Guideline

Effective from: January 2024
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Medicine – Antimicrobial Therapeutic Drug Monitoring

NSQHS STANDARDS

4. Medication Safety | 3.Healthcare-Associated Infection | 1. Clinical Governance | 2. Partnering with Consumers

Purpose and intent

To provide support for clinicians interpretating therapeutic drug monitoring (TDM) for antimicrobials, ensuring a consistent and appropriate approach.

This guideline provides guidance about antimicrobial concentrations in plasma or serum. For concentration analysis from other sites (e.g. cerebrospinal fluid (CSF) or urine), contact the Infectious Diseases service or ID/AMS pharmacist for advice.

Please note: This is not an antimicrobial prescribing guideline. It should be used to guide interpretation of antimicrobial TDM only. For specific prescribing information (e.g. drug interactions, starting doses, toxicity not related to serum concentrations and monitoring parameters), consult other resources. Prescribing of antimicrobials should always follow local antimicrobial stewardship procedures.

Refer to Metro North Vancomycin Management in Adult Patients procedure for specific details regarding vancomycin (or the relevant local guideline) and Queensland Health Aminoglycoside dosing in adults guideline for aminoglycosides.

Scope and target audience

This guideline aims to provide support for all Metro North Hospital and Health Service (MNHHS) staff (permanent, temporary and casual), undergraduate students (Medical, Nursing and Midwifery) and Australian Defence Force personnel (Medical, Nursing and Midwifery) on placement within MNHHS.

Background

Therapeutic drug monitoring (TDM) allows individualisation of drug dose by checking plasma or serum drug concentrations and adjusting the dose so that the drug concentration is within a target range. TDM is recommended in specific circumstances to ensure effectiveness of an antimicrobial and minimise likelihood of toxicity related to drug overexposure.

Not all patients require TDM. TDM should occur at the discretion of the treating clinician.

Consider TDM for the following patients:

- those with kidney dysfunction or suspected augmented renal clearance (see below)
- those with liver dysfunction
- other conditions likely to cause pharmacokinetic changes (e.g. cystic fibrosis, critically unwell patients)
- those at extremes of weight (less than 50 kg or more than 120 kg, or a BMI less than 20 or more than 30 kg/m^2)
- elderly (older than 80)
- hypoalbuminemia (< 24 g/L)
- difficult to treat pathogens (i.e., high minimum inhibitory concentration (MIC))
- difficult to treat sites of infection (e.g., deep-seated infections—bone and joint infections, CNS infections)
- those with drug interactions potentially affecting drug concentrations
- those with non-resolving infections
- those with suspected drug toxicity (particularly if an exposure toxicity relationship is known for the drug)
- those on drugs with a narrow therapeutic index (e.g., cefepime, azole antifungals).

Augmented renal clearance

Augmented renal clearance (traditionally defined as a GFR above 130 mL/min/1.73m^2) describes patients with increased clearance of drugs due to increased kidney function. It has been traditionally described in critically unwell patients but should be suspected in those with a creatinine concentration within the reference range who are aged younger than 55 years, presenting after trauma or neurosurgical intervention or a significant burn, or those with sepsis or pancreatitis.

Repeat sampling for TDM

After a dose change, check a repeat antimicrobial concentration once 4 – 5 half lives of the drug have passed at the new dose. Specific advice is given in the ‘sample collection’ section of each drug monograph. If the drug concentration is within range and no dose change is made, rechecking the drug concentration may not be needed unless the concentration is suspected to have changed (eg in the setting of kidney or liver injury, kidney function improvement or development of drug toxicity).

Process

General advice for TDM

Take plasma samples for TDM after at least 4 to 5 drug half-lives have passed, i.e. once at steady state, though this can change based on dosing administration method and whether a loading dose was given.

Aim to collect blood via venepuncture from the ‘opposite arm’ (i.e. not the arm where the antimicrobial is being administered). Peripherally inserted central catheter (PICC) lines may be used for sample collection in specific circumstances, after adequate flushing of the line, though drug concentrations from a PICC line may be inaccurate (see relevant local procedures).

Interpret drug concentrations in the context of the patient’s organ function (i.e. is the patient’s kidney function stable).

A minimum inhibitory concentration (MIC) is needed to determine effectiveness of the antimicrobial. For patients where a pathogen is isolated, an MIC can be requested from the microbiology laboratory. If this is not available, use the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints as an estimate.

Process for TDM:

The medical officer or pharmacist should document when a blood sample is needed on the National Standard Medication Chart and in the patient notes. For inpatient electronic prescribing, a TDM placeholder can be added as a prompt for nursing staff, see the PowerChart Medication Level Needed Guide.

For the dose before a TDM sample time, if drug administration occurs outside the documented time on the prescription, document the actual time of drug administration and contact the pharmacist to check if TDM is still appropriate.

Unless drug toxicity is strongly suspected do not withhold the dose after sampling. If drug toxicity is suspected, the medical officer must note to withhold the drug on the prescription and communicate the plan with nursing staff. In addition, medical staff must document in the patient notes.

Samples should be sent to Pathology Queensland immediately after collection. See individual drug monographs for sample handling information.

Table 1 outlines relevant antimicrobials and current frequency of testing. This list of medications and days of test performance may change. The HPLC laboratory processes samples in the lab Monday to Saturday, for drugs analysed daily, if the sample can get to the lab by 10am, results are available the same day. If results are urgent, call the HPLC laboratory staff to ensure the sample is processed that day.

Table 1 - TDM undertaken by the HPLC laboratory at Pathology Queensland

Assays run daily (Mon-Sat)*		**Assays run weekly (usually Wednesday)**
• aciclovir	• ertapenem	• azithromycin
• ampicillin	• flucloxacillin	• bedaquiline
• amoxicillin	• fluconazole	• cefoxitin
• benzylpenicillin	• ganciclovir	• clarithromycin
• cefalotin	• itraconazole	• clofazimine
• cefazolin	• meropenem	• ethambutol
• cefepime	• moxifloxacin	• isoniazid
• ceftazidime	• piperacillin+tazobactam	• linezolid
• ceftolozane+tazobactam	• posaconazole	• pyrazinamide
• ceftriaxone	• teicoplanin	• rifampicin
• ciprofloxacin	• voriconazole	• tigecycline

*Samples at the HPLC lab by 10am will have results available same day (for those processed daily).

TDM targets for beta-lactam drugs

Concentrations reported by Pathology Queensland for beta-lactams are the unbound (free) values.

For intermittent beta-lactam dosing, it is recommended that the unbound (or free) drug concentration is above the MIC for the entire dosing interval (denoted as 100% fT>MIC). For patients on a beta-lactam continuous infusion, aim for 4 times above the MIC at any time during the dosing interval.

