AMS

DIAMS
(DAILY INTEGRATION OF ANTIMICROBIAL STEWARDSHIP)

PROLONGED / EXTENDED INFUSION OF ANTIBIOTICS IN ADULT PATIENTS

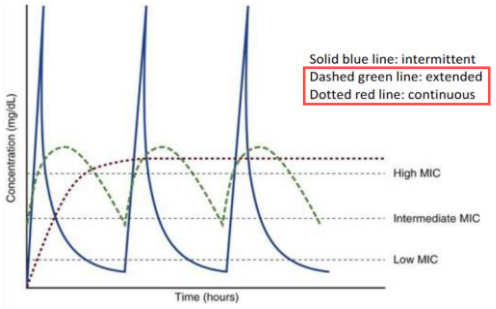
Revised: 26 June 2023

Ampicilin + Sulbactam | **Cefepime Inj.** | **Cloxacillin Inj.** | **Ceftazidime Inj.**

Imipenem + Cilastatin Inj. | **Meropenem Inj.** | **Piperacillin + Tazobactam** | **Vancomycin Inj.**

What is Prolonged Infusion?

- Administration of antibiotics over a prolonged duration:
  - **Over 3-4 hours per dose (extended infusion)**
  - **Over 24 hours (continuous infusion)**
- Applicable to time-dependent antibiotics such as ***Beta-lactam antibiotics.***
- Prolonged infusion improves the efficacy of the antibiotics by increasing the time of free drug concentration above the MIC (% fT > MIC).



In what situation prolonged infusion is needed?

Prolonged infusions are at least equally effective or in certain circumstances (such as critical illness), more effective than traditional intermittent infusions. For example:

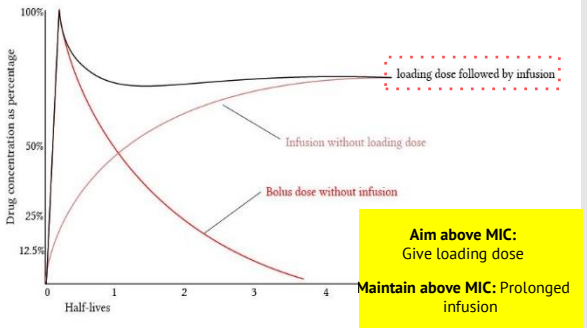
1. **Less susceptible pathogens** - pathogens with high MIC (i.e., intrinsic resistance or tendency to acquire resistance during therapy); such as *P. aeruginosa, A. baumannii & CREs.*
   - Patients with an elevated risk of drug-resistant pathogens:
     i. Frequent healthcare exposures
     ii. Prior repeated antibiotic exposures
2. **Patients with altered pharmacokinetics -** patients with augmented renal clearance (ARC) (CrCl >120 mL/min) such as:
   - Critically ill *(may also have other variable pharmacokinetics such as altered volumes of distribution (Vd), abnormal fluid balance, and/or changes in protein binding)*
   - Young patients and/or patients with traumatic brain injury (TBI) - (predisposition to ARC)
   - Obese patients
3. **Severe infections**
   - Central nervous system (CNS) infections, complicated melioidosis, cystic fibrosis & necrotizing fasciitis

Which antibiotics to give Prolonged Infusion?

- Piperacillin/Tazobactam (Tazocin)
- Cephalosporins (Ceftazidime & Cefepime)
- Carbapenems (Meropenem & Imipenem/Cilastatin)
- Others: (Cloxacillin, Ampicillin/Sulbactam (Unasyn) & Vancomycin) – *in specific cases only*

How to give Prolonged Infusion?

1. A **LOADING DOSE (LD)** should be given (usually over 30-60 min) to achieve rapid attainment of therapeutic concentration.
   - The usual loading dose is the high end of normal dose (or even higher doses).
   - Loading dose generally not affected by patient's renal function
2. Followed by **MAINTENANCE DOSE (MD)** using prolonged infusion. MD should be started at the **next standard admin time.**



By: AMS Team (Dr Syamhanin Adnan, Izyana Munirah, Hannah Mahir & Adam Ashraf Jaafer) & PRIC (Ang Li Min, Chong Kai Qian & Abby Ang).

Only for internal circulation. For further enquiries, kindly contact ext 4126.

