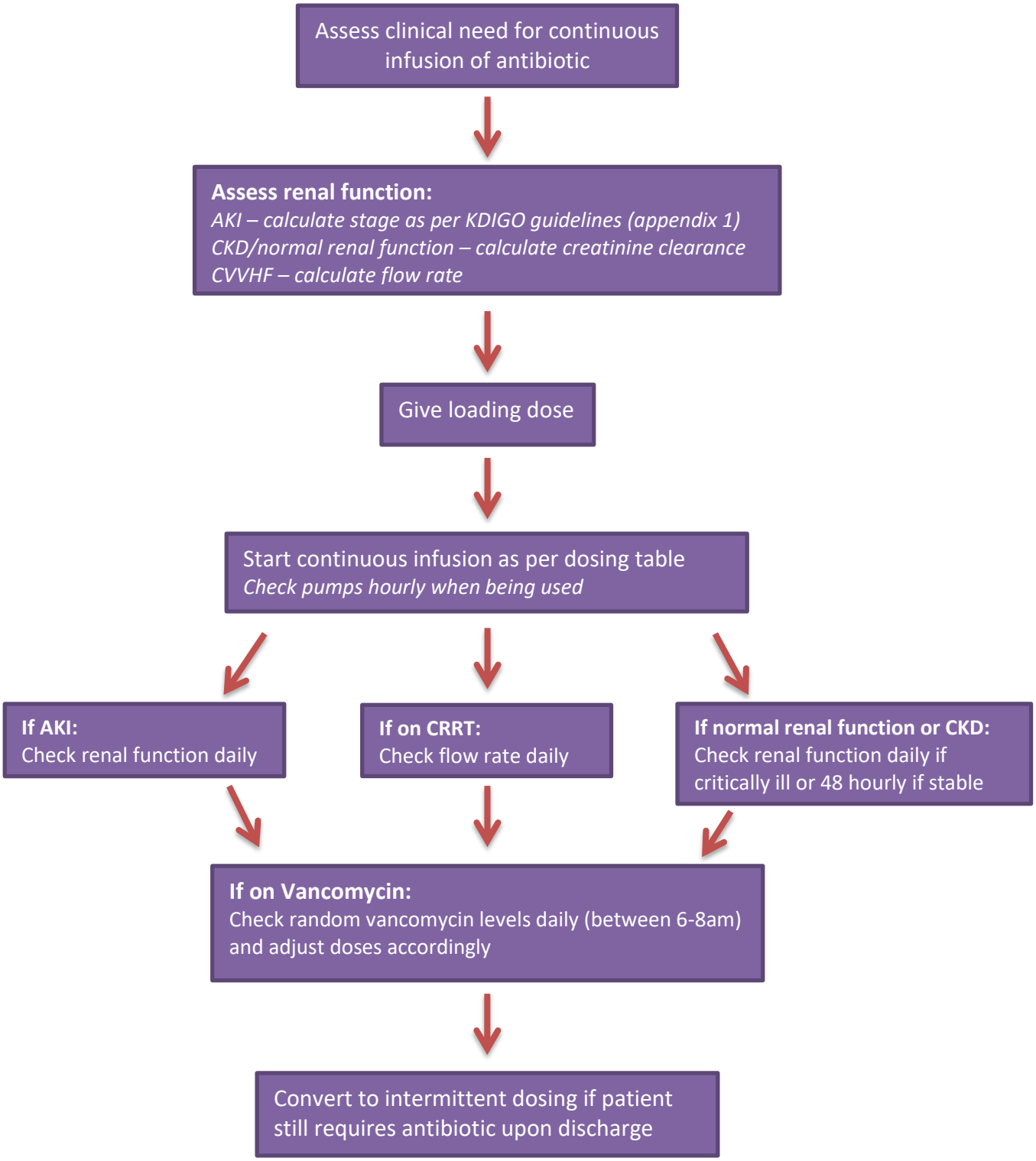
University Hospitals Sussex NHS Foundation Trust

Continuous Infusions of Vancomycin, Piperacillin-Tazobactam and Meropenem

For use on Intensive Care Only



Optimal antibiotic dosing is essential in ICU patients and can often be challenging due to the altered pharmacokinetics and pharmacodynamics seen in critically ill patients. For certain time dependent antibiotics, such as vancomycin, meropenem and piperacillin-tazobactam, a continuous infusion is seen as a logical alternative compared to intermittent infusions. This is supported by pharmacokinetic studies showing a better target attainment using a continous dosing approach.

