Management of Common HSgB Infections (MoCHIs)

HSgB Treatment Algorithm for Resistant Gram-Negative (GNR) Infection

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AmpC Producing Enterobacterales (AmpC-E)

Click on the antibiotic for dosing info!

Culture grew AmpC producing Enterobacterales

***Serratia marcescens* OR**
***Providencia spp* OR**
Morganella morganii

Follow susceptibility testing

⚠ In **severe infection & high bacterial burden*** conditions, there is a risk of treatment failure.
➔ **refer to ID** if indicated.

High bacterial burden eg:
undrained abscesses, infective endocarditis, ventriculitis, etc

***Citrobacter freundii* OR**
***Enterobacter cloacae* complex OR**
Klebsiella aerogenes

⚠ **CAUTION!**
NOT RECOMMENDED to use **Pip-Tazo/ Ceftriaxone / Ceftazidime** even if the C & S result shows sensitive.

***Enterobacter cloacae* complex** consists of:

E. cloacae	*E. hormaechei*	*E. asburiae*
E. kobei	*E. ludwigii*	

Uncomplicated Cystitis[#]

Nitrofurantoin[a]
OR
TMP-SMX (Bactrim)[a]
OR
Single dose Aminoglycoside[a]

Other Infections

Cefepime MIC ≤ 2 µg/ml
Cefepime

Cefepime MIC 4 - 8 µg/ml
Depending on severity:
Cefepime
OR
Carbapenem
(severe infection)[b]

Cefepime MIC > 8 µg/ml
Carbapenem

***STEP-DOWN THERAPY[c]:**
TMP-SMX (Bactrim)[a]
OR
Ciprofloxacin[a]

Note:
a) Confirm susceptibility before choosing the antibiotics.
b) Definition of **severe infection**: patient in septic shock. Refer Appendix 1
c) Criteria for **step-down therapy**:
   i. Susceptibility to the recommended Abx is demonstrated,
   ii. Patients are hemodynamically stable,
   iii. Reasonable source control measures have occurred,
   iv. Concerns about insufficient intestinal absorption are not present.

Carbapenem-Resistant *Acinetobacter baumannii* (CRAB)

Click on the antibiotic for dosing info!

Culture grew *Acinetobacter baumannii*

Identify whether the culture is a colonizer or a pathogen

*Acinetobacter in non-sterile sample can be a **colonizer** & thus may not require treatment.*
Clinical correlation is important to prevent unnecessary antibiotic therapy.

Colonizer:
No treatment required

Infection:
Establish severity of infection

Refer to Infection Severity Assessment [Click Here]

Mild Infection[b]

Ampicillin-Sulbactam Sensitive?

YES → **Ampicillin-Sulbactam As Monotherapy**

NO → **Cefoperazone-Sulbactam Sensitive?**

YES → **Cefoperazone-Sulbactam (High Dose) As Monotherapy**

NO → **Polymyxin B** *(Non-UTI Infection)* OR **Colistin** *(Urinary Infection)* OR **Minocycline**[a] *(Non-UTI Infection)*

If not responding, treat as per moderate-severe infection

Moderate to Severe Infection[c]

TWO Drugs Combination Therapy*

*** Until clinical improvement is observed***

First Agent

Ampicillin-Sulbactam* (High Dose)
** For moderate-severe disease, Unasyn is recommended regardless of Unasyn susceptibility*

PLUS

Second Agent

- **Polymyxin B** *(Non-UTI Infection)*
  OR
- **Colistin** *(Urinary Infection)*
  OR
- **Minocycline**[a] *(Non-UTI Infection)*

Note:
a. Confirm susceptibility before choosing the antibiotics.
b. **Mild infection:** Good source control and no evidence of severe sepsis or septic shock. E.g., cystitis and tracheitis.
c. **Moderate to severe infection:** Any infection that raises significant clinical concern or does not meet mild infection criteria, such as severe sepsis or septic shock, undrained abscesses, and CRBSI (if catheter has not been removed). Refer Appendix 1
d. **NOT RECOMMENDED:**
   i. **Polymyxin + Carbapenem** combination:
   Need to have 3rd agent. But use with Unasyn increases risk of toxicities with multiple β-lactam agents (neurologic adverse events)
   ii. **Nebulized antibiotics** as adjunctive therapy - lack of benefit observed in clinical trials, concerns regarding unequal distribution in infected lungs, and the potential for respiratory & complications such as bronchoconstriction

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Stenotrophomonas maltophilia

Click on the antibiotic for dosing info!

