Laboratory Medicine & Pathobiology
UNIVERSITY OF TORONTO

Guidance on Antimicrobial Therapeutic Ranges and Critical Values

Recommendations endorsed by the LMP Quality Council

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Purpose

This document summarizes our findings for antimicrobial therapeutic ranges and critical values from hospitals within the Greater Toronto Area (GTA), in collaboration with the respective Pharmacy/Infectious Disease departments. The intention of this document is to act as a guide and/or reference for clinical laboratories with respect to reporting levels of antimicrobial drugs that require therapeutic drug monitoring (TDM).

Executive summary

- Assays for common antimicrobials requiring TDM are not analytically equivalent and this must be considered when attempting to use harmonized therapeutic ranges and/or critical values
- Therapeutic ranges used for vancomycin and aminoglycosides are generally similar across institutions, especially for interpretation of trough samples
  - It is still important to consider other factors when interpreting levels in blood such as: severity of infection, dosing strategy, or specific patient population
- Currently, only two laboratories in the GTA offer voriconazole testing so therapeutic ranges and critical values are all harmonized
- Consider incorporating quality assurance practices specific to TDM antimicrobial assays to ensure delivery of high-quality service

Analytical variance

An important concept within laboratory testing that is often overlooked is the analytical variance that occurs within a laboratory and/or between laboratories. Variance within a laboratory is often referred to as imprecision while variance between laboratories is often referred to as bias. While imprecision can be largely controlled with internal quality assurance processes, bias is not so easily managed. This is largely due to inherent differences in the manufacturing and development of testing reagents between the major in vitro diagnostic (IVD) companies. Bias becomes concerning with assays that employ the use of antibodies and/or are interpreted against "universal" ranges/cutoffs – vancomycin is a prime example of a TDM assay that fits both these attributes.

Below, we illustrate analytical variance with empirical vancomycin data from several hospital laboratories within the GTA. Four patient plasma pools were generated with concentrations reflecting subtherapeutic (approximately 5 mg/L), near subtherapeutic (approximately 10 mg/L), near supratherapeutic (approximately 15 mg/L) and supratherapeutic ranges (approximately 25 mg/L). Across the 8 participating laboratories, there was representation from five IVD companies as well as five different types of immunoassays.

