Guideline

Effective from: May 2023 Review date: June 2025

Medicine – Antimicrobial Therapeutic Drug Monitoring











Purpose and intent

To provide a guide for clinicians to support consistent and appropriate therapeutic drug monitoring (TDM) for antimicrobials.

This guideline provides guidance regarding antimicrobial concentrations in plasma or serum. For concentration analysis in 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 <u>Vancomycin Management in Adult Patients</u> procedure for specific details regarding vancomycin and Queensland Health <u>Queensland Health Aminoglycoside dosing in adults guideline</u> 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/m²)
- 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)
- patients with drug interactions potentially affecting drug concentrations
- patients with non-resolving infections
- patients 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/1.73m²) 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

If a dose change has been made, check a repeat antimicrobial concentration after 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 (i.e. in the setting of kidney 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, i.e. 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 the PKPD target for 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) clinical breakpoint as an estimate. If the MIC of a pathogen is very low, the drug dose required to achieve the PKPD target can also be quite low. In general, it is not recommended to reduce the dose below the standard dose (considering site of infection and the patient's renal function), unless toxicity is strongly suspected based on drug concentration.

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 in the setting of altered medication administration times.

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

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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	
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^{*}Samples at the HPLC lab by 10am will have results available same day (only 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 -10 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.

Vancomycin and aminoglycoside drug monitoring is covered separately—see local or area based guidelines.

Summary table of target concentrations for intermittent infusion

Drug	Minimum concentration ¹	Maximum concentration		
Ampicillin/amoxicillin (unbound,	8 mg/L (Enterobacterales)	50 mg/L		
trough)	4 mg/L (Enterococcus sp)			
	0.5 mg/L (Streptococcus pneumoniae)			
Benzylpenicillin (unbound, trough)	0.125 mg/L (penicillin susceptible Staphylococcus sp)	50 mg/L		
	0.25 mg/L (Streptococcus group A, B, C and G)			
Cefazolin (unbound, trough)	2 mg/L (Staphylococcus aureus)	20 mg/L ²		
Cefepime (unbound, trough)	1 mg/L (Enterobacterales) 8 mg/L (<i>Pseudomonas sp</i>)	20 mg/L		
Ceftazidime (unbound, trough)	1 mg/L (Enterobacterales) 8 mg/L (<i>Pseudomonas sp</i>)	50 mg/L		
Ceftolozane + tazobactam³ (trough, unbound)	2 mg/L (Enterobacterales) 4 mg/L (<i>Pseudomonas sp</i>)	50 mg/L		
Ceftriaxone (unbound, trough)	1 mg/L (Enterobacterales)	20 mg/L ²		
Ciprofloxacin (total)	Peak concentration > 5mg/L (<i>Pseudomonas sp</i>) AUC:MIC > 125 mg*hr/L	Trough concentration < 5 mg/L		
Flucloxacillin (unbound, trough)	1 mg/L (S. aureus)	20 mg/L		
Fluconazole (total, trough)	2 mg/L (C <i>andida sp</i>)	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	Piperacillin:	Piperacillin:		
(unbound, trough)	8 mg/L (Enterobacterales)	130 mg/L		
	16 mg/L (<i>Pseudomonas sp</i>)	Tazobactam:		
	Tazobactam: 2 mg/L	20 mg/L		
Posaconazole (total, trough)	0.5 mg/L (prophylaxis)	3 mg/L		
	1 mg/L (treatment)			
Teicoplanin (total trough)	>15 mg/L (uncomplicated infection) >20 mg/L (serious infection)	40 mg/L - 60 mg/L (see monograph)		
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, other pathogen MICs available from EUCAST breakpoints table, see <u>EUCAST: Clinical breakpoints and dosing of antibiotics</u>. If a pathogen has reported intermediate susceptibility to an antimicrobial – seek expert advice (the target trough concentration may be higher). Due to reporting of I (or SDD) 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 <u>augmented renal clearance</u>
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m²)
- 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 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)
- 4mL 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°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 - 10 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.