Culture grew *Stenotrophomonas maltophilia*

Identify whether the culture is a colonizer or a pathogen

*Stenotrophomonas in non-sterile sample can be a **colonizer** & thus may not require treatment.*
Clinical correlation is important to prevent unnecessary antibiotic therapy.

Colonizer:
No treatment required

Infection:
Establish severity of infection

Refer to Infection Severity Assessment [Click Here]

Mild Infection[b]

Monotherapy

Preferred
1. TMP-SMX (Bactrim)[a]
Alternative
2. Minocycline[a] *(Non-UTI*/Non-BSI* Infection)*
3. Levofloxacin[a]

** **UTI:** Urinary Tract Infection*
** **BSI:** Bloodstream Infection*

Moderate to Severe Infection[c]

Initiate combination therapy until clinical improvement is observed. Then, step-down to TMP-SMX (Bactim) monotherapy

Preferred
1. TMP-SMX (Bactrim)[a,d] **PLUS / MINUS** Minocycline[a] *(Non-UTI Infection)*
Alternative
2. TMP-SMX (Bactrim)[a,d] **PLUS / MINUS** Levofloxacin[a]

NOT RECOMMENDED to use **Ceftazidime**[e] or **Polymyxin**[e] even if the C & S result shows sensitive.

Note:
a. Confirm susceptibility before choosing the antibiotics.
b. **Bactrim Alternative** - In situation whereby TMP-SMX (Bactrim) is not an option:
   a. Combination of minocycline and levofloxacin can be considered if the isolate is susceptible to both agents.
   b. If the combination of minocycline and levofloxacin is not an option, and TMP-SMX can't be administered because the patient has an IgE-mediated hypersensitivity reaction, rapid desensitization of TMP-SMX can be performed if the isolate is susceptible.
   c. If intolerance or resistant to all the above agents, combination of Ceftazidime-avibactam plus Aztreonam may be considered.
c. **NOT RECOMMENDED:**
   i. **Ceftazidime:** Regardless of the severity, due to intrinsic β-lactamases, likely to render ceftazidime ineffective + inaccurate MICs.
   ii. **Polymyxin:** No CLSI susceptibility criteria, hetero-resistance & challenges in accuracy and reproducibility of polymyxin MICs.

Extended-spectrum β lactamases producing Enterobacterales (ESBL-E)

Click on the antibiotic for dosing info!

Culture grew ESBL-E

Site of Infection?

CAUTION!
NOT RECOMMENDED to use **Piperacillin-Tazobactam/ Cefepime** even if the C & S result shows sensitive.

Uncomplicated Cystitis

Nitrofurantoin[a]
OR
TMP-SMX (Bactrim)[a]
OR
Single dose Aminoglycoside[a]
OR
Fosfomycin[a,b] – *For E.coli only*
OR
Ertapenem [a] – *For pregnant pts or when above agents cannot be used*

Pyelonephritis OR complicated UTI

Carbapenem[a]

STEP-DOWN THERAPY [c]

REFER ID or AMS FOR SUITABILITY OF STEP-DOWN THERAPY[c]
TMP-SMX (Bactrim)[a]
OR
Ciprofloxacin[a]
OR
(Once daily dosing) [a,d] – **For urinary source infection, TDM required**

Infections outside the Urinary Tract or UTI with systemic involvement

Carbapenem[a]

STEP-DOWN THERAPY [c]

REFER ID or AMS FOR SUITABILITY OF STEP-DOWN THERAPY[c]
TMP-SMX (Bactrim)[a]
OR
Ciprofloxacin[a]
OR
(Once daily dosing) [a,d] – **For urinary source infection, TDM required**

Note:
a) Confirm susceptibility before choosing the antibiotics.
b) **Fosfomycin:** Not suitable for Enterobacterales other than *E. coli* due to the possibility of harbouring FosA gene in other Enterobacterales that deactivate Fosfomycin.
c) Criteria for **step-down therapy**:
   i. Susceptibility to the recommended Abx is demonstrated,
   ii. Patients are hemodynamically stable,
   iii. Reasonable source control measures have occurred,
   iv. Concerns about insufficient intestinal absorption are not present.
d) **Aminoglycosides**: Refer to pharmacist for TDM monitoring.