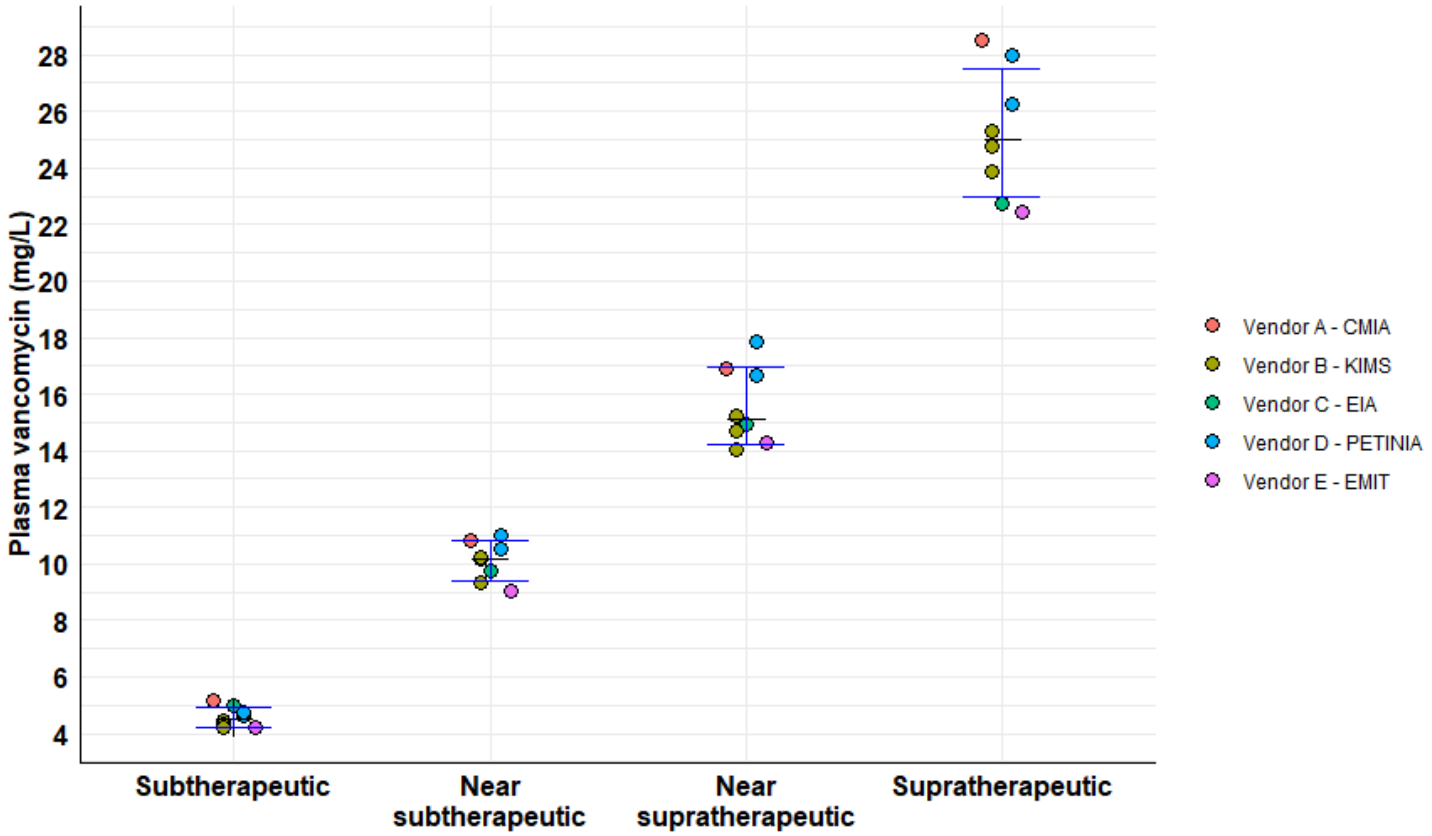

Figure 1. Vancomycin assay variation across GTA laboratories. Inter-laboratory variation in vancomycin measurements across various concentrations. The blue error bars represent inter-laboratory standard deviations based on the mean of all measurements within each concentration category (sub-, near sub-, near supra-, and supra-therapeutic).

Guidance on Antimicrobial Therapeutic Ranges and Critical Values

Laboratory reporting guidance

Across the GTA hospitals, the TDM test menu for antimicrobials includes: vancomycin, aminoglycosides (tobramycin, gentamicin, amikacin) and voriconazole. While individual hospitals may not necessarily perform all tests in-house, most hospitals still offer this test menu with some being referred out to other institutions (see Appendix 1 for more details).

To assess the landscape of therapeutic ranges and/or critical values used across institutions for these antimicrobial tests, Pharmacy and Infectious Disease groups were engaged for their input on guidance documents, clinical practice and other relevant information. Below, we summarize our findings for each of the five tests. For more information on treatment resources and/or algorithms, refer to the cited references and engage with your local Pharmacy/Infectious Disease clinicians.

1. Vancomycin

Description: Vancomycin is a glycopeptide antibiotic typically used to treat a number of bacterial infections, especially for Gram-positive bacteria that are unresponsive to other antibiotics.

All GTA hospitals provide reporting for **trough** levels and the therapeutic ranges are generally consistent:

- Trough target levels of 8 – 15 mg/L are appropriate for most infections where vancomycin is indicated.
- Trough target levels of 15 – 20 mg/L can be considered in patients with serious or deep-seated infections that require more aggressive dosing severe sepsis, endocarditis, infections involving the central nervous system, bone & joint infections, and serious infections involving methicillin-resistant *S. aureus* (e.g. bacteremia, pneumonia).
- Though there is no concentration that definitively correlates with toxicity, the majority of GTA laboratories use > 20 mg/L as a threshold for critical results.

Some GTA hospitals also provide reporting for **peak** and **random** levels and the therapeutic ranges are generally consistent:

- Post-dose target levels should be within 30 – 40 mg/L
- Random target levels should be less than 30 mg/L
- There is less agreement for the critical thresholds for peak or random results used by GTA laboratories (refer to Biochemistry and Haematology Critical Values)

It is important to note that there is a current paradigm shift from trough monitoring of vancomycin towards Bayesian calculation of area under the curve (AUC). While this change is most pronounced in the US, Canadian centers are moving towards this and there are likely a significant portion of centers that use a combination of trough-based and AUC-based monitoring.

References

1. Rybak MJ, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Disease Pharmacists. Am J Health Syst Pharm. 2020 May 19;77(11):835-864.
2. Vancomycin Monitoring and Adjustment. (2018). Sinai Health System – University Health Network. Antimicrobial Stewardship Program.
3. Vancomycin Empiric Dosing Guidelines. (2016) Vancouver Coastal Health.
4. Aminoglycosides – Guidelines for use. (2019). Sunnybrook Health Sciences Centre.
5. Jorgensen SCJ, McIntyre M, Curran J, So M. Vancomycin Therapeutic Drug Monitoring: A Cross-Sectional Survey of Canadian Hospitals. Can J Hosp Pharm. 2023 Jul 5;76(3):203-208. doi: 10.4212/cjhp.3337. PMID: 37409147; PMCID: PMC10284285.

