

Antimicrobial Reference Laboratory

Guideline Ranges for TDM

**2022 – 2023**

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**General Laboratory details**

Antimicrobial Reference Laboratory

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Laboratory Opening hours are Monday to Friday 9am to 5:15pm

| **Important Changes This Version** | **New Analytes Available (from May 2021)** |
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| \*ISONIAZID Sample Requirements:  **Isoniazid (and metabolite) degrade quickly in serum/plasma. Please provide whole blood (un-centrifuged) in ‘Fluoride/Oxalate’ (FX) tubes.**  Initial 2h post dose sample required. If slow absorption suspected a further 6h post dose sample may be drawn  Sent via Dx or Royal Mail  Blood must reach ARL within 5 days at Room Temperature | ISONIAZID  (+ N-Acetyl ISONIAZID)\* |

**TDM preface**

Despite advances in antimicrobial therapy, a significant proportion of patients with infection suffer with negative clinical outcomes driven by non-modifiable factors such as age, co-morbidities and severity of infection. With rising antimicrobial resistance (AMR) and a decline in the availability of newer agents, optimising the existing therapeutic agents by applying pharmacokinetic/pharmacodynamic (PK/PD) principles has become a priority in clinical practice.

Therapeutic drug monitoring (TDM) of antimicrobial agents has been used for a number of antimicrobials for decades; mainly to monitor efficacy and prevent dose-related adverse drug reactions.

In recent years, application of TDM has been extended across a wider range of agents as an Antimicrobial Stewardship Strategy (AMS) against growing AMR.

Modern healthcare professionals/organisations are faced with more complex clinical needs with age (extremes of low and high), body habitus with a wide range of Body Mass Indices (BMI), multi-organ co-morbidities and polypharmacy leading to drug-drug interactions. There is a growing pressure amongst clinicians to adopt new technologies to achieve “precision dosing” with a widespread use of TDM in the belief that such intervention will improve patient outcomes. However, hard evidence in the form of Randomised Controlled Trials (RCT) to support such a notion are lacking.

Therefore, therapeutic ranges quoted in this document should be used as a “guide” in terms of patient management rather than as a therapeutic “target” to achieve taking into consideration all the infection related factors including host, pathogen, clinical and antimicrobial options.

We welcome discussion from clinicians in terms of indications, timings, sample type/container, logistics, transport and interpretation of results on a case-by-case basis. Therefore, please do not hesitate to contact us via above details during the days and timings specified in this document.

**Aminoglycosides**

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| --- | --- | --- | --- |
| **Agent** | **Risk group** | **Expected levels**  **(Guide-lines)**  **(mg/L)** | **Re-assay interval\***  **(days)** |
| Gentamicin  Tobramycin  (Once-daily)a | All patients on 2nd-4th dose; earlier if changing renal function or other risk factors. | Pre: <1 mg/L  Post: >10 mg/L  or  8h post (5 mg/kg): 1.5-6 mg/L  or follow Hartford nomogram  (but note this is for 7 mg/kg) | 6-8 |
| Gentamicin  (Once-daily 5 mg/kg)b | Neonatal sepsis | Pre: < 2 mg/L BUT <1 mg/L after 3rd dose  Post: >8 mg/L |  |
| Gentamicin  Tobramycin  (BD or TDS)c-d | All patients on 2nd-4th dose; earlier if changing renal function or other risk factors. | Gram Negative pneumonia  Pre: <2 mg/L  Post: >7 mg/L  Infective endocarditis (IE)  Pre: <1 mg/L  Post: 3-5 mg/L | 3-7 |
| Amikacin  (Once-daily)a,f |  | Pre: <5 mg/L  Post: 40-45† mg/L | 6-8 |
| Amikacin (BD or TDS)c |  | Pre: <10 mg/L  Post: 20-30 mg/L | 3-7 |
| Streptomycin  (7.5 mg/kg BD)d-e | All patients after 2nd-4th dose. | Infective endocarditis;  Pre: <3.0 mg/L  Post: 10-25 mg/L | 7-28 |