Continuous infusions should be used when there is a confirmed clinical indication for the specified antibiotic, with consideration given to local antimicrobial guidance and sensitivities.

Vancomycin

Background

Vancomycin displays time dependent antimicrobial activity, where efficacy is correlated to the time that the serum concentration exceeds the minimum inhibitory concentration (MIC), rather than the attainment of peak concentrations. There is evidence that continuous infusions of vancomycin are as efficacious as intermittent infusions in critical care patients, with a decreased likelihood of nephrotoxicity and a perceived simpler process to monitor serum levels

Indication

Vancomycin is indicated for the treatment of the following infections:

- Complicated skin and soft tissue infections
- Bone and joint infections
- Community acquired pneumonia (CAP)
- Hospital acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP)
- Infective endocarditis
- Bacteraemia that occurs in association with, or is suspected to be associated with any of the above

Contra-indications

Hypersensitivity to the active substance or to any of the excipients
Vancomycin should be avoided in patients with previous hearing loss

Cautions

Use with care in patients with renal insufficiency, including anuria, as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations

Adverse effects

- Flushing of the upper body (“red man syndrome”), exanthema and mucosal inflammation, pruritus, urticaria
- Renal insufficiency manifested primarily by increased serum creatinine and serum urea
- Hypotension
- Tinnitus, possibly preceding onset of deafness, should be regarded as an indication to discontinue treatment
- Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25g

Interactions

Concurrent or sequential administration of vancomycin with other potentially neurotoxic or/and nephrotoxic active substances may potentiate the nephrotoxicity and/or ototoxicity of vancomycin and consequently requires careful monitoring of the patient

Monitoring
Therapeutic drug monitoring (see below)

Dose
Loading dose
35mg/kg based on **actual** body weight
Use a reduced loading dose of 25mg/kg for obese patients (BMI ≥30)
Maximum 3g loading dose

Route	Maximum concentration	Maximum rate
Peripheral line	5mg/ml	10mg/minute
Central line	10mg/ml	10mg/minute

Continuous infusion
Start continuous infusion immediately after the loading dose has been given. Dosing is dependent on renal function, with consideration given to acute changes in renal function and if the patient requires continuous renal replacement therapy (CRRT).

For patients without an acute kidney injury:

Calculate Creatinine Clearance (CrCl) using calculator (available on via calculators on Microguide). For obese patients, use ideal body weight to calculate CrCl. Do **NOT** use eGFR.

Creatinine clearance	Starting dose
≥81ml/min	40mg/kg/day
50-80ml/min	25mg/kg/day
25-49ml/min	14mg/kg/day
≤24ml/min	7mg/kg/day

Round doses to the nearest 250mg

For patients with an acute kidney injury (not on CRRT):
Calculate stage of AKI according to KDIGO guidelines *(appendix 1)*. Do **NOT** use eGFR or CrCl.

AKI stage	Starting dose
Stage 1	25mg/kg/day
Stage 2	14mg/kg/day
Stage 3	7mg/kg/day

AKI stages should be assessed on a daily basis

For patients requiring continuous venovenous haemofiltration (CVVHF):
Dosing is based on the intensity of the renal replacement therapy

CVVHF intensity	Starting dose infused over 24 hours
10 to 15ml/kg/hr	1g
15.1 to 20ml/kg/hr	1.25g
20.1 to 25ml/kg/hr	1.5g
25.1 to 30ml/kg/hr	1.75g
>30ml/kg/hr	2g