2. Aminoglycosides

Description: Aminoglycosides are antimicrobials usually reserved for treatment of gram negative organisms not susceptible to other, less toxic antibiotic therapy. Aminoglycosides may very rarely be used in combination with other antimicrobials ("synergy") in select infections due to gram positive bacteria such as *Enterococcus* spp. infective endocarditis. The drugs within this class that are often measured for TDM are gentamicin, tobramycin and amikacin.

Across most GTA hospitals, the consensus – supported by Clinical Pharmacist stakeholders – is that the trough levels for the three aminoglycosides should be "undetectable" or below the lower reportable limit for extended interval dosing. However, this does not necessarily apply with other dosing strategies (synergy, "traditional" multiple daily dosing). Due to the various aminoglycoside assays that are offered within the GTA, the trough target range/cutoff can vary depending on the limit of quantification for the particular assay. Furthermore, some hospitals will report different trough targets depending on several factors such as: (1) dosing strategy (defined daily, multiple daily, synergy), (2) type of infection, and (3) specific patient population (neonates, critically ill). Some of the trough cutoffs observed are:

- Gentamicin: < 0.5 mg/L, < 1.0 mg/L, < 2.0 mg/L
- Tobramycin: < 0.5 mg/L, < 1.0 mg/L, < 2.0 mg/L
- Amikacin: < 2.3 mg/L, < 4.0 mg/L, < 8.0 mg/L, < 10 mg/L

Nearly all GTA hospitals also report peak levels for all aminoglycosides but the target ranges are variable as they depend on several factors similar to trough levels (as described above).

Given these complexities, laboratories can work with pharmacists to enhance the reporting of aminoglycoside levels by including guidance on interpretation. As an example, Unity Health recently revised their aminoglycoside reporting through collaboration between the laboratory and pharmacy to provide detailed guidance on interpretation (see Appendix 1).

There is generally good agreement for critical thresholds among the GTA hospitals for the aminoglycoside levels whether it is trough or peak sampling (refer to Biochemistry and Haematology Critical Values). However, it is important to note that there is no agreed upon concentration that definitively correlates with toxicity.

References

1. Initiating Intravenous (IV) Aminoglycoside Therapy Safely in Adult Inpatients. (2023). Sinai Health System – University Health Network Antimicrobial Stewardship Program.

3. Voriconazole

Description: Voriconazole is an antifungal agent that can be used to treat apergillosis, candidiasis, coccidioidomycosis, histoplasmosis, penicilliosis and infections by *Scedosporium* or *Fusarium*.

For voriconazole, the trough target level range is 1 - 5 mg/L and toxicity should be considered for trough levels > 6 mg/L. At the time of this document, only two GTA hospitals offers voriconazole TDM testing and both report a therapeutic range of 1- 5 mg/L and a critical limit of > 6 mg/L.

While nearly all GTA hospitals use the same therapeutic range, Lexicomp provides infection-specific ranges that can be considered depending on institutional practices:

- Invasive aspergillosis: target > 1 – 1.5 mg/L; maintain < 6 mg/L to prevent toxicity
- CNS aspergillosis: target 2 – 5 mg/L
- Endophthalmitis: target 2 – 5 mg/L

References

1. Lexicomp Online, Voriconazole Lexi-Drugs Online. Waltham, MA: UpToDate, Inc.; July 30, 2021. Accessed August 9, 2021.
2. Patterson TF, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. 2016 Aug 15;63(4):31-360.
3. Voriconazole Monitoring and Adjustment. (2023). Sinai Health System – University Health Network Antimicrobial Stewardship Program.

Quality laboratory management of antimicrobial TDM assays

To ensure delivery of quality laboratory service for antimicrobial TDM assays, we recommend integrating the following practices into your laboratory quality management system:

1. Standardize nomenclature across your institution

It is important to standardize the nomenclature used for the different types of blood samples that can be drawn for TDM in the context of dosing schedule. Whether your institution/health system uses pre-dose/post-dose or trough/peak, it is important to standardize these descriptors in alignment with Pharmacy and Infectious Disease stakeholders. Furthermore, the laboratory should establish unique orderables for each time-specific blood sample to enable appropriate target levels/canned comments to be reported with results. Order entry should also prompt for last dose date and time.

2. Ensure appropriate turnaround time for referred out TDM tests

Very few GTA hospitals offer all five of these antimicrobial TDM tests in-house, which means a significant portion of these are referred out to external institutions. As a result, turnaround time (TAT) for these results is extended which may delay patient treatment/management. Even though there is little a laboratory can control with referred out tests in these regards, it is important to communicate the expected TAT to relevant stakeholders to ensure that they are aware and to confirm that there are no patient safety issues related to delayed TAT.

3. Maintain constant communication with Pharmacy and/or Infectious Disease stakeholders

As the primary clinicians who manage antimicrobial treatment and dosing, it is essential that the laboratory maintains an open channel of communication with Pharmacy and Infectious Disease stakeholders. Topical issues that should be discussed could include: assay changes, reviewing old nomograms, and ensuring alignment between Pharmacy guidelines and laboratory reporting.

