toxicologist or call the national poison centre.

National Poison Center, Malaysia		
Day	**Time**	**Contact**
Weekdays	8:00am-10:00pm	+604-6536 999
Weekends & Public Holidays	8:00am-5:00pm	+604-6536 999

Laboratory investigations

- A careful history may obviate the need for blood tests.
- Other investigations may be required depending on the type of poison ingested.

Investigation	Indication
Blood glucose	All cases with altered sensorium
Blood gas analysis	Patients with respiratory insufficiency, hyperventilation or suspected metabolic acid base disturbance. (A high anion gap is seen in methanol, paraldehyde, iron, ethanol, salicylate poisoning etc.)
Electrolytes	Hypokalemia may occur in acute poisoning, i.e. salicylate / theophylline
Acetaminophen & salicylate level	Should be performed in any case of suspected toxicological exposure as acetaminophen & salicylate are often being co-ingested
ECG	Detection of dysrhythmia i.e. widened QRS or prolonged QT interval. Tricyclic antidepressant poisoning may manifest as myocardial depression, ventricular fibrillation or ventricular tachycardia
Radiology	Suspected ingestion of metallic objects, iron salts.

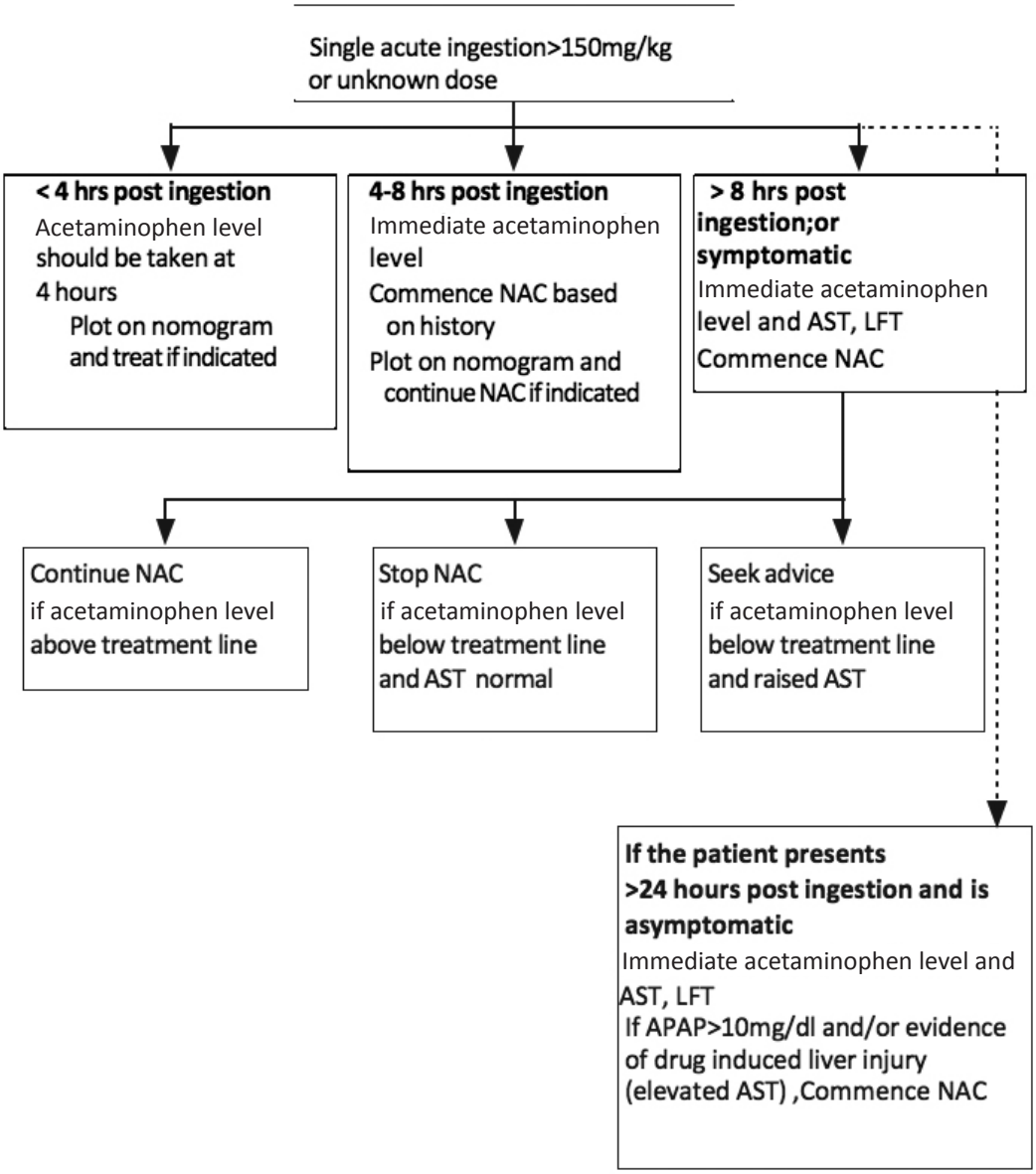
Topics that will be covered:

1. Paracetamol/Acetaminophen (APAP)
2. Salicylate (Acetylsalicylic acid-ASA)
3. Household Products
    - Household bleaches
    - Multipurpose cleaners
    - Detergents
    - Hydrocarbons
    - Mothballs
4. Insecticides
5. Herbicides
6. Antihypertensives
7. Oral Hypoglycaemic Agents
8. Opioids
9. Ethanol and Toxic Alcohols
10. Sympathomimetics
11. Psychiatric drugs – Antidepressants
12. Toxidromes

PARACETAMOL/ ACETAMINOPHEN (APAP)

- Acetaminophen is a common poisoning in the paediatric population. Acute intentional ingestion is more commonly seen in adolescents while chronic poisoning is seen in preschool ages due to therapeutic errors.
- A single ingestion of >150mg/kg acetaminophen can cause significant toxicity. Patients may be asymptomatic if presented early, or symptomatic with nausea, vomiting and abdominal pain. If left untreated, patients may progress to liver failure.
- Treatment involves the administration of N-acetylcysteine (NAC), a precursor to facilitate the synthesis of glutathione.

MANAGEMENT ALGORITHM FOR ACUTE SINGLE INGESTION OF ACETAMINOPHEN



Key points

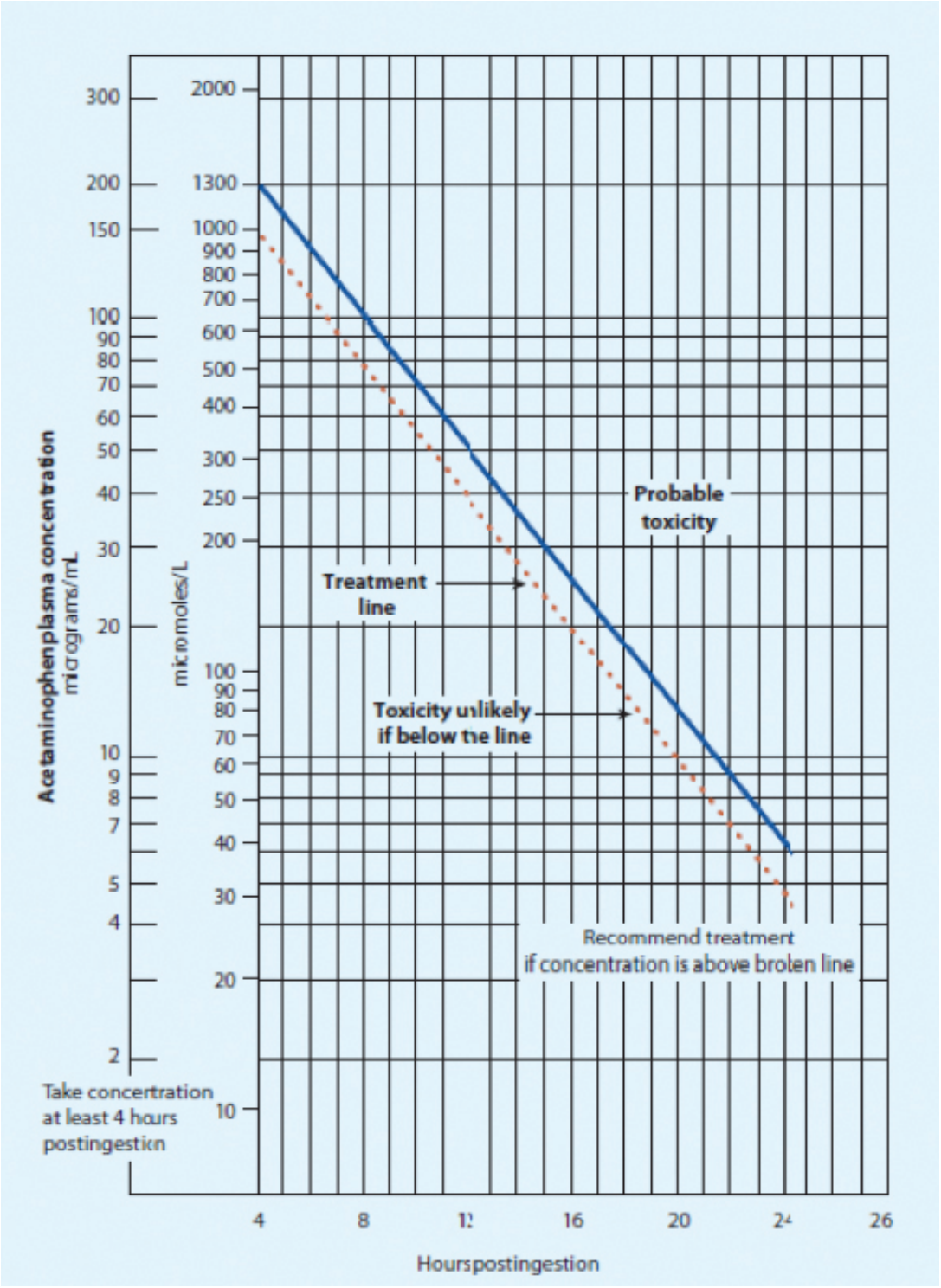
- As history may be inaccurate especially in intentional poisonings it is important to correlate with clinical features and laboratory investigations
- Age <2 years is an independent risk factor for development of toxicity
- Acetaminophen level should be repeated 4 hours from the first level to identify "nomogram crossers" which can be seen in ingestions of extended release formulations and a small proportion of immediate release preparations.
  **Nomogram crossers are roughly seen in 10% of population where the initial APAP level is below treatment line but the level declines slowly that subsequent level is above the treatment line on the RM nomogram.
- Rumack-Matthew (RM) nomogram is used only for acute single ingestions with known time of ingestion.
- For single ingestions of unknown time, measure the APAP and AST. If APAP is >10ug/ml and/or AST is elevated, initiate NAC therapy.
- Patients who present > 8 hours of ingestion of potentially toxic dose or with symptoms of toxicity (right upper quadrant pain, nausea, vomiting) should be given NAC immediately.
- Evidence of hepatotoxicity in acute acetaminophen poisoning is usually delayed beyond 24hours. A normal AST in the initial stage of poisoning does not rule out hepatotoxicity.

Labs for monitoring	frequency
APAP	• **4 hours post ingestion** for acute single ingestions or stat for *RSTI/unknown time of ingestion/unreliable history followed by • **4 hours from the first level** taken followed by • **4 hours prior to end of NAC** if using 20 hour protocol • Repeat level daily until APAP is undetectable
AST, LFT, coagulation profile	• At presentation then • 4 hours prior to end of NAC if using 20 hour protocol then • daily if patient is on extended prescribed protocol
RBS, Renal Profile	At presentation and repeat as per required
Lactate	Daily if evidence of hepatic injury (increasing AST)

*RSTI = Repeated supratherapeutic ingestion

- Consult toxicologist if the APAP level is >300ug/ml in acute single ingestions or in massive overdose (>30g acetaminophen ingested).

Rumack Matthew Nomogram (RM Nomogram)



Repeated Supratherapeutic Ingestion (RSTI) of acetaminophen

- This type of poisoning is commonly seen in febrile infants and children where overzealous dosing of acetaminophen was given to maximize the effect or due to dosing error (failure to read medication label and dose).
- This poisoning has a higher risk of potential hepatotoxicity as the dose of acetaminophen is given beyond the prescribed frequency (e.g. QID or 4 hourly or even less).
- Consider RSTI acetaminophen poisoning in children who have ingested:-
  - >200mg/kg/day over 24 hours or
  - >150mg/kg/day over 48 hours or
  - For children < 6years old, >100mg/kg/day over 72 hours or more
- Since RSTI poisoning in children is unintentional, these patients generally present late with symptoms or with an elevated AST/ALT.
- The decision to start NAC therapy depends very much on the potential risk of hepatotoxicity.
- APAP level and AST/LFT should be measured immediately once diagnosis has been established.
- As the patient has taken multiple doses rather than a single dose the RM Nomogram cannot be used.
- Start NAC therapy if the AST is elevated, regardless of the APAP level. NAC should also be started if the measured APAP > 10ug/ml with or without elevation of AST.

Indication to initiate NAC therapy in RSTI

APAP	>10ug/ml	>10ug/ml	<10ug/ml	<10ug/ml
AST	elevated	normal	elevated	normal
Initiate NAC	yes	yes	yes	no

Intravenous Acetaminophen

- 10-fold dosing errors has been reported in young children due to confusion (between mg and ml) and incorrect route (oral given intravenously).
- There is limited experience with intravenous acetaminophen poisoning.
- The RM nomogram has not been extensively studied with intravenous compared to oral acetaminophen, hence should not be used to determine risk of hepatotoxicity and the initiation of NAC therapy.
- Due to paucity of data, it is reasonable to start NAC if the patient was given a single dose of >60mg/kg iv acetaminophen. Continue NAC until the APAP is undetectable.
- For patients on multiple therapeutic dosing of iv acetaminophen who present with evidence of hepatotoxicity (elevated AST), start NAC and continue until APAP is undetectable and hepatotoxicity resolves.

N-Acetylcysteine (NAC)

- NAC is the antidote used to treat acetaminophen poisoning.
- Other than being a precursor to glutathione, NAC also provides cysteine as a substrate for sulphation. This is important as majority of the metabolism of APAP in children is through sulphation instead of glucuronidation as seen in adults.
- NAC has been shown to benefit patients with APAP induced liver injury (elevated AST) even with undetectable APAP levels
- It is available in iv and oral form

Dosing regimen iv NAC:

Weight	Dilution
≥ 40kg	Loading 200mg/kg in 500mls D5% over 4 hours followed by 100mg/kg in 1000mls D5% over 16 hours or more
≥20kg- <40kg	Loading 200mg/kg in 250mls D5% over 4 hours followed by 100mg/kg in 500mls D5% over 16 hours or more
<20kg	Loading 200mg/kg in 7ml/kg D5% over 4 hours followed by 100mg/kg in 14ml/kg D5% over 16 hours or more

- NAC delivery should have as minimal interruption as possible to ensure continuous hepato-protection. The transition between the first to the second bag of iv NAC should not be delayed.
- Adverse reactions can be seen with iv NAC. Symptoms include flushing, aching, rashes, angioedema, bronchospasm and hypertension.
- If adverse reactions occur, iv NAC should be withheld. Administer antihistamine and corticosteroids and restart the infusion after an hour at a slower rate.
- Most adverse reactions are mild and can be easily treated with low incidence of recurrence.
- For persistent severe adverse reactions despite treatment, iv NAC can be switched to oral NAC if the patient is able to tolerate orally well.
- Defervescent oral NAC tablets (600mg/tab) can be used as an alternative to iv NAC, however caution should be practiced when using in very young children or patients on sodium restriction due to its sodium content.
- **Dosing regimen oral NAC**: loading dose 140mg/kg. 4 hours after the loading dose, 70mg/kg should be given every 4 hours for an additional 17 doses
  - Dissolve the defervescent tablets in 100 - 150mls water. For children <20kg dissolve 4.8g oral NAC (defervescent tablets) in 100mls water (48mg/ml). Calculate the dose required based on body weight.
    E.g. for a 10kg child, loading dose 1.4g (140mg/kg) = 1400 X 1/48= 29mls
  - Nausea and vomiting can occur with oral NAC. Antiemetics can be used to facilitate the delivery of oral NAC.
- NAC may cause mild prolongation of prothrombin time (PT) and INR (≤2) without any evidence of liver injury. This adverse effect of NAC should be considered when assessing patients for coagulopathy.

- NAC should be continued beyond prescribed 'protocol length' (beyond 20 hours) at a rate of 6.25mg/kg/hr if there is evidence of one or more of the following:
  - Ongoing hepatic injury / increasing AST
  - Detectable APAP
  - INR>2
  - encephalopathy
- The decision to discontinue NAC depends on the patient's clinical course
- NAC can be discontinued if
  - Patient is clinically improving
  - INR<2
  - Improving encephalopathy (if present)
  - AST reduced by >50% of peak or <1000 iu/L

Prediction of liver failure requiring transplant

- King's College Criteria (KCC) can be used to predict patients who may require liver transplant and early referral to a transplant centre.

King's College Criteria (KCC)
Either of the following predicts a survival rate <20% 1. Arterial pH<7.3 or lactate > 3 mmol/L after fluid resuscitation Or 2. All of the following Creatinine >292 umol/L Prothrombin Time>100s or INR>6.5 Grade III or IV encephalopathy

- When determining KCC, adverse effects of NAC (prolonged PT/ INR) should be taken into consideration.
- If vitamin K is used and is effective in correcting prolonged PT/INR, this would indicate a viable liver.
- Fresh frozen plasma (FFP) or Prothrombin complex concentrate (PCC) should only be given when there is evidence of bleeding or risk of bleeding (performing invasive procedures) and not solely for correction of prolonged PT/INR. Correcting the PT/INR with exogenous clotting factors does not indicate an improvement in hepatic function, but instead will alter the interpretation when determining KCC.

SALICYLATE (Acetylsalicylic Acid- ASA)

- Ingestion of medicated oils containing methyl salicylate is a common cause of pediatric salicylate poisoning in Malaysia.
- Medicated oils can come with various concentrations of methyl salicylate and a lick or taste can sometimes prove fatal for children <6 years old.
- Ingestion of more than 150mg/kg is toxic.
- The primary toxicity of salicylate is to the brain.
- Because of its acidic pKa (pH3.5), salicylate toxicity worsens with acidosis, causing a shift of salicylate intracellularly, in particular the CNS and exerting its toxicity.
- The principle of managing salicylate poisoning is to create pH conditions and concentration gradients that favours the exit of salicylate from the CNS and enhance renal elimination.
- The initial evaluation of salicylate poisoning consists of close assessment of the respiratory rate, depth and acid base status.
- In the early phase of poisoning, respiratory alkalosis occurs due to direct stimulation of salicylate to the respiratory center. Over time, this progresses to mixed acid base (respiratory alkalosis and metabolic acidosis) and finally metabolic acidosis.
- Respiratory alkalosis may be transient or absent in very young children due to limited ventilatory reserve.
- A mixed acid base picture with acidemia warrants urgent intervention as the CNS protective effect of alkalemia is already lost.
- Always CHECK UNITS used in measured serum levels (mmol/l vs mg/L vs mg/dL). Errors in interpretating serum levels based on different units used/reported or unit conversion errors (e.g. mg/L to mg/dL) has resulted in disastrous salicylate fatalities.