In some circumstances, i.e., clinically stable, low risk patients who have already completed a few days of therapy, a target of being above the MIC for at least half the dosing interval (denoted as 50% fT>MIC) may be appropriate. In this setting, check a drug concentration halfway through the dosing interval (if dosing is at 8am, 4pm and 12am take a sample at 12pm or 8pm) and check it is above the MIC of the pathogen you are treating.

For infections in tissues that are difficult to penetrate (e.g., CNS infections) or in patients who are critically unwell, use a target of 4 times above the MIC at the end of the dosing interval. Take a trough concentration (i.e. a sample within 60 minutes of the next dose) and aim for a concentration 4 times above the MIC of the pathogen you are treating.

Summary table of target concentrations for intermittent infusion

Drug	Minimum concentration[1]	Maximum concentration
Ampicillin/amoxicillin (unbound, trough)	8 mg/L (Enterobacterales) 4 mg/L (*Enterococcus sp*) 0.5 mg/L (*Streptococcus pneumoniae*)	50 mg/L
Benzylpenicillin (unbound, trough)	0.125 mg/L (penicillin susceptible *Staphylococcus sp*) 0.25 mg/L (*Streptococcus* group A, B, C and G)	50 mg/L
Cefazolin (unbound, trough)	2 mg/L (*S. aureus*)	20 mg/L[2]
Cefepime (unbound, trough)	1 mg/L (Enterobacterales) 8 mg/L (*Pseudomonas sp*)	20 mg/L
Ceftazidime (unbound, trough)	1 mg/L (Enterobacterales) 8 mg/L (*Pseudomonas sp*)	50 mg/L
Ceftolozane + tazobactam[3] (trough, unbound)	2 mg/L (Enterobacterales) 4 mg/L (*Pseudomonas sp*)	50 mg/L
Ceftriaxone (unbound, trough)	1 mg/L (Enterobacterales)	20 mg/L[2]
Ciprofloxacin (total)	Peak concentration > 5mg/L (*Pseudomonas sp*) AUC:MIC > 125 mg*hr/L	Trough concentration >5 mg/L
Daptomycin (total)	(for Staphylococcal infections) AUC:MIC >666 mg*hr/L, or trough concentrations >3.2mg/L	Trough concentration >19.5 mg/L
Flucloxacillin (unbound, trough)	1 mg/L (*S. aureus*)	20 mg/L
Fluconazole (total, trough)	2 mg/L (C*andida sp*)	50 mg/L
Ganciclovir	Depends on indication, see ganciclovir monograph	
Itraconazole (total, trough)	1-2 mg/L	4 mg/L
Linezolid (total, trough)	2 mg/L	7 mg/L
Meropenem (unbound, trough)	2 mg/L	44 mg/L
Piperacillin+tazobactam (unbound, trough)	Piperacillin: 8 mg/L (Enterobacterales) 16 mg/L (*Pseudomonas sp*) Tazobactam: 2 mg/L	Piperacillin: 130 mg/L Tazobactam: 20 mg/L
Posaconazole (total, trough)	0.5 mg/L (prophylaxis) 1 mg/L (treatment)	3 mg/L
Teicoplanin (total trough)	>15 mg/L (uncomplicated infection) >20 mg/L (serious infection)	60 mg/L
Voriconazole (total, trough)	1 mg/L (or 2 mg/L for CNS or bulky disease)	5.5 mg/L

1: Use individual patient MIC if available, or use breakpoint MICs available from EUCAST, see EUCAST: Clinical breakpoints and dosing of antibiotics. If a pathogen has reported intermediate susceptibility to an antimicrobial – seek expert advice (the target trough concentration may be higher). Due to routine reporting of I for *Pseudomonas* spp. for some drugs, these targets have been included.
2: Concentrations above 20 mg/L are used as they are more than 10 times above the breakpoint MIC, though toxicity is not usually seen below 50 mg/L.
3: Target concentrations based on ceftolozane concentration.

Antimicrobial TDM monographs

Cefazolin Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected augmented renal clearance
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Age older than 80
- Significant staphylococcal infections, other difficult to treat pathogens (i.e. high MIC)
- Non-resolving infections

General pharmacokinetics:

Protein binding: 73-87%
Half-life: 2 hours
Excretion: renal clearance, primarily glomerular filtration, to a lesser extent, tubular secretion.

Sample collection should occur at least 12 hours after dose initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube no gel (lithium heparin)
- 6 mL Red top tube no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing*:*

- Collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time), this will show if 100% fT > MIC is being achieved.

Continuous infusions*:*

- concentrations should be the same at any time during continuous infusion, but usually a sample at the end of the infusion (i.e. while still running but just before infuser or infusion bag change) is recommended. Do not stop infusion for a sample, and do not take a sample from the line where the drug is being infused.

Sample handling

Sample must be delivered to laboratory as soon as possible, within 2 hours of collection. Test is performed Mondays to Saturdays. If samples get to pathology before 10am, results are available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20^{o}C.

Pathology Queensland reports the unbound concentration for cefazolin.

Target range: unbound trough concentration above the pathogen's MIC (e.g. 2 or 4 mg/L) to below 20 mg/L.

Effectiveness: 100% fT > MIC, which equates to a concentration above the MIC at the end of the dosing interval. If no specific MIC is available for the patient, aim for an unbound (free) cefazolin concentration at the end of the dosing interval of above 2 mg/L for *Staphylococcus aureus*, or 4 mg/L for susceptible Gram-

negative pathogens. For patients on a continuous infusion, aim for 4 times above the MIC. See also Targets for beta-lactam drugs.

For patients on dialysis (where cefazolin is being dosed 3 times a week after dialysis), check a concentration before dialysis and aim to be above the MIC.

Toxicity: not well defined, seizures have occurred with very high concentrations in the context of kidney failure. In general, concentrations above 20mg/L are not required and can prompt dose review.

Dose adjustment (see also repeat sampling)

If the concentration is low:

- Increase the dosing frequency (i.e. from 8-hourly to 6-hourly, preferred over increasing the dose) or change to an extended infusion (administer the infusion over half the dosing interval) or continuous infusion.

Beta-lactam concentrations can be boosted by probenecid, discuss with Infectious Diseases and check drug interactions.

If the concentration is high, consider withholding drug and decreasing the dose.

For more information, see CONTACTS.

Cefepime Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected augmented renal clearance
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Age older than 80
- Suspected cefepime-induced neurotoxicity
- Difficult to treat pathogens (i.e. high MIC) or non-resolving infections.

General pharmacokinetics

Protein binding: 16%

Half-life: 2 hours

Excretion: almost exclusively by renal mechanisms, primarily glomerular filtration.