HOSPITAL SUNGAI BULOH
JABATAN FARMASI HOSPITAL SUNGAI BULOH

AMS

DIAMS
(DAILY INTEGRATION OF ANTIMICROBIAL STEWARDSHIP)

PROLONGED / EXTENDED INFUSION OF ANTIBIOTICS IN ADULT PATIENTS

Revised: 26 June 2023

Ampicilin + Sulbactam | Cefepime Inj. | Cloxacillin Inj. | Ceftazidime Inj.
Imipenem + Cilastatin Inj. | Meropenem Inj. | Piperacillin + Tazobactam | Vancomycin Inj.

Drug / Indication	Choose the usual recommended dose based on indication & disease severity (refer to HSgB ABX Guideline or DIAMS). Then, choose the renal adjusted dose corresponding to the patient's CrCl.
Ampicilin + Sulbactam (Unasyn) Inj. ➢ Only for high dose Unasyn for the treatment of MRO Acinetobacter[1,2] REFER MoCHIs Resistant GNR Infection Algorithm	**Loading Dose:** (Should be administered **STAT**) ○ 9 g in 200 ml NS. Administer over 30 mins **Maintenance Dose:** (Should be started at the **next standard administration time**) ○ 9 g Q8H over 4 hours[1] *Dilute each dose in at least 200ml diluents (NS, D5 or LR) **No data on renal dosing adjustment for extended infusion administration*
Cefepime Inj. ➢ For patients diagnosed with indications requiring Cefepime 2g q8h (such as severe Infections, CNS Infection & cystic fibrosis)	**Loading Dose:** (Should be administered **STAT**) ○ 2 g in 50-100 ml diluents (NS or D5). Administer over 30 mins. **Maintenance Dose:** (Should be started at the **next standard administration time**) **Renal Function** / **Dosing** ≥ 60 mL/min — 2 g Q8H over 3-4 hours 30 – 59 mL/min — 2 g Q12H over 3-4 hours 10 – 29 mL/min — 1 g Q12H over 3-4 hours <10 mL/min or IHD — 1 g Q24H over 3- 4 hours * Dilute each dose in 50-100 ml diluents (NS or D5).
Cloxacillin Inj. ➢ The recommendation is **ONLY** for Continuous Infusion ➢ Can be considered in patients with severe/ deep-seated infection **AND** hypoalbuminemia (Alb < 20) – Cloxacillin is highly protein-bound (95%) REFER MoCHIs Staph aureus Bacteremia Algorithm	**Loading Dose:** (Should be administered **STAT**) ○ 2 g in 50-100 ml diluents (NS or D5). Administer over 30 mins. **Maintenance Dose:** (Should be started **IMMEDIATELY AFTER** the loading dose) ○ 12 g as continuous infusion over 24 hours[4] • **Central line:** Dilute 2 g in 50 mL diluents (NS or D5), administer over 4 hours. • **Peripheral line:** Dilute 2 g in 100 mL diluents (NS or D5), administer over 4 hours.

By: AMS Team (Dr Syamhanin Adnan, Izyana Munirah, Hannah Mahir & Adam Ashraf Jaafer) & PRIC (Ang Li Min, Chong Kai Qian & Abby Ang).

Only for internal circulation. For further enquiries, kindly contact ext 4126.

HOSPITAL SUNGAI BULOH
JABATAN FARMASI HOSPITAL SUNGAI BULOH

DIAMS
(DAILY INTEGRATION OF ANTIMICROBIAL STEWARDSHIP)

PROLONGED / EXTENDED INFUSION OF ANTIBIOTICS IN ADULT PATIENTS

Revised: 26 June 2023

Ampicilin + Sulbactam | Cefepime Inj. | Cloxacillin Inj. | Ceftazidime Inj.
Imipenem + Cilastatin Inj. | Meropenem Inj. | Piperacillin + Tazobactam | Vancomycin Inj.

Drug / Indication	Choose the usual recommended dose based on indication & disease severity (refer to HSgB ABX Guideline or DIAMS). Then, choose the renal adjusted dose corresponding to the patient's CrCl.

Ceftazidime Inj.

- Extended infusion can be considered in patients diagnosed with melioidosis or pseudomonas infection.

REFER DIAMS ABX Renal Dose for specific indication for dosing

Loading Dose: (Should be administered **STAT**)

- 2 g in 50-100 ml diluents (NS or D5). Administer over 30 mins.

Maintenance Dose: (Should be started at the **next standard administration time**)

Renal Function	Usual Recommended Dose	
	2g Q8H	2g Q6H
> 50 mL/min	2 g Q8H over 4 hours	2 g Q6H over 4 hours
30 – 49 mL/min	2 g Q12H over 4 hours	2 g Q8H over 4 hours
< 30 mL/min	Use intermittent infusion	Use intermittent infusion

* Dilute each dose in 50-100 ml diluents (NS, D5 or Hartmann's Solution).