Clinical Manifestations of Salicylate poisoning	
General	Hyperpyrexia, profuse sweating and dehydration
CNS	Tinnitus, delirium, seizures, cerebral oedema, coma, Reye's syndrome
Respiratory	Hyperventilation
GIT	Epigastric pain, nausea, vomiting, UGIH, acute hepatitis
Renal	Acute renal failure
Metabolic	Hyper/hypoglycaemia, anion gap metabolic acidosis, hypokalaemia
Cardiovascular	Non-cardiogenic pulmonary oedema
Investigations: FBC, PCV, BUSE/Serum creatinine, LFT/PT/PTT, RBS; ABG Serum salicylate level at 4 hours after ingestion	

Management

- All symptomatic patients should be closely monitored and any patients presenting with mixed acid base picture should initiate urgent intervention.
- Principles of managing salicylate poisoning:
  - limit absorption by using AC
  - enhance renal elimination by alkalinizing the urine
  - reduce CNS toxicity by correcting the acidosis
  - restore intravascular volume and correct hypoglycaemia.
- Send salicylate level every 4 hours until peak is seen. All salicylate levels must be accompanied by a blood gas, serum K, urine pH.
- Interpretation of serum salicylate levels must be done concurrently with the patient's acid base status (venous blood gas).
- A declining salicylate level with concurrent metabolic acidosis suggests shift of salicylate from the plasma to intracellular (CNS) indicating worsening toxicity rather than improvement.
- It is imperative to remember that any conditions contributing to acidosis in the patient will worsen CNS toxicity.
- Sedation and intubation in this case can prove fatal as compensatory mechanism to correct the acidosis is lost, causing a rise in PCO2 and a rapid fall in serum pH.
- Hyperbilirubinemia in neonates can cause a falsely elevated serum ASA levels. If there is a concern for falsely elevated salicylate levels, contact lab personnel for other methods in measuring ASA levels.
- Patients presenting with coma, stupor or delirium in salicylate toxicity should liberally be given dextrose even with normal blood sugar levels. Hypoglycorrhachia is known to occur in salicylism and can worsen neurotoxicity.
- Treat hypoglycaemia with 2-5ml/kg of 10% dextrose.
- MDAC (multidose activated charcoal) can be given if the patient present early <4 hrs of ingestion (*refer contraindications to AC). Start with 1g/kg loading dose followed by 0.5g/kg every 4-6 hourly for 36 hours. Risk of vomiting, aspiration and intestinal obstruction must be considered when using MDAC.

Guide to urinary alkalization in salicylate poisoning:

- Urinary alkalization can enhance renal elimination of salicylate by 30%.
  - o Start with loading $NaHCO_3$ 8.4% , 1-2mmol/kg iv bolus then dilute 75 mls 8.4% $NaHCO_3$ in 425 ml 5% dextrose and run at twice maintenance fluid requirement. Titrate rate to achieve target urine pH >7.5
- Start urinary alkalization for symptomatic patients, or acid base shows mixed respiratory alkalosis and metabolic acidosis with a normal pH or acidemia, or ASA > 30mg/dl.
- Urinary alkalization can be discontinued when the patient is clinically improving and the serum ASA levels < 20 mg/dl with a normal serum pH.

Parameters to monitor while performing urinary alkalization	Frequency
Urine PH	HOURLY - aim TARGET URINE pH >7.5 - titrate up bicarbonate infusion to achieve targeted urine pH
Venous blood gas (serum pH)	HOURLY until target URINE pH has been achieved, then 4-6 hourly - maintain SERUM pH between 7.4-7.55 - Do not allow SERUM pH to exceed >7.55 while on bicarbonate infusion - if SERUM pH has exceeded >7.55 and targeted URINE pH has not been achieved despite increasing dose of bicarbonate, then the bicarbonate infusion can no longer be increased and consider hemodialysis if serum ASA is increasing
Serum K	2-4 hourly Keep serum K>4, correct immediately if K<4 -hypokalemia will result in failure to achieve alkaline urine as renal compensation kicks in by reabsorbing K and exchanging with H resulting in acidic urine
Renal profile (creatinine), Ca	As per when needed to look for acute kidney injury, hypocalcemia
ASA level	2-4 hourly until peak is seen then as per when required *Ensure that when levels are declining, SERUM pH is >7.4

- Extra corporeal removal (hemodialysis) should be considered in any of the following:
  - ASA levels >100mg/dl or >90mg/dl with renal impairment
  - Altered mental status
  - ARDS or
  - If standard treatment with urinary alkalinisation fails and
    - ASA levels > 90mg/dl or
    - ASA levels >80mg/dl in presence of renal impairment or
    - Serum pH <7.2
- Continue hemodialysis until patient is clinically improving and ASA level<20mg/dl or hemodialysis was performed for at least 4-6 hours while ASA levels were not available.
- Exchange transfusion can be used for neonates or when HD is unavailable.
- Intermittent hemodialysis is preferred.
- Urinary alkalinisation must be initiated and continued while awaiting hemodialysis. During hemodialysis, urinary alkalinisation with $NaHCO_3$ can be withheld as the bicarbonate is supplied by the HD.
- It is imperative to continue $NaHCO_3$ therapy for urinary alkalinisation once HD has been completed to ensure ongoing renal excretion of salicylate.

HOUSEHOLD PRODUCTS

Management

- Based on a demographic study analyzed by the Malaysia National Poison Centre from 2006 to 2015, the most cases reported under the household products classification include cleaners, bleaches and disinfectants. Others include hydrocarbons like kerosene and other household products such as mothballs etc.
- Household products can be divided into two, product that can be potentially dangerous and also minimally toxic.
- To call a situation as minimally toxic ingestion, healthcare personnel must be able to:
  1. Identify the minimally toxic product and it's ingredients
  2. Know the amount of the minimally toxic product taken
  3. Obtain reliable history
  4. Assess that patient is asymptomatic following that minimally toxic product ingestion
  5. Have a differential diagnoses such as allergic reaction, aspiration or non-accidental injury in the mind if the presentation skewed from asymptomatic to presence of signs and symptoms that is not expected for minimally toxic ingestion.

Household Bleaches

- Household bleaches can be divided **into chlorine base bleach (whitening bleach)** or **oxygen bleach (color-safe bleach).**

Chlorine based bleach

- Chlorine based bleach chemical content include sodium hypochlorite of around minimal concentration (~5%).
- It is a weak alkali and weak oxidizing agent and mainly caused oropharyngeal or upper GI irritation with signs and symptoms of nausea, vomiting and epigastric pain.
- When chlorine based bleaches are mixed with other substances like toilet cleaners *(acids)* or glass cleaner *(ammonia)*, it can cause the release of chlorine or chloramine gas respectively, especially in enclosed space. Patient may inhales the chlorine or chloramine gas that can cause shortness of breath or bronchospasm.
- Management for chlorine or chloramine gas inhalation is also supportive. Bronchodilators and steroids can be used. Nebulized sodium bicarbonate has been used with good outcome. Patient should be admitted until symptoms resolve. Patient that developed respiratory distress may need to be intubated and put on ventilatory support.

Oxygen bleach

- Oxygen bleach (colour-safe bleach) chemical content would include low hydrogen peroxide or peroxide-releasing compound of around minimal concentration (~6%).
- Hydrogen peroxide toxicity is mainly due to the release of oxygen gas causing venous or arterial gas embolism. Each ml of 3% hydrogen peroxide releases around 10ml of oxygen gas.
- Ingestion of hydrogen peroxide with concentration > 10% can cause GIT irritation includes hemorrhagic gastritis, gastric perforation, mucosal burn or systemic gas embolisation.
- Inhalation can cause acute lung injury or respiratory distress.
- Ocular exposure can cause corneal ulcer or perforation.
- Dermal exposure can cause burn or gangrene.

- The management for bleach ingestion is generally supportive. Gastrointestinal decontamination is NOT recommended in single use agent. OGDS usually is not recommended either. The patient can be observe for improvement of signs and symptoms and encouraged to take orally.

Multipurpose Cleaners

- Examples of multipurpose cleaners are Magiclean, Cif etc.
- It may contain detergents and a glycol ether solvent (e.g. 2-butoxyethanol, a toxic alcohol).
- Other common additives include sodium hydroxide, hydrocarbons (e.g. pine oil) and antiseptic (e.g. alkanolamine).
- The ingredients are of low concentration in household products. Accidental ingestion typically produces local irritant effects only. No treatment is required.
- Intentional ingestion of large volume (typically >150ml) may produce GI corrosive effects.
- In rare occasion with massive volume ingestion (typically >500ml), toxic alcohol effects secondary to glycol ether poisoning have been reported. Typical clinical features of glycol ether poisoning include anion gap metabolic acidosis, elevated osmol gap, CNS depression and renal impairment.

- Mainstay of treatment is supportive.
- Gastrointestinal decontamination is generally NOT indicated and maybe harmful.
- Accidental ingestion of small volume with symptoms limited to oropharyngeal irritating effects does not require treatment. Patients should be observed for symptoms progression or swallowing difficulties for at least several hours.
- Patients with symptoms suggestive of GI tract corrosive effect should be admitted for surgical assessment and upper endoscopy.
- For massive ingestion, monitor serial arterial blood gasses, osmol and anion gap. Consider hemodialysis in the presence of significant unexplained anion gap metabolic acidosis or an abnormal high osmol gap. (*refer topic on toxic alcohol)

Detergents

- Detergent is used in many cleaning products.
- It mainly contain surface active agents (surfactant) consist of:
  1. Anionic surfactant type:
     - Most common surfactant in bath soap, shampoo, general laundry detergents
     - Example are alkyl groups, ammonium lauryl sulfate, sodium groups
     - It can cause irritant effect
  2. Non-ionic surfactant type:
     - Common in heavy duty laundry detergent
     - Example are alkylpolyethoxylates, PEG groups, polysorbate groups
     - Produce less local irritation than anionic
  3. Cationic surfactant type :
     - Disinfectants, industrial products, fabric softener, swimming pool algicides
     - Example: benzalkonium chlorides
     - 10-15% are caustic. 0.1-0.5% caused significant mucosal irritation. Esophageal or GIT burns are possible with ingestion of few mls of concentrated solution. CNS depression that progress to coma and shock are rare
  4. Detergent pods contain surfactants and harmful chemicals. When bit into it can burst and can cause choking, chemical burns to airway mucosa and coma

- Proteolytic/amylolytic enzymes are used in laundry detergents and presoaks to loosen soil and remove stain. Product contained these enzymes, can likely caused emesis.

- Clinical effects:
  - Oral ingestion - immediate spontaneous vomiting, or intractable vomiting, diarrhea or haematemesis with large ingestions
  - Eye exposure - mild to severe corrosive injury depending on products
  - Skin exposure - mild erythema or rash
- Management includes:
  - Do not induce emesis
  - Early intubation to secure airway if suspected chemical burns to airway mucosa
  - Rehydrate with iv fluids for symptomatic treatment
  - Irrigate with copious amount of water in case of eye exposure
  - Endoscopy is rarely required

Hydrocarbons

- Hydrocarbons are organic compounds made up primarily of carbon and hydrogen atoms. They are commonly used as solvent, fuel, lubricating oil, wax or polish.
- Aromatic hydrocarbons are commonly abused by adolescents and young adults.
- The following are the hydrocarbons groups:

Class	Group Toxicity	Examples
Light chain aliphatic hydrocarbons - straight chain	Low viscosity and high volatility leading to high risk of aspiration Ingestion: GI irritant effects, CNS toxicity, high risk of aspiration pneumonitis. Inhalation: CNS toxicity	**Butane, isobutane:** Gas fuel(LPG), lighter fuel, refrigerant **n-hexane:** Industrial solvent, fuel, lighter fluid, brake-cleaning fluids, rubber cement, glues, spray paints, coatings, silicones **Naphtha:** industrial solvent, shoe polish, lighter fluid **Gasoline** **Kerosene** **Turpentine substitute** **Diesel**
Long chain aliphatic hydrocarbons - branched chain	High viscosity and low volatility Ingestion less likely to be aspirated. Poorly absorbed from the GI tract with no significant systemic toxicity. May cause a mild laxative effect. Significant inhalational exposure unlikely due to low volatility	**Mineral oil:** Baby oil, cosmetics, lubricant, brake fluid, furniture polish **Heavy fuel oil**
Aromatic hydrocarbons - containing benzene ring(s)	Ingestion: high potential for CNS toxicity, may cause cardiac arrhythmias. GI irritant effects. Inhalation: CNS toxicity, cardiac arrhythmia & sudden death(Sudden sniffer's death).	**Benzene:** industrial solvent, gasoline additive **Toluene and xylene:** thinner **Naphthalene:** moth repellant **Pine tar, coal tar, creosote:** shampoo, soap, antiseptic, laxative

Class	Group Toxicity	Examples
Halogenated hydrocarbons - containing chlorine, bromine or fluoride	Ingestion or inhalation: CNS toxicity, cardiac arrhythmias, renal and hepatic toxicity	**Methylene chloride:** industrial solvent, paint stripper **Chloral hydrate:** sedative agent **Chloroform (trichloromethane), carbon tetrachloride:** industrial solvent **Trichloroethane, trichloroethylene:** typewriter correction fluid, colour film cleaners, spot removers, fabric cleaning solution, adhesives, paint stripper, degreasers **Tetrachloroethylene:** dry cleaning solvent **Freons:** phased out refrigerant & aerosol propellants Halons (Bromochlorodifluoromethane[BCF] & **Bromotrifluoromethane [BTM]):** specialised fire extinguishers
Essential oils - volatile oils extracted from plants	Ingestion or inhalation of concentrated preparations: aspiration pneumonitis, GI irritation and CNS toxicity	**Camphor:** moth repellant, cold rub, medicinal oil, cough mixture **Eucalyptus oil, menthol, peppermint oil:** perfume, aromatherapy, cosmetics **Pine oil:** household cleansing products and antiseptic **Turpentine oil:** medicinal oil

- Hydrocarbons with inherent toxicity (pneumonic: CHAMP)
  - Camphor- seizure
  - Halogenated- cardiac, liver & renal toxicity
  - Aromatic- cardiotoxic, benzene is carcinogenic
  - Metal containing- heavy metal poisoning
  - Pesticides in a hydrocarbon solvent- pesticide toxicity

Clinical Features

- Pulmonary:
  - Aspiration is the main concern in hydrocarbons ingestion. Symptoms to suggest aspiration: choking and coughing during ingestion.
  - Rapid onset aspiration pneumonitis. Symptoms including shortness of breath, coughing and wheezing usually presented within 30 minutes after ingestion. Condition may rapidly progress to respiratory failure.
- Central nervous system:
  - Rapid onset CNS toxicity with agitation or impaired consciousness.
  - Seizure may occur early and is the typical presentation of camphor poisoning.
  - Irreversible CNS damage is associated with prolonged exposure to hydrocarbons. The primary pathology is white matter degeneration (leukoencephalopathy). The clinical features include ataxia, spasticity, dysarthria and dementia (Painter's syndrome).
- Cardiac:
  - Halogenated and aromatic hydrocarbons cause cardiotoxicity by sensitizing the myocardium to endogenous catecholamines.
  - Dysrhythmia-induced sudden death, termed the *"sudden sniffing death syndrome"* is well-described after inhalational abuse of these hydrocarbons.

- Individual hydrocarbon toxicity:
  - Halogenated hydrocarbons, particularly carbon tetrachloride and chloroform are hepatotoxic.
  - Ascending peripheral neuropathy may occur after exposure to n-hexane (normal hexane), methyl-N-butyl stone (MnBK) or possibly to toluene.
  - Aniline, nitrobenzene and nitrite containing hydrocarbons may cause methaemoglobinaemia.
  - Halogenated hydrocarbons and toluene are nephrotoxic. Chronic toluene abuse can cause transient renal tubular acidosis. Clinical findings are a hyperchloremic metabolic acidosis, hypokalemia and aciduria.
  - Methylene chloride, a commonly encountered paint stripper is metabolised by liver P450 to carbon monoxide. Delayed CO poisoning may occur.
  - Benzene is haematotoxic, and is associated with haemolysis, aplastic anaemia, and haematologic malignancies. These effects are not found in other aromatic hydrocarbons.
  - Chloracne: severe form generalised acne eruption after exposure to halogenated aromatic hydrocarbons (e.g. dioxins, polychlorobiphenyls).

Management

- Mainstay of treatment is supportive and aspiration prevention.
- GI decontamination is not indicated after ingestion of aliphatic hydrocarbons.
- Hydrocarbons with significant systemic toxicity: gastric aspiration with nasogastric tube (for hydrocarbons in liquid form) within 1-2 hours post ingestion in patient with adequate airway protection may be attempted.
- Supportive management for aspiration pneumonitis and CNS toxicity. Consider airway protection in patients with impaired consciousness.
- Prophylactic steroid and antibiotic use has no proven efficacy in limiting acute lung injury in hydrocarbon pneumonitis.
- Special considerations:
  - Beta-blockers (esmolol 0.025-0.1 mg/kg/min IV or propranolol 1-2 mg IV) is the antiarrhythmic drug of choice in aromatic or halogenated hydrocarbons induced ventricular tachycardia and ventricular fibrillation.
  - N-acetylcysteine should be given as early as possible and preferably within 16 hours after chloroform or carbon tetrachloride ingestion or significant inhalational exposure.
  - Steroids can be used to treat chemical pneumonitis induced by aspiration of mineral oils. Consult medical toxicologist

Mothballs

Mothballs or other forms of moth repellants (e.g. cake type, tablets type, hanger types) can be classified according to its active ingredients:

1. Camphor
2. Naphtalene
3. Paradichlorobenzene
4. Pyrethroids
5. Incense woods

Clinical Effects

Camphor:

- Rapid onset generalised tonic-clonic seizures is the classical presentation of camphor toxicity after ingestion.
- Onset of symptoms within 5-20 minutes after ingestion, peaks within 90 minutes.
- Other neurological effects including hallucination, agitation, CNS depression and coma have been reported.

Naphthalene:

- Significant naphthalene toxicity typically presents with delayed onset of haemolysis.
- Neurological symptoms including dizziness, headache and lethargy are reported after exposure.
- Toxicity can occur following ingestion, inhalation or dermal absorption.
- Metabolised in the liver to form the toxic metabolite alpha-Naphthol which is responsible for naphthalene induced oxidant stress.
- Toxic dose of naphthalene is highly variable and mainly depends on the G6PD status of the exposed individual. Hemolysis is more likely to occur in newborn infants, patients with severe G6PD deficiency or sickle cell disease.
- Heamolysis usually becomes clinically evident within 1-2 days after acute exposure. Anaemia secondary to haemolysis usually peaks at 3-5 days post exposure.
- Crosses placenta, can cause fetal haemolysis and methaemoglobinaemia.

Paradichlorobenzene:

- Low human toxicity. Toxicity upon ingestion limited to gastrointestinal effect with nausea and vomiting.
- Chronic inhalation abuse by bagging has resulted in skin and neurological symptoms.

Mothball Recognition

Identifying the mothball ingredient is important for your management plan. Floating test is readily available tests for mothball identification.

	Float in water	Float in saturated salt water
Camphor	Yes	Yes
Naphtalene	No	Yes
Paradichlorobenzene	No	No

Management

Camphor:

- Airway protection with endotracheal intubation in patients with impaired consciousness.
- Consider GI decontamination with gastric lavage and activated charcoal for a potentially life-threatening overdose after airway protection.
- Seizures control: benzodiazepines.
- Asymptomatic patient after an observation period of 6 hours is medically cleared.

Naphthalene:

- Obtain baseline FBC, G6PD status and urinalysis for RBCs.
- Home monitoring for symptoms of haemolysis including jaundice, dark urine and lethargy.
- Follow up FBC, serum haptoglobin, urinalysis with re-evaluation within 24-48 hours.
- Subsequent follow up 5 days post ingestion is recommended in order to detect any delayed onset of haemolysis.

Paradichlorobenzene:

- Unintentional exposures do not require any treatment.