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/m²)
- 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 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)
- 4mL 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 cefepime.

Target range: unbound trough concentration above the MIC (e.g. 1 or 8 mg/L) to below 20 mg/L for intermittent infusion, for continuous infusion aim for between 16 to 32 mg/L.

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 a random concentration of 16 to 32 mg/L. See also Targets for beta-lactam drugs.

Toxicity: Neurotoxicity appears dose (or exposure) 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.

Ceftriaxone Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected <u>augmented renal clearance</u>
- 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/m²)
- 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 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)
- 4mL 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 trough concentration 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.

Ciprofloxacin Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected <u>augmented renal clearance</u>
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m²)
- 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 200µL of plasma or serum (~0.5mL blood). Use any of:

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

Intermittent dosing:

- For AUC based monitoring—collect 2 samples, one sample 2 hours after the dose and one 6-8 hours after the dose.
- For peak concentration—collect a sample 30 minutes after infusion completed or 2 hours after an 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 AUC₀₋₂₄/MIC of >125 mg*hr/L.

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

- an AUC₀₋₂₄/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 a 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 AUC₀₋₂₄ 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).

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/m²)
- 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 to 1.5 hours

Metabolism: In patients without kidney failure, metabolism is usually <10%, but 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 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)
- 4mL 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 patients on a continuous infusion, aim for 4 - 10 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).

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.

Fluconazole Therapeutic Drug Monitoring

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

- Kidney dysfunction or suspected <u>augmented renal clearance</u>
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m²)
- 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 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)
- 4mL 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 $\geq 55-100$ mg*hr/L is recommended for candidemia, a simpler approach to TDM is to <u>aim for a trough concentration above the MIC of the pathogen</u> (i.e. above 2 mg/L for susceptible candida).

Toxicity: Toxicity exposure relationships are not well defined.

Dose adjustment (see also <u>repeat sampling</u>) 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.

Ganciclovir Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected <u>augmented renal clearance</u>
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m²)
- 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 200µL of plasma or serum (~0.5mL blood). Use any of:

- 6mL Green top tube no gel (lithium heparin)
- 4mL Purple top tube (EDTA)
- 5mL 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 <u>prophylaxis or maintenance therapy</u> 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 <u>initial IV treatment (induction therapy)</u> 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.

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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.

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 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)
- 4mL 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°C.

Target range:

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 (seek expert advice):

- 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 H₂ antagonists and proton pump inhibitors
- Ensure itraconazole solution is taken on empty stomach

If the concentration is high:

Decrease dose or dosing frequency.

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

- 4.5mL light green top tube gel (lithium heparin)
- 5mL 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 AUC₀₋₂/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 AUC₀₋₂₄ 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; 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.

Meropenem Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected <u>augmented renal clearance</u>
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m²)
- 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 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)
- 4mL 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 - 10 times above the MIC. See also <u>Targets for beta-lactam drugs</u>.

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.

Piperacillin + Tazobactam Therapeutic Drug Monitoring

Consider TDM in patients with:

- Kidney dysfunction or suspected <u>augmented renal clearance</u>
- Liver dysfunction
- Extreme weight (less than 50 kg or more than 120 kg or BMI less than 20 or more than 30 kg/m²)
- 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 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)
- 4mL 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 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 - 10 times above the MIC. See also **Targets for beta-lactam drugs.**

Toxicity: Not well defined. Neurotoxicity has been associated with unbound piperacillin concentrations above 130 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.

Posaconazole Therapeutic Drug Monitoring

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

General pharmacokinetics

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

Protein binding: > 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 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)
- 4mL 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 -20°C.

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 reference Chau et al).

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 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.

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 40-60 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 (also associated with 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.

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If toxicity is occurring (i.e. thrombocytopenia, increased creatinine) consider changing drug – discuss with ID.

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 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)
- 4mL 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.

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

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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	New document
Changes to practice from previous version	New document
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:	
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AUTHORISATION

Hospital and Health Service

Authorising Officer Signature: Date:

Executive Director, Royal Brisbane and Women's Hospital

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