Severn Pathology
North Bristol NHS Trust

Antimicrobial Reference Laboratory

GUIDELINE RANGES FOR TDM

2024 – 2025

Antimicrobial Reference Laboratory – Guideline Ranges 2024 – 2025

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General Laboratory details

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

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Important Changes: This Version
Updated with the following changes - Page 3 Non-serum sample identification required on the request forms (biohazard) Page 8 Rifampicin – sample timings added Rifabutin – sample timings added

Please state if a non-serum sample is being sent clearly on the request form and if there is a biohazard risk.

For sample requirements, request from and further information please visit our website:
www.nbt.nhs.uk/severn-pathology/pathology-services/antimicrobial-reference-laboratory

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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 between 2nd-4th dose; earlier if changing renal function or other risk factors e.g. Age	Pre: <1 mg/L Post: >10 mg/L or 8h post (on 5 mg/kg dose): 1.5 - 6 mg/L or follow Hartford nomogram[a] (patient is on 7 mg/kg dose)	3
Gentamicin (Once-daily 5 mg/kg)[b]	Neonatal sepsis	Pre: < 2 mg/L BUT <1 mg/L after 3rd dose Post: >8 mg/L	3
Gentamicin Tobramycin (BD or TDS)[c-d]	All patients on 2nd-4th dose; earlier if changing renal function or other risk factors.	Gram Negative sepsis or pneumonia Pre: <2 mg/L Post: 5 – 10 mg/L Infective endocarditis (IE) Pre: <1 mg/L Post: 3-5 mg/L	3
Amikacin (Once-daily)[a,f]		Pre: <5 mg/L Post: 40 - 45† mg/L	6-8
Amikacin (BD or TDS)[g]		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

[a]Nicolau et al. 1995. Antimicrobial Agents & Chemotherapy 39:650-655.

[b]NICE Clinical Guideline 149, 2012.

[c]British National Formulary, https://bnf.nice.org.uk/drugs/gentamicin/ [access date 10/03/2023]

[d]Elliott et al. 2004. Journal of Antimicrobial Chemotherapy 54: 971-81.

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

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

[g]BNF V 3.2.8 Sep 2023 https://bnf.nice.org.uk/drugs/amikacin/#monitoring-requirements

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)
Vancomycin[a-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
Teicoplanin[e-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
Daptomycin[g]	Patients with CPK elevation, high dose therapy (>6 mg/kg) or renal impairment	(6 - 8mg/kg dose) Pre: 5 - 25 mg/L or Pre: 10 - 25mg/L in severe sepsis or deep-seated infection Pre: >24.3 mg/L associated with increased risk of toxicity[g]	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

[a]Jeffres et al. 2006. Chest 130: 947-55. Lodise et al. 2008. Antimicrobial Agents & Chemotherapy 52: 1330-6.

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

[c]Ingram et al. 2008. Journal of Antimicrobial Chemotherapy 62: 168-171.

[d]Wysocki et al, 2001. Antimicrobial Agents and Chemotherapy 45: 2460-2467.

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

[f]Lamont et al, 2009. Journal of Antimicrobial Chemotherapy 64: 181-187.

[g]Bhavnani 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.

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

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

[l] Hanai et al. 2022. Journal Antimicrobial Chemotherapy 77: 869-879.

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Antifungal agents

Agent	Risk group	Expected levels (Guide-lines) (mg/L)	Re-assay interval* (days)
Flucytosine[a]	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
Isavuconazole[e]	Not routinely monitored but may be useful in complex cases or in renal impairment	Pre: 2 - 4 mg/L (usually)^	4-8
Itraconazole[a-b]	Routine in 1st week of therapy. Measure 4-7 days after starting therapy	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
Fluconazole[a]	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
Posaconazole[a-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
Voriconazole[a,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.

[a]Vermes et al. 2000. Journal of Antimicrobial Chemotherapy 46: 171-179. Ashbee et al. 2014. J. Antimicrobial Chemotherapy 69:1162-1176.

[b]Andes 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.

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

[d]Pascual et al. 2012. Clinical Infectious Diseases 55:381-90.

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

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Agents used in Mycobacterial infection[a]

Agent	Risk group	Expected levels (Guide-lines) (mg/L)	Re-assay interval* (days)
Streptomycin[b] (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
Streptomycin[c] (25 mg/kg BIW)	All patients after 2nd-4th dose.	Pre: <1 mg/L Post: 65 - 80 mg/L	7-28d
Rifampicin[c] ARL recommends: PRE dose sample: up to 1h before dose POST dose samples: ORAL 1, 2 and 4h after dose I.V. 1h after dose	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
ISONIAZID[f] (+N-Acetyl-ISONIAZID)	Patients with poor clinical progression + checking for acetylation status	Post: (2hr) 3 - 5 mg/L	Depending on levels & progression
Ethambutol[c]	Patients with poor clinical progression or significant renal dysfunction	Pre: <1 mg/L Post: 2 - 6 mg/L	Depending on levels & progression
Rifabutin[d] ARL recommends: PRE dose sample: up to 1h before dose POST dose samples: ORAL 1, 2 and 4h after dose I.V. 1h after dose	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
Levofloxacin[d]	Patients being treated for MDR TB.	Pre: 0.5 - 2 mg/L Post: 8 - 13 mg/L	Depending on levels & progression
Cycloserine[d]	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
Moxifloxacin[d]	Patients being treated for MDR TB.	Pre: 0.3 - 0.7 mg/L Post: 3 - 5 mg/L	Depending on levels & progression
Linezolid[e] (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

[a]Assuming 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.

Continued…….

[b]British National Formulary, Edition 67. 2014 section 5.1.9.
[c]Peloquin 2017. Microbiol Spectrum 5:1-8. Pasipanodya et al. 2013. J. Infectious Diseases 208:1464-73.
[d]Holland 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
[e]Schecter 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
[f]Potter *et al*, 2020. MDRTB ADR Monitoring Guidance. TB Drug Monographs

Other agents

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Agent	Risk group	Expected levels (Guide-lines) (mg/L)	Re-assay interval* (days)
Aciclovir and its metabolite CMMG[f]	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
Ganciclovir[a]	Young children, renally impairment or unstable renal function	Pre: 0.5 -1.0 mg/L (prophylaxis) Pre: 1.0 – 2.0 mg/L (therapy) Post: 7 - 9 mg/L (Ganciclovir) Post: 5 - 7 mg/L (Valganciclovir)	4-8
Chloramphenicol[b]	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-trimoxazole[d] (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
Colistin[e]	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

[a]Luck et al. 2011 International Journal of Antimicrobial Agents 37:445-448. Marston et al J Antimicrob Chemother 2021; 76: 2356–2363. Franck et al Clin Pharmacol Ther, 112: 233-276. https://doi.org/10.1002/cpt.2431

[b]British National Formulary for Children. 2018-19 p354

[c]Joos et al. 1995. Antimicrobial Agents & Chemotherapy 39:2661-2666.

[d]Brown. 2014. Ann Int Care 4:13-22

[e]Nation et al. 2014. Lancet Infectious Diseases S1473-3099. Gregorie et al. 2017. Clin Pharmacokinet 56:1441-1460.

[f]Hellden et al. 2003. Nephrol. Dial. Transplant 18: 1135-1141