Sample collection should occur at least 12 hours after dose initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing*:*

- collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time), this will show if 100% fT > MIC is being achieved.

Continuous infusions*:*

- concentrations should be the same at any time during continuous infusion, but usually a sample at the end of the infusion (i.e. while still running but just before infuser or infusion bag change) is recommended. Do not stop infusion for a sample, and do not take a sample from the line where the drug is being infused.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20^{o}C.

Pathology Queensland reports the unbound concentration for cefepime.

Target range: unbound trough concentration above the MIC (e.g. 1 or 8 mg/L) to below 20 mg/L (for intermittent infusion).

Effectiveness: 100% fT > MIC, which equates to a concentration above the MIC at the end of the dosing interval. If no pathogen specific MIC is available for the patient, aim for an unbound (free) concentration of cefepime above 1 mg/L for Enterobacterales (or 8 mg/L for *Pseudomonas* spp.) at the end of the dosing interval. For patients on a continuous infusion, aim for 4 times above the MIC. See also Targets for beta-lactam drugs.

Toxicity: Neurotoxicity is dose dependent, though a definitive toxicity threshold has not been found. Aim for a trough concentration below 20 mg/L or for those on continuous infusion, a random concentration below 35 mg/L.

Dose adjustment (see also repeat sampling)

If the concentration is below the MIC of the pathogen you are treating:

- Increase the dosing frequency (e.g. from 12 hourly to 8 hourly, preferred over increasing the dose) or change to an extended infusion (administer the infusion over half the dosing interval).

If the concentration is high:

- Consider withholding drug and decreasing the dose.

For more information, see CONTACTS.

Ceftriaxone Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected augmented renal clearance
- Liver dysfunction
- Hypoalbuminemia (< 24 g/L)
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Difficult to treat pathogens (i.e. high MIC) or non-resolving infections

General pharmacokinetics:

Protein binding: 83-95%
Half-life: 8 hours
Excretion: 33-67% excreted unchanged in urine, remainder secreted in bile

Sample collection should occur at least 12 hours after dose initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube no gel (lithium heparin)
- 6 mL Red top tube no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing*:*

- collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time), this will show if 100% fT > MIC is being achieved.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Pathology Queensland reports the unbound concentration for cefazolin.

Target range: unbound trough concentration above the pathogen's MIC (e.g. 1 mg/L) to below 20 mg/L.

Effectiveness: 100% fT > MIC, which equates to a concentration above the MIC at the end of the dosing interval. If no specific MIC is available for the patient, aim for an unbound (free) ceftriaxone concentration at the end of the dosing interval of above 1 mg/L for Enterobacterales. See also Targets for beta-lactam drugs.

Toxicity: not well defined. In general, concentrations above 20 mg/L are not required and can prompt dose review.

Dose adjustment (see also repeat sampling)

If the concentration is below the MIC increase the dosing frequency (i.e. from daily to 12-hourly, preferred over increasing the dose).

If the concentration is high, consider withholding drug and decreasing the dose.

For more information, see CONTACTS.

Ciprofloxacin Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected augmented renal clearance
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Age older than 80
- (for oral therapy) Suspected poor gastrointestinal absorption
- Difficult to treat pathogens (i.e. high MIC) or non-resolving infections

General pharmacokinetics

Absorption (bioavailability): 70%

Protein binding: 20-40%

Half-life: 4 hours

Metabolism: 33-50% drug cleared by nonrenal mechanisms

Excretion: 50-75% renal excretion (exceeds creatinine clearance due to significant proximal tubular secretion).

Sample collection should occur 24 hours after drug initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 4.5 mL light Green top tube – gel (lithium heparin)
- 5 mL Gold top tube – gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing*:*

- For AUC based monitoring—collect 2 samples, one sample 2 hours after dose and one 6-8 hours post dose.
- For peak concentration—collect a sample 30 minutes after infusion completed or 2 hours post oral dose.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Pathology Queensland reports the total concentration for ciprofloxacin.

Target range: (total concentration) Cmax of 10 x MIC or an AUC_{0-24}/MIC of >125 mg*hr/L.

Effectiveness (for Gram-negative pathogens): the PKPD targets for ciprofloxacin are either:

- an AUC_{0-24}/MIC of >125 mg*hr/L (contact ID/AMS pharmacist to help with AUC calculation) or
- a Cmax 10 times above the MIC (see above for sample timing).

The MIC breakpoint for Enterobacterales is 0.25 mg/L and for *Pseudomonas* spp. is 0.5 mg/L – if an individual patient specific MIC is not available, use these as the MIC target.

Toxicity: Dose-dependent toxicity is not well defined, concentrations significantly above the targets can prompt dose review (e.g., a trough concentration above 5 mg/L or an $AUC_{0\text{-}24}$ above 500 mg*hr/L).

Dose adjustment (see also repeat sampling)

If the concentration is low:

- Ensure drug is not being administered with aluminium, magnesium, calcium, iron or zinc (significant decrease in bioavailability).
- Increase the dose or frequency.

If the concentration is high:

- Decrease dosing frequency (i.e., from 12-hourly to 24-hourly).

For more information, see CONTACTS

Daptomycin Therapeutic Drug Monitoring

Consider TDM in patients with:

- Hypoalbuminemia (< 24 g/L)
- Kidney dysfunction or suspected augmented renal clearance
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Difficult to treat pathogens (i.e. high MIC) or non-resolving infections.

General pharmacokinetics

Protein binding: 90-93%, Half-life: 8-9 hours (if CrCl > 80 mL/min), 18-30 hours (end stage renal disease).

Renally cleared (minimal to no active tubular secretion of daptomycin); daptomycin is not metabolised.

Sample collection should occur after at least 2 doses (48 hours) of daptomycin have been given at the same dose.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing*:*

- collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time).
- for calculation of AUC, seek advice from ID/AMS teams.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10 am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20 °C.

Pathology Queensland reports the total concentration for daptomycin.

Effectiveness: daptomycin efficacy has been linked to achieving an AUC/MIC ratio of > 666 mg*hr/L (total concentration) for staphylococcal infections. If calculation of AUC is not possible, an alternative is to aim for a (total) trough concentration above 3.2 mg/L. For enterococcal infections, where the MIC may be above 1 mg/L, seek expert advice.

Toxicity: daptomycin total trough concentrations above 19.5 mg/L and 24.3 mg/L have been associated with increased creatinine phosphokinase (CPK).

Dose adjustment (see also repeat sampling)

For patients with low concentrations increase the daily dose, doses up to 12 mg/kg have been used (particularly for enterococcal infections). If doses above 12 mg/kg are needed, seek expert advice.