Carbapenem-Resistant Enterobacterales (CRE)

Click on the antibiotic for dosing info!

Culture grew CRE

*CRE can be a **colonizer** in non-sterile samples (especially from rectal swab) & thus may not require treatment.*
Clinical correlation is important to prevent unnecessary antibiotic therapy.

Urinary infections (UTI)

Uncomplicated cystitis

Follow susceptibility testing

Preferred (if susceptible):

Nitrofurantoin[a]
OR
TMP-SMX (Bactrim)[a]
OR
Fosfomycin[a,b] *(if E. coli)*

Pyelonephritis/ Complicated UTI

Ciprofloxacin[a]
OR
TMP-SMX (Bactrim)[a]
OR
Amikacin q24h[a,c]
OR
Meropenem[d]
(high-dose, extended infusion)
OR
Colistin

Infections outside the Urinary Tract or UTI with systemic involvement

Ceftazidime-Avibactam SENSITIVE AND Non-Carbapenemase (Non-CP CRE) OR Carbapenemase Producing (CP-CRE) - KPC or OXA

If Meropenem MIC ≤ 1

Meropenem *(high-dose, extended infusion)*

If Meropenem MIC 2 - 8

PREFERRED	ALTERNATIVE
Ceftazidime-Avibactam *(mono-therapy)*	**Meropenem** *(high-dose, extended infusion)* **PLUS** **Polymyxin B** *(If Non-Urinary source)* **or** **Colistin** *(If Urinary source)* **or** **Amikacin**[a,c]

If Meropenem MIC > 8

PREFERRED	ALTERNATIVE
Ceftazidime-Avibactam *(mono-therapy)*	**Polymyxin B** *(If Non-Urinary source)* **OR** **Colistin** *(If Urinary source)*

Ceftazidime-Avibactam RESISTANT OR Carbapenemase Producing (CP-CRE); presumed/confirmed NDM

Polymyxin B *(If Non-Urinary source)*
OR
Colistin *(If Urinary source)*

ALTERNATIVE

Ceftazidime-Avibactam
PLUS
Aztreonam

**If feasible, conduct an Aztreonam plus Ceftazidime-Avibactam synergy test to confirm the sensitivity of this combination*

Note:
a) Confirm susceptibility before choosing the antibiotics.
b) **Fosfomycin:** Not suitable for Enterobacterales other than *E. coli* due to the possibility of harbouring FosA gene in other Enterobacterales that deactivate Fosfomycin.
c) **Aminoglycosides**: Refer to pharmacist for TDM monitoring.
d) **Meropenem** monotherapy can be used ONLY when Meropenem MIC ≤ 1

