Continuous infusions of Piperacillin/Tazobactam & Meropenem (DCCM only)

Piperacillin/Tazobactam

Background

Beta-lactam antibiotics display a time dependent activity for bactericidal killing, where efficacy is correlated to the time the free plasma drug concentration remains above the minimum inhibitory concentration (MIC) of the targeted pathogen. Continuous infusions of piperacillin/tazobactam produce higher and sustained concentrations above the MIC, benefitting critically ill patients with a high level of illness severity. When compared to intermittent dosing, improved outcomes have been demonstrated for continuous piperacillin/tazobactam infusions in critically ill patients.

Indication

Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
Complicated intra-abdominal infections
Empirical therapy of a range of severe infections prior to availability of sensitivities
Febrile neutropenia (usually in combination with an aminoglycoside)

Contraindications

Hypersensitivity to active substances, any other penicillin- antibacterial agent or to any of the excipients
History of acute severe allergic reaction to any other beta-lactam active substances (e.g. cephalosporin, monobactam or carbapenem).

Exclusions

Patients on IHD or CAPD are excluded from this guideline as they would derive little benefit from the change in pharmacokinetics. These patients should remain on regular intermittent dosing schedules dosed appropriately for their degree of renal impairment.

Cautions

Neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function
Piperacillin/ tazobactam can cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis. If patients develop a skin rash they should be monitored closely and Piperacillin + Tazobactam discontinued if lesions progress.

Adverse effects

The most commonly reported adverse effect is diarrhoea.
The most serious adverse reactions include pseudo-membranous colitis and toxic epidermal necrolysis.

Dosing - see next page

Monitoring

Monitor renal function daily in critically unwell patients and adjust dose accordingly.
Ensure infusion pumps are checked hourly whilst being used.

Transfer to non-critical wards

Convert infusion to equivalent intermittent dose
Stop infusion at a suitable time and give dose immediately.

Piperacillin/ Tazobactam

Loading dose

A loading dose is always required prior to starting a continuous infusion

- Patients who have already received a dose of Piperacillin+ Tazobactam in the last 6 hours do NOT require a loading dose and can be started on the continuous infusion immediately.

The continuous infusion should be started immediately after the loading dose

Loading dose	Reconstitution and dilution
4.5g as a slow bolus over 5 minutes	Reconstitute each 4.5g vial with 20mL Sodium chloride 0.9%

Maintenance dosing (starts immediately after loading dose)

Most patients, regardless of kidney function and following on from the loading dose, should receive the full dose of 18g/24 hours (dosed as 4.5g every 6 hours where each dose is run over 6 hours).

A dose adjustment may be required in very low body weight patients or poor kidney function. Seek advice from a critical care pharmacist.

Initial 48 hours (All)

All patients in the initial 48 hours AND for patients with normal kidney function after 48 hours	
	18g per 24 hours (= 4.5g over 6 hours every 6 hours)

After 48 hours:

For CrCl >40mL/min, no dose adjustment required- continue current maintenance dose.

Patients with normal renal function or CKD	
CrCl	
>40mL/min	18g/ 24 hours (= 4.5g over 6 hours every 6 hours)
20-40mL/min	13.5g/ 24 hours (= 4.5g over 8 hours every 8 hours)
<20mL/min	9g/ 24 hours (= 4.5g over 12 hours every 12 hours)

Acute kidney injury (as per KGDIGO guidelines- see Appendix 1) Requires daily assessment	
AKI stage	
Stage 1	18g/ 24 hours (= 4.5g over 6 hours every 6 hours)
Stage 2	13.5g/ 24 hours (= 4.5g over 8 hours every 8 hours)
Stage 3 **(excluding CVVHDF)**	9g/ 24 hours (= 4.5g over 12 hours every 12 hours)

Requiring CVVHDF	
	18g/ 24 hours (= 4.5g every 6 hours over 6 hours)

Piperacillin/ tazobactam

Preparation and administration

Piperacillin/tazobactam contains a penicillin -please check allergy status before starting therapy.