For patients with supratherapeutic concentrations, decrease the dose or frequency (48-hourly dosing is recommended in patients with creatinine clearance less than 30 mL/min).

For more information, see CONTACTS

Flucloxacillin Therapeutic Drug Monitoring

Consider TDM in patients with:

- Hypoalbuminemia (< 24 g/L)
- Liver dysfunction, kidney dysfunction or suspected augmented renal clearance
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Age older than 80
- (for oral therapy) Suspected poor gastrointestinal absorption
- Difficult to treat pathogens (i.e. high MIC) or non-resolving infections.

General pharmacokinetics

Absorption (bioavailability): 40-55%, Protein binding: 90-95%, Half-life: 0.75 hours

Metabolism: In patients without kidney failure metabolism us usually <10%; this is increased in kidney failure

Excretion: predominantly via the kidney (by both glomerular filtration and tubular secretion).

Sample collection should occur at least 12 hours after dose initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing*:*

- collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time), this will show if 100% fT > MIC is being achieved.

Continuous infusions*:*

- concentrations should be the same at any time during continuous infusion, but usually a sample at the end of the infusion (i.e. while still running but just before infuser or infusion bag change) is recommended. Do not stop infusion for a sample, and do not take a sample from the line where the drug is being infused.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Pathology Queensland reports the unbound concentration for flucloxacillin.

Target range: unbound trough sample above pathogen's MIC (e.g. 1 mg/L) to below 20 mg/L.

Effectiveness: 100% fT > MIC, which equates to a level above the MIC at the end of the dosing interval. If no pathogen specific MIC is available for the patient, aim for an unbound (free) concentration above 1 mg/L at the end of the dosing interval. For clinically stable patients, aim for 50% fT>MIC, aiming for a

flucloxacillin concentrations above the MIC halfway through the dosing interval. For patients on a continuous infusion, aim for 4 times above the MIC. See also Targets for beta-lactam drugs.

Toxicity: Not well defined. In general, trough concentrations above 20 mg/L (unbound) are not required and should prompt a dose decrease. Neurotoxicity has been shown to be dose dependent and may improve with a dose decrease, other toxicities (hepatotoxicity) are likely idiosyncratic.

Dose adjustment (see also repeat sampling)

If the concentration is below the MIC of the pathogen you are treating:

- increase the dosing frequency (i.e. from 6-hourly to 4-hourly, preferred over increasing the dose) or (if IV) change to an extended infusion (administer the infusion over half the dosing interval) or continuous infusion
- (if oral) consider giving the drug in the fasting state (1 hour before food)
- review for drug interactions (including concomitant voriconazole or posaconazole).

Beta-lactam concentrations can be boosted by probenecid, discuss with Infectious Diseases and check drug interactions.

If the concentration is high, consider withholding drug and decreasing the daily dose—flucloxacillin has linear pharmacokinetics (if kidney function is stable) so halving the dose roughly halves the drug concentration.

For more information, see CONTACTS

Fluconazole Therapeutic Drug Monitoring

TDM is generally not needed for fluconazole. If there is strong clinical suspicion of altered pharmacokinetics, it can be considered. Patients may include those with:

- Kidney dysfunction or suspected augmented renal clearance
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Age older than 80
- Potential drug interactions affecting fluconazole concentration.
- Difficult to treat pathogens (i.e. high MIC)
- Severe non-resolving infections
- (for oral therapy) Suspected poor gastrointestinal absorption

General pharmacokinetics

Absorption (bioavailability): above 90%

Protein binding: 10%

Half-life: 20-50 hours

Metabolism: 11% drug cleared by nonrenal mechanisms

Excretion: 80% renal excretion

Sample collection should occur 4 days after drug initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing:

- At least 4 days after starting or a dose change, collect a trough sample (i.e. within 60 minutes of the next dose, provided the previous dose was given on time).

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Pathology Queensland reports the total concentrations for fluconazole.

Target range: a trough concentration above the pathogen's MIC

Effectiveness: although 24-hour AUC/MIC ratio of ≥ 55–100 mg*hr/L is recommended for candidemia, a simpler approach to TDM is to aim for a trough concentration above the MIC of the pathogen (i.e. above 2 mg/L for susceptible candida).

Toxicity: Toxicity exposure relationships are not well defined.

Dose adjustment (see also repeat sampling) can be made linearly up to doses of 800mg, i.e. doubling the dose doubles the drug concentration. New dose = (desired concentration/actual concentration) * current dose.
For more information, see CONTACTS

Ganciclovir Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected augmented renal clearance
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Age older than 80
- Non-resolving infections.

General pharmacokinetics

Protein binding: 1-2%

Half-life: 3.5 hours

Excretion: renal excretion by glomerular filtration and active tubular secretion.

Sample collection should occur at least 48 hours after drug initiation or a dose change (intermittent infusion) or after at least 24 hours if using a continuous infusion.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 4 mL Purple top tube (EDTA)
- 5 mL Gold top tube – gel (Clotted)

Intermittent dosing*:*

- At least 48 hours after starting or changing the dose collect a trough sample (i.e. within 60 minutes of the next dose, provided the previous dose was given on time).
- To measure AUC, at least 48 hours after starting or changing the dose, take a peak sample (1 hour after administration) and another sample 6 hours after administration (or as directed by dosing software)

Continuous infusion

- After at least 24 hours on continuous infusion, a sample can be taken at any time, although at just before bag or infuser change is recommended. Do not stop infusion for a sample, and do not take a sample from the line where the drug is being infused.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Pathology Queensland reports the total concentration of ganciclovir**.**

Effectiveness: for prophylaxis or maintenance therapy aim for a trough concentration of 1 - 2 mg/L or an AUC of 40-60 mg*hr/L (if on continuous infusion correlates with a random concentration of 1.6 to 2.5 mg/L).

Higher exposures of a trough concentration of 2 - 4mg/L or an AUC of 80-120 mg*hr/L or have been proposed as targets for initial IV treatment (induction therapy) based on expert opinion or *in vitro* data. Prolonged exposure to these higher targets increases the risk of toxicity. Higher target concentrations may be required for resistant CMV where high dose ganciclovir is being used.

For patients on a continuous infusion, the drug concentration (mg/L) * 24(hrs) = 24-hour AUC (mg*hr/L). **Toxicity:** Not well defined. If trough concentration exceeds 5mg/L consider dose reduction, especially if haematological toxicity also present.
Dose adjustment (see also repeat sampling) Ensure the patient is receiving dose appropriate for renal function according to local guidelines. For dose adjustment, contact ID/AMS pharmacist.
For more information, see CONTACTS

Itraconazole Therapeutic Drug Monitoring

All patients receiving itraconazole may be considered for therapeutic drug monitoring

General pharmacokinetics:

Protein binding: 99.8%
Half-life: 15-42 hours
Excretion: less than 2% excreted unchanged in urine, predominantly hepatically metabolised

Sample collection: The first concentration can be checked after 10-14 days of dosing (if a loading dose was used, sampling may be able to performed earlier). Resampling can occur 7 days after a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Gel tubes have the potential to interfere with this assay. Using gel tubes may result in specimen rejection.