\* Assuming initial results are within the expected range

aNicolau et al. 1995. Antimicrobial Agents & Chemotherapy 39:650-655.

bNICE Clinical Guideline 149, 2012.

cBritish National Formulary, Edition 67. 2014 section 5.1.4.

dElliott et al. 2004. Journal of Antimicrobial Chemotherapy 54: 971-81.

eNote: these are different to the AHA Scientific Statement ranges. Baddour et al. 2015. Circulation 132:1435-86.

fJenkins et all. 2016. Journal of Antimicrobial Chemotherapy 71: 2754-59. † Guideline levels not available; these are levels that are routinely seen.

Hartford nomogram link https://clincalc.com/Aminoglycoside/

**Glycopeptides/Lipopeptides/Oxazolidinones**

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| --- | --- | --- | --- |
| **Agent** | **Risk group** | **Expected levels**  **(Guide-lines)**  **(mg/L)** | **Re-assay interval\***  **(days)** |
| Vancomycina-d | All patients on >2-4 days therapy. Patients receiving other nephrotoxic drugs.  Assay at 2nd-4th dose. | Pre: 10-15 mg/L but 15-20 mg/L in complicated infection  OR  Steady state during continuous infusion: 20-25 mg/L | 6-8 |
| Teicoplanine-f,j | a) Skin and soft tissue infection  b) Bone and Joint infection  d) Infective endocarditis  e) OPAT on 25 mg/kg 3x per week | Pre: 15-30 but <60 mg/L  Pre: 20-40 but <60 mg/L  Pre: 30-40 but <60 mg/L  Pre: 20-30 mg/L | 6-8 |
| Daptomycing | Patients with CPK elevation, high dose therapy (>6 mg/kg) or renal impairment | Pre: 5-20 mg/L or  Pre: 10-20 mg/L in severe sepsis  Pre: >20 mg/L associated with increased risk of toxicity | 6-8 |
| Linezolid  (600mg BD)h-i | Patients on long-term therapy (>28d) or if on agents with potential drug interactions | Pre: 2-8 mg/L  Post: 12-26 mg/L | 8-16 |

\*Assuming initial results are within the expected range

aJeffres et al. 2006. Chest 130: 947-55. Lodise et al. 2008. Antimicrobial Agents & Chemotherapy 52: 1330-1336.

bBritish National Formulary. 2008. Number 55. Rybak et al. 2009. Am J Health-Syst Pharm. 66:82–98.

cIngram et al. 2008. Journal of Antimicrobial Chemotherapy 62: 168-171.

dWysocki et al, 2001. Antimicrobial Agents and Chemotherapy 45: 2460-2467.

eTeicoplanin: Summary of Product Characteristics. 2013. European Medicines Agency. Assessment report: Targocid and associated names. 2014. EMEA/H/A-30/1301. European Medicines Agency.

fLamont et al, 2009. Journal of Antimicrobial Chemotherapy 64: 181-187.

gBhavnani et al. 2010. Clinical Infectious Diseases 50: 1568-74. Falcone et al. 2013. J. Infection Chemotherapy 19 :732-9, DiPaolo et al. 2013. Int J. Antimicrobial Agents 42 :250-5, Falcone et al. 2013. CID 57 :1568-76, Reiber et al. 2015 Therapeutic Drug Monitoring, 37 :634-40. .

hPea et al. 2012. JAC 67:2034-42. Dong et al. 2014. Eur J. Clinical Microbiology & Infectious Diseases, Epub 12/02/14

iMatsumoto et al. 2014. International Journal of Antimicrobial Agents 44:242-7. Cattaneo et al. 2016. Expert Opin Drug Metab. Toxicol. 12:533-44

I Hanai et al. 2022. Journal Antimicrobial Chemotherapy 77: 869-879.