Note: A maximum dose of **4g/day** should be used. Please contact pharmacy if levels remain subtherapeutic at this dose

Administration

For **central** administration: Prepare 500mg vancomycin in 50ml of sodium chloride 0.9% (10mg/ml) and repeat as necessary

For **peripheral** administration into a large vein green cannula: Prepare 500mg vancomycin in 100ml sodium chloride 0.9% (5mg/ml) and repeat as necessary

Ensure infusion pumps are checked **hourly** whilst being used

See *Appendix 2* for infusion rates

Therapeutic Drug Monitoring

Take blood for vancomycin level every morning at 6-8am.
Label the sample (in gold topped clotted bottle): '*Random vancomycin level'*
Adjust total daily dose according to the level as shown below

Vancomycin level	Dose change required
<15mg/L	Increase by 500mg per day
15-25mg/L	No change
>25mg/L	Decrease by 500mg per day*
>30mg/L	Stop infusion for 6 hours and restart at lower dose (discuss with ward pharmacist)

**If patient is already only receiving 500mg per day, reduce dose to 250mg per day*

Transfer to non-critical care wards

Vancomycin should be converted to intermittent dosing before being transferred to ward areas
Dosing should be based on the total daily dose of vancomycin

Doses up to 1g in 24 hours should be prescribed every 24 hours
Doses between 1.25g and 3g should be divided into two doses and prescribed every 12 hours
Doses over 3.25g should be divided into three doses and prescribed every 8 hours
Round doses to the nearest 250mg
Contact pharmacy for advice if doses cannot be divided equally

Start intermittent dosing and document when to re-check levels as shown below

Last vancomycin level	Converting to intermittent dosing	Re-check next vancomycin level
<15mg/L	Contact pharmacy for advice	
15-20mg/L	Stop infusion at a suitable time and start intermittent dosing immediately	Pre-dose level before the fourth intermittent dose*
20-25mg/L	Stop infusion and start intermittent dosing 8-12 hours later	Pre-dose level before the fourth intermittent dose*
>25mg/L	Contact pharmacy for advice	

**If the patient is on once daily dosing, re-check next vancomyin level pre-dose before the second intermittent dose*

Piperacillin-Tazobactam

Background

Beta-lactam antibiotics display time dependent activity for bacterial killing, where efficacy is correlated to the time that free plasma drug concentrations remain 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 urinary tract infections (including pyelonephritis)
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections (including diabetic foot infections)
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Contra-indications

Hypersensitivity to the 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).

Cautions

Neurological complications in the form of convulsions may occur when high doses are administered, especially in patients with impaired renal function

Tazocin may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis. If patients develop a skin rash they should be monitored closely and Tazocin discontinued if lesions progress.

Adverse effects

The most commonly reported adverse reaction is diarrhoea
Among the most serious adverse reactions are pseudo-membranous colitis and toxic epidermal necrolysis

Interactions

Piperacillin may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid substance toxicity.

Dose

Loading dose

A loading dose is always required prior to starting a continuous infusion
The continuous infusion should be started immediately after the loading dose

Patients who have already received a dose of piperacillin/tazobactam in the last 8 hours do **NOT** require a loading dose and can be started on the continuous infusion immediately

Loading Dose	Reconstitution and Dilution
4.5g as a slow IV bolus over 5 mins	Reconstitute each vial with 20ml sodium chloride 0.9%

Continuous infusion

Initial 48 hours:

	Dose	Reconstitution and Dilution	Infusion Rate	Equivalent Intermittent Dose
Maintenance dose: 1st 48 hours (all patients)	13.5g/24hours	Reconstitute each 4.5g vial with 20mL sodium chloride 0.9% and add to 250mL sodium chloride 0.9%. Final volume = 310mL (44mg/mL)	12.9ml/hour (over 24 hours)	4.5g every 8 hours

For nosocomial pneumonia, pseudomonas infections, resistant infections (on advice of microbiology) and bacterial infections in neutropenic patients the recommended dose is 18g/24hours (equivalent to 4.5g QDS)

After 48 hours:

Not in AKI or on CRRT				
If CrCl >20ml/min	Continue infusion of 13.5g/24 hours	Reconstitute each 4.5g vial with 20mL sodium chloride 0.9% and add to 250mL sodium chloride 0.9%. Final volume = 310mL (44mg/mL)	12.9ml/hour (over 24 hours)	4.5g every 8 hours
If CrCl ≤20ml/min	Reduce infusion to 9g/24 hours	Reconstitute each 4.5g vial with 20mL sodium chloride 0.9% and add to 250mL sodium chloride 0.9%. Final volume = 290mL (31mg/mL)	12.1ml/hour (over 24 hours)	4.5g every 12 hours

Acute Kidney Injury *(as per KDIGO guidelines – see Appendix 1). Requires daily assessment*				
Stage 1 or 2	Continue infusion of 13.5g/24 hours	Reconstitute each 4.5g vial with 20mL sodium chloride 0.9% and add to 250mL sodium chloride 0.9%. Final volume = 310mL (44mg/mL)	12.9ml/hour (over 24 hours)	4.5g every 8 hours
Stage 3	Reduce infusion to 9g/24 hours	Reconstitute each 4.5g vial with 20mL sodium chloride 0.9% and add to 250mL sodium chloride 0.9%. Final volume = 290mL (31mg/mL)	12.1ml/hour (over 24 hours)	4.5g every 12 hours

Requiring CRRT				
On CVVHF	Continue infusion of 13.5g/24 hours	Reconstitute each 4.5g vial with 20mL sodium chloride 0.9% and add to 250mL sodium chloride 0.9%. Final volume = 310mL (44mg/mL)	12.9ml/hour (over 24 hours)	4.5g every 8 hours

For nosocomial pneumonia, pseudomonas infections, resistant infections (on advice of microbiology) and bacterial infections in neutropenic patients the recommended dose is 18g/24hours (equivalent to 4.5g QDS) in patients on CRRT or with a CrCl ≥40ml/min and not in AKI stage 2-3.

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

Transfer to non-critical care wards

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

Meropenem

Background

As with other beta-lactam antibiotics, meropenem displays time dependent bactericidal activity, where efficacy is correlated to the time that free plasma drug concentrations remain above the minimum inhibitory concentration (MIC) of the targeted pathogen. It has been demonstrated that continuous infusions of beta lactam antibiotics 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 and ventilator-associated pneumonia.
- Broncho-pulmonary infections in cystic fibrosis
- Complicated urinary tract infections
- Complicated intra-abdominal infections
- Complicated skin and soft tissue infections
- Acute bacterial meningitis
- Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above

Contra-indications

- Hypersensitivity to meropenem or any other carbapenem antibacterial agent.
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of beta lactam antibacterial agent (e.g. penicillins or cephalosporins).

Cautions

- Hepatic function should be closely monitored during treatment with meropenem due to the risk of hepatic toxicity
- Seizures have infrequently been reported during treatment with carbapenems, including meropenem
- Antibiotic-associated colitis and pseudomembranous colitis have been reported with meropenem, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of meropenem

Adverse effects

The most frequently reported adverse effects are: diarrhoea, rash, nausea/vomiting and injection site inflammation.
The most commonly reported meropenem-related laboratory adverse events are thrombocytosis and increased hepatic enzymes.

Interactions

The concomitant use of meropenem and valproic acid/sodium valproate is not recommended

Dose

Loading dose

A loading dose is always required prior to starting a continuous infusion
The continuous infusion should be started immediately after the loading dose

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

Loading Dose	Reconstitution and Dilution
1g as a slow IV bolus over 5 mins	Reconstitute each vial with 20ml water for injection

Continuous infusion

Initial 48 hours:

	Dose	Reconstitution and Dilution	Infusion Rate	Equivalent Intermittent Dose
Maintenance dose: 1st 48 hours (all patients)	3g/24hours	Reconstitute a 1g vial with 20ml sodium chloride 0.9% and add to 100ml sodium chloride 0.9%. Final volume = 120ml (8.3mg/ml) **Note: only ONE vial to be reconstituted at a time due to drug stability issues >8hours**	15ml/hour (over 8 hours)	1g every 8 hours