INSECTICIDES

Common Insecticides in Malaysia		
Chemical Group	**Active Ingredient**	**Formulations/Uses**
Organosphosphates	Malathion, Chlorpyrifos, *nerve gases (Sarin, tabun, soman, agent VX)	Liquid: Anti termites, acaricide, soil borne pests, Gas: * chemical warfare
Organochlorines	Lindane (gammahexa-chlorocyclohexane)	Topical liquid: Treatment for scabies, lice
Carbamates	Carbofuran, carbaryl	Liquid: to control beetles, borers, nematodes and weevils
Pyrethrins/ Pyrethroids	Allethrin, Cypermethrin, Dimethrin, Permethrin	Spray/ solid coil: to control flying insects in homes and industries (mosquitoes, cockroaches)

Pyrethrins/pyrethroids

- Found in household insecticide sprays (e.g. Baygon, Shieldtox, Ridsect) and mosquito coils sold at supermarkets and department stores
- Pyrethrins are naturally occurring insecticides derived from the chrysanthemum plant. Toxicity from ingestion or dermal exposure is relatively low in humans although seizures has been reported in large ingestions
- Hypersensitivity reactions (acute bronchospasm, anaphylaxis) and direct irritant effects are more commonly seen. There is no specific antidote. Treatment is supportive, wash exposed dermal areas with copious amount of soap and water. Treat bronchospasm and anaphylactic reactions accordingly

Organochlorines

- Lindane is commonly used as a pharmaceutical treatment for lice and scabies
- Any ingestion of lindane in a child with symptoms warrants close medical observation
- Symptoms include GI irritation, vomiting, drowsiness, seizures, tachycardia
- 1g of lindane topically can result in seizures in children, which typically occurs between 1-6 hours post exposure
- Treat seizures with benzodiazepines and barbiturates. Avoid phenytoin
- Activated charcoal can be given if presented within 1 hour of ingestion of liquid lindane preparation provided the patient is able to protect airway (* refer topic on activated charcoal)
- Pancytopenia and aplastic anemia has been reported in repeated exposure to lindane
- There is no specific antidote

Carbamates

- Symptoms are similar to organophosphate poisoning
- Overt muscarinic symptoms can be treated with iv atropine (*refer organophosphate poisoning)
- Pralidoxime is rarely indicated but can be considered in severe carbamate poisoning in conjunction with atropine if there is presence of acute cholinergic crisis
- Pralidoxime is contraindicated if the carbamate is carbaryl

Organophosphates

- Organophosphates (OP) inhibits acetylcholinesterase enzyme and prevents the breakdown of neurotransmitter acetylcholine. This action causes continuous stimulation of cholinergic receptors (both muscarinic and nicotinic) resulting in acute cholinergic crisis
- OPs undergo “aging” where inhibition of acetylcholinesterase enzymes becomes irreversible thus rendering the enzyme useless
- Cholinergic stimulation can present with muscarinic symptoms (DUMBBELS- diaphoresis, urination, miosis, bradycardia, bronchorrhea, emesis, lacrimation, salivation) or nicotinic symptoms (mydriasis, tachycardia, hypertension, fasciculations, paralysis)
- It is important to remember that muscarinic symptoms (DUMBBELS) are not always initially predominant or clinically dramatic. Some OPs may present with predominant nicotinic symptoms (mydriasis, tachycardia) or even a mixture of both nicotinic and muscarinic symptoms
- The main contributor to mortality in acute OP poisoning is hypoxia either from bronchorrhea (muscarinic) or hypoventilation from respiratory muscle paralysis (nicotinic)
- Atropine is used to treat ***muscarinic*** symptoms only. The aim in atropinisation is to achieve drying of the bronchial secretions so that gas exchange is feasible to correct hypoxia and/or for cardiac stability by keeping MAP>60mmHg in severe bradycardia causing hypotension
- Pralidoxime is an oxime that reverses the acetylcholinesterase enzyme inhibition by the OP provided aging has not occurred. Recent multiple publications with meta analysis have not shown benefit of pralidoxime in improving outcomes for OP poisoning. Its use remains controversial

Management

- Resuscitate and stabilise the patient as necessary.
- Remove contaminated clothing and wash exposed areas copious amount of soap and water.
- Examine the patient for signs and symptoms of a cholinergic toxidrome (nicotinic- muscle fasciculation/ weakness, fatigue, seizures or muscarinic- salivation, lacrimation, urination, diarrhea, GI upsets, emesis, sweating, miosis, bradycardia, bronchospasm, hypotension).
- If there is hypoxia, determine the underlying cause. If it is due to bronchorrhea, give IV Atropine 0.02mg/kg every 5 minutes, doubling the dose each time, till secretions have reduced. If it is due to hypoventilation from respiratory muscle paralysis, intubate and support ventilation.
- Atropine administration is guided by the drying of secretions rather than the heart rate or pupil size.
- Once atropinisation has been achieved, a continuous infusion of atropine can be started at 0.025mg/ kg/hr. Patients on atropine infusion needs to be monitored for atropine toxicity (over atropinisation - tachycardia, flushing, agitation/restlessness, urinary retention, absent bowel sounds).
- Atropine infusion can be tapered down once the acute cholinergic symptoms have resolved.
- Intermediate syndrome can be seen in some OP poisoning. It is a syndrome of delayed muscle weakness without any cholinergic symptoms. Intermediate syndrome can occur between 24-96 hours after acute poisoning, and after resolution of acute cholinergic crisis. Patients who develop intermediate syndrome will have prolonged respiratory paralysis that may last from a few days to weeks. Support ventilation until muscle paralysis improves.
- Avoid the use of succinylcholine as a muscle relaxant for intubation as its action can be prolonged with acetylcholinesterase enzyme inhibition in OP poisoning.
- Treat hypotension with norepinephrine and epinephrine.
- Dopamine is not recommended to treat hypotension.

HERBICIDES

- Common herbicides seen in Malaysia are glyphosate and paraquat.
- Glyphosate which is now the primary content of Roundup® may cause significant GI injury and is managed symptomatically.
- Paraquat is sold as a green liquid.
- All patients who present with a history of herbicide ingestion must have a urine paraquat level on arrival. Test should be repeated if negative at 4 to 6 hours post ingestion if the first test was performed at less than 4 hours post ingestion.
- Patients who have ingested paraquat may present with the following :
  - Difficulty breathing (early)
  - Diarrhea and vomiting
  - Dysphagia and drooling of saliva
  - Ulcers in the mouth and esophagus
  - Jaundice and liver failure
  - Renal failure

Management

Paraquat

- Remove contaminated clothes and wash skin with soap and water.
- Avoid unnecessary administration of oxygen, unless significant hypoxia.
- Gastric lavage is not recommended as paraquat is corrosive and may cause gastrointestinal injury. Some herbicides are also mixed with hydrocarbons. In large intentional ingestions, secure the airway and a Ryle's tube can be inserted gently, with stomach contents aspirated to remove any toxins in the stomach.
- Administer activated charcoal at a dose of 1g/kg in paraquat poisoning if the patient present early, within 1 hour of ingestion.
- Ensure good hydration to correct hypovolemia from GI loss.
- There is no specific antidote.
- Multiple treatment modalities including immunosuppression with corticosteroids and cyclophosphamide, NAC, high doses of vitamin C,E and glutathione has not shown improvement in outcome in human or animal studies and is currently not recommended.
- Patients with confirmed paraquat poisoning who develop respiratory distress and shock have a poor prognosis. Palliative care with oxygen and analgesics should be administered for patient comfort.

Glyphosate

- Glyphosate has a relative low toxicity unlike paraquat, toxicity is mainly from the co-formulation and surfactants e.g. polyoxyethyleneamine.
- Glyphosate is corrosive in high concentrations.
- Glyphosate is ***not the same as organophosphate insecticide***. It does not inhibit acetylcholinesterase enzymes and thus do not clinically exhibit any acute cholinergic symptoms in poisoning.
- Main toxicity is GI irritation, presenting with severe vomiting and diarrhea.
- Avoid gastric lavage, but in large ingestions, gastric aspirate using NG tube can be attempted if the patient presents early.
- Hydration is key to volume replacement.
- Hemodialysis can be considered in severe poisoning with multiorgan failure.

ANTIHYPERTENSIVES

Beta-Blockers (BB)

- BB are widely used in the treatment of hypertension, ischemic heart disease, arrhythmias, thyrotoxicosis, etc.
- Propranolol is the most lethal beta -blocker in poisoning.
- Sotalol is unique among beta blockers for its inhibition on the potassium channel resulting in prolonged QTc and torsades de pointes.
- Other beta blockers are less toxic and about 1/3 of the overdosed patients remained asymptomatic.

Pharmacokinetics and Pharmacology

- BB are well absorbed with a rapid onset of action, peaks within 1-4 hours (longer for sustained-release preparations).
- Lipid solubility has a role in determining toxicity and elimination:
  - High lipid solubility:
    Usually hepatic metabolism.
    Can pass Blood Brain Barrier (BBB) and have CNS effects; delirium, coma and seizures.
    Example: Propranolol which is highly lipid soluble. Its elimination half-life ranges from 2-3 hours in therapeutic dose to 14 hours in overdose.
  - Poor lipid solubility (high water solubility)
    Renal elimination.
    Examples: Atenolol is the most renal-dependent BB concerning excretion and renal failure may cause its accumulation and toxicity. (Half-life extends from 6 hours to 73 hours in renal failure patients with CrCl <5 ml/min.) It also has the smallest Vd (0.8 L/kg) among the beta blockers and is minimally protein bound (<5%), which makes it amenable to haemodialysis and haemoperfusion. Membrane stabilising activity may affect toxicity:
  - Membrane stabilising activity (e.g. propranolol) has the potential to cause sodium channel blockade and resultant dysrhythmias.
- Alpha-adrenergic blockade:
  - Carvedilol: nonselective beta-adrenergic antagonist with alpha 1 blocking activity.
  - Labetalol: both alpha and beta antagonism in the following ratio: oral 1:3 and IV 1:7
  - Therefore, it is important to identify the particular beta blocker in the management of overdose.

Clinical Manifestations

- About 1/3 remain asymptomatic.
- Co-morbid conditions like CCF, sick sinus syndrome or co-ingestion of other cardioactive toxins increase likelihood of toxicity.
- Cardiovascular toxicity: hypotension, bradycardia, CCF, QRS and QT prolongation on ECG.
- Respiratory depression and apnea.
- CNS: delirium, coma, seizures; seizures (28%) is also frequently reported in propranolol poisoning. Occurs most often in the setting of hypotension.
- Hypoglycemia (relatively common in children after beta blocker ingestion).
- Bronchospasm appears to occur only in susceptible patients.
- Toxicity generally manifests early within 6 hours.

Management

- Ensure ABCs.
- GI decontamination can be considered; activated charcoal 1 g/kg within 1-2 hours post ingestion.
- Treatment options for hypotension and bradycardia (generally follow the listed sequence with increased severity but needs individual consideration):
  - Atropine: 0.5 mg IVI in adult or 0.02 mg/kg in children (minimum 0.1 mg, up to 3 mg in severe cases)
  - High dose insulin (HDI): *refer section on calcium channel blocker poisoning for dose regimen.
  - Glucagon: Bolus: 2-5 mg IV over 1 minute up to 10 mg (50 mcg/kg in children). Maintenance: 2-5 mg /hour in D5% (20-50 mcg/kg/hour in children) titrated clinically.
  - Inotropes and vasopressors: Adrenaline or Noradrenaline is a reasonable first choice. Maintain a low dose, escalating doses of catecholamines may have a deleterious effect.
  - Pacing, intra-aortic balloon pump, phosphodiesterase inhibitors, extra-corporeal circulation.
  - Treatment for prolonged QRS in propranolol poisoning: $NaHCO_3$ 1-2 mEq/kg IV bolus for QRS more than 100 msecs.
  - Intralipid: can be considered for the rapidly collapsing patient who is not responsive to other treatment modalities that has been optimised. Initial dose 20% 1.5 ml/kg bolus over 1 minute followed by infusion at 15 ml/kg/hour for 30-45 minutes. Repeat bolus can be given. Recommended maximum cumulative dose of 12 ml/kg. Caution: intralipid can cause fat embolism and acute pancreatitis. Consult medical toxicologist.

Calcium Channel Blockers (CCB)

- CCB are used for angina, hypertension, arrhythmias and migraine prophylaxis.
- CCB poisoning is one of the most lethal overdoses by prescribed drugs.
- Generally, non-dihydropyridine (verapamil, diltiazem) is more dangerous than dihydropyridine.
- Sustained released preparations result in delayed onset and prolonged symptoms.
- Verapamil is the most dangerous CCB in overdose.

Pharmacokinetics and Pharmacology

- The drug is well absorbed orally.
- Volume of distribution ranges from 5.5. L/kg (verapamil) to 5.3 L/kg (diltiazem) to 0.8 L/kg (nifedipine).
- Hepatic metabolism via cytochrome CYP3A.
- Potential for drug-drug or drug-food interaction with protease inhibitors, macrolide antibiotics and grapefruit juice.
- Verapamil and diltiazem may decrease clearance of drugs like carbamazepine, theophylline, HMG-CoA reductase inhibitors, most HIV-protease inhibitors.
- Onset is rapid (1-2 hours) for regular preparations and can be delayed (up to 12-18 hours) for SR preparations.
- Decreased functional actin-myosin complexes result in depressed contractile force. Impedes Ca^{2+} influx responsible for spontaneous phase 4 depolarisation in pacemaker cells.
- All CCBs inhibit L-type voltage-gated slow calcium channels. This decreases calcium influx into cardiac and smooth muscle cells. In myocardium this causes decreased contractility and conduction.
- In peripheral vasculature there is relaxation and peripheral vasodilatation.
- Each CCB has varying affinity for the different L-type Ca^{2+} channels, however, selectivity may be lost in massive overdose.

Clinical Manifestations

- Presentation is often rapid and fulminant with immediate release formulations. With SR preparations signs may be delayed 6-8 hours. Delayed effect up to 15 hours has been reported.
- Reflex tachycardia and peripheral flushing may be the first signs in CCB overdose especially with dihydropyridines (nifedipine, amlodipine).
- Cardiovascular: hypotension, bradycardia, dysrhythmias, cardiogenic shock.
- CNS depression is uncommon and should prompt for consideration of co-ingestions. Dizziness, altered mental status, seizures, stroke, coma may occur in the setting of cardiogenic shock.
- Pulmonary: acute lung injury/ARDS.
- Hyperglycaemia: insulin release from pancreatic beta islet cells also calcium mediated. In CCB overdose, decreased calcium influx leads to decreased insulin release. This is usually the early sign of CCB toxicity.
- Ischemic bowel injury: reported in significant CCB overdose and is often a complication that limits adequate GI decontamination.

Management

- Ensure ABCs.
- GI decontamination: activated charcoal 1 g/kg within 1-2 hours post ingestion.
- Treatment options for hypotension and bradycardia (generally follow the listed sequence with increased severity but need individual consideration):
  - Atropine: 0.5 mg IV in adult or 0.02 mg/kg in children (minimum 0.1 mg up to 3 mg in severe cases).
  - Calcium: increased extracellular calcium creating a concentration gradient across the cell membrane promoting intracellular calcium flux. This is a high priority in the treatment of CCB toxicity. IV calcium gluconate 10% 0.7ml/kg is recommended to be given over 2 minutes. Up to 3 doses can be given. Effect is transient and re-dosing is often required. Monitoring of serum Ca levels is required in repeated dose and infusion. Calcium concentration of up to 2 times upper limit of normal or ionised calcium level of 2 mmol/L can be tolerated in treatment of CCB poisoning.
  - High dose insulin (HDI) - Consult a medical toxicologist:
    i. Standard therapy for severe CCB overdose. Take 30 mins to 1 hour to have effect.
    ii. Supported by animal studies and human cases series, demonstrated increased myocardial contractility without producing ischemia and improved survival.
    iii. HDI may exert its beneficial effects through increased inotropy, increased intracellular glucose transport and vascular dilatation.
    iv. Goals of HDI is to maintain perfusion of essential vascular beds and organs not to increase BP or MAP alone. Clinical parameters like adequate urine output, clear mentation and biochemical markers like lactate levels is more relevant as compared to blood pressure and pulse alone.
    v. Start with 0.5-2 unit/kg/hour and titrate up to 10 unit/kg/hour. Aim to improve MAP>60mmHg, titrate up to achieve target.
    vi. Some centres would also advocate a bolus dose of 0.5 to 1 unit/kg/hour before starting the infusion.
    vii. Adverse effects:
      a. Hypoglycemia and electrolyte imbalance especially hypokalaemia.
      b. Insulin receptor mechanism for hypoglycemia is saturable at a dose much below the insulin use for HDI therapy. Clinical experience shows that hypoglycemia can be managed easily.
      c. Frequent blood sugar check (every 10-20 minutes when HDI dose is titrated, every 30-60 minutes once insulin dose is stable). Dextrose infusion at 0.5g/kg/hr can be started to maintain blood sugar level between 5.5 mmol/L to 11 mmol/L.
      d. Monitor serum potassium (hourly during titration and every 6 hours once stable). Consider supplement if potassium concentration falls below 2.8-3.0 mmol/L. Keep serum K between 2.8-3.2, do not over correct K to “normal range” as this is not true hypokalemia and potassium will rebound once toxicity resolves.

- Inotropes and vasopressors:
  i. Escalating dose of catecholamines can increase blood pressure and heart rate but they also increase SVR which may result in decreases in cardiac output and perfusion of vascular beds. The increased myocardial oxygen demand that results from catecholamines and vasopressors may be deleterious in the setting of hypotension and decreased coronary perfusion.
  ii. As HDI therapy takes 30 minutes to 1 hour to take effect catecholamines are often started before HDI can take full effect.
  iii. Adrenaline or noradrenaline is a reasonable initial choice.
  iv. Inotrope dose should be titrated down if there is adequate response from HDI and calcium therapy.
- Pacing, intra-aortic balloon pump, phosphodiesterase inhibitors, extra-corporeal circulation.
- Intralipid: can be considered for the rapidly collapsing patient who is not responsive to other treatment modalities that has been optimised. Initial dose 20% 1.5 ml/kg bolus over 1 minute followed by infusion at 15 ml/kg/hour for 30-45 minutes. Repeat bolus can be given. Recommended maximum cumulative dose of 12 ml/kg. Caution: intralipid can cause fat embolism and acute pancreatitis. Consult medical toxicologist.

ORAL HYPOGLYCAEMIC AGENTS (OHA)

Sulphonylureas

- Sulphonylureas (SU) is a class of OHA used to treat diabetes mellitus (DM). Its major mechanism of action is to stimulate the endogenous insulin release from pancreatic beta cells.

Clinical presentation in overdose

- Hypoglycaemia is a major concern.
- Onset of hypoglycaemia symptoms can be delayed up to 18- 24 hours.
- Sulphonylureas stimulate insulin release from the pancreas.
- Clinical features of hypoglycaemia include neurological manifestations such as drowsiness, weakness, confusion, coma, seizure or cerebral edema and sympathomimetic manifestations such as sweating, tachycardia and hypertension.
- Single tablet ingestion can result in hypoglycaemia, especially in children.

Investigations and management

- Consider GI decontamination with activated charcoal if airway is protected.
- Monitor for hypoglycaemia.
- Consider further investigations in patients presenting with unexplained hypoglycaemia and suspected SU exposure.
- In any overdose (even single tablet in non-DM patient or in children), observation for at least 24 hours is recommended.
- If hypoglycaemia occurs treat conventionally with IV dextrose (0.5-1g/kg Dextrose 25% in children and D10% in neonates) followed by food (frequent small snacks) if the patient is able to tolerate orally.
- ***Avoid continuous infusion of iv hypertonic dextrose***. Encourage patients to take orally (carbohydrates and protein) as frequently as possible. Since sulphonylureas increases insulin release, continuous hypertonic dextrose infusions will only result in transient hyperglycaemia followed by a fall in plasma glucose and possibly back to hypoglycaemic levels.
- Aim to maintain serum glucose between 5.5-8mmol/l
- Glucagon is not recommended as antihypoglycaemic in sulphonylurea poisoning as its action in delayed and it can stimulate insulin release from the pancreas resulting in prolonged hypoglycaemia.
- For refractory hypoglycemia consider octreotide in addition to dextrose and food.

Use of octreotide in SU overdose

- Octreotide is the synthetic analogue of somatostatin. It counteracts the hypoglycaemic effects of SU by inhibiting pancreatic beta cell insulin release.
- Consider in patients with SU poisoning presenting with refractory hypoglycaemia (e.g. requiring repeated IV dextrose bolus or escalating dose of dextrose infusion to maintain normal blood glucose).
- Recommended dose is 50 mcg (1 mcg/kg in children) subcutaneous injection every 6 hours for 24 hours. Further doses may be required for SU with long duration of action.
- After stopping octreotide, the patient should be observed for another 24 hours for recurrent hypoglycaemia.

Metformin

- Metformin is a biguanide antidiabetic agent used for the treatment of type II diabetes mellitus. Its pharmacological effects are mainly mediated by inhibition of hepatic gluconeogenesis and enhanced peripheral glucose utilisation.

