Severn Pathology
North Bristol NHS Trust

Antimicrobial Reference Laboratory

GUIDELINE RANGES FOR TDM

2021 – 2022

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Important Changes This Version	New Analytes Available (from May 2021)
ISAVUCONAZOLE now 2-4mg/L	ISONIAZID (+ N-Acetyl ISONIAZID)*

*ISONIAZID Sample Requirements: Blood drawn into Sodium Oxalate tube (Grey top) Initial 2h post dose sample required. If slow absorption suspected a further 6h post dose sample may be drawn Blood centrifuged in the laboratory and Plasma aliquoted into a secondary tube Sent via Dx or Royal Mail Plasma must reach ARL within 5 days at Room Temperature

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Agent	Risk group	Expected levels (Guide lines) (mg/L)	Re assay interval* (days)
Aminoglycosides			
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 8 h 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 < 2mg/L BUT <1 mg/L after 3rd dose Post >8mg/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

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

[b]NICE Clinical Guideline 149, 2012.

[c]British National Formulary, Edition 67. 2014 section 5.1.4.

[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.

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

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Glycopeptides/Lipopeptides/Oxazolidinones			
Vancomycin[a-d]	All patients on >2-4 days therapy. Patients receiving other nephrotoxic drugs. Assay at 2nd-4th dose.	Pre dose 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]	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	Pre dose 5-20 mg/L or Pre dose 10-20mg/L in severe sepsis Pre dose levels >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

[a]Jeffres et al. 2006. Chest 130: 947-55. Lodise et al. 2008. Antimicrobial Agents & Chemotherapy 52: 1330-1336.
[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

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Antifungal agents			
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	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
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]			
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]	Patients with poor clinical progression	Pre <0.5mg/L (ideally) Post <4mg/L sub-therapeutic Post 4-8mg/L usually adequate Post 8-24mg/L ideal	Depending on levels & patient progression
ISONIAZID[f] (+N-Acetyl-ISONIAZID)	Patients with poor clinical progression + checking for acetylation status	Post (2hr) 3-5mg/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]	Patients who fail to respond to treatment. Patients on agents with CYP P450 interactions	Pre <0.1mg/L (usually) Post 0.45-0.9 mg/L	Depending on levels & patient 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 10-20mg/L Post (3-4h) 20-35mg/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 <5mg/L (ideally) Post 12-26mg/L Pre 2-8 mg/L (usually) Post 12-26 mg/L	Depending on levels & progression

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* 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.
[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

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Other agents			
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 dose 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 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.
[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

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