Vials of piperacillin/tazobactam are available in a 4g/0.5g i.e 4.5g strength

Reconstitution

- Reconstitute each 4.5g vial with 20mL Sodium chloride 0.9%.
- Swirl until dissolved. Reconstitution generally occurs in 5-10 minutes.

Dilution

- For maintenance infusions, reconstitute each 4.5g vial as above and then further dilute to 50mL with Sodium chloride 0.9% in a 50mL syringe.
- Glucose 5% is an alternative diluent if necessary, and may be preferred in hypernatraemia.

Administration

- Can be given by a central or peripheral line
- Use Guardrails DCCM: Pip/Tazo continuous **Nexus CC syringe pump**
- Continuous infusions will require doses being given back to back, so a flush is not required, with the exception being the end of a course of piperacillin/tazobactam.

Meropenem

Background

As with other beta-lactam antibiotics, meropenem displays time dependent bactericidal activity, where efficacy is correlated to the time the free plasma drug concentration remains above the minimum inhibitory concentration (MIC) of the targeted pathogen. Continuous infusions of meropenem result in consistent attainment of drug exposure above the MIC, resulting in superior bacteriological efficacy when compared to intermittent infusions in critically ill patients.

Indication

Severe pneumonia including hospital-acquired and ventilator-associated pneumonia
Acute bacterial meningitis
Febrile neutropenia
Mixed aerobic/ anaerobic infections including ESBL-producing gram negative infections.
Presumptive therapy of a wide range of severe infections prior to availability of sensitivities

Contraindications

Hypersensitivity to meropenem or any other carbapenem antibiotic

Exclusions

Patients on IHD or CAPD are excluded from this guideline as they will derive little benefit from the change in pharmacokinetics. These patients should remain on regular intermittent dosing schedules dosed appropriately for their degree of renal impairment.

Cautions

Hepatic function should be closely monitored during treatment due to the risk of hepatic toxicity
Seizures have been infrequently reported during treatment with carbapenems, including meropenem
Severe allergic reaction (e.g. severe skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reactions with eosinophilia and systemic symptoms (DRESS) to any other type of beta-lactam antibacterial (e.g. penicillin, cephalosporin).
Antibiotics associated colitis and pseudo-membranous colitis have been reported with meropenem- consider this diagnosis in patients who present with diarrhoea during or subsequent to meropenem.

Adverse effects

Most commonly reported adverse effects: diarrhoea, rash, nausea, vomiting & injection site inflammation.
Most commonly reported lab adverse events: thrombocytosis, increased hepatic enzymes.

Interactions

Concurrent use of meropenem and sodium valproate should be avoided. Valproate levels can fall significantly (by 80-90%) within 24 hours of starting meropenem with a strong correlation to induction of seizures. An additional antiepileptic agent should be considered if there isn't an alternative antibiotic.

Dose- see standard and increased dosing section on next pages

A loading dose is always required prior to starting a continuous infusion

- Patients who have already received a dose of meropenem in the last 8 hours do NOT require a loading dose and can be started on the continuous infusion immediately.

The continuous infusion should be started immediately after the loading dose

Monitoring

Monitor renal function daily in critically unwell patients and adjust dose accordingly.
Ensure infusion pumps are checked hourly whilst being used.

Transfer to non-critical wards

Convert infusion to equivalent intermittent dose
Stop infusion at a suitable time and give dose immediately.

Meropenem dosing regime

Standard dosing regimen

Most patients, regardless of kidney function and following on from the loading dose, should receive the full dose of either 3g /24 hours (dosed as 1g every 8 hours, where each dose is run over 8 hours).

High dose 'increased exposure' regimen

When clinically necessary the usual dose may be increased to 6g/24 hours (dosed as 2g every 8 hours where each dose is run over 8 hours). Examples of indications requiring high dose regime: CNS infections, resistant or complex infections, pseudomonal infections and patients at increased risk of augmented renal clearance e.g. (pre-) morbid obesity or as dictated by therapeutic drug monitoring.

Dose adjustments

Dose adjustments may be required in patients with low body weight or with poor kidney function.
Therapeutic drug monitoring is available at Christchurch (send away) and may be recommended by ID team.