Imipenem + Cilastatin Inj.

- Extended infusion can be considered in patients diagnosed with severe/ deep-seated infection or resistant gram-negative infections.

Loading Dose: (Should be administered **STAT**)

- 500 mg in 50-100 ml diluents (NS or D5). Administer over 30 mins.

OR

- 1,000 mg in 100 ml diluents (NS or D5). Administer over 60 mins.

Maintenance Dose: (Should be started at the **next standard administration time**)

- For dose 500 mg: Dilute in 50-100 ml diluents (NS or D5).
- For dose 1,000 mg: Dilute in 100 ml diluents (NS or D5).

Renal Function	Usual Recommended Dose[5]		
	500mg Q6H	1000mg Q8H	1000mg Q6H
> 70 mL/min	500 mg Q6H over 3 hours	1,000 mg Q8H over 3 hours	1,000 mg Q6H over 3 hours
41 – 70 mL/min	500 mg Q8H over 3 hours	500 mg Q8H over 3 hours	750 mg Q8H over 3 hours
15 – 40 mL/min	250 mg Q6H over 3 hours	250 – 500 mg Q6-8H over 3 hours	500 mg Q6H over 3 hours
< 15 ml/min or HD	Use Intermittent infusion		

By: AMS Team (Dr Syamhanin Adnan, Izyana Munirah, Hannah Mahir & Adam Ashraf Jaafer) & PRIC (Ang Li Min, Chong Kai Qian & Abby Ang).

Only for internal circulation. For further enquiries, kindly contact ext 4126.

HOSPITAL SUNGAI BULOH
JABATAN FARMASI HOSPITAL SUNGAI BULOH

DIAMS
(DAILY INTEGRATION OF ANTIMICROBIAL STEWARDSHIP)

PROLONGED / EXTENDED INFUSION OF ANTIBIOTICS IN ADULT PATIENTS

Revised: 26 June 2023

Ampicilin + Sulbactam | Cefepime Inj. | Cloxacillin Inj. | Ceftazidime Inj.
Imipenem + Cilastatin Inj. | Meropenem Inj. | Piperacillin + Tazobactam | Vancomycin Inj.

Drug / Indication	Choose the usual recommended dose based on indication & disease severity (refer to HSgB ABX Guideline or DIAMS). Then, choose the renal adjusted dose corresponding to the patient's CrCl.
Meropenem Inj. ➢ Extended infusion can be considered in patients requiring Meropenem 2g Q8H (such as Severe Infections, CNS Infection & resistant gram-negative infections) **REFER MoCHIs Drug Resistant GNR Algorithm**	**Loading Dose:** (Should be administered **STAT**) ○ 2 g in 50-100 ml NS. Administer over 30 mins. **Maintenance Dose:** (Should be started at the **next standard administration time**) **Renal Function** / **Dosing**[8] ≥ 50 mL/min: 2 g Q8H over 3 hours 30 – 49 mL/min: 1 g Q8H over 3 hours 10 – 29 mL/min: 1 g Q12H over 3 hours < 10 ml/min or HD: Use Intermittent infusion * Dilute each dose in 50-100 ml NS.
Piperacillin + Tazobactam (Tazocin) Inj. ➢ Extended infusion can be considered in patients requiring Piperacillin/ Tazobactam 4.5g Q6H (such as severe Infections, necrotizing fasciitis & cystic fibrosis)	**Loading Dose:** (Should be administered **STAT**) ○ 4.5 g in 50-100 ml diluents (WFI, NS or D5). Administer over 30 mins **Maintenance Dose:** (Should be started at the **next standard administration time**)[6] **Renal Function** / **Dosing** ≥ 20 mL/min: 4.5 g Q8H over 4 hours < 20 mL/min or IHD: 4.5g Q12H over 4 hours * Dilute each dose in 50-100 ml diluents (WFI, NS or D5).

By: AMS Team (Dr Syamhanin Adnan, Izyana Munirah, Hannah Mahir & Adam Ashraf Jaafer) & PRIC (Ang Li Min, Chong Kai Qian & Abby Ang).

Only for internal circulation. For further enquiries, kindly contact ext 4126.