**Antifungal agents**

|  |  |  |  |
| --- | --- | --- | --- |
| **Agent** | **Risk group** | **Expected levels**  **(Guide-lines)**  **(mg/L)** | **Re-assay interval\***  **(days)** |
| Flucytosinea | Routine within 72h of starting therapy. | Pre: 20-50 mg/L  Post: 50-100 mg/L  Pre dose concentrations <20 mg/L have been associated with treatment failure and emergence of resistance.  Post dose concentrations >100 mg/L have been associated with toxicity. | 4-8 |
| Isavuconazolee | Not routinely monitored but may be useful in complex cases or in renal impairment | Pre: 2-4 mg/L (usually)^ | 4-8 |
| Itraconazolea-b | Routine in 1st week of therapy. Measure 4-7 days after starting therapy | By Chromatographic assay  Prophylaxis: Pre: 0.5-4.0 mg/L  Therapy: Pre: 1.0-4.0 mg/L  All pre dose levels to be kept below 4.0 mg/L | 4-8 |
| Fluconazolea | Not routinely monitored but may be useful in complex cases or renal failure | AUC:MIC ratio of >100, call for advice on sampling. | 4-8 |
| Posaconazolea-c | Routine in majority of patients. Measure 3-8 days after starting therapy | Prophylaxis: Pre: 0.7-3.75 mg/L  Therapy: Pre: 1.0-3.75 mg/L  All pre-dose levels to be kept below 3.75 mg/L | 4-8 |
| Voriconazolea,b,d | Routinely within 5d of starting therapy | Prophylaxis and therapy  Pre: 1.0-5.5 mg/L or 2.0-5.5 mg/L for bulky or disseminated infections | 4-8 |

\*Assuming initial results are within the expected range.

aVermes et al. 2000. Journal of Antimicrobial Chemotherapy 46: 171-179. Ashbee et al. 2014. J. Antimicrobial Chemotherapy 69:1162-1176.

bAndes et al. 2009. Antimicrobial Agents and Chemotherapy 53: 24-34. Dolton et al. 2015.Current Opinion in Infectious Diseases 27:493-500. Chau et al. 2014 Intern Med J 44:1364-88.

cDolton et al. 2012. Antimicrobial Agents and Chemotherapy 56: 2806-2813. Dekkers et al. 2016. Curr Fung Infect Rep 10:51-61.

dPascual et al. 2012. Clinical Infectious Diseases 55:381-90.

eBorman et al. 2020. Med Mycol 58 (7): 996-999. ^ Levels that are routinely seen and not true expected levels.

**Agents used in Mycobacterial infectiona**

|  |  |  |  |
| --- | --- | --- | --- |
| **Agent** | **Risk group** | **Expected levels**  **(Guide-lines)**  **(mg/L)** | **Re-assay interval\***  **(days)** |
| Streptomycinb  (15 mg/kg OD) | All patients after 2nd-4th dose. | Pre: <5 mg/L in <50y patients  Pre: <1 mg/L in >50y patients  Post: 15-40 mg/L | 7-28d |
| Streptomycinc  (25 mg/kg BIW) | All patients after 2nd-4th dose. | Pre: <1 mg/L  Post: 65-80 mg/L | 7-28d |
| Rifampicinc | Patients with poor clinical progression | Pre: <0.5 mg/L (ideally)  Post: <4 mg/L sub-therapeutic  Post: 4-8 mg/L usually adequate  Post: 8-24 mg/L ideal | Depending on levels & progression |
| ISONIAZIDf  (+N-Acetyl-ISONIAZID) | Patients with poor clinical progression + checking for acetylation status | Post: (2hr) 3-5 mg/L | Depending on levels & progression |
| Ethambutolc | Patients with poor clinical progression or significant renal dysfunction | Pre: <1 mg/L  Post: 2-6 mg/L | Depending on levels & progression |
| Rifabutind | Patients who fail to respond to treatment.  Patients on agents with CYP P450 interactions | Pre: <0.1 mg/L (usually)  Post: 0.45-0.9 mg/L | Depending on levels & progression |
| Levofloxacind | Patients being treated for MDR TB. | Pre: 0.5-2 mg/L  Post: 8-13 mg/L | Depending on levels & progression |
| Cycloserined | All patients after 4th-6th dose. | Pre: 10-20 mg/L  Post: (3-4h) 20-35 mg/L  Levels to be kept below 35 mg/L | 10-30d |
| Moxifloxacind | Patients being treated for MDR TB. | Pre: 0.3-0.7 mg/L  Post: 3-5 mg/L | Depending on levels & progression |
| Linezolide  (600 mg OD oral)  (600 mg BD oral) | Patients being treated for MDR TB. | Pre: <5 mg/L (ideally)  Post: 12-26 mg/L  Pre: 2-8 mg/L (usually)  Post: 12-26 mg/L | Depending on levels & progression |