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Suggested ADULT Dosage of Antibiotics (With Normal Renal and Liver Functions)		
Antibiotic Group	**Antibiotics**	**Suggested Dosage**
Aminoglycoside	**Amikacin**	• Uncomplicated cystitis: 15 mg/kg[a] IV, single dose • Pyelonephritis or cUTI: 15 mg/kg[a] IV once, then refer to TDM level for subsequent dose & interval
	Gentamicin	• Uncomplicated cystitis: 5 mg/kg/dose[a] IV, single dose • Pyelonephritis or cUTI: 7 mg/kg[a] IV once, then refer to TDM level for subsequent dose & interval
	[a] *Aminoglycosides dosing: Use adjusted body weight (AdjBW) for patients with body weight of > 120% of ideal body weight (IBW)*	
Carbapenem	**Ertapenem**	• 1 gm IV q24H, infused over 30 minutes
	Imipenem-Cilastatin	• Uncomplicated cystitis: 500 mg IV q6H, infused over 30 minutes • All other infections: 500 mg IV q6H, infused over 3 hours
	Meropenem	**AmpC-E / ESBL:** • Non-CNS infections: 1 gm IV q8H, infused over 30 minutes • Severe / CNS infections: 2 gm IV q8H, infused over 30 minutes **CRE:** • Uncomplicated cystitis (if Meropenem MIC ≤ 1): 1 gm IV q8H, infused over 30 mins • All other infections: 2 g LD over 30 mins, then 2 gm IV q8H, infused over 3 hours
Cephalosporin	**Cefepime**	• Uncomplicated cystitis: 1 gm IV q8H, infused over 30 minutes • All other infections: 2 g LD over 30 mins then 2 gm IV q8H, infused over 3 hours
Novel Beta-Lactam, Beta-Lactamase Inhibitor (BLBLI)	**Ceftazidime-Avibactam**	• 2.5 gm IV q8H, infused over 3 hours • *Note: To be used with Aztreonam. Administer both drugs simultaneously. Both drugs are Y-site compatible.*
Fluoroquinolone	**Ciprofloxacin**	• Uncomplicated cystitis: 400 mg IV q12H **or** 500 mg PO q12H • All other infections: 400 mg IV q 8H **or** 750 mg PO q12H
	Levofloxacin	• 750 mg IV/PO q24H
Polymyxins	**Colistin**	• Refer to Hospital Antibiotic Guidelines/DIAMS - Renal dose for dosing
	Polymyxin B	• Refer to Hospital Antibiotic Guidelines/DIAMS - Renal dose for dosing
Sulbactam-based combination	**Ampicillin-Sulbactam**	• Unasyn sensitive Acinetobacter: 3 gm IV q4-6H, infused over 30 minutes • Unasyn resistant/mod-severe infection: 9 gm IV q8H, infused over 4 hours (High dose)
	Cefoperazone-Sulbactam	• 4 gm IV q6H
Tetracycline	**Minocycline**	• 200 mg IV/PO q12H • *Note: Minocycline monotherapy is not advisable for the treatment of bloodstream infections and urinary tract infections.*
Others	**Aztreonam**	• 2 gm IV q8H, infused over 3 hours *Note: To be used with Ceftazidime-avibactam. Administer both drugs simultaneously. Both drugs are Y-site compatible.*
	Fosfomycin	• Uncomplicated cystitis: 3 gm PO x 1 dose
	Nitrofurantoin	• Immediate-release (IR) formulation: 100 mg PO q6H • Sustained-release (SR) formulation: 100 mg PO q12H
	TMP-SMX (Bactrim)	• Cystitis / Pyelonephritis: TMP 160 mg (= 2 tabs or vials) PO/IV q12H • Other Non-UTI Infection: 8-12 mg/kg/day (TMP component) IV/PO, given in 2 to 3 divided doses (*Note: Consider max dose of 960 mg TMP/day*)

Appendix 1: Infection Severity Assessment

There is no specific guidance available in assessing the severity of infection.
Here are some examples of infections that could be classified as mild or moderate to severe infections.

Mild infections:

- Skin and soft tissue infection
- Urinary tract infection
- Catheter-related infection including bloodstream infection

*However, these infections may be considered severe when a patient presents with organ dysfunction or septic shock.

Moderate to severe infections:

- Infection causing organ dysfunction
- Septic shock
- Moderate to severe Pneumonia
- Infective endocarditis
- Meningitis
- Ventriculitis
- Necrotizing fasciitis

In addition, some infections may be classified as mild or moderate infections depending on patients' condition. These include:

- Bone and joint infection
- Prosthetic joint infection

High-burden infections:

Include infections such as:

- Infective endocarditis (IE)
- Meningitis
- Infections prior to source control
  (e.g., abscesses, necrotizing fasciitis, osteomyelitis, prosthetic infections).

Extracted from:
Consensus Guidelines on Treatment Of Multidrug Resistant Gram Negatives, 1st Edition, 2024,
Malaysian Society of Infectious Diseases and Chemotherapy (MSIDC)

References:

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