Loading dose

Standard dose regimen	1g as a slow bolus over 5 minutes
High dose regimen	2g as short infusion over 15-30 minutes (Reconstitute TWO x 1g vials and add to 100mL bag 0.9% Sodium chloride)

Maintenance infusion (starts immediately after loading dose)

Initial 48 hours (All)

All patients in the initial 48 hours AND for patients with normal kidney function after 48 hours	
Standard dose regimen	3g/ 24 hours (= 1g over 8 hours every 8 hours)
High dose regimen	6g/ 24 hours (= 2g over 8 hours every 8 hours)

After 48 hours

For CrCl ≥50mL/min, no dose adjustment required- continue current maintenance dose.

Patients with normal renal function or CKD		
CrCl	**Standard dosing regime**	**High dose regimen**
>50mL/min	3g/ 24 hours (= 1g over 8 hours every 8 hours)	6g/ 24 hours (= 2g over 8 hours every 8 hours)
26-50mL/min	3g/ 24 hours (= 1g over 8 hours every 8 hours)	4g/ 24 hours (= 1g over 6 hours every 6 hours)
<25mL/min	2g/ 24 hours (= 1g over 12 hours every 12 hours)	3g/ 24 hours (= 1g over 8 hours every 8 hours)

Acute kidney injury (as per KGDIGO guidelines- see Appendix 1) Requires daily assessment		
AKI stage	**Standard dosing regimen**	**High dose regimen**
Stage 1	3g/ 24 hours (= 1g over 8 hours every 8 hours)	6g/ 24 hours (= 2g over 8 hours every 8 hours)
Stage 2	3g/ 24 hours (= 1g over 8 hours every 8 hours)	6g/ 24 hours (= 2g over 8 hours every 8 hours)
Stage 3 **(excluding CVVHDF)**	2g/ 24 hours (= 1g over 12 hours every 12 hours)	2g/ 24 hours (= 1g over 12 hours every 12 hours)

Requiring CVVHDF	
Standard dosing regimen	3g/ 24 hours (= 1g every 8 hours over 8 hours)
High dose regimen	3g/ 24 hours (= 1g every 8 hours over 8 hours)

Meropenem

Preparation and administration

Please check allergy status before starting therapy.

**** Only make ONE infusion immediately prior to being used owing to drug stability issues ****

- **2g in 50mL are only stable for 8 hours**
- **1g in 50mL are only stable for 12 hours**

Vials of meropenem are available in a 1g strength

Reconstitution

- Reconstitute each 1g vial with 20mL Sodium chloride 0.9%.
- Swirl until dissolved. Reconstitution generally occurs in 5-10 minutes.

Dilution

- For continuous infusions, reconstitute each vial as above. Draw up the required number of vials and then further dilute to 50mL with Sodium chloride 0.9% in a 50mL syringe.
- Glucose 5% CANNOT be used for continuous infusions.
- ONLY use 2g in 50mL for 2g q8h dosing owing to stability
- **Only make ONE infusion immediately prior to being used owing to drug stability issues**

Administration

- Can be given by a central or peripheral line
- Use Guardrails DCCM: Mero continuous **Nexus CC syringe pump**
- Continuous infusions will require doses being given back to back, so a flush is not required, with the exception being the end of a course of meropenem.

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Scope	All staff in DCCM
Author/Edited by	DCCM pharmacists
Endorsed	Approved by DCCM Quality Group & AMS Committee

Appendix 1: KDIGO criteria for acute kidney injury

Stage	Serum creatinine (SCr)	Timing	Urine output
1 or	Increase 1.5 – 1.9 x baseline SCr Increase in SCr by ≥26.5 µmol/L	7d 48h	<0.5 mL/kg/h for 6-12h
2	Increase in 2.0 – 2.9 x baseline SCr	7d	<0.5mL/kg/h for ≥ 12h
3 or or	Increase in ≥ 3 x baseline SCr Increase in SCr to ≥353.6 µmol/L Initiation of renal replacement therapy	7d 7d	<0.3 mL/kg/h for ≥ 24h or Anuria for ≥ 12h