Pharmacokinetics and pathophysiology

- Metformin is not metabolised in humans. It is excreted in urine unchanged. Renal insufficiency impairs metformin excretion leading to high plasma metformin concentrations and toxicity even at therapeutic doses. The duration of action for standard release preparations was reported to be 1.3-4.5 hours.
- Metformin inhibits hepatic elimination of lactate. Metformin associated lactic acidosis (MALA) is a life threatening complication of metformin toxicity. MALA was reported in two groups of patients:
  - Intentional metformin overdose.
  - Patients with renal impairment taking therapeutic doses of metformin.
- In addition patients with pre-existing illnesses predisposing to lactate accumulation (e.g. liver disease, alcohol abuse, major illnesses causing hypotension and poor tissue perfusion) have high chance of developing MALA. With modern intensive care the first group of patients usually have favourable prognosis, while the reported mortality rate in second group of patients is around 50%.

Clinical presentation in overdose

- Mild poisoning cases present with GI disturbance only (e.g. nausea and vomiting).
- Severe poisoning cases typically present with MALA, which is diagnosed by the presence of elevated serum lactate and anion gap metabolic acidosis.
- The initial presentation of MALA can be non-specific with symptoms including tachypnea, abdominal pain, nausea, vomiting, malaise, myalgia and dizziness. Patients with worsening lactic acidosis will deteriorate into multi-organ failure with impaired consciousness, hypothermia, hypotension, renal failure, ventricular arrhythmias and respiratory insufficiency.
- Hypoglycaemia is not a common presentation in metformin poisoning unless the patient has massive overdose or has concomitant hypoglycaemic agents poisoning.

Investigations

- Blood glucose, blood gases, anion gap, serum lactate concentration and renal function.
- CXR, ECG and other baseline investigations as clinically indicated.
- Investigations for precipitating cause of MALA (e.g. UTI).

Management of metformin overdose

- Mainstay of management is supportive.
- Administer activated charcoal for significant overdose.
- For cases with mild symptoms and no metabolic disturbances an observation period for 6 hours post ingestion is recommended.

Management for MALA

- Early intensive care and hemodialysis are recommended.
- Ensure adequate fluid resuscitation. Consider IV sodium bicarbonate 1-2 mEq/kg for significant metabolic acidosis.
- Hemodialysis (HD) with bicarbonate dialysate can be life saving especially in patients with renal impairment. HD effectively removes both circulating metformin and lactate. Early HD is usually recommended as patients can deteriorate rapidly with unstable hemodynamics.
- Hemofiltration (e.g. CVVH) can be considered for patients with unstable hemodynamics and HD is not feasible.

OPIOIDS

- Opioid poisoning presents with a myriad of symptoms including pinpoint pupils, bradypnea or apnea, bradycardia and hypotension, depressed consciousness. (Opioid toxidrome, *refer toxidrome table)
- Some synthetic opioids like tramadol are seizuregenic and can cause hypoglycemia and acute serotonin toxicity
- Methadone can cause QT prolongations and cardiac arrhythmias (torsades des pointes)
- Synthetic opioids like methadone and tramadol will not test positive in a urine drug screen for opioids/ opiates. A negative Urine Drug Screen (UDS) does not rule out the absence of a drug. Always correlate clinical symptoms to a toxidrome.
- Dextromethorphan is a unique morphinan drug that is commonly abused by adolescents for its euphoric effects. It is available over the counter as cough and cold medication. In high doses it acts on opioid receptors. It also inhibits serotonin reuptake and can cause serotonin toxicity. It is partially reversed with naloxone.
- *Ingestion or exposure to any substance abuse or narcotics warrants a referral to SCAN team for further investigation.*

Management

- Assist ventilation with a bag-valve-mask device immediately if patient is bradypneic and hypoxic. Prepare equipment for intubation.
- IV Naloxone is the antidote used to treat opioid poisoning.
- Most opioid poisoning in children is unintentional, hence the use of naloxone and the risk of developing complications is low. If the patient is not opioid naïve, caution should be practiced when giving naloxone (use lower doses) to avoid precipitating opioid withdrawal in the patient .
- The aim of using naloxone is to reverse respiratory depression to avoid intubation and mechanical ventilation. Complete restoration of consciousness level is not the necessary endpoint in naloxone therapy. Start at:
    - 0.1mg/kg bolus for children weighing 5-20kg. If no improvement in respiratory rate in 2 minutes, administer 2mg, then 4 mg, then 10mg then 15mg. If still no improvement in RR, consider other causes of respiratory depression
    - 2mg bolus for children weighing>20kg. If no improvement in RR in 2 minutes, give 4mg then 10mg, then 15mg. Consider other causes if no improvement of respiratory depression

- Higher doses of naloxone may be required for opioid reversal in children in view of higher doses per kg body weight.
- Repeat dosing may be required or a maintenance infusion. For naloxone infusion, give a loading dose at 50% of effective reversal dose, followed by 2/3 the effective reversal dose per hour. E.g. the patient received 2mg, 4mg and 10mg of naloxone to reverse respiratory depression. Total reversal dose =16mg. To start naloxone infusion, give loading iv naloxone 8mg bolus followed by 10mg/hr infusion.
- Continue to monitor respiration closely preferably in an intensive care unit.
- Naloxone reversal is short duration. Overdoses on long acting opioids such as methadone will require longer duration of treatment and observation. Naloxone can cause noncardiogenic pulmonary oedema, cardiac dysrhythmias and hypertension
- All patients on naloxone infusion should be monitored closely in a critical care setting.
- If high doses of naloxone did not reverse respiratory depression and level of consciousness, proceed to intubation and further resuscitation. Investigate for other causes of reduced consciousness and respiratory depression.
- Continue to monitor for signs of respiratory depression up to 24 hours once patient is off naloxone.
- Monitor for seizures and hypoglycemia in tramadol exposure. Seizure may occur even at therapeutic levels.

ETHANOL AND TOXIC ALCOHOLS

- Any alcohol ingestion in children requires clarification on type of alcohol ingested, either ethanol or a toxic alcohol (methanol, isopropyl alcohol, ethylene glycol).
- Ethanol and toxic alcohol ingestions can cause profound CNS depression, hypoglycemia and hypothermia especially in infants and very young children.
- A small sip of a concentrated alcoholic beverage may cause significant ethanol intoxication and coma in a young child. Always consider co-ingestions with other drugs in any child presenting with a toxic coma.
- Toxic alcohols can be found in most household products.
- Ingestions of toxic alcohols can cause wide anion gap metabolic acidosis.
- Patients may present with vomiting, blurring or loss of vision, ataxia, hypoglycemia, respiratory distress, unexplained metabolic acidosis, coma or cardiovascular collapse.

Alcohol type	Sources	Metabolite	Intervention	
			Fomepizole/ oral ethanol	Dialysis
Ethanol	Alcoholic beverages, mouthwash, perfumes	Non toxic (CO_2 and H_20 as final product)	-	+/-
Methanol	Automobile coolant and anti-freeze, windshield wiper fluid, paint and varnish remover	Toxic (formic acid) Causes blindness Metabolic acidosis with wide anion gap	+	+
Ethylene glycol	Automobile coolant and anti-freeze, solvents	Toxic (oxalic acid) Causes acute kidney injury Hypocalcemia Metabolic acidosis with wide anion gap	+	+
Isopropanol (isopropyl alcohol)	Rubbing alcohol, hand sanitizers, solvents	Non toxic (acetone)	-	+/-

Management

- Resuscitate and stabilise as necessary. Alcohols can cause respiratory depression and coma, protect airway and intubate if needed.
- Check blood glucose level and correct hypoglycemia with intravenous dextrose.
- Gastric lavage is rarely indicated due to rapid absorption of toxic alcohols. Activated charcoal is not recommended.
- Fluid resuscitation for hypotension due to vasodilation.
- Sodium bicarbonate may be administered in methanol and ethylene glycol poisoning with severe acidemia to trap and enhance renal clearance of formate and favour the formation of less toxic metabolites. Aim to achieve serum pH >7.2.
- Send serum methanol/ethylene glycol/ethanol.
- The key in managing toxic alcohols is to prevent formation of toxic metabolites and enhance elimination of these toxic alcohols (parent compounds) and its formed toxic metabolites. This is achieved by blocking the aldehyde dehydrogenase (ADH) enzyme with ethanol or fomepizole and dialysis.

- ADH blockade with ethanol or fomepizole will result in a longer half life of the toxic alcohol due to inhibition of its metabolism. Dialysis is used to eliminate the toxic alcohol and its toxic metabolites from the plasma.
- Oral ethanol may be used to buy time while obtaining fomepizole and while awaiting hemodialysis. Caution: oral ethanol can cause CNS depression, hypothermia, hypoglycaemia, transaminitis and pancreatitis. For effective ADH blockade with ethanol, serum ethanol needs to be frequently monitored and maintained > 100mg/dL. This may be challenging if lab support for serum ethanol is not readily available. Dose: give loading dose 0.8g/kg 20% oral ethanol diluted in fruit juice (A 20% V/V concentration yields 200mg/ml). Maintenance dose: 80mg/kg/hr 20% oral ethanol diluted in juice.
- Aim a narrowing of anion gap while on oral ethanol. If anion gap widens and metabolic acidosis worsens (without the availability of serum ethanol), this may indicate inadequate ADH blockade with oral ethanol and the oral dose needs to be increased.
- Intravenous ethanol is not recommended for pediatric patients.
- Fomepizole is an excellent ADH blocker. It is the antidote of choice for toxic alcohol poisoning. Due to its high cost, it is available only in selected centers. Loading dose 15mg/kg iv fomepizole diluted in 100mls dextrose 5% and infuse over 30 minutes, followed by maintenance dose 10mg/kg every 12 hours. Maintenance dose needs to be adjusted every 48 hours (after 5 doses).
- Please discuss with a medical toxicologist if fomepizole is indicated for treatment to avoid wastage, and dose adjustment due to autoinduction of its own metabolism.
- Both fomepizole and oral ethanol doses needs to be increased/adjusted during hemodialysis. Consult medical toxicologist.
- Monitor the patient's acid base balance, serum lactate, blood sugar, liver enzymes, renal function and anion gap closely.
- Isopropyl alcohol can cause deep CNS depression and gastrointestinal bleed. Treatment is supportive.
- Indication for hemodialysis in methanol poisoning:
  - Severe methanol poisoning
  - Coma, seizures, new vision deficit, metabolic acidosis (serum pH<7.15) or persistent metabolic acidosis despite antidote and supportive measures
  - Serum methanol >50 mg/dL in the absence of an ADH blockade
  - If there is renal impairment

SYMPATHOMIMETICS

- Amphetamine was first synthesised in 1887.
- In 1980s there was an outburst of "designer drugs" in response to the legislation of amphetamine control. More than 200 chemicals are derived from the basic amphetamine structure and are collectively known as amphetamine derivatives or amphetamine-like substances.
- Two examples are 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) and methamphetamine.

Pharmacology

- The primary mechanism of action is the release of endogenous catecholamines such as noradrenaline, serotonin and dopamine, resulting in sympathomimetic poisoning and psychomotor agitation.
- Methamphetamine is usually in a form of crystal and can be rapidly absorbed by inhalation, ingestion and injection. It has greater CNS potency than other amphetamines and longer half life around 19-34 hours. The duration of effect may last more than 24 hours.
- Clinical effects of MDMA begin 15-60 minutes after ingestion and lasts 1-6 hours typically. The half-life is around 8 hours and occasionally effects may be present for more than 24 hours.

Clinical Features

- Typical CNS stimulant effects.
- "Tweaking" is described as psychomotor agitation and psychiatric symptoms similar to schizophrenia (paranoid, hallucinations, agitation, delusions) in methamphetamine users. Patients are the greatest danger to themselves and others through violent acts.
- "Met-bug" is described as visual or tactile hallucinations of "bugs" experienced by methamphetamine user. The patient may have self-harm behavior secondary to the hallucination.
- MDMA will cause euphoria, increased alertness, jaw clenching, tooth grinding (bruxism) and restless movement in "therapeutic dose" and generally has less sympathetic effect, much more euphoria compared with amphetamine/methamphetamine.
- MDMA was reported to cause significant hyponatremia, probably due to increased release of vasopressin and its commonly occurred in the morning after using MDMA.
- The serotonergic activity of MDMA is as risk factor for serotonin syndrome, particularly when combined with SSRIs.
- Pneumothorax and pneumomediastinum has been reported.
- Acute cerebral (infarction or hemorrhage) or cardiac (e.g. arrhythmias, ischemia) events are common causes of death.
- Chronic use of MDMA causes permanent damage of serotonergic neurons in the brain.

Investigations

- Bedside urine toxicology kit for drugs of abuse detecting amphetamine, methamphetamine and MDMA as separate entities. Positive results are generally expected up to several days after their use.
- Clinical utility of bedside kit is limited as both false positive (e.g. pseudoephedrine) or false negative are really common. Caution in interpretating urine drug screening, always correlate clinical symptoms to UDS finding.
- Hyponatremia is common in MDMA use. Check sodium level in any patient with altered mental status.
- CT brain, ECG, CXR, blood test such as FBC, RP, LFT, CK(CE) and others as clinically indicated.

Treatment

- Rapid "cooling", use of benzodiazepines (BZD) and supportive measures are the mainstay of treatment. Hyperthermia needs to be treated aggressively as it contributes to mortality in sympathomimetic toxicity.
- Avoid physical restraints as it worsens rhabdomyolysis and acute kidney injury.
- Use benzodiazepines to control agitation in titrated manner. Give intravenous BZD, repeated every 5-10 minutes as necessary until patient "calms down". Large doses of BZD may be required to control agitation for certain cases. Calming the patient down reduces the risk of rhabdomyolysis and acute kidney injury. Start with bolus midazolam 0.05-0.1mg/kg for children <5 yrs, 0.025-0.05mg/kg for children age 6-12 years. Double the dose every 5-10 minutes until the patient is calm. Aim to calm the patient, and not sedation. There is no ceiling limit for benzodiazepine in managing sympathomimetic toxicity. Once patient is calm, midazolam infusion can be started to maintain catecholamine suppression, reduce agitation and hypertension, improve hyperthermia and reduce the risk of rhabdomyolysis.
- For severe rhabdomyolysis (high creatinine kinase and urine myoglobinuria), urinary alkalinisation can be used to prevent myoglobin deposition in renal tubules. (* refer urinary alkalinisation in salicylate poisoning).
- Anti-pyschotics use to control agitation in acute sympathomimetic toxicity is not recommended due to its unfavorable risk-benefit consideration (lowers seizure threshold and risk of developing acute serotonin syndrome/neuroleptic malignant syndrome).
- IV fluids to treat hypotension from volume loss.
- Serotonin syndrome/ toxicity can be seen with some stimulants like methamphetamine, MDMA and amphetamine. Suspect acute serotonin toxicity if the patient has tremors, hypereflexia, clonus (spontaneous or inducible), ocular clonus, tachycardia, altered mental state. (* refer management of acute serotonin toxicity in SSRI/antidepressants).
- Treatment for seizures:
  - Benzodiazepine
  - Phenytoin is NOT recommended
  - Rule out hyponatremia and intracranial pathology
- Treatment for hypertensive emergencies:
  - Benzodiazepine and "calm down" patient first
  - Titrate with short acting nitrates e.g. GTN; nitroprusside
  - Consider phentolamine, calcium channel blockers if inadequate response.

PSYCHIATRIC DRUGS - ANTIDEPRESSANTS

Antidepressants	
Class	**Example**
Tricyclic antidepressants (TCA)	Amitriptyline
Selective serotonin reuptake inhibitors (SSRI)	Citalopram, Escitalopram, Fluoxetine, Sertraline, Fluvoxamine
Nonselective monoamine reuptake inhibitors	Venlafaxine, Duloxetine
Others	Mirtazapine, Bupropion

- The newer generation of psychiatric drugs such as selective serotonin reuptake inhibitors (SSRI) and nonselective serotonin reuptake inhibitors (NSRI) are safer compared to tricyclic antidepressants.
- As a result they are prescribed more often then TCAs but may still cause significant toxicity in children.

Management

SSRI

- There is no specific antidote. Monitor for signs of serotonin syndrome (agitation, tremors, hyperlexia, confusion, tachycardia, hypertension, dilated pupils, loss of muscle coordination, muscle rigidity, sweating, vomiting, diarrhea and headache). In severe serotonin syndrome, patient may develop high fever, seizures, irregular heart beat, rhabdomyolysis and unconsciousness.
- Treatment for serotonin syndrome is supportive.
- Benzodiazepines e.g. IV Diazepam can be administered for seizures and to control agitation. Avoid physical restraints, as this will worsen rhabdomyolysis. Avoid phenytoin for seizures.
- Good hydration is required to enhance drug elimination and treat rhabdomyolysis.
- Treat hypotension with fluids resuscitation.
- Monitor ECG for QT prolongation.
- Stop all drugs that may cause serotonin toxicity.
- Cyproheptadine (serotonin antagonist) is rarely indicated as serotonin toxicity generally resolves within 24 hours. It can be considered in severe serotonin toxicity although evidence to support its use is currently lacking. Consult medical toxicologist for input in severe cases.

Tricyclic Antidepressant (TCA)

- Patients can present with hypotension from vasodilatation, cardiac dysrhythmias from sodium channel and potassium channel blockade, CNS depression and seizures.
- Deaths in TCA poisoning are related to Na channel blockade effect causing life threatening arrhythmias and seizures.
- Principle of treatment is to overcome Na channel blockade and reduce binding of TCA to Na channels with sodium bicarbonate.
- Intubate and protect airway if airway is compromised or patient is comatose.
- Place patient on continuous ECG monitoring to look for QRS widening, QT prolongation, cardiac conduction abnormality.
- Monitor for arrhythmias, hypotension, altered sensorium or seizures, which usually occurs within the first 6 hours after ingestion.
- Treatment should be instituted for widened QRS complex and wide complex arrhythmias. QRS widening (QRS >100ms) can be corrected with sodium bicarbonate 8.4% bolus at 1-2mmol/kg. Repeat boluses until QRS narrows or until serum pH>7.55. Aim narrowing of QRD < 100ms.
- Since TCA can cause potassium channel blockade and QT prolongation, monitor serial serum K, Ca and Mg. Keep K>4, Ca> 2.1 and Mg> 0.9.
- Keep patient on continuous cardiac monitoring for QT prolongation and torsades de pointes. If QT > 450ms with the presence of any arrhythmias, administer bolus IV $MgSO_4$ 25-50mg/kg dilute in 10ml dextrose 5% over 10-15mins. Repeat if necessary 5-15 minutes later. If in doubt, consult a medical toxicologist
- Use ACLS/APLS guidelines to treat life threatening arrhythmias.
- Identify the antidepressant taken to anticipate other possible complications
- Treat seizures with benzodiazepines and barbiturates. Do not use phenytoin as it will worsen sodium channel blockade.
- Hemodialysis/PD is not effective as tricyclics are protein bound. Important to avoid the use of flumazenil for reversal of co-ingestion of benzodiazepines as this can precipitate tricyclic induced seizure activity.