Intermittent dosing*:*

- collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time).

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20^{o}C.

Effectiveness: the concentration goal considered adequate for treatment of active fungal infections is 1–2 mg/L using HPLC. The target trough concentration most often suggested for prophylaxis is above 0.5 mg/L. Itraconazole is metabolised to hydroxyitraconazole, which has roughly equivalent antifungal activity to the parent drug.

Toxicity: avoid trough concentrations above 4 mg/mL.

Dose adjustment (see also repeat sampling). Brands of itraconazole are not bioequivalent.

If the concentration is low:

- Increase Itranox dose by 25–50%; if taking Itranox capsules, also consider switching to itraconazole solution or Lozanoc capsules.
- Ensure Itranox capsules are taken with food, and avoid H_2 antagonist and proton pump inhibitor
- Ensure itraconazole solution is taken on empty stomach

If the concentration is high:

- Decrease dose or dosing frequency.

For more information, see CONTACTS

Linezolid Therapeutic Drug Monitoring

All patients receiving linezolid for longer than 2 weeks should be considered for therapeutic drug monitoring, along with any patient with a creatinine clearance of less than 30mL/min or frail or elderly patients (e.g. aged over 70 years).

General pharmacokinetics:

Protein binding: 31%
Half-life: 5 hours
Excretion: 65% clearance is nonrenal, approximately 30% drug is renally cleared.

Sample collection should occur 3-5 days after drug initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 4.5 mL light green top tube - gel (lithium heparin)
- 5 mL gold top tube – gel (Clotted)

Intermittent dosing:

- collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time).

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Target range: aim for a linezolid total trough concentration between 2 – 7 mg/L (for long term use, aim for the lower end of the target range).

Effectiveness: Maximum efficacy is demonstrated at %T>MIC of above 85% and an AUC_{0-2}/MIC ratio of 80–120 mg*hr/L. Traditionally a Cmin (trough concentration) above 2 mg/L has been used as the efficacy target, which for pathogens with an MIC of 1 mg/L, will provide an adequate AUC. For pathogens with an MIC of 2 mg/L, a trough concentration of 5 – 8 mg/L may be required to achieve the desired AUC, which comes with an increased risk of toxicity.

Toxicity: Linezolid-induced thrombocytopenia has been reported at trough concentrations above 7 – 10 mg/L and $AUC_{0–24}$ of 300 – 350 mg*hr/L**.** For long-term use (i.e. for MDR TB) aim for a trough concentration of 2 mg/L to minimise toxicity.

Dose adjustment (see also repeat sampling)

If the concentration is low: increase dose or dosing frequency to get to 600 mg 12-hourly. For patients with a trough concentration below 2 mg/L on 600 mg 12-hourly, seek expert advice, consider increasing to 600 mg 8-hourly, but trough concentrations must be rechecked within 48 hours, and this dose should only be used for a short period of time (i.e. a few days while critically unwell).

If the concentration is above 7 mg/L: if using twice daily dosing, decrease to daily dosing, if using 600mg daily decrease to 300mg daily. Recheck trough concentration after at least 48 hours at the same dose.

Check for drug interactions, including clarithromycin (increases linezolid concentrations) and rifampicin (decreases linezolid concentrations).

For more information, see CONTACTS

Meropenem Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected augmented renal clearance
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Age older than 80
- Difficult to treat pathogens (i.e. high MIC) or non-resolving infections

General pharmacokinetics

Protein binding: 2%

Half-life: 1 hour

Metabolism: 30% metabolism to inactive metabolite

Excretion: 70% renal clearance, primarily glomerular filtration

Sample collection should occur at least 12 hours after dose initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing*:*

- collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time), this will show if 100% fT > MIC is being achieved.

Continuous infusions*:*

- concentrations should be the same at any time during continuous infusion, but usually a sample at the end of the infusion (i.e. while still running but just before infuser or infusion bag change) is recommended. Do not stop infusion for a sample, and do not take a sample from the line where the drug is being infused.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Pathology Queensland reports the unbound concentration for meropenem.

Target range: unbound trough concentration above the MIC (e.g. 2 mg/L) to below 44 mg/L.

Effectiveness: 100% fT > MIC, which equates to a level above the MIC at the end of the dosing interval. If no pathogen specific MIC is available for the patient, aim for an unbound (free) trough concentration of

meropenem above 2 mg/L. For patients on a continuous infusion, aim for 4 times above the MIC. See also **Targets for beta-lactam drugs**.

Toxicity: Neurotoxicity and nephrotoxicity have been associated with total trough concentrations above 44.45 mg/L (unbound > 43.6 mg/L) and should prompt a dose decrease.

Dose adjustment (see also repeat sampling)

If the concentration is below the MIC of the pathogen you are treating:

- Increase the dosing frequency (e.g. from 8-hourly to 6-hourly, preferred over increasing the dose) or use an extended infusion (i.e. give the drug over 3 or 4 hours, ideally the extended infusion runs over half the dosing interval).

If the concentration is high:

- Consider withholding drug and decreasing the dose.

For more information, see CONTACTS

Piperacillin + Tazobactam Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected augmented renal clearance
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m^2)
- Age older than 80
- Difficult to treat pathogens (i.e. high MIC) or non-resolving infections

General pharmacokinetics

Protein binding: piperacillin 16-30% tazobactam 23-48%

Half-life: 1 hour (both piperacillin and tazobactam)

Excretion: 80% predominantly via the kidney (by both glomerular filtration and tubular secretion).

Sample collection should occur at least 12 hours after dose initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing*:*

- collect a trough sample (within 60 mins of the next scheduled dose, provided the dose before given at the scheduled time), this will show if 100% fT > MIC is being achieved.

Continuous infusions*:*

- concentrations should be the same at any time during continuous infusion, but usually a sample at the end of the infusion (i.e. while still running but just before infuser or infusion bag change) is recommended. Do not stop infusion for a sample, and do not take a sample from the line where the drug is being infused.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20^{o}C.

Pathology Queensland reports the unbound concentration for piperacillin.

Target range: an unbound piperacillin trough concentration above the pathogen's MIC (e.g. 8 or 16 mg/L) to below 130 mg/L. The target for tazobactam is a concentration above 2 mg/L and below 20 mg/L for nonbacteraemic ESBL infections.