\* Assuming initial results are within the expected range; BIW: twice a week

aAssuming that patients are on standard (usually daily) therapy, for patients on intermittent therapy please call to discuss expected levels as these will vary depending on dosing regimen used.

bBritish National Formulary, Edition 67. 2014 section 5.1.9.

cPeloquin 2017. Microbiol Spectrum 5:1-8. Pasipanodya et al. 2013. J. Infectious Diseases 208:1464-73.

dHolland et al. 2009. Pharmacotherapy 29:503-10. Srivastava et al. 2013. European Respiratory Journal, 42:1449-53. Ramachandran et al, 2015, Drug Safety, 38:253-69. Peloquin 2017. Microbiol Spectrum 5:1-8. Hwang et al.2013. Int J. Tuberc Lung Dis 17:1257-66. Park.et al. 2017. AAC 59:4429-4435

eSchecter et al. 2010. CID 50: 49-55; McGee et al. 2009. Antimicrobial Agents & Chemotherapy 53: 3981-3984. Dong et al. 2014. Eur J. Clinical Microbiology & Infectious Diseases, Epub 12/02/14

fPotter *et al*, 2020. MDRTB ADR Monitoring Guidance. TB Drug Monographs

**Other agents**

|  |  |  |  |
| --- | --- | --- | --- |
| **Agent** | **Risk group** | **Expected levels**  **(Guide-lines)**  **(mg/L)** | **Re-assay interval\***  **(days)** |
| Aciclovir and its metabolite CMMGf | Patients with renal impairment, on high dose therapy or exhibiting CNS effects | For Aciclovir, interpretation of levels needs to be patient specific  CMMG: Measured in Pre-dose levels ONLY.  Pre: CMMG <2.6 mg/L. Elevated CMMG levels are associated with increased risk of neurotoxicity. | 6-8 |
| Ganciclovira | Young children, renally impairment or unstable renal function | Pre: 0.5-1.0 mg/L  Post: 7-9 mg/L (Ganciclovir)  Post: 5-7 mg/L (Valganciclovir) | 4-8 |
| Chloramphenicolb | All patients but especially neonates. | Pre: Ideally <10 mg/L but must be <15 mg/L  Post: (2h) 10-25 mg/L | 5-7 |
| Co-trimoxazoled  (sulphamethoxazole + trimethoprim)c | High-dosage therapy (PCP) or renal impairment. | Sulphamethoxazole;  Pre: <100 mg/L, Post: 120-150 but <200 mg/L  Trimethoprim;  Pre: 5-7 mg/L, Post: 5-10 but <20 mg/L | 6-8 |
| Colistine | Patients on IV treatment | Pre: 2-4 mg/L | Day 2-3 (if patient received a loading dose)  Re-assay 5-7d |

\*Assuming initial results are within the expected range

aLuck et al. 2011 International Journal of Antimicrobial Agents 37:445-448.

bBritish National Formulary for Children. 2018-19 p354

cJoos et al. 1995. Antimicrobial Agents & Chemotherapy 39:2661-2666.

dBrown. 2014. Ann Int Care 4:13-22

eNation et al. 2014. Lancet Infectious Diseases S1473-3099. Gregorie et al. 2017. Clin Pharmacokinet 56:1441-1460.

fHellden et al. 2003. Nephrol. Dial. Transplant 18: 1135-1141