TOXIDROMES				
Toxidrome	Example	Common findings	Other findings	Potential Interventions
Opioid	Heroin Morphine	CNS depression, miosis, respiratory depression	Hypothermia, bradycardia, acute lung injury	Ventilation or naloxone
Sympathomimetic	Cocaine Amphetamine	Psychomotor agitation, mydriasis, diaphoresis, tachycardia, hypertension, hyperthermia	Seizures, rhabdomyolysis, myocardial infarction	Cooling, sedation with benzodiazepines, hydration.
Cholinergic	Organophosphates Carbamates	Salivation, lacrimation, diaphoresis, vomiting, urination, defecation, muscle fasciculations, weakness, bronchorrhea	Bradycardia,miosis, seizures,respiratory failure, paralysis	Airway protection and ventilation, atropine, pralidoxime
Anticholinergic	Scopalamine Atropine	Altered mental status, mydriasis, dry/ flushed skin, urinary retention, decreased bowel sounds, hyperthermia, dry mucus membranes	Seizures, dysrhythmias, rhabdomyolysis	Physostigmine (if appropriate), sedation with benzodiazepines, cooling, supportive management
Salicylates	Aspirin Salicylate Oils	Altered mental status, metabolic acidosis, tinnitus, hyperpnea, tachycardia, diaphoresis, vomiting	Low grade fever, ketonuria, acute lung injury	MDAC, alkalinise urine with potassium repletion, hemodialysis, hydration
Hypoglycemia	Sulfonylureas Insulin	Altered mental status, diaphoresis, tachycardia, hypertension	Slurring of speech, seizures	Intravenous glucose, oral feeding if able, frequent capillary blood for glucose measurement, octreotide
Serotonin Syndrome	Pethidine SSRI TCA Amphetamines	Altered mental status, hyperreflexia, hyperthermia, mydriasis, increased muscle tone	Intermittent whole body tremor	Cooling, sedation with benzodiazepines, hydration, supportive management

Section 20

CHILD PSYCHIATRY

Chapter 115:
Children & Young People's Mental Health

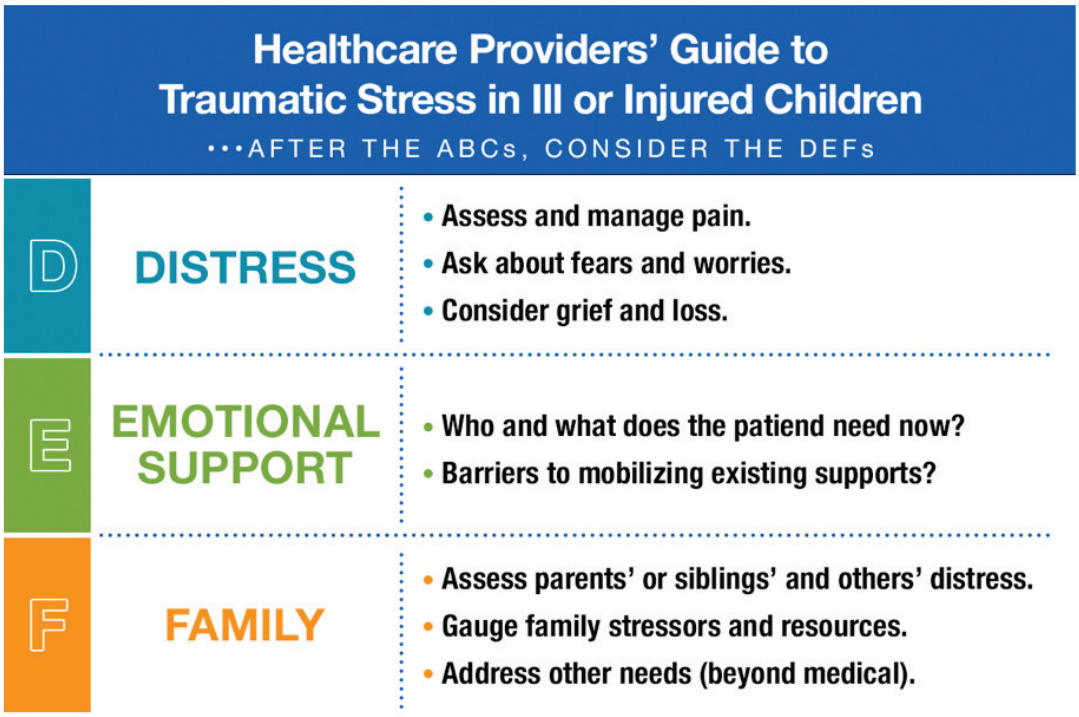
Common Red Flags indicating potential mental health issues in children

Parents' /caregivers' capacity to provide history that is accurate is essential especially with children and young people as one of the earliest red flags across the ages would be changes in the pattern of behaviour that remain despite strategies to manage them.

Some common behaviour and emotion red flags

- Ongoing behaviour problems at daycare, school or at home
- Hyperactivity or constant movement that is beyond regular playing
- Unusual fears or worries
- Not taking part in activities like playtime at the playground or extracurricular activities
- Persistent sadness that lasts two weeks or more
- Withdrawing from or avoiding social interactions
- Hurting oneself or talking about hurting oneself
- Talking about death or suicide
- Outbursts or extreme irritability
- Changes in appetite
- Frequent physical symptoms such as abdominal aches and headaches
- Possible worsening of existing medical conditions despite adequate treatment provided, such as more episodes of AEBA, or flare of eczema

Trauma-Informed Paediatric Care



The D-E-F framework can help health care providers in Paediatrics to identify, address and prevent traumatic stress responses in children and young people.

Pocket Cards for D-E-F
https://www.healthcaretoolbox.org/sites/default/files/images/pdf/DEFpocketcards.pdf

Nursing Assessment tool
https://www.healthcaretoolbox.org/sites/default/files/images/pdf/DEFNursingAssessmentFormFINAL.pdf

When to refer?

Consider referrals when the patient and family /caregivers would benefit from further support. This excludes SCAN related situations.

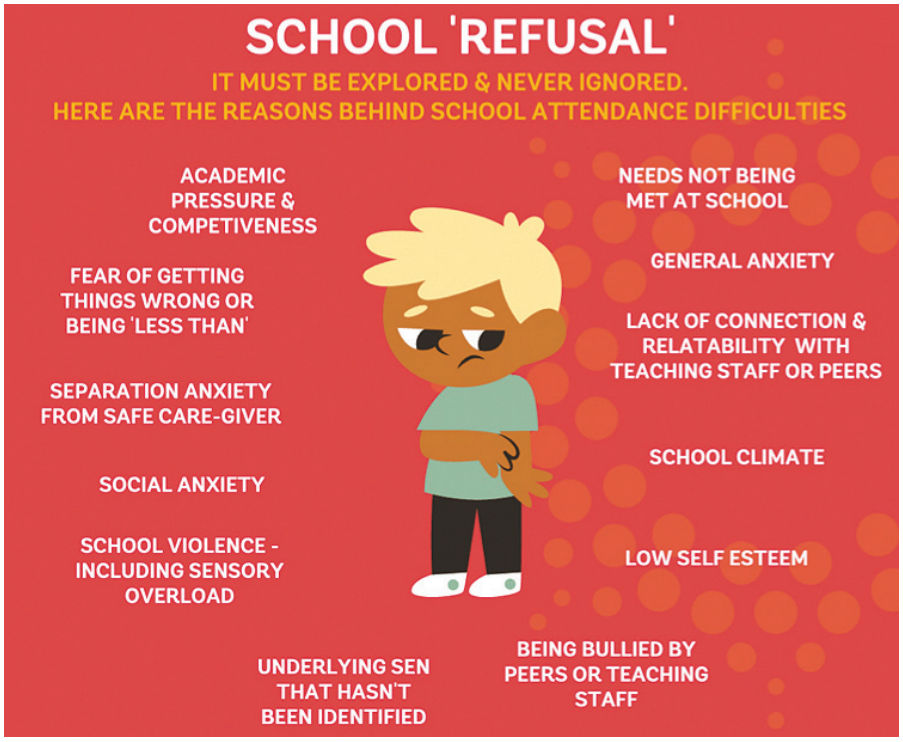
1. Mention the concerns you have identified:
   a. "I am concerned that you /your child may be experiencing difficult feelings or thoughts. It may be useful to speak to our social worker /counsellor /mental health professional who can help your family more.
2. Involve the child and family in the decision to seek help as this would ensure participation and not seem intrusive.

Short screening tools that would be useful
https://cps.ca/en/mental-health-screening-tools

Adverse Childhood Events
https://centerforyouthwellness.org/aceq-pdf/

School refusal

School refusal rates have been increasing after the Covid-19 pandemic. Many children and young people may be having significant emotional distress especially anxiety and depression. They may present to Paediatrics with physical symptoms with no identifiable underlying medical issues. It would be useful to screen these children and young people and their parents for the possibility of school refusal.



Screening assessment tools

Screen for Child Anxiety Related Disorders (SCARED)
*able to screen for significant school avoidance, anxiety disorder, panic disorder, significant somatic symptoms, generalised anxiety disorder, separation anxiety disorder and social anxiety disorder

Child
https://www.aacap.org/App_Themes/AACAP/docs/member_resources/toolbox_for_clinical_practice_and_outcomes/symptoms/ScaredChild.pdf

Parent
https://www.aacap.org/App_Themes/AACAP/docs/member_resources/toolbox_for_clinical_practice_and_outcomes/symptoms/ScaredParent.pdf

SChool REfusal EvaluatioN (SCREEN)

Young People (10-16 years)
https://www.insa.network/images/Georgines_uploads/SCREEN_English.pdf (questionnaire)
https://www.insa.network/images/Georgines_uploads/User_Manual_SCREEN.pdf (key)

Obsessive Compulsive Disorder (OCD)

The average age of onset is about 10 years, although children as young as 5 or 6 years may be diagnosed with OCD. Though children can start showing symptoms of OCD around age 3, this is extremely rare. Children may have OCD when unwanted thoughts, and compulsive behaviours happen frequently, take up a lot of time (more than an hour a day), interfere with their activities, or make them very upset. Generalised Anxiety Disorder, mood disorders, and Autism Spectrum Disorder are often comorbid with OCD. Comorbid depression is associated with increased OCD symptom severity and functional impairment.

Screening tool for OCD
https://www.ementalhealth.ca/index.php?ID=14&m=survey

Conversion Disorder (Functional Neurological Symptom Disorder)

Functional neurological disorder (FND) is a multi-network brain disorder that encompasses a broad range of neurological symptoms. The common presenting symptoms in Paediatrics include numbness, weakness, seizure-like events, or abnormal gait or movements.

This diagnosis is often considered when presenting symptoms cannot be fully explained by neurological or other medical conditions, or by substance use, and are not intentionally produced. Often, many of these children have underlying psychological distress or difficulties in their home environment. A separate diagnosis of Factitious Disorder is given if symptoms are malingered.

One of the key features is that the symptoms may be inconsistent, often changing during examination. An accepting rather than a judgmental approach towards symptoms is helpful.

Differentiating features of conversion disorder symptoms

SYMPTOM	DISTINGUISHING FEATURES AND PRESENTATION
Blindness	In conversion disorder, the child, though complaining of recent onset of blindness, neither sustains injury while manoeuvring around the clinic room nor displays any expected bruises or scrapes. The pupillary reflex is present, thus demonstrating the intactness of the optic nerve, chiasm, tract, lateral geniculate body, and mesencephalon.
Deafness	In conversion deafness, the blink reflex to a loud and unexpected sound is present, thus demonstrating the intactness of the brain stem.
Psychogenic nonepileptic seizures	Children with psychogenic nonepileptic seizures generally lack response to treatment with antiepileptic drugs or have a paradoxical increase in seizures with antiepileptic drug treatment. The negative history of injury or loss of control of bladder or bowel during the seizure episode is also significant.
Tremor	When weights are added to the affected limb, patients with functional tremor tend to have greater tremor amplitude, whereas in those with organic tremor, the tremor amplitude tends to diminish.
Dystonia	Useful distinguishing features include an inverted foot or "clenched fist," adult onset, a fixed posture that is apparently present during sleep, and the presence of severe pain.
Paralysis	In conversion paralysis, the child loses the use of half of his or her body or of a single limb, but the paralysis does not follow anatomical patterns and is often inconsistent upon repeat examination.
Syncope	The conversion child may report feeling faint or fainting, but no autonomic changes are identified, such as pallor, and there is no associated injury. In addition, the fainting spells have a "swooning" character to them, heightening the drama of these events.
Aphonia	Conversion aphonia may be suspected when the child is asked to cough, for example, during auscultation of the lungs. In contrast with other aphonias, the cough is normally full and loud.
Anaesthesia	Conversion anaesthesia may occur anywhere, but it is most common on the extremities. One may see a typical "glove and stocking" distribution; however, unlike the "glove and stocking" distribution that may occur in a polyneuropathy, the areas of conversion anaesthesia have a very precise and sharp boundary, often located at a joint.
Paraplegia	In conversion paraplegia, one finds normal, rather than increased, deep tendon reflexes, and the Babinski sign is absent. In doubtful cases, the issue may be resolved by demonstrating normal motor evoked potentials.

Section 21

PAEDIATRIC EMERGENCY

Chapter 116:
Anaphylaxis

Introduction

Anaphylaxis is likely when all of the following 3 criteria are met:

- Sudden onset and rapid progression of symptoms (minutes to hours)
- Life-threatening Airway and/or Breathing and/or Circulation problems
- Skin and/or mucosal changes (flushing, urticaria, angioedema)

Life threatening features are as follows:

- Airway problems:
  - Airway swelling e.g. throat and tongue swelling.
  - Hoarse voice.
  - Stridor.
- Breathing problems:
  - Shortness of breath (bronchospasm, pulmonary oedema).
  - Wheeze.
  - Confusion caused by hypoxia.
  - Cyanosis is usually a late sign.
  - Respiratory arrest.
- Circulation problems
  - Shock.
  - Cardiovascular collapse with faintness, palpitations, loss of consciousness.
  - Cardiac arrest
- The following supports the diagnosis:
  - Exposure to a known allergen for the patient
- Other considerations:
  - Skin or mucosal changes alone are not a sign of an anaphylactic reaction
  - Skin and mucosal changes can be subtle or absent in up to 20% of reactions (some patients can have only a decrease in blood pressure, i.e., a Circulation problem)
  - There can also be gastrointestinal symptoms (e.g. vomiting, abdominal pain, incontinence)

Key points to severe reaction

- Previous severe reaction.
- History of increasingly severe reaction.
- History of asthma.
- Treatment with β blocker.

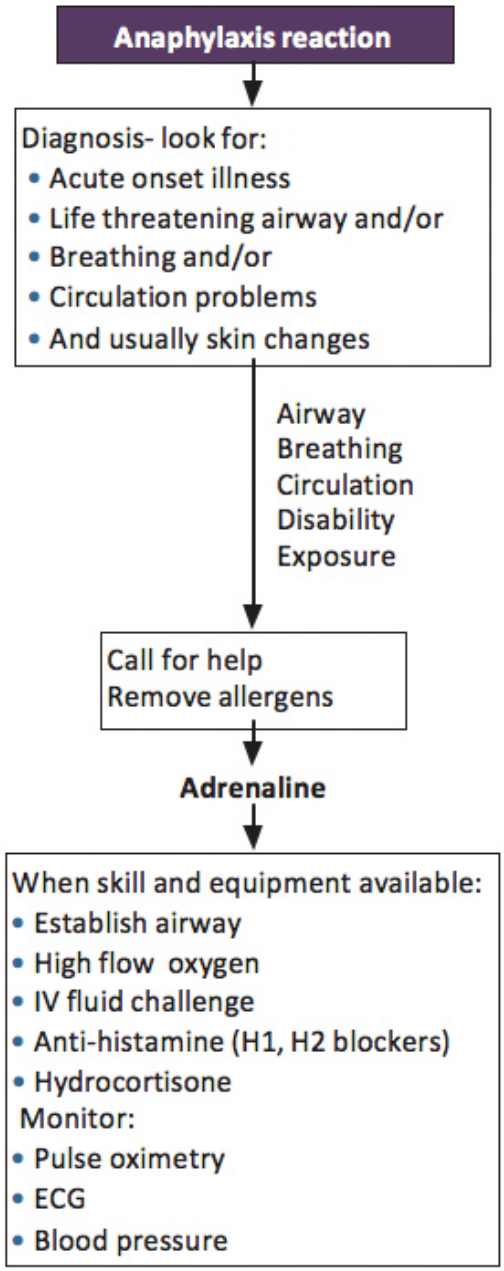
Time course for fatal anaphylactic reactions.

When anaphylaxis is fatal, death usually occurs very soon after contact with the trigger. Fatal food reactions cause respiratory arrest typically after 30–35 minutes; insect stings cause collapse from shock after 10–15 minutes; and deaths caused by intravenous medication occur most commonly within 5 minutes

Approach to treatment (see following pages)

The clinical signs of critical illness are generally similar because they reflect failing respiratory, cardiovascular and neurological system. Use ABCDE approach to recognise and treat anaphylaxis.

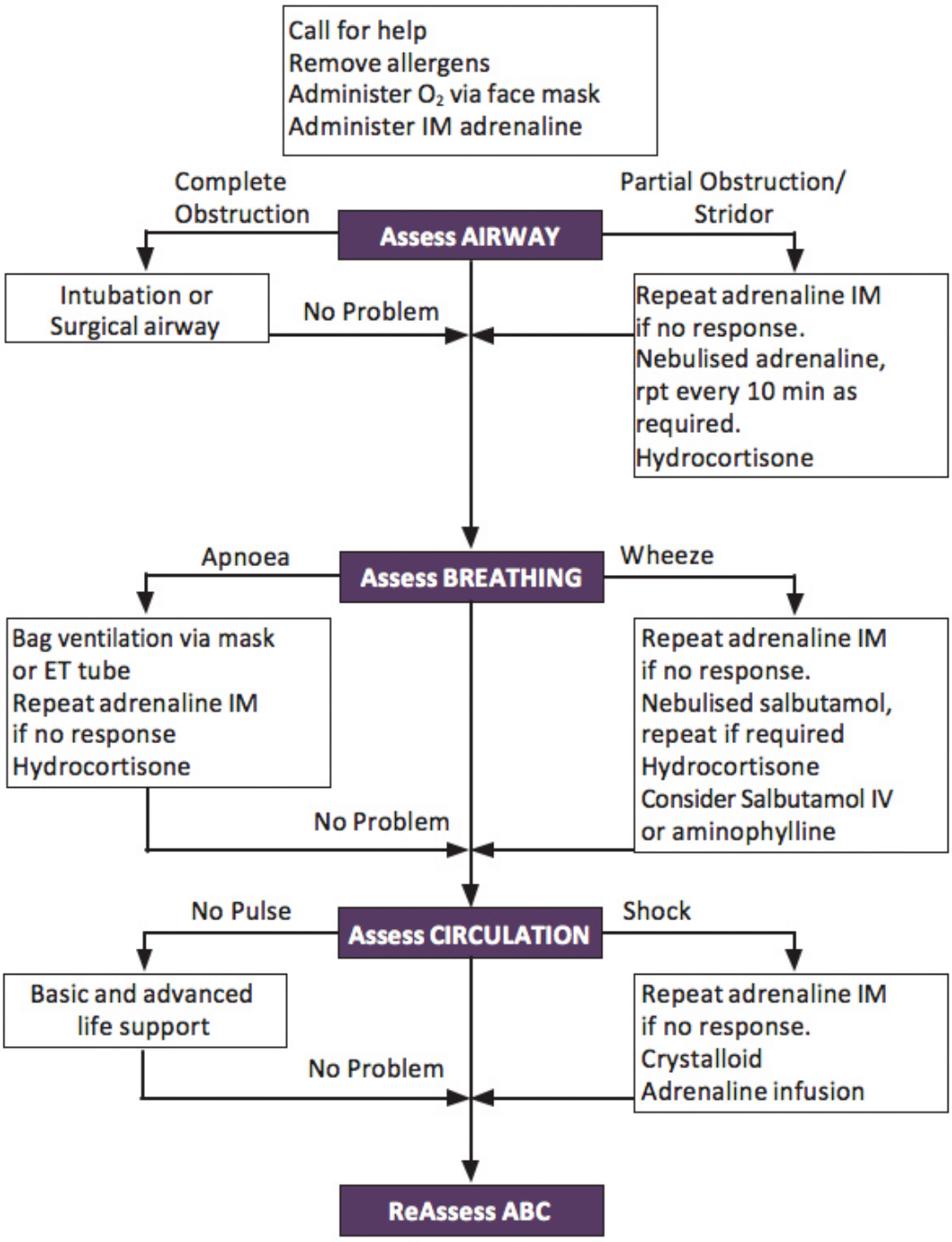
GENERAL MANAGEMENT AND ASSESSMENT



Emergency treatment in anaphylaxis				
Drugs in anaphylaxis	Dosage by age			
	< 6 months	6 mths to 6 years	6 years-12 years	> 12 years
Adrenaline IM- pre hospital practitioners	150 micrograms (0.15ml of 1000)		300micrograms (0.3ml of 1:1000)	500microgram (0.5ml of 1:1000)
Adrenaline IM- in hospital practitioners (rpt after 5 mins if no improvement)	10 micrograms/kg 0.1ml/kg of 1:10000 (infants/young children) OR 0.01ml/kg of 1:1000 (older children)			
Adrenaline IV	Start with 0.1microgram/kg/min and titrate up to 5microgram/kg/min*			
Crystalloid	20 mls/kg			
Hydrocortisone ** (IM or Slow IV)	25mg	50mg	100mg	200mg

*If hypotension persist despite adequate fluid (CVP>10), obtain echocardiogram and consider infusing noradrenaline as well as adrenaline.
** Dose of intravenous corticosteroid should be equivalent to 1-2mg/kg/dose of methylprednisolone every 6 hours (prevent biphasic reaction).
Oral prednisolone 1m/kg can be used in milder case.
Antihistamine are effective in relieving cutaneous symptoms but may cause drowsiness and hypotension.
If the patient is on β-blocker, the effect of adrenaline may be blocked; Glucagon administration at 20-30µg/kg, max 1mg over 5 minutes followed by infusion at 5-15µg/min is useful.
Continue observation for 6-24 hours depending on severity of reaction because of the risk of biphasic reaction and the wearing off of adrenaline dose.