Effectiveness: 100% fT > MIC, which equates to a level above the MIC at the end of the dosing interval. If no pathogen specific MIC is available for the patient, aim for an unbound (free) trough concentration of piperacillin above 8 mg/L (or 16 mg/L for *Pseudomonas* spp.). For patients on a continuous infusion, aim for 4 times above the MIC. See also **Targets for beta-lactam drugs.**

Toxicity: Not well defined. Neurotoxicity have been seen with total piperacillin concentrations of 150 mg/L. Unbound piperacillin concentrations above 130 mg/L or tazobactam concentrations above 20 mg/L should prompt a dose decrease.

Dose adjustment (see also repeat sampling)

If the concentration is below the MIC of the pathogen you are treating:

- Increase dosing frequency (i.e. from 8- hourly to 6-hourly, preferred over increasing the dose) or change to an extended infusion (administer the infusion over half the dosing interval) or continuous infusion.

If the concentration is high:

- Consider withholding drug and decreasing the dose.

For more information, see CONTACTS

Posaconazole Therapeutic Drug Monitoring

All patients receiving posaconazole for longer than 5 days may be considered for therapeutic drug monitoring (TDM). Patients with mucositis or diarrhoea often have low posaconazole concentrations and require proactive TDM.

General pharmacokinetics

Absorption (bioavailability): depends on the formulation, 54% for modified release tablet

Protein binding: above 98%

Half-life: 25-31 hours

Metabolism: hepatic metabolism, predominantly glucuronide conjugates, with only minor amounts of oxidative (CYP450 mediated) metabolites, less than 0.1% of posaconazole is excreted unchanged in urine.

Sample collection should occur 5-7 days after drug initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing:

At least 5 days (ideally 7 days) after drug initiation or a dose change collect a trough sample up to 60 mins before the next scheduled dose, provided the previous dose was given on time.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20ºC.

Pathology Queensland reports the total concentration for posaconazole. Evidence for the target ranges is weak, but general guidance is given below (for more information see Chau et al reference).

Target range: above 0.5 mg/L (prophylaxis) or 1 mg/L (treatment) to less than 3 mg/L.

Effectiveness: prophylaxis: above 0.5 mg/L, treatment: above 1.0 mg/L

Toxicity: although the drug is well tolerated, dose reduction should be considered if adverse effects occur and the posaconazole concentration is >3 mg/L. Apparent mineralocorticoid excess is a dose dependant side effect of posaconazole, occurring more commonly in patients with a concentration above 2 mg/L.

Dose adjustment (see also repeat sampling)

For modified-release tablet: If subtherapeutic, increase from 300 mg daily to 400 mg daily (consider 200 mg BD to improve chance of achieving trough target) and if dose is being taken in fasted state administer with a high fat meal. Recheck after 5 – 7 days.

For suspension: more reliable absorption with modified release tablets, ideally switch product. If continuing on suspension, ensure patient takes suspension with food and/or acidic beverage, and avoid H_2 antagonists and proton pump inhibitors. For prophylaxis increase dose to 200 mg four times a day or 300 mg three times a day. For treatment, increase to 400 mg three times daily. Recheck after 5-7 days.

For more information, see CONTACTS

Teicoplanin Therapeutic Drug Monitoring

When to consider TDM – consider TDM in all patients receiving teicoplanin for treatment of infection.

General pharmacokinetics

Protein binding: 90-95%

Half-life: 70-100 hours

Excretion: renally excreted

Sample collection: take the first sample on day 4, then recheck concentrations if needed after 5-7 days.

Minimum volume 200µL of plasma or serum (~0.5mL blood). Use any of:

- 6mL Green top tube – no gel (lithium heparin)
- 6mL Red top tube – no gel (Clotted).

Gel tubes have the potential to interfere with this assay. Using gel tubes may result in specimen rejection.

Intermittent dosing:

- On day 4 of treatment, collect a trough sample within 60 minutes of the next dose (provided the previous dose as given on time), after a dose change, recheck concentration after 5-7 days.

Important information for the request form:

- Time of blood sample collection
- Time and date of last dose
- Dosing regimen
- Infection details

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Target range: total concentration above 15 mg/L (uncomplicated infection) or above 20 mg/L (severe infection) to below 60 mg/L.

Effectiveness: Although the 24-hour area under the curve to MIC ratio (AUC/MIC) is likely the most important PD index correlating with efficacy, trough concentrations are used as a surrogate.

Aim for total drug trough concentrations above 15 mg/L in uncomplicated infection, or above 20 mg/L for severe *Staphylococcal* infections such as critically ill patients or those with endocarditis or osteomyelitis.

Toxicity: nephrotoxicity may be more likely with a trough concentration above 60 mg/L. Teicoplanin induced thrombocytopenia appears dose dependent (and linked to lower baseline platelet counts) and may be associated with trough concentrations > 40mg/L

Dose adjustment (see also repeat sampling)

Dose adjustments can be made linearly (i.e. double the dose to double the concentration) depending on the target concentration. For concentrations above 60 mg/L, either decrease the dose or the dosing

frequency and monitor for adverse effects. Linear dose adjustments can be made by: new dose = (desired concentration/actual concentration) * current dose. If toxicity is occurring (i.e. thrombocytopenia, increased creatinine) consider changing drug – discuss with ID.
For more information, see CONTACTS

Voriconazole Therapeutic Drug Monitoring

All patients receiving voriconazole for longer than 5 days may be considered for therapeutic drug monitoring.

General pharmacokinetics (notoriously complex for voriconazole)

Absorption (bioavailability): above 90%

Protein binding: 60-80%

Half-life: 6 hours (varies between 3-46 hours)

Metabolism: hepatic metabolism via CYP2C9, CYP2C19 (major metabolic enzyme), CYP3A4.

Excretion: Inactive metabolites excreted in urine (80%) and faeces (20%).

Sample collection should occur 5-7 days after drug initiation or a dose change.

Minimum volume 200 µL of plasma or serum (~0.5 mL blood). Use any of:

- 6 mL Green top tube – no gel (lithium heparin)
- 6 mL Red top tube – no gel (Clotted)
- 4 mL Purple top tube (EDTA)

Intermittent dosing:

Between 5-7 days after drug initiation or a dose change take a trough sample, up to 60 mins before the next scheduled dose, provided the previous dose was given on time.

Sample handling

Sample must be delivered to laboratory as soon as possible, ideally within 2 hours of collection. Test performed Mondays to Saturdays. If samples get to pathology before 10am, results available same day.

Instructions for referring laboratories

Centrifuge, separate plasma within 2 hours of collection, and store and transport plasma frozen at -20°C.