For CNS infections, pseudomonas infections and resistant infections (on advice of microbiology) double the loading dose into the same volumes as above

After 48 hours:

Not in AKI or on CRRT				
If CrCl >26ml/min*	Continue infusion of 3g/24hours	Reconstitute a 1g vial with 20ml sodium chloride 0.9% and add to 100ml sodium chloride 0.9%. Final volume = 120ml (8.3mg/ml)	15ml/hour (over 8 hours)	1g every 8 hours
If CrCl ≤25ml/min**	Reduce infusion to 2g/24 hours	Reconstitute a 500mg vial with 10ml sodium chloride 0.9% and add to 50ml sodium chloride 0.9%. Final volume = 60ml (8.3mg/mL)	10ml/hour (over 6 hours)	1g every 12 hours

Acute Kidney Injury *(as per KDIGO guidelines – see Appendix 1). Requires daily assessment*				
Stage 1 or 2*	Continue infusion of 3g/24hours	Reconstitute a 1g vial with 20ml sodium chloride 0.9% and add to 100ml sodium chloride 0.9%. Final volume = 120ml (8.3mg/ml)	15ml/hour (over 8 hours)	1g every 8 hours
Stage 3	Reduce infusion to 2g/24 hours	Reconstitute a 500mg vial with 10ml sodium chloride 0.9% and add to 50ml sodium chloride 0.9%. Final volume = 60ml (8.3mg/mL)	10ml/hour (over 6 hours)	1g every 12 hours

Requiring CRRT				
On CVVHF	Continue infusion of 3g/24hours	Reconstitute a 1g vial with 20ml sodium chloride 0.9% and add to 100ml sodium chloride 0.9%. Final volume = 120ml (8.3mg/ml)	15ml/hour (over 8 hours)	1g every 8 hours

**For CNS, pseudomonas and resistant infections double the maintenance doses into the same volume*
*** For CNS, pseudomonas and resistant infections (on advice of microbiology) increase dose to 3g/24 hours*

Monitor renal function daily in critically unwell patients and adjust dosing accordingly
Ensure infusion pumps are checked **hourly** whilst being used
Ensure only **ONE** vial to be reconstituted at a time due to drug stability issues >8hours

Transfer to non-critical care wards

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

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Appendix 1

KDIGO criteria for acute kidney injury

Stage	Serum Creatinine (SCr)	Timing	Urine output
1	Increase 1.5 – 1.9 x Baseline SCr	7 d	< 0.5 mL/kg/h for 6 – 12 h
or	Increase in SCr by ≥ 26.5 µmol/L (≥0.3 mg/dL)	48 h	
2	Increase 2.0 – 2.9 x baseline SCr	7 d	< 0.5 mL/kg/h for ≥ 12 h
3	Increase ≥3.0 x baseline SCr	7 d	< 0.3 mL/kg/h for ≥ 24 h
or	Increase in SCr to ≥ 353.6µmol/L (≥ 4.0 mg/dL)	7 d	*or*
or	Initiation of renal replacement therapy		Anuria for ≥ 12 h

Appendix 2

The infusion rates for differing doses of vancomycin by continuous infusion:

Vancomycin (total daily dose)	Infusion rate via central line in ml/hour (10mg/ml)	Infusion rate via peripheral line in ml/hour (5mg/ml)
4000mg	16.7	33.3
3750mg	15.6	31.3
3500mg	14.6	29.2
3250mg	13.5	27.1
3000mg	12.5	25
2750mg	11.5	22.9
2500mg	10.4	20.8
2250mg	9.4	18.8
2000mg	8.3	16.7
1750mg	7.3	14.6
1500mg	6.3	12.5
1250mg	5.2	10.4
1000mg	4.2	8.3
750mg	3.1	6.3
500mg	2.1	4.2
250mg	1.1	2.1