SPECIFIC TREATMENT AND INTERVENTION



Discharge Planning

- Prevention of further episodes
- Education of patients and caregivers in the early recognition and treatment of allergic reaction
- Management of co-morbidities that increase the risk associated with anaphylaxis
- An adrenaline pen should be prescribed for those with history of severe reaction to food, latex, insect sting, exercise and idiopathic anaphylaxis and with risk factor like asthma.

Chapter 117:
Recognition and Assessment of Pain

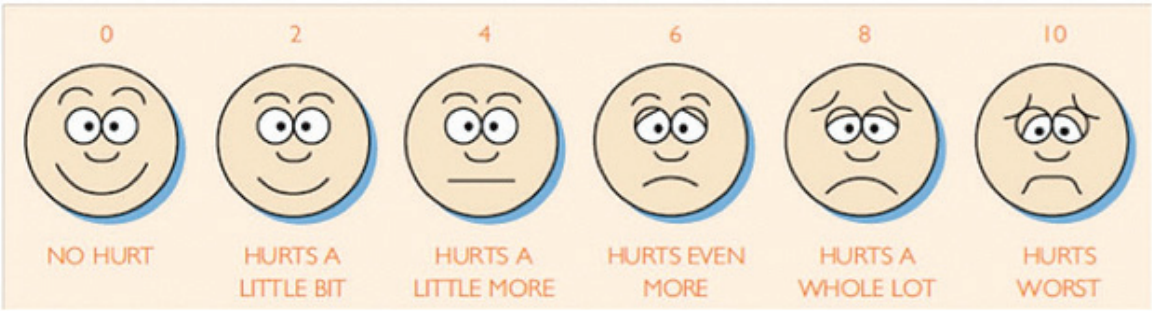
The health care provider should decide on an appropriate level of pain relief for a child in pain and also before a diagnostic or therapeutic procedure.
We can assess a child in pain using an observational-based pain score or a self-assessment pain score. Repeated assessment needs to be done to guide further analgesia.

Observational-based Pain Score: The Alder Hey Triage Pain Score				
No.	**Response**	**Score 0**	**Score 1**	**Score 2**
1	Cry or voice	No complaint or cry Normal conversation	Consolable Not talking negative	Inconsolable Complaining of pain
2	Facial expression – grimace*	Normal	Short grimace <50% time	Long grimace >50% time
3	Posture	Normal	Touching / rubbing / sparing / limping	Defensive / tense
4	Movement	Normal	Reduced or restless	Immobile or thrashing
5	Colour	Normal	pale	Very pale / 'green'
*grimace – open mouth, lips pulled back at corners, furrowed forehead and /or between eye-brows, eyes closed, wrinkled at corners. Score range from 0 to 10				

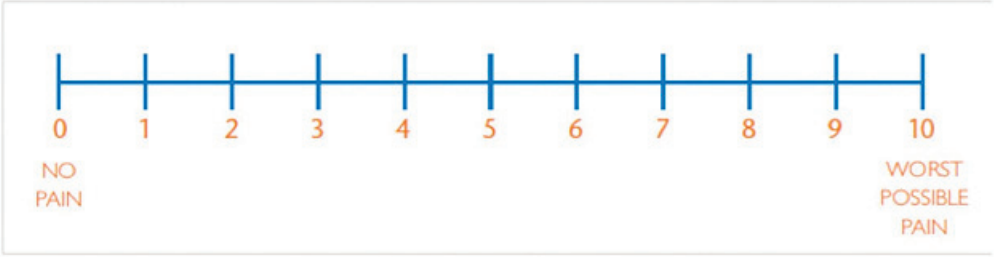
Self Assessment Pain Score:

The two examples are FACES Pain Scale (Wong & Baker) and Verbal Pain Assessment Scale (Likert Scale).

FACES Pain Scale - The child is more than 3 years old and he or she is asked to choose a face on the scale which best describes his / her level of pain. Score is 2, 4, 6, 8, or 10.



Verbal Pain Assessment Scale
A child who is more than 8 years old is asked to rate his or her pain by circling on any number on the scale of 0 to 10.



Chapter 118:
Sedation and Analgesia for Diagnostic and Therapeutic Procedures

Definitions

- *Sedation* – reduces state of awareness but does not relieve pain.
- *Analgesia* – reduces the perception of pain.

Levels of sedation

Procedural sedation means minimal or moderate sedation / analgesia.

- *Minimal* sedation (anxiolysis): drug-induced state during which the patient responds normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected.
- *Moderate* sedation / analgesia: drug-induced depression during which the patient responds to verbal commands either alone or accompanied by
- light tactile stimulation. The airway is patent and spontaneous ventilation is adequate. Cardiovascular function is adequate.

Note:

- Avoid deep sedation and general anesthesia in which the protective airway reflexes are lost and the patient needs ventilatory support.
- However, some children require general anesthesia even for brief procedures whether painful or painless because of their level of distress.

Levels of sedation

- Patients undergoing diagnostic or therapeutic procedures.

Contraindications

- Blocked airway including large tonsils or adenoids
- Increase intracranial pressure
- Reduce level of consciousness prior to sedation
- Respiratory or cardiovascular failure
- Neuromuscular disease
- Child too distressed (may need higher level of sedation or even anaesthesia)

Patient selection

The patients should be in Class I and II of the ASA classification of sedation risk.

- Class I – a healthy patient
- Class II – a patient with mild systemic disease, no functional limitation

Preparation

- Consent
- Light restraint to prevent self injury

Personnel

- At least a senior medical officer, preferably PLS or APLS trained.
- A nurse familiar with monitoring and resuscitation.

Facilities

- Oxygen source
- Suction
- Resuscitation equipment
- Pulse oximeter
- ECG monitor
- Non-invasive BP monitoring
- Defibrillator

Fasting

- Recommended for all major procedures:
  Nil orally: no solid food for 6 hours
  no milk feeds for 4 hours
- May allow clear fluids up to 2 hours before, for infants
  (Note that it is difficult to sedate a hungry child)

Venous access

- Vein cannulated after applying local anaesthesia for 60 minutes, preferably done the day before.

Sedation for Painless Procedures

- *Non-pharmacologic measures* to reduce anxiety, e.g. let the mother feed, hold and talk to the child"
  - Behavioural management, child friendly environment
- Medication
  - Oral Chloral hydrate (drug 1 in table) should be used.

Note:

- Opioids should not be used.
- Sedatives such as benzodiazepine and dissociative anaesthesia ketamine should be used with caution and only by experienced senior medical officers.
- A few children may need general anaesthesia and ventilation even for painless procedure such as MRI brain if the above fails.

Sedation for Painful Procedures

- *Non-pharmacologic measures* to reduce anxiety
  - Behavioural management, child friendly environment.
- Local anaesthesia
  - Topical: Lignocaine EMLA ® 5% applied with occlusive plaster for 60 minutes to needle puncture sites, e.g. venous access, lumbar puncture, bone marrow aspiration.
  - Subcutaneous Lignocaine infiltrated to the anaesthetised area prior to prolonged needling procedure, e.g. insertion of chest drainage.
  - Medications
- Many sedative and analgesic drugs are available; however, it is advisable to use the following frequently used medications:

1. *Narcotics (analgesia)* also have sedative effects
   - Fentanyl
   - Naloxone (narcotic reversal)
     - For respiratory depression* caused by narcotics.
   - Morphine - general dissociative anaesthesia
2. Benzodiazepines (sedatives) have no analgesia effects
   - Diazepam
   - Flumazenil (benzodiazepine reversal)
     - Can reverse respiratory depression* and paradoxical excitatory reactions
   - Midazolam.
3. Ketamine (to be used by senior doctors preferably in the presence of an anaesthesia doctor).
   Adverse effects include
   - Increased systemic, intracranial and intraocular pressures.
   - Hallucinogenic emergence reactions (usually in older children).
   - Laryngospasm.
   - Excessive airway secretions.

**provide bag-mask positive pressure ventilation whilst waiting for reversal agent to take effect.*

Post sedation monitoring and discharge

Patient can be discharged when:

- Vital signs and SaO_2 normal.
  And
- Arousable.
- Baseline level of verbal ability and able to follow age-appropriate commands.
- Sit unassisted (if appropriate for age).

Drug dosages used for sedation and analgesia in children			
Drug	**Dose**	**Onset of action**	**Duration of action**
Chloral Hydrate	Oral 25 - 50 mg/kg; Maximum 2g. For higher doses, i.e. 50 -100 mg/kg, please consult paediatrician or anaesthesiologist	15 – 30 mins	2 -3 hours
Narcotics			
Morphine	IV >1 year: 200-500 mcg/kg <1 year: 80 mcg/kg	5 – 10 mins	2 – 4 hours
Fentanyl	IV 1 – 2 mcg/kg	2 – 3 mins	20 -60 mins
Benzodiazepines			
Midazolam	IV 0.05 – 0.1 mg/kg, maximum single dose 5 mg; may repeat up to maximum total dose 0.4 mg/kg (10 mg)	1 -2 mins	30 – 60 mins
Diazepam	IV 0.1 - 0.2 mg/kg	2 - 3 mins	30 – 90 mins
Ketamine	IV 0.5 - 2.0 mg/kg	1 – 2 mins	15 – 60 mins
Reversal agents			
Naloxone	Repeated small doses IV 1 - 10 mcg/kg every 1-2 mins		
Flumazenil	IV 0.01 – 0.02 mg/kg every 1 -2 minutes up to a maximum dose of 1 mg		

Section 22

PRACTICAL PROCEDURES

Chapter 119:
Practical Procedures

Selective sedation and pain relief is important before the procedures.
(please refer to chapter on **Sedation and Analgesia for Diagnostic and Therapeutic Procedures**)

Introduction

APLS courses have been conducted in Malaysia since October 2010.
Kindly refer to the latest APLS textbook 7th Ed 2023 for further details:

- Chapter 19: Practical procedures: airway and breathing
- Chapter 20: Practical procedures: circulation

1. AIRWAY ACCESS - ENDOTRACHEAL INTUBATION

Please request for assistance from a senior doctor in Paediatrics or Anaesthesiology Department whenever necessary. Other methods of opening airways are not described here, e.g. Guedel airway, nasopharyngeal airway, laryngeal mask airway and surgical airway.

- Securing and maintaining a patent airway is very important in a patient with respiratory or cardiopulmonary failure or cardiac arrest.

Indications

- To maintain and protect airway, in children with impaired CNS function or airway obstruction.
- In respiratory failure, when bag-mask ventilation or continuous positive airway pressure (CPAP) is insufficient to maintain oxygenation and/or ventilation.
- Need for prolonged positive pressure ventilation.
- To facilitate elective or emergency surgical procedures.
- Congenital diaphragmatic hernia (newborn).

Contra-indications

- If the operator is inexperienced in intubation, perform bag-mask ventilation (contraindicated in diaphragmatic hernia) till help arrives.

Equipment

- Monitoring: ECG monitor, blood pressure (rapid cycling), pulse oximetry, capnography (if available).
- Self-inflating bag and mask with high flow oxygen.
- Laryngoscope. (May consider video laryngoscope if available)
- Blades:
  - Straight blade for infants, curved blades for an older child.
  - Size 0 for neonates, 1 for infants, 2 for children.
- Endotracheal tube – prepare appropriate size as shown below.
- Stylet (optional, not always necessary).
- Suction catheter and device.

Estimated Size of ETT (mm) and Length
2.5 for < 1kg 3.0 for 1-2kg 3.5 for 2-3kg 3.5 - 4.0 for > 3kg For Children > 1 year: Uncuffed ETT size (mm) = 4+(age (years) /4) Cuffed ETT size (mm) = 3.5+(age (years) /4)
Oral ETT length (cm) = 12 + (age (years) /2) Oral ETT length for neonates (cm) = 6 + Weight (in kg) OR Nasal-Tragus length (NTL) + 1cm

- Scissors and adhesive tape.
- Sedation (Midazolam + Morphine, consider Ketamine if experienced).
- Consider preparing inotropes / vasopressors and IV fluid bolus for unstable patients, if needed.
- Consider muscle relaxant (Rocuronium or Succinylcholine).

Procedure

1. Position infant with head in midline and slightly extended (sniffing position in a child).
2. Continue bag and mask ventilation up to 3 minutes if necessary (omit this pre-oxygenation step in cardiac arrest) with 100% oxygen till well saturated. In newborns adjust FiO_2 accordingly until oxygen saturation is satisfactory between 94 to 98%.
3. Medication used for induction of anaesthesia prior to intubation:
   - Consider induction with IV Ketamine 1 to 2 mg/kg (can be used safely in head injury, caution in patients with hypertension or glaucoma).
   - Consider muscle relaxant if no contraindication, e.g. IV Succinylcholine (1-2 mg/kg) or Rocuronium (1-2 mg/kg). *Caution: Intubator must be able to bag the patient well (with adequate chest rise) and have good intubation skills before giving muscle relaxant.*
   - ***Relative contra-indications for Succinylcholine*** are burns, spinal cord injury, neuromuscular disorders, malignant hyperthermia, hyperkalaemia and renal failure.
   - Sedation with IV Midazolam (0.1-0.2 mg/kg) and IV Morphine (0.1-0.2 mg/kg) may also be used.
4. Monitor the child's vital signs continuously throughout the procedure.
5. Insert a nasogastric tube either before induction or as soon as possible afterwards, aspirate gastric contents and leave a 50ml syringe attached.
6. Once child is fully sedated / muscle relaxed, introduce the laryngoscope blade between the tongue and the palate with left hand and advance to the back of the tongue while maintaining head position with the right hand.
7. When epiglottis is seen, lift blade upward and outward to visualize the vocal cords. Suction secretions if necessary.
8. Using the right hand, insert the ETT from the right side of the infant's mouth; a stylet may be required.
9. Keep the glottis in view and insert the ETT between the vocal cords until the desired length.
10. If intubation is not done within 30 seconds, the attempt should be aborted and oxygenation re-established before a further attempt.
11. Once intubated, remove laryngoscope and hold the ETT firmly in place. Connect to the self-inflating bag and continue bag-mask ventilation.
12. Confirm the ETT position by looking for equal chest expansion, listen to air entry over both axillae and over the stomach. $ETCO_2$ capnography should be used if available, to definitively confirm tube placement.
13. Secure the ETT with adhesive tape and connect to the ventilator.
14. If a cuffed ETT is use, inflate the cuff to achieve adequate seal, and check cuff pressure, ensure <25 cmH_20.
15. Order and review a chest x-ray to confirm optimal ETT tip position below the vocal cords but above the carina (at the level of T1-T3).

Complications

- Oesophageal intubation (ETT may be in-situ initially, then dislodged).
- Right lung intubation.
- Trauma to the upper airway.
- Hypoxia.
- Aspiration of gastric contents.
- Subglottic stenosis (late).

2. BREATHING – Positive Pressure Ventilation

- After opening the airway, start ventilation using a self-inflating bag with an appropriate-sized face mask, or through the ETT of an intubated child.
- Provide supplemental oxygen, and titrate to keep SpO_2 between 94-98%.
- Aim for gentle chest rise. Avoid excessive tidal volumes and rapid ventilation, which may cause gastric distension, inhibit ventilation and increase risk of aspiration.
- In a critically ill child with respiratory failure, adjust the ventilation rate according to age (between 15-30 per minute).
- In cardiac arrest, bag-mask ventilation is provided with a ratio of 2 ventilations to 15 chest compressions while performing CPR.
- Following intubation, aim for a ventilation rate at the lower limit of normal for age, with uninterrupted chest compressions.

Age	Ventilation rate in cardiac arrest
Infant	25 breaths per minute
1-8 years	20 breaths per minute
9-12 years	15 breaths per minute
>12 years	10-12 breaths per minute

3. CHEST COMPRESSION

1. Start IMMEDIATE chest compressions if:
   - There are no signs of life.
   - There is no pulse.
   - There is a slow pulse (less than 60 beats per minute) with poor perfusion.
2. Chest compressions should be delivered over the lower half of the sternum, at a rate of 100-120 compressions per minute.
3. A ratio of 15 compressions to 2 ventilations is maintained, whatever the number of rescuers. Once the child has been intubated, compressions should be continuous, with ventilations via ETT at the appropriate rate.
4. Rescuers performing compressions should change every 2 minutes, to avoid fatigue and maintain optimal performance.
5. The chest should be compressed to one third of the anterior-posterior diameter, about 4 cm for an infant and 5 cm for a child.
6. Allow for complete chest recoil in between compressions.
7. The child in cardiac arrest receiving uninterrupted CPR should be connected to a cardiac monitor as soon as possible to ascertain whether it is a non-shockable (asystole or pulseless electrical activity) or shockable (ventricular fibrillation or pulseless ventricular tachycardia) rhythm.
8. Adrenaline should be given immediately for non-shockable rhythms.
9. Immediate defibrillation should be performed for shockable rhythms.
10. If no help has arrived after 1 minute of CPR, emergency services should be contacted. Apart from this, CPR should be uninterrupted unless the child shows signs of life.

4. BLOOD SAMPLING & VASCULAR ACCESS

4.1. VENEPUNCTURE & PERIPHERAL VENOUS LINE

Indications

- Blood sampling.
- Intravenous fluid, medications and blood components.

Equipment

- Glove
- Alcohol swab.
- Tourniquet.
- Topical anaesthetic (TA), e.g. Lignocaine EMLA® 5%, or ethyl chloride spray for rapid cannulation.
- Catheter 24 G, 22 G or needle sizes 25, 23, 21 G.
- Heparinised saline, T-connector, rubber bung for setting an IV line.

Technique

1. Identify the vein for venepuncture. Secure the identified limb and apply tourniquet or equivalent. Note that the peripheral veins will be collapsed in a child with peripheral vasoconstriction, e.g. in circulatory shock or high fever.
2. Local warming, transillumination techniques (under 2 years) or ultrasound guidance, if available, may facilitate venous access.
3. Non-pharmacologic techniques such as parental presence, oral sucrose or distraction may reduce pain and anxiety in awake children.
4. TA may be applied with occlusive plaster an hour earlier or spray with ethyl chloride for a short procedure.
5. Clean the skin with alcohol swab.
6. Puncture the skin and advance the needle or catheter in the same direction as the vein at a 15-30 degree angle.
7. In venepuncture, blood is collected once blood flows out from the needle. The needle is then removed and pressure applied once sufficient blood is obtained.
8. In setting an intravenous line, the catheter is advanced a few millimetres further. Once blood appears at the hub, then withdraw the needle slightly while advancing the catheter over the needle.
9. Remove the tourniquet and flush the catheter with heparinised saline.
10. Secure the catheter and connect it to either rubber bung or IV drip.
11. Immobilise the joint above and below the site of catheter insertion with restraining board and tape.

Complications

- Haematoma or bleeding.
- Thrombophlebitis after a few days.
- Extravasation can lead to soft tissue injury resulting in limb or digital loss and loss of function.

This complication is of concern in neonates, where digital ischaemia, partial limb loss, nerve damage, contractures of skin and across joints can occur.

Extravasation injury (prevention is the priority) Signs include:

- Pain, tenderness at insertion site especially during infusion or giving slow bolus drugs.
- Redness.
- Swelling.
- Reduced movement of affected site.
- *(Note – the inflammatory response can be reduced in neonates especially preterm babies)*

Inspection of injection sites

- The insertion site should be observed for signs of extravasation:
- At least every 4 hours for ill patients.
- Sick preterm in NICU: should be done more often, even every hour for continuous infusion.
- Each time before, during and after slow bolus or infusion.
- Consider re-siting the intravenous catheter every 48 to 72 hours.