Pathology Queensland reports the total concentration for voriconazole.

Target range: total trough concentration above 1 mg/L (2 mg/L for CNS infection, bulky or multifocal disease) to below 5.5 mg/L.

Effectiveness: For prophylaxis and treatment aim for a trough concentration between 1 to 5.5 mg/L.

For CNS infection, bulky disease or multifocal source: aim for 2 to 5.5 mg/L.

If an MIC is available for an individual patient, a trough concentration of 2 to 5 times above the MIC can be used as a target.

Toxicity: Neurological toxicity, visual disturbance and hepatotoxicity are more common with voriconazole concentrations above 5.5 mg/L.

Dose adjustment (see also repeat sampling)

Voriconazole has nonlinear kinetics, so drug concentrations after a dose change are not easily predicted.

If concentration is low, check for drug interactions that may be reducing voriconazole concentration (e.g. flucloxacillin, rifamycins, antiepileptics, antiretrovirals, barbiturates). Coadministration of omeprazole or pantoprazole can increase voriconazole concentrations. Taking voriconazole in the fasted state (1 hour before or 1 hour after eating) can increase bioavailability.

CYP2C19 genotype testing has been suggested if patients remain subtherapeutic on voriconazole with 2 samples and appropriate dose adjustments and patient adherence.

Adjust the dose based on the drug concentration:

- 0.0–0.5 mg/L: increase dose by 50% or decrease dosing frequency from 12-hourly to 8-hourly
- between 0.5 and 1.0 mg/L: increase dose by 25%
- above 5.5 mg/L and asymptomatic: decrease dose by 25%;
- above 5.5 mg/L with drug-related toxicities (and need to continue voriconazole): hold one dose and decrease subsequent doses by 50%.

After dose adjustment recheck the concentration after 5-7 days.

For more information, see CONTACTS

Partnering with consumers

Patients and family members are to be encouraged and given the opportunity to ask questions, clarify information and identify goals relating to antimicrobial treatment. Staff are responsible for providing information in a way that is understandable and that meets their needs and are to check consumer's understanding of discussions.

Legislation and other authority

Medicine and Poisons Act 2019

Medicines and Poisons (Medicines) Regulation 2021

References

1. Thomas P. Bechtel, Richard L. Slaughter, M.Sc., Timothy D. Moore, M.Sc., Seizures associated with high cerebrospinal fluid concentrations of cefazolin, American Journal of Hospital Pharmacy, Volume 37, Issue 2, 1 February 1980, Pages 271–273.
2. Huwyler T, Lenggenhager L, Abbas M, Ing Lorenzini K, Hughes S, Huttner B, Karmime A, Uçkay I, von Dach E, Lescuyer P, Harbarth S, Huttner A. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. Clinical Microbiology and Infection.2017;23(7):454-9.
3. Pais GM, Chang J, Barreto EF, Stitt G, Downes KJ, Alshaer MH, Lesnicki E, Panchal V, Bruzzone M, Bumanglag AV, Burke SN, Scheetz MH. Clinical Pharmacokinetics and Pharmacodynamics of Cefepime. Clin Pharmacokinet. 2022 Jul;61(7):929-953.
4. Erwin Dreesen, Matthias Gijsen, Omar Elkayal, Pieter Annaert, Yves Debaveye, Joost Wauters, Mats O Karlsson, Isabel Spriet, Ceftriaxone dosing based on the predicted probability of augmented renal clearance in critically ill patients with pneumonia, Journal of Antimicrobial Chemotherapy, Volume 77, Issue 9, September 2022, Pages 2479–2488.
5. Wallenburg E, Ter Heine R, de Lange DW, van Leeuwen H, Schouten JA, Ten Oever J, Kolwijck E, Burger DM, Pickkers P, Gieling EM, de Maat MM, Frenzel T, Brüggemann RJ. High unbound flucloxacillin fraction in critically ill patients. J Antimicrob Chemother. 2021 Nov 12;76(12):3220-3228.
6. Imani S, Buscher H, Marriott D, Gentili S, Sandaradura I. Too much of a good thing: a retrospective study of β-lactam concentration-toxicity relationships. J Antimicrob Chemother. 2017 Oct 1;72(10):2891-2897.
7. Quinton MC, Bodeau S, Kontar L, Zerbib Y, Maizel J, Slama M, Masmoudi K, Lemaire-Hurtel AS, Bennis Y. Neurotoxic Concentration of Piperacillin during Continuous Infusion in Critically Ill Patients. Antimicrob Agents Chemother. 2017 Aug 24;61(9):e00654-17.
8. Kalaria SN, Gopalakrishnan M, Heil EL. A Population Pharmacokinetics and Pharmacodynamic Approach To Optimize Tazobactam Activity in Critically Ill Patients. Antimicrob Agents Chemother. 2020 Feb 21;64(3):e02093-19.
9. Abdul-Aziz, M.H., Alffenaar, JW.C., Bassetti, M. et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: a Position Paper#. Intensive Care Med 46, 1127–1153 (2020).
10. Ewoldt TMJ, Abdulla A, Rietdijk WJR, Muller AE, de Winter BCM, Hunfeld NGM, Purmer IM, van Vliet P, Wils EJ, Haringman J, Draisma A, Rijpstra TA, Karakus A, Gommers D, Endeman H, Koch BCP. Model-informed precision dosing of beta-lactam antibiotics and ciprofloxacin in critically ill patients: a multicentre randomised clinical trial. Intensive Care Med. 2022 Dec;48(12):1760-1771.
11. Märtson AG, Edwina AE, Kim HY, Knoester M, Touw DJ, Sturkenboom MGG, Alffenaar JC. Therapeutic Drug Monitoring of Ganciclovir: Where Are We? Ther Drug Monit. 2022 Feb 1;44(1):138-147.

12. Olesja Rissling, Marcel Naik, Susanne Brakemeier, Danilo Schmidt, Oliver Staeck, Arnim Hohberger, Hans-Hellmut Neumayer, Klemens Budde, High frequency of valganciclovir underdosing for cytomegalovirus prophylaxis after renal transplantation, Clinical Kidney Journal, Volume 11, Issue 4, August 2018, Pages 564–573.

13. Therapeutic Guidelines [digital]. Melbourne: Therapeutic Guidelines Limited; 2022 Mar.

14. Chau MM, Daveson K, Alffenaar JC, Gwee A, Ho SA, Marriott DJE, Trubiano JA, Zhao J, Roberts JA; Australasian Antifungal Guidelines Steering Committee. Consensus guidelines for optimising antifungal drug delivery and monitoring to avoid toxicity and improve outcomes in patients with haematological malignancy and haemopoietic stem cell transplant recipients, 2021. Intern Med J. 2021 Nov;51 Suppl 7:37-66.