HOSPITAL SUNGAI BULOH
JABATAN FARMASI HOSPITAL SUNGAI BULOH

DIAMS
(DAILY INTEGRATION OF ANTIMICROBIAL STEWARDSHIP)

PROLONGED / EXTENDED INFUSION OF ANTIBIOTICS IN ADULT PATIENTS

Revised: 26 June 2023

Ampicilin + Sulbactam | Cefepime Inj. | Cloxacillin Inj. | Ceftazidime Inj.
Imipenem + Cilastatin Inj. | Meropenem Inj. | Piperacillin + Tazobactam | Vancomycin Inj.

Drug / Indication	Choose the usual recommended dose based on indication & disease severity (refer to HSgB ABX Guideline or DIAMS). Then, choose the renal adjusted dose corresponding to the patient's CrCl.

Vancomycin Inj.

- The recommendation is **ONLY** for Continuous Infusion
- Consider for severe infections (such as CNS Infection & complicated MRSA infection) **AND** unable to achieve therapeutic concentration using intermittent dosing (ie pharmacokinetically challenging cases such as obesity, augmented renal clearance)

REFER HSgB Vancomycin protocol for intermittent dosing

Loading Dose: (Should be administered **STAT**)*

Weight	Dosing[7]
< 40 kg	500 mg in 100 ml NS or D5 over 1 hour
41-69 kg	1,000 mg in 250 ml NS or D5 over 2 hours
⩾ 70 kg	1,500 mg in 250 ml NS or D5 over 2.5 hours

* Consult TDM Pharmacist for loading dose requirement for patient already receiving intermittent vancomycin infusion.

Maintenance Dose: (Should be started **IMMEDIATELY AFTER** the loading dose)

Renal function	Dosing[7]
⩾ 100 mL/min	1,250 mg Q12H over 12 hours
80 - 99 mL/min	1,000 mg Q12H over 12 hours
60 - 79 mL/min	750 mg Q12H over 12 hours
30 - 59 mL/min	500 mg Q12H over 12 hours
< 30 mL or HD	Refer to TDM Pharmacy (ext: 4124)

* Dilute each dose in 100-250 ml diluents (NS or D5) (max concentration: 10mg/ml).

***** Serum level should be taken 24 hours after initiation of vancomycin infusion. Dosing adjustment should be made based on TDM recommendations.***

By: AMS Team (Dr Syamhanin Adnan, Izyana Munirah, Hannah Mahir & Adam Ashraf Jaafer) & PRIC (Ang Li Min, Chong Kai Qian & Abby Ang).

Only for internal circulation. For further enquiries, kindly contact ext 4126.

HOSPITAL SUNGAI BULOH
JABATAN FARMASI HOSPITAL SUNGAI BULOH

References:

1. Tamma PD et al., (2023) Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. IDSA 2023; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed 26 June 2023.
2. Housman, S. T., et al., (2013). In vitro pharmacodynamics of human-simulated exposures of Ampicillin/sulbactam, Doripenem and tigecycline alone and in combination against multidrug-resistant Acinetobacter baumannii. *JAC*, *68*(10). doi.org/10.1093/jac/dkt197
3. Guide to Antimicrobial Therapy in the Adult ICU, 2017
4. Courjon, J., et al., (2020). A population pharmacokinetic analysis of continuous infusion of Cloxacillin during Staphylococcus aureus bone and joint infections. *AAC*, *64*(12). doi.org/10.1128/aac.01562-20
5. Ibrahim et al., (2017) Extended infusion versus intermittent infusion of imipenem in the treatment of ventilator-associated pneumonia. Drug Des Devel Ther. 2017; 11: 2677–2682 doi.org/10.2147/DDDT.S143021
6. Ram et al. Extended vs Bolus Infusion of Broad-Spectrum β-Lactams for Febrile Neutropenia: An Unblinded, Randomized Trial. Clin Infect Dis 2018 Sep 28;67(8):1153-1160 doi.org/10.1093/cid/ciy258
7. Ministry of Health, Malaysia Clinical Pharmacokinetics Pharmacy Handbook. Second edition. 2019. Chapter 15: Vancomycin.
8. Johns Hopkins POC-IT Guides
9. UCDMC Extended Infusion. Beta-Lactam Guideline. UC Davis Health. (2020).
10. Sanford Guide to Antimicrobial Therapy (Last updated: 13th April 2021).

By: AMS Team (Dr Syamhanin Adnan, Izyana Munirah, Hannah Mahir & Adam Ashraf Jaafer) & PRIC (Ang Li Min, Chong Kai Qian & Abby Ang).