If moderate or serious extravasation occurs, especially in the following situation:

- Preterm babies.
- Delay in detection of extravasation.
- Hyperosmolar solutions or irritant drugs (e.g. glucose concentration > 10%, sodium bicarbonate, calcium solution, ALL inotropes, blood products, cloxacillin, fusidic acid, acyclovir, TPN).

Consider:

- Immediately stop infusion, inform senior colleague and counsel parents.
- Refer to plastic surgeon / orthopaedic surgeon urgently.
- Elevate the affected limb and provide analgesia as needed.
- Performing 'subcutaneous saline irrigation' as soon as possible for severe extravasation injuries, especially in neonates *(ref Davies et al. Preventing the scars of neonatal intensive care. Arch Dis Child Fetal Neonatal Ed 1994;70: F50-F51)*.
  Give IV morphine for analgesia, then perform numerous subcutaneous punctures around the extravasated tissue and flush slowly with generous amount of normal saline to remove the irritant. Ensure that the flushed fluid flows out through the multiple puncture sites.

Pitfalls in peripheral venous cannulation

- If the patient is in shock, the venous backflow (or arterial backflow in the event of accidental arterial cannulation) may be sluggish.
- BEWARE! An artery can be accidentally cannulated, e.g. brachial artery at the cubital fossa and the temporal artery at the side of the head of a neonate, and be mistaken for venous access. Check for resistance to flow during slow bolus or infusion (e.g., frequent alarming of the perfusor pump), skin blanching, pulsation in the backflow or a rapid backflow. Rapid bolus or infusion of drugs into an artery can cause ischaemia of the limb. Where in doubt, gently remove the IV cannula.
- Ensure prescribed drug is given by the proper mode of administration. Some drugs can only be given by slow infusion (e.g. fusidic acid) instead of slow bolus in order to reduce tissue damage from extravasation.
- Avoid medication error (correct patient, correct drug, correct dose, correct route).
- Avoid nosocomial infection.

4.2 ARTERIAL BLOOD SAMPLING & PERIPHERAL ARTERIAL LINE CANNULATION

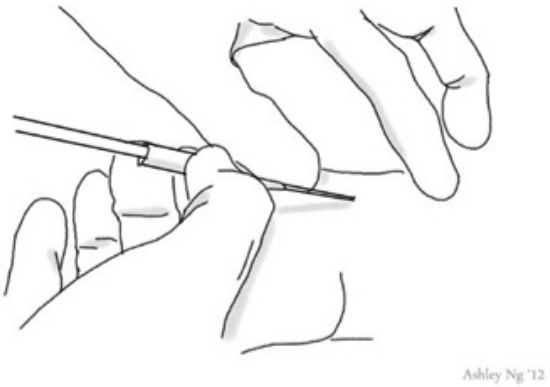
Note: this is a very painful procedure and should be done with proper analgesia in a closely monitored setting.

Indications

- Arterial blood gases.
- Invasive blood pressure monitoring.
- Frequent blood sampling.

Contraindications

- Avoid sites with skin infection or absent collateral circulation (risk of limb ischaemia).
- Do not set arterial line if child cannot be monitored closely.



Equipment

- Topical anaesthetic (TA) like lignocaine EMLA® 5%.
- Alcohol swab.
- Needle size 27 G, 25 G; Catheter size 24, 22 G
- Heparinised saline in 5cc syringe (1 ml for neonate), T-connector.
- Heparinised saline (1u/ml) for infusion.

Procedure

1. The radial pulse is identified. Other sites that can be used are posterior tibial (posterior to medial malleolus while the ankle is in dorsiflexion) and dorsalis pedis artery (dorsal midfoot between the first and second toes while the ankle is in plantar flexion).
2. Ultrasound guidance can improve success rate and reduce complications.
3. TA may be applied with occlusive plaster an hour before procedure.
4. Clean the skin with alcohol swab.
5. Dorsiflex the wrist slightly. Puncture the skin and advance the catheter in the same direction as the radial artery at a 30-40^0 angle.
6. The catheter is advanced 2-3 millimetres further when blood enters the hub, then withdraw the needle while advancing the catheter.
7. Ensure good flow, then flush gently with heparinised saline.
8. Once the peripheral artery is successfully cannulated:
   - Ensure that the arterial line is functioning. The arterial pulsation is usually obvious in the tubing.
   - Connect to T-connector, 3-way stop-cock (red colour), and syringe pump. May consider Luer-lock arterial line tubing in older children, to reduce risk of accidental disconnection and bleeding.
   - Label the arterial line and the time of insertion.
9. Run the heparinised saline at an appropriate rate:
   - 0.5 to 1.0 mL per hour for neonates.
   - 1.0 mL (preferred) or up till 3.0 mL per hour for invasive BP line (stop if skin mottling or blanching).
10. Immobilize the joint above and below the site of catheter insertion with restraining board and tape, ensuring the tape is not too tight.

Complications and Pitfalls

- Arteriospasm, which may lead to ischaemia and gangrene, especially in neonates.
- Haematoma or thrombosis
- Infection (rare)

Precautions

Prevention of digital, distal limb ischaemia and gangrene

- AVOID end arteries e.g. brachial (in cubital fossa) and temporal artery (side of head) in babies (BEWARE - both these arteries can be accidentally cannulated and mistaken as 'veins' especially in ill patients with shock).

Circulation chart

Perform observations and circulation charting of distal limb every hour in the NICU/PICU, and whenever necessary to detect for signs of ischaemia, namely:

- Colour - pale, blue, mottled.
- Cold, clammy skin.
- Capillary refill > 2 seconds.

Treatment of digital or limb ischaemia (prevention is the priority) This is difficult as the artery involved is of small calibre**.**

- Remove IV cannula.
- Confirm thrombosis with ultrasound doppler.
- May consider warming the contralateral unaffected lower limb to induce reflex vasodilatation of the affected leg.
- Ensure good peripheral circulation and blood pressure
- Anticoagulant drugs and thrombolytic agents should be considered
- Refer orthopaedic surgeon if there are concerns of persistent ischaemia or gangrene.

Reminders:

- PREVENTION of limb ischaemia is of utmost importance.
- Early detection of ischaemia is very important in order to avoid irreversible ischaemia.
- If the patient is in shock, the risk of limb ischaemia is greater.
- Small and preterm babies are at greater risk for ischaemia.
- No fluid or medication other than heparinized saline can be given through arterial line. This mistake can occur if the line is not properly labelled, or even wrongly labelled and presumed to be a venous line.

4.3. INTRAOSSEOUS ACCESS

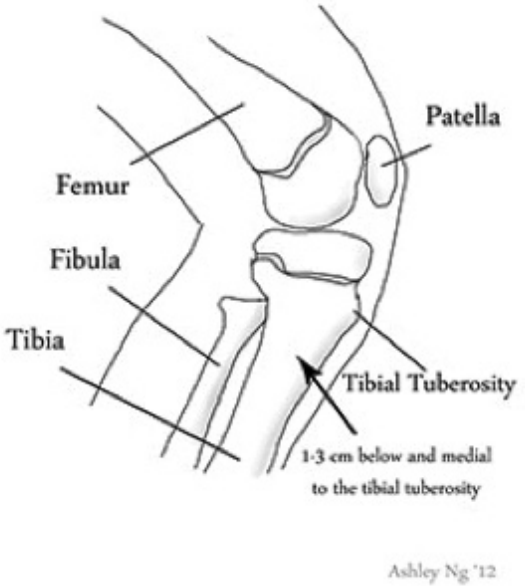
Intraosseous (IO) infusion can be used for all paediatric age groups.

Sites:

- Most common site is the proximal tibia (all age groups)
- Infant – distal femur
- Child – anterior superior iliac spine, distal tibia, distal femur
- Adolescent/adult - distal tibia, medial malleolus, anterior superior iliac spine, distal radius, distal ulna, proximal humerus.

All fluids, blood products and IV medications can be given via the IO route.

IO needles should be removed as soon as definitive vascular access is obtained, usually within 24 hours after insertion, to reduce infection risk.



Indications

- Emergency access for IV fluids and medications when other methods of vascular access have failed.
- In time-critical circumstances, e.g. decompensated shock with severe vasoconstriction or cardiac arrest, IO access may be the INITIAL means of vascular access.

Contraindications

- Fractures, crush injuries near the access site or a proximal ipsilateral bone. IO itself can cause fractures especially in young infants.
- Conditions in which the bone is fragile e.g. osteogenesis imperfecta.
- Previous attempts to establish access in the same bone.
- Infection over the overlying tissues.
- Prosthesis or orthopaedic procedure near the insertion site.

Equipment

- Sterile dressing set.
- EZ-IO drill set if available (Insert according to manufacturer guidance).
- Intraosseous needle (appropriate size)
- Syringes for aspiration.
- Local anaesthesia.

Procedure (handheld needle technique)

1. Immobilize the lower limb.
2. Support the limb with linen.
3. Clean and drape the area, and administer local anaesthetic at the insertion site (in conscious patients).
4. Insert the IO needle aseptically, at 90° to the skin, 1-3 cm below and medial to the tibial tuberosity (over the flat part of the tibia).
5. Push through the skin until bone is felt.
6. Avoid the growth plate, and advance the needle at a 90° angle with a rotational motion, until a 'give' is felt.
7. Remove the trocar while stabilizing the needle cannula.
8. Aspirate bone marrow with a 5cc syringe to confirm access. Failure to aspirate does not mean the insertion has failed, and placement can also be confirmed by flushing fluids without difficulty or signs of extravasation.
9. Infuse a small amount of saline and observe for swelling at the insertion site or posterior to the insertion site. Fluid should flow in easily and no swelling must be seen. (Swelling indicates that the needle has penetrated through the posterior cortical bone, and must be removed).
10. Connect the cannula to tubing and IV fluids. Secure with a dressing.
11. Monitor closely for any extravasation of fluids.

Complications

- Cellulitis.
- Osteomyelitis.
- Extravasation of fluids/compartment syndrome.
- Damage to growth plate.
- Fracture of bone especially in young infant.

4.4 NEONATES

4.4.1 CAPILLARY BLOOD SAMPLING



Ashley Ng '12

Indications

- Capillary blood gases
- Capillary blood glucose
- Serum bilirubin

Equipment

- Lancet or heel prick device
- Alcohol swab

Procedure

1. Either prick the medial or lateral aspect of the heel
2. For the poorly perfused heel, warm with gauze soaked in warm water.
3. Clean the skin with alcohol swab
4. Stab the sterile lancet to a depth of 2.5mm, then withdraw it. Intermittently squeeze the heel gently when the heel is re-perfused until sufficient blood is obtained.

Complications

- Cellulitis.
- Osteomyelitis.

4.4.2. UMBILICAL ARTERY CATHETERISATION (UAC)

An invasive procedure and should be done under supervision in a NICU setting.

Indications

- For repeated blood sampling in ill newborn especially those on ventilator.
- Occasionally it is used for continuous BP monitoring and infusion.

Contraindications

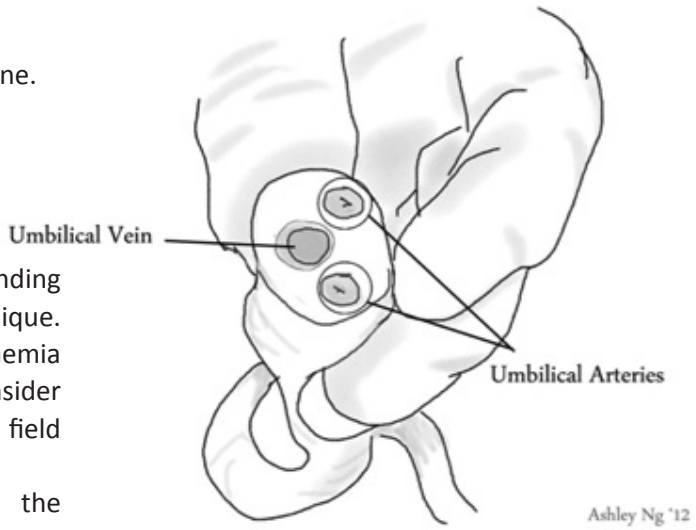
- Local vascular compromise in lower extremities
- Peritonitis
- Necrotising enterocolitis
- Omphalitis

Prior to procedure

- Examine the infant's lower extremities and buttocks for any signs of vascular insufficiency.
- Palpate femoral pulses for their presence and equality.
- Evaluate the infant's legs, feet, and toes for any asymmetry in colour, visible bruising, or vascular insufficiency.
- Document the findings for later comparison. Do not set if there is any sign of vascular insufficiency.

Equipment

- UAC/UVC set.
- Umbilical artery catheter, appropriate size.
  - Size 3.5 F for infants < 1.5kg
  - Size 5 F for infants > 1.5kg
- 5 cc syringes filled with heparinized saline.
- Three-way tap.
- Heparinized saline (1u/ml) for infusion.



Procedure

1. Clean the umbilicus and the surrounding area using standard aseptic technique. In order to observe for limb ischaemia during umbilical arterial insertion, consider exposing the feet in term babies if the field of sterility is adequate.
2. Catheterise the umbilical artery to the desired position.
   The formula for UAC is:
   - (Birth weight in kg x 3) + 9 + 'stump length' in cm (read length from the upper end of the stump) *(high position: tip above diaphragm between T6-9)*
   - Birth weight in kg + 7 cm *(low position is no longer recommended)*

3. Hold the stump gently (not taut) and cut the umbilicus horizontally leaving behind a 1 cm stump. If you pull the stump taut before cutting, you will end up with the arteries protruding 2 mm beyond the umbilicus jelly and this make successful cannulation more difficult.
   There are 2 arteries and 1 vein. The artery is smaller in diameter, white and constricted. Hold the stump upright with your fingers or artery forceps. Gentle and patiently dilate the lumen of the artery with a probe.
   Insert the catheter to the desired distance.
4. Ensure the successful and correct cannulation of one umbilical artery.
   - Tips for successful catheterisation of the umbilical artery:
     - In a fresh and untwisted umbilical stump, the two arteries can be clearly distinguished from the vein.
     - Stand to the left side of the baby if you are right-handed and direct the catheter posteriorly and inferiorly in the direction of the lower limbs.
     - The blood withdrawn is bright red.
     - Visible arterial pulsations can be seen in the column of blood withdrawn into the catheter. However, this pulsation may not be seen in very preterm babies and babies in shock, using the closed system.
   - In *accidental cannulation* of the umbilical vein, the catheter tip can be in the left atrium (via the foramen ovale from the right atrium into left atrium) or in the left ventricle giving a backflow of oxygenated blood.
   - Stick the label of the catheter onto patient's folder for future reference (brand and material of catheter) in the event of limb ischaemia or thrombosis of femoral artery occurring later.
5. Observe for signs of arterial ischaemia to the lower limbs and buttocks (colour, cold skin, capillary refill delayed, poor dorsalis pedis and posterior tibial pulses) during and after the procedure due to arterial vasospasm. An assistant lifts slightly the edge of the drape without compromising the sterility field to inspect the lower limbs circulation.
6. If there are no complications (limb ischaemia – see pitfalls), secure the UAC to avoid accidental dislodgement.
7. Perform a chest and abdominal X-ray to ascertain the placement of UAC tip
   - Between T 6-9 vertebra *(high position)* - preferred
   - At the L 3-4 vertebra *(low position)*

   Withdraw (do not push in, to maintain sterility) the catheter to the correct position, if necessary.
8. Monitor the lower limbs and buttock area for ischaemic changes 2-4 hourly
9. Infuse heparinised saline continuously through the UAC at 0.5 to 1 U/hr to reduce the risk of catheter occlusion and thrombotic events.
10. Note the catheter length markings every day and compare with the initial length (to check for catheter migration).
11. Remove the UAC as soon as no longer required to reduce the incidence of thrombus formation and long line sepsis.

Complications

- Bleeding from accidental disconnection and open connection.
- Embolisation of blood clot or air in the infusion system.
- Vasospasm or thrombosis of aorta, iliac, femoral or obturator artery leading to limb or buttock ischaemia.
- Thrombosis of renal artery (hypertension, haematuria, renal failure), mesenteric artery (gut ischaemia, necrotising enterocolitis).
- Vascular perforation of umbilical arteries, haematoma and retrograde arterial bleeding.
- Nosocomial infection.

4.4.3. UMBILICAL VEIN CATHETERISATION (UVC)

Indications

- UVC is used for venous access in neonatal resuscitation.
- As a venous access in preterm babies especially ELBW babies (<1000g) and also in sick babies in shock with peripheral vasoconstriction.
- For doing exchange transfusion for severe neonatal jaundice.

Contraindications

- Omphalitis, omphalocoele
- Necrotising enterocolitis
- Peritonitis

Equipment

- UVC set.
- Umbilical venous catheter, appropriate size
  - Size 3.5 F for infants < 1.5kg
  - Size 5 F for infants > 1.5kg
- 5 cc syringes filled with heparinized saline.
- Three-way tap.
- Heparinized saline (1u/ml) for infusion.

Procedure

1. Clean umbilicus and its surroundings using standard procedures.
   In order to observe for limb ischaemia during insertion (in the event of accidental arterial catheterisation), consider exposing the feet in term babies whilst maintaining field of sterility.
2. Formula for insertion length of UVC:
   [0.5 x UAC cm (high position)] + 1 cm.
   Or
   (Birth weight in kg x 1.5) + 5.5 + stump length in cm
3. Perform the umbilical venous cannulation
   - Tips for successful UV catheterisation:
     - In a fresh (first few hours of life) and untwisted umbilical stump, the umbilical vein has a thin wall, is patulous and is usually sited at the
     - 12 o'clock position. The two umbilical arteries which have a thicker wall and in spasm, and sited at the 4 and 8 o'clock positions. However, in a partially dried umbilical cord, the distinction between the vein and arteries may not be obvious.
     - The venous flow back is sluggish and without pulsation (in contrast to the arterial pulsation of UAC).
     - The blood is dark red in colour.
     - Stand to the right of the baby (if you are right handed).
     - Tilt the umbilical stump inferiorly at an angle of 45 degrees from the abdomen. Advance the catheter superiorly and posteriorly towards the direction of the right atrium.
   - Measurement of Central venous pressure
     - The UVC tip is sited in the upper IVC (inferior vena cava).
       The right atrial pressure in a term relaxed baby normally ranges from -2 to + 6 mmHg (i.e. -3 cm to + 9 cm water).
     - Negative intrathoracic pressure and air embolism
     - In a crying baby, the negative intrathoracic pressure can be significant during deep inspiration.

- Ensure that no air embolism occurs during the procedure especially in the presence of negative pressure when the catheter tip is in the right atrium.
- Air embolism can occur if the baby takes a deep inspiration when the closed UVC circuit is broken.
- Stick the label of the catheter onto the patient's folder for future reference (brand and material of catheter) in the event of thrombosis occurring in the cannulated vessel.

4. If there are no complications, secure the UVC to avoid accidental migration of the catheter.
5. If the UVC is for longer term usage such as for intravenous access / TPN, perform chest and abdominal radiograph to ascertain the tip of the catheter is in the inferior vena cava above the diaphragm.
6. Consider removing the UVC after 5-7 days to reduce incidence of line sepsis or thrombus forming around the catheter.

Complications

- Infections.
- Thrombo-embolic – lungs, liver, even systemic circulation
- Pericardial tamponade, arrhythmias, hydrothorax
- Portal vein thrombosis and portal hypertension (manifested later in life)

Pifalls

- The umbilical artery can be mistakenly cannulated during umbilical venous catheterisation.

4.5 CENTRAL VENOUS ACCESS: FEMORAL VEIN CANNULATION IN CHILDREN

- The routes of central venous access include peripherally inserted central catheter - PICC (e.g. through cubital fossa vein into SVC) and femoral, external / internal jugular and subclavian veins.
- These lines must be inserted by trained senior doctors in selected seriously ill children requiring resuscitation and emergency treatment.
- The benefits of central venous access must be weighed against the numerous potential complications arising from the procedure.
- This includes pneumothorax and life-threatening injuries of the airway, lungs, great vessels and heart.
- The Seldinger technique of central line insertion applies to all sites and the femoral vein cannulation technique is described.
- Ultrasound-guided insertion may be used, when available, to increase the success rate and decrease complications. (refer APLS 7th Ed).