15. H. Ruth Ashbee, Rosemary A. Barnes, Elizabeth M. Johnson, Malcolm D. Richardson, Rebecca Gorton, William W. Hope, Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology, Journal of Antimicrobial Chemotherapy, Volume 69, Issue 5, May 2014, Pages 1162–1176.

16. Ji HH, Tang XW, Zhang N, Huo BN, Liu Y, Song L, Jia YT. Antifungal Therapy with Azoles Induced the Syndrome of Acquired Apparent Mineralocorticoid Excess: a Literature and Database Analysis. Antimicrob Agents Chemother. 2022 Jan 18;66(1):e0166821.

17. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018 May;24 Suppl 1:e1-e38.

18. Lopez-Garcia B, Luque S, Roberts JA, Grau S. Pharmacokinetics and preliminary safety of high dose linezolid for the treatment of Gram-positive bacterial infections. J Infect. 2015 Nov;71(5):604-7.

19. Alsultan A. Determining therapeutic trough ranges for linezolid. Saudi Pharm J. 2019 Dec;27(8):1061-1063.

20. Hanai Y, Takahashi Y, Niwa T, Mayumi T, Hamada Y, Kimura T, Matsumoto K, Fujii S, Takesue Y. Clinical practice guidelines for therapeutic drug monitoring of teicoplanin: a consensus review by the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. J Antimicrob Chemother. 2022 Mar 31;77(4):869-879.

21. Philip R Selby, Aaron J Heffernan, David Yeung, Morgyn S Warner, Sandra L Peake, Uwe Hahn, Ian Westley, Sepehr Shakib, Jason A Roberts, Population pharmacokinetics of posaconazole in allogeneic haematopoietic stem cell transplant patients, Journal of Antimicrobial Chemotherapy, 2024, dkae006.

22. Galar A, Muñoz P, Valerio M, Cercenado E, García-González X, Burillo A, Sánchez-Somolinos M, Juárez M, Verde E, Bouza E. Current use of daptomycin and systematic therapeutic drug monitoring: Clinical experience in a tertiary care institution. Int J Antimicrob Agents. 2019 Jan;53(1):40-48.

23. Falcone M, Russo A, Cassetta MI, Lappa A, Tritapepe L, d'Ettorre G, Fallani S, Novelli A, Venditti M. Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? J Infect Chemother. 2013 Aug;19(4):732-9. doi: 10.1007/s10156-013-0559-z.

Related documents

Blood collection from a peripherally inserted central catheter must be in accordance with the (RBWH) 001899: Central Venous Access Device (CVAD) Management and (STARS) Central Venous Access Device (CVAD) Management 006981 (for both, see section on Blood Collection)

Metro North Medication management Policy

Metro North Medicines: Prescribing Requirements Procedure

Metro North Medicines Administration Procedure

Metro North Vancomycin Management in Adult Patients Procedure
Queensland Health Aminoglycoside dosing in adults guideline
Metro North Infection Control: Preventing and Controlling Healthcare - Associated Infection Policy
Metro North Peripheral Intravenous Cannulation & Venepuncture Resource Package

Appendix 1- Definition of terms

Term	Definition
100% fT > MIC	100% free (unbound drug) time above the MIC
50% fT > MIC	50% free (unbound drug) time above the MIC
AMS	Antimicrobial stewardship
AUC	Area under the curve – unless specified, in this document these are for a 24-hour period at steady state.
CrCl	Creatinine clearance (calculated using Cockcroft Gault equation)
ESBL	Extended spectrum beta-lactamase
GFR	Glomerular filtration rate
HPLC	High-performance liquid chromatography
MIC	Minimum inhibitory concentration: the lowest concentration of an antimicrobial that inhibits visible growth of a bacterium or bacteria.
PICC	Peripherally inserted central catheter
TDM	Therapeutic drug monitoring
100% fT > MIC	100% free (unbound drug) time above the MIC

Appendix 2 – Useful contacts

- Pathology Queensland HPLC Laboratory (sampling and results): 3646 0028.
- Contact the local AMS pharmacist or Infectious Diseases, ICU or relevant speciality (e.g., haematology) for more information about concentration interpretation.
- Herston Infectious Diseases Institute (HeIDI) Senior Pharmacist (Research): 3647 0802.

Document history

Author	Senior Pharmacist (Research), Herston Infectious Diseases Institute (HeIDI), Royal Brisbane and Women's Hospital, Metro North Health
Custodian	Director, Herston Infectious Diseases Institute, Royal Brisbane and Women's Hospital, Metro North Health
Risk rating	Medium
Compliance evaluation and audit	Review of clinical incidents relating to therapeutic drug monitoring Ad hoc audits to assess quality of antimicrobial TDM Pre post implementation audit to be undertaken in collaboration with Herston institute of infectious diseases.
Replaces Document/s	Medicine – Antimicrobial Therapeutic Drug Monitoring V1.0
Changes to practice from previous version	Addition of Daptomycin to Summary Table on page 5. Addition of Daptomycin Therapeutic Drug Monitoring on page 13. Additional information added Flucloxacillin Therapeutic Drug Monitoring on page 14. Additional information added to Posaconazole Therapeutic Drug Monitoring on page 26. Correction to references. Addition of references 21 – 23.
Education and training to support implementation	Communication of guideline at pharmacy and ID meetings across MNHHS. Education sessions have been offered to all pharmacy sites in MNHHS (completed at RBWH and STARS). Added to RBWH AMS webpage and other MNHHS AMS webpages as developed.
Consultation	**Key stakeholders** RBWH ID department TPCH ID department Redcliffe ID department Caboolture ID department AMS pharmacists across MNHHS Clinical Pharmacology Dept RBWH ICU RBWH HPLC laboratory and Microbiology laboratory Pathology Queensland
Marketing Strategy	A Metro North Policy, Procedure and Protocol Staff Update will be published online each month to update staff of all new and updated policies, procedures and protocols. This update will be emailed to all Safety and Quality Units in each

	clinical directorate and a broadcast email sent to all Metro North staff with a link to the published update.
Key words	TDM, antimicrobial, AMS, therapeutic drug monitoring, drug levels, medication, assay, HPLC, unbound, beta-lactam, beta lactam

Custodian Signature Date 09/05/2024

Director, Herston Infectious Diseases Institute, Royal Brisbane and Women's Hospital, Metro North Hospital and Health Service

AUTHORISATION

Authorising Officer Signature Date 13/05/2024

Executive Director, Royal Brisbane and Women's Hospital

The original signed version is kept in file at the Herston Infectious Diseases Institute, Royal Brisbane and Women's Hospital, Metro North.