Indications

- Seriously ill ventilated paediatrics patient especially with difficult peripheral vein access.
- To monitor central venous pressure.
- Longer term intravenous access (compared to IO access).
- Haemodialysis.

Contraindications

- Absence of trained doctors for this procedure.
- Bleeding and clotting disorders.
- Risk of contamination of the cannulation site by urine and faeces for femoral vein cannulation.

Equipment

- Sterile set.
- Lidocaine (Lignocaine) 1% for local anaesthetic, 2 mL syringe, 23 G needle.
- 5 mL syringe and normal saline, paediatric infusion set and 3-way tap.
- Seldinger cannulation set – syringe, needle, guide wire, catheter.
- Sterile dressing.

Procedure

1. In a ventilated child, give a dose of analgesia (e.g. Morphine / Fentanyl) and sedation (e.g. Midazolam).
2. In the supine position, expose the chosen leg and groin in a slightly abducted position. Elevate the hips slightly.
3. Identify the landmark by palpating the femoral artery pulse in the mid-inguinal region. The femoral vein is medial to the femoral artery, 5-6 mm in infants, 10-15 mm in adolescents. Ultrasound guidance is recommended for this procedure, when available.
4. Clean and drape the inguinal region.
5. Infiltrate local anaesthetic at the insertion site.
6. Insert the saline filled syringe and needle at a 45° angle to the skin and parallel to the femoral artery pulsation. The needle enters the skin 2-3 cm below the inguinal ligament, and the vein 1-2 cm below the inguinal ligament. Aspirate gently and advance needle in-line with the leg.
7. When there is a backflow of blood into the syringe, stop advancing, and disconnect the syringe from the needle. The guide wire is then promptly and gently inserted through the needle, and into the vein.
8. Withdraw the needle gently and carefully without risking damage to the guide wire including kinking (will lead to difficulty or inability to remove guide wire after catheter insertion) and fracturing the guide wire.
9. Insert the dilator over the wire into the vein, then remove dilator and insert the catheter over the wire. Take care to avoid displacement of the wire either into the patient or out of the vein.
10. Make sure the end of the wire is sticking out of the catheter, before inserting the catheter into the vein.
11. Once the cannula has been inserted, remove the guide wire and draw blood from all the lumina, flush immediately and lock the catheter.
12. Suture the catheter in place. Attach the infusion tubing, and tape the tubing securely in place.

Pitfalls

- Do not lose or kink the guide wire (inserted too deep into patient).
- Do not fracture the guide wire with the needle.
- Take care not to accidentally cannulate the femoral artery (blood pressure could be low in a patient with shock and mistaken for the femoral vein).
- Beware of local haematoma at insertion site.
- Always check the distal perfusion of the leg and toes before and after procedure.

5. BODY FLUID SAMPLING

5.1. LUMBAR PUNCTURE

Indications

- Suspected meningitis / encephalitis.
- Intrathecal chemotherapy for oncology patients.
- In selected patients being investigated for neurometabolic disorders.

Contraindications

- Increased intracranial pressure (signs and symptoms, raised blood pressure, fundoscopic signs). Perform CT scan or MRI brain before lumbar puncture.
- Haemodynamic instability
- Bleeding disorder - platelet count <50,000/mm^3, prolonged PT or APTT.
- Skin infection over the site of lumbar puncture
- Patient with hypertensive encephalopathy

Equipment

- Sterile set.
- Sterile bottles for CSF, bottle for RBS (random blood sugar).
- Spinal needle 20-22G, length 1.5 inch with stylet; length 3.5 inches for children > 12 years old.

Procedure

1. Give sedation (e.g. Midazolam), apply local anaesthetic (e.g. EMLA).
2. Take a random blood sugar sample (RBS) after lumbar puncture.
3. Place child in lateral recumbent position with neck, body, hips and knees flexed. Monitor oxygen saturation continuously.
4. Visualise a vertical line between the highest point of both iliac crests and its transection with the midline of the spine (at level between vertebrae L 3-4).
5. Clean area using standard aseptic techniques: povidone-iodine and 70% alcohol.
6. Gently puncture skin with spinal needle at the identified mark and point towards the umbilicus. The entry point is distal to the palpated spinous process L4.
7. Gently advance a few millimetres at a time until there is a backflow of CSF (there may be a 'give' on entering the dura mater before the CSF backflow). Collect the CSF in the designated bottles.
8. Gently withdraw needle, spray with op-site, cover with gauze and bandage.
9. Ensure that the child lies supine for the next 4 to 6 hours, continue monitoring child till he or she recovers from the sedation.

Complications

- Headache or back pain following the procedure (from arachnoiditis).
- Brain herniation associated with raised ICP. Look at brain imaging and exclude raised ICP clinically before doing lumbar puncture.
- Bleeding into CSF, or around the cord (extraspinal haematoma).

5.2. CHEST TUBE INSERTION

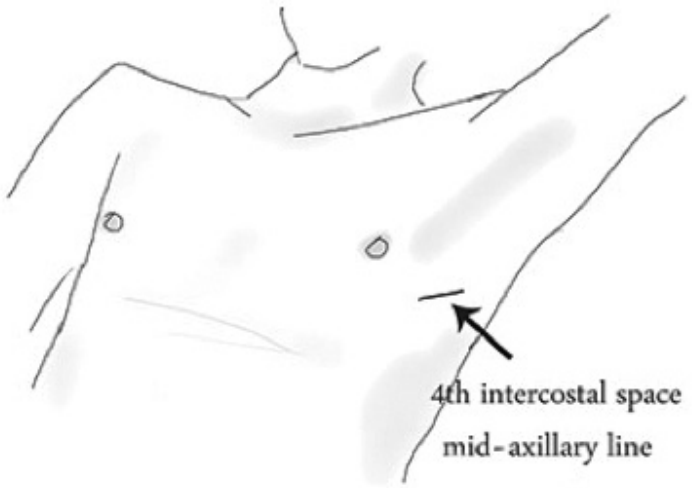
Indications

- Pneumothorax with respiratory distress. In tension pneumothorax, perform a needle thoracocentesis before chest tube insertion.
- Significant pleural effusion.
- Empyema.

NEEDLE THORACOCENTESIS

1. Indicated in tension pneumothorax as an emergency measure to decompress the chest until a chest tube is inserted.
2. Done under strict aseptic technique. Attach a 10ml syringe already filled with 2ml sterile normal saline to a 16 to 20 gauge angiocatheter. Gently insert catheter perpendicularly through the second intercostal space, over the top of the third rib, at the midclavicular line while applying a small negative pressure as the needle is advanced. Air will be aspirated on successful needle thoracocentesis. When this happens, remove the syringe and needle while leaving the catheter in situ to allow the tension pneumothorax to decompress. Then, insert a chest tube as described below as soon as feasible.

SITE FOR CHEST TUBE INSERTION



Equipment

- Suturing set.
- Local anaesthetic +/- sedation.
- Chest tube, appropriate size.
- 8 Fr for < 2 kg body weight
- Infants: 10 Fr for > 2kg body weight
- Older children: 12-18 Fr depending on size
- Underwater seal with sterile water.
- Suction pump – optional.

Procedure

1. Sedate the child.
2. Position the child with ipsilateral arm fully abducted.
3. Clean and drape the skin.
4. Infiltrate local anaesthetic into the skin at 4th or 5th intercostal space on the mid-axillary line. "Triangle of safety" – anterior to mid-axillary line, posterior to pectoral groove and above 5th Intercostal space.
5. Check approximate length of the chest tube to be inserted as it follows the curve of the chest. Tip of the chest tube should be sited at the highest point of the thorax (for pneumothorax) and lowest dependent part of the thorax (for pleural effusion).
6. ***Open Insertion Method***
   - The open method (without the metal introducer) of chest tube cannulation is the preferred method. The closed method (with the introducer) is dangerous and NOT recommended.
   - Make a small incision in the skin just above the 5th rib. Use the blunt dissecting forceps to dissect through the subcutaneous tissue and puncture the parietal pleura with the tip of the clamped forceps. Put a sterile gloved finger into the incision and clear the path into the pleura. This may be difficult in a small child. Advance the chest drain tube into the pleural space during expiration.
   - For drainage of air, roll the child slightly to the opposite side for easier manoeuvring and advancement of the chest tube anteriorly. Place the tip of the chest tube at the incision. Point the catheter tip anteriorly and superiorly, and slowly advance the chest tube.
   - For drainage of empyema, maintain the child in the supine position, direct the catheter tip posteriorly and inferiorly, and proceed with the rest of the procedure.
   - Connect the chest tube to underwater seal.
   - The water should bubble (if pneumothorax present) and the fluid column fluctuates with respiration if chest tube is in the pleural space.
   - Secure the chest tube with sutures in children or sterile tape strips in neonates.
   - Connect the underwater seal to low-pressure continuous suction (negative pressure usually -10 to -20 mmHg) if necessary for empyema.
   - Confirm the chest tube position with a chest X-ray.

Complications

- Malposition.
- Bronchopulmonary fistula
- Vascular injury
- Intrathoracic or Intraabdominal organ injury
- Re-expansion pulmonary oedema (clamp for 1 hour after draining 10ml/kg pleural fluid, to reduce risk).

5.3. PERICARDIOCENTESIS

This is a specialised procedure ideally performed in the cardiac unit or ICU. Occasionally it may be performed as a life-saving procedure by a senior paediatric doctor.

Indications

- Symptomatic collection of air.
- Blood or other fluids / empyema in pericardial sac.

Equipment

- Suturing set.
- Angiocatheter – size 20 G for newborn, 18 G for older children.
- T-connector. 10 cc syringes
- 3-way stopcock.

Procedure

1. The patient should be given analgesia and sedation and be ventilated.
2. Place patient in supine position and on continuous ECG monitoring.
3. Clean and drape the subxiphoid area. Give local anaesthesia.
4. Insert the angiocatheter at about 1cm below the xiphoid process at angle of 45° to the skin and advance slowly, aiming at the tip of the left shoulder while applying light negative pressure with the syringe. Stop advancing the catheter if there is cardiac arrhythmia.
5. Once fluid or air is aspirated, withdraw the needle about 3 mm and advance the catheter into the patient.
6. Remove the needle, rapidly connect the hub of the catheter to a previously prepared T-connector, 3-way stopcock and a 10 cc syringe.
7. Remove as much fluid or air as possible by manipulating the 3-way stopcock.
8. Secure the catheter in place.
9. Send any aspirated fluid for cell count, biochemistry and culture.
10. Perform CXR to confirm positioning and look for any complication.
11. The catheter should be removed within 72 hours. If further aspiration is required, surgical placement of a pericardial drain is an option. Consider early cardiology/ cardiothoracic consultation.
12. If point of care ultrasound is available, this can confirm presence of pericardial fluid and guide aspiration. With ultrasound guidance, parasternal and apical approaches may be feasible.

Complications

- Perforation of heart chambers leading to cardiac tamponade.
- Haemo/ pneumo – pericardium
- Cardiac arrhythmias
- Pneumothorax
- Infection/ Bleeding

5.4. ABDOMEN

5.4.1. GASTRIC LAVAGE

Indications

- Removal of ingested toxins
- Removal of meconium from stomach for newborn

Equipment

- Nasogastric tube size 8-12 Fr
- Syringes: 5cc for neonate, 20 cc for older children
- Sterile water

Procedure

1. Put the wrapped infant in a supine slight head-up position. A child should be in a comfortable sitting position held by the guardian or health care provider.
2. Estimate the length of *nasogastric* tube inserted by measuring the tube from the nostril to the tragus of the ear, and to a point halfway between the xiphoid process and the umbilicus.
3. For *orogastric* tube insertion, the estimated insertion length is measured from the angle of the mouth to the ear lobe and to a point halfway between the xiphoid process and the umbilicus.
4. Lubricate the tip of the tube with KY jelly. Insert the tube gently.
5. Confirm position by aspirating stomach contents. Re-check by plunging air into stomach whilst listening with a stethoscope, or check acidity of stomach contents with pH paper.
6. Perform gastric lavage until the aspirate is clear.
7. If indicated, leave activated charcoal or specific antidote in the stomach.

Complications

- Discomfort.
- Trauma to upper gastrointestinal tract
- Aspiration of stomach contents into lungs.

5.4.2. ABDOMINAL PARACENTESIS

Indications

- Diagnostic procedure.
- Drain ascites.

Equipment

- Dressing set.
- Cannula size 16, 18, 20, 22G (depending on size of child and purpose of paracentesis)
- 10cc Syringes.

Procedure

1. Supine position. Catheterize to empty the bladder.
   Clean and drape abdomen. Give local anaesthesia and sedation.
2. Site of puncture is at a point in the outer 1/3 of a line drawn from the umbilicus to the anterior superior illiac spine.
3. Insert the catheter (connected to a syringe) at 45° aiming superiorly into the peritoneal cavity in a slight 'Z' track fashion (by pulling the skin inferiorly before needle insertion and release skin soon after that before pushing needle into peritoneum).

4. Aspirate while advancing the catheter until fluid is seen in the syringe. Remove the needle and reconnect the catheter to the syringe and aspirate the amount required. Use a three-way tap if large amounts need to be removed.
5. Once complete, remove the catheter (if paracentesis is for diagnostic purpose). Cover puncture site with sterile dry gauze.

Complications

- Infection
- Perforation of hollow viscus (usually does not lead to complications)
- Leakage of ascitic fluid (typically when Z-track not performed properly)
- Hypotension if excessive amount is removed quickly
- Abdominal wall hematoma or bleeding

5.4.3 PERITONEAL DIALYSIS

(See **Chapter on Acute Dialysis**)

This procedure is like abdominal paracentesis. However, dialysate or normal saline needs to be infused into the peritoneum through a small catheter to 'float' the intestines (create an ascites) before insertion of peritoneal dialysis catheter.

5.4.4 BLADDER CATHETERISATION

Indications

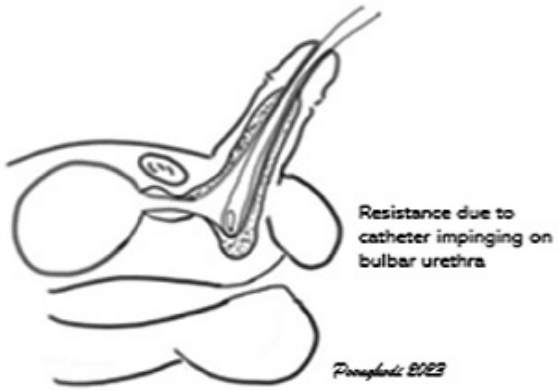
- Obtain urine specimen to look for urinary tract infection
- Monitor urine output
- Relieve urinary retention
- Obtain urine specimen for microscopy and culture
- Preparation for imaging procedure such as micturating cystourethogram (MCUG)

Equipment

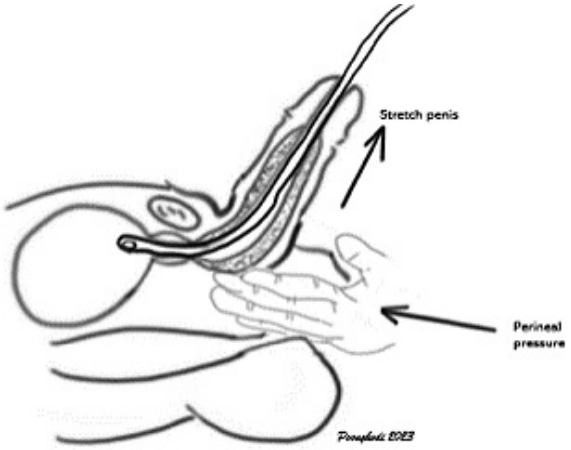
- Dressing Set.
- Urinary catheter of appropriate size
  Newborns : 5-6 Fr
  Older Children : 8-10 Fr
- LA / K-Y jelly.
- Syringe and sterile water for injection.

Procedure

1. Position the child in a frog-leg position. Clean the genitalia with sterile water /saline and drape the perineum.
2. In girls, separate the labia majora with fingers to expose the urethral opening.
   Pass catheter in gently until urine is seen then advance a few centimetres further.
3. In boys, hold the penis perpendicular to the body. There may be some resistance as the catheter tip reaches the bladder neck.
   If there is resistance to insertion – slightly withdraw the catheter, stretch penis further, and apply gentle perineal pressure before inserting the catheter again
   Pass catheter in gently until urine is seen then advance the catheter a few centimetres further.



Resistance during insertion



Apply gentle perineal pressure

5. Secure the catheter with adhesive tape to the lower part of the abdomen and connect the catheter to a urine bag.
   Remove catheter after urine collection if the purpose is to obtain urine for microscopy and culture and sensitivity.
6. Connect the catheter to the urine bag / Remove the catheter after the procedure.

Preparation for Micturating cystourethogram (MCUG)

- Trimethoprim 4 mg/kg BD for 3 days (one day before, on the day of and one day after the procedure) should be given as periprocedural antibiotic prophylaxis. (Adjust to 2 mg/kg BD for 3 days if eGFR < 15ml/min/1.73m2)
- If oral medication is not feasible, alternative such as IV/IM Gentamicin may be given before the procedure.
- IV/IM Cefuroxime/Ceftriaxone should be considered in children with kidney impairment and dose adjusted appropriately

NOTE:

The catheter should be inserted until urine drains out and not more than 7cm in young boys and 5cm in young girls.

- Important to ensure that the length of the catheter introduced is appropriate to avoid knotting of the catheter in the bladder

Complications

- Infection
- Bleeding and trauma especially in a fearful struggling child which may lead to urethral stricture later on.

5.4.5 SUPRAPUBIC BLADDER TAP

This procedure is seldom used nowadays as most doctors use in-out urethral catheterization or urine bag obtain urine specimen. It may be difficult to obtain a urine sample but if successful, the urine is not contaminated by perineal bacteria and will indicate a true positive urinary tract infection.

Indications

- Urine culture in a young infant.

Equipment

- Dressing set.
- Needle size 21, 23 G
- Syringe 5cc.
- Urine culture bottle.

Procedure

1. Make sure bladder is palpable. Give a drink to patient half to 1 hour before procedure.
2. Position the child in supine position. Clean and drape the lower abdomen. Topical anaesthesia is optional in paediatric as it is considered to cause as much pain as aspiration procedure itself.
3. It is encouraged to use ultrasound to increase success rate. On ultrasound, the bladder appears anechoic with posterior enhancement.
4. Insert the needle attached to a 5cc syringe perpendicular or slightly caudally to the skin, 1 cm above the midline of the pubic symphysis.
5. Aspirate while advancing the needle till urine is obtained. Ideally the needle is visualized entering the bladder with ultrasound guidance.
6. Withdraw the needle and syringe.
7. Pressure dressing over the puncture site.
8. Send urine for culture and microscopy.
9. The specimen bottle/laboratory request form must be labelled as suprapubic aspiration sample as any amount of microorganism yielded would be significant.

Complications

- Microscopic haematuria from trauma to bladder mucosa.
- Infection
- Viscus perforation (this may be minimized with ultrasound guidance

5.5. BONE MARROW ASPIRATION AND TREPHINE BIOPSY

Indications

- Examination of bone marrow in a patient with haematologic or oncologic disorder.

Contraindications

- Bleeding tendency, platelet count < 50,000/mm^3.
- Consider transfusion of platelet concentrates prior to procedure.

Equipment

- Bone marrow set (Islam) 16 – 18 G

Procedure

1. Sedate child, monitor continuously with pulse oximeter.
2. Position child - either as for lumbar puncture or in a prone position.
3. Identify site for aspiration - posterior iliac crest preferred, upper anterior-medial tibia for child < 3 months old.
4. Clean skin using standard aseptic technique with povidone-iodine and 70% alcohol. Give local anaesthetic.
5. Make a small skin nick over the PSIS (posterior superior iliac spine). Hold the trocar firmly and gently enter the cortex by a twisting action.
   A 'give' is felt as the needle enters the bone marrow.
6. Trephine biopsy is usually done before marrow aspiration.
7. Withdraw needle, spray with op-site, cover with gauze and crepe bandage.
8. Lie child supine for the next 4 to 6 hours and observe for blood soaking the gauze in a child with bleeding diasthesis.

Complications

- Bleeding, haematoma
- Infection

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