4. Consider periodic assessment between institutions of patient samples with known TDM values to ensure consistency and accuracy

Given the analytical variance that occurs with antimicrobial TDM assays (as described above), it can be good practice for laboratories to engage with each other in periodic assessment of known patient samples. In maintaining awareness of the variance between different IVD vendor assays (for the same antimicrobial), laboratories can assess the equivalence of their results with other institutions.

Appendix 1 – Unity Health Aminoglycoside Reporting

To ensure delivery of quality laboratory service for antimicrobial TDM assays, we recommend integrating the following practices into your laboratory quality management system:

	Appending Comment
Tobramycin	For traditional ("conventional") dosing method: • Pre-dose: < 2.0 mg/L for adults and pediatrics • ½ hour post-dose: 4.0 – 10.0 mg/L (pediatrics 5.0-10.0 mg/L) For extended interval ("once daily") dosing method: • pre < 1.0 mg/L for adults • Collect level 8-12 hrs post-dose for adults; 3 hr and 6 hr post-dose for pediatrics and use nomogram for interpretation. Refer to guidelines for Aminoglycoside dosing at your institution. • For further assistance with interpretation contact unit pharmacist.
Gentamicin	For traditional ("conventional) dosing method: • Pre-dose: < 2.0 mg/L for adults and pediatrics • ½ hour post-dose: 4.0 – 10.0 mg/L (pediatrics 5.0-10.0 mg/L) When used for synergy in the treatment of gram positive endocarditis in adults: • Pre-dose: < 1.0 mg/L • ½ hour post-dose: 3.0 - 4.0 mg/L For extended interval("once daily") dosing method: • Pre-dose: < 1.0 mg/L for adults • Collect level 8-12 hours post dose for adults; 3 hr and 6 hr post dose for pediatrics and use nomogram for interpretation. Refer to guidelines for Aminoglycoside dosing at your institution. • For further assistance with interpretation; contact unit pharmacist.
Amikacin	For traditional ("conventional) dosing method in adults: • pre < 8 mg/L • ½ hour post-dose: • 20 - 30 mg/L • For Urinary tract infection: 15 – 30 mg/L For extended interval("once daily) dosing method in adults: • pre < 1.0 mg/L • Collect level 8-12 hours post dose and use nomogram for interpretation. Refer to guidelines for Aminoglycoside dosing at your institution. • For further assistance with interpretation; contact unit pharmacist • For pediatrics, contact pediatric pharmacist for therapeutic drug monitoring targets.

Appendix 2 – Hospital Laboratory TDM Information

Amikacin

Hospital	Vendor	Assay Principle
Halton Healthcare	Referred out	
Headwaters Healthcare Centre	Referred out	
Humber River Hospital	Referred out	
Joseph Brant Hospital	Referred out	
Lakeridge Health	Referred out	
Mackenzie Health	Referred out	
Markham Stouffville Hospital	Referred out	
Michael Garron Hospital	Referred out	
North York General Hospital	Referred out	
Scarborough Health Network	Referred out	
Sinai Health	Referred out	
St. Michael's Hospital, Unity Health	Roche	KIMS
St. Joseph's Health Centre, Unity Health	Roche	KIMS
Sunnybrook Health Sciences Centre	Referred out	
The Centre for Addiction and Mental Health	Referred out	
The Hospital for Sick Children	Abbott	
Trillium Health Partners	Referred out	
William Osler Health System	Referred out	
Women's College Hospital	Referred out	
University Health Network	Abbott	PETINIA

KIMS kinetic interaction of microparticle in solution; PETINIA particle enhanced turbidimetric inhibition immunoassay.

Gentamicin

Hospital	Vendor	Assay Principle
Halton Healthcare	Abbott	PETINIA
Headwaters Healthcare Centre	Referred out	
Humber River Hospital	Beckman	EMIT
Joseph Brant Hospital	Siemens	PETINIA
Lakeridge Health	Siemens	PETINIA
Mackenzie Health	Beckman	EMIT
Markham Stouffville Hospital	Beckman	EMIT
Michael Garron Hospital	Referred out	
North York General Hospital	Referred out	
Scarborough Health Network	Beckman	EMIT
Sinai Health	Referred out	
St. Michael's Hospital, Unity Health	Roche	CEDIA
St. Joseph's Health Centre, Unity Health	Beckman	EMIT
Sunnybrook Health Sciences Centre	Roche	KIMS
The Centre for Addiction and Mental Health	Referred out	
The Hospital for Sick Children	Roche	KIMS
Trillium Health Partners	Siemens	PETINIA
William Osler Health System	Siemens	PETINIA
Women's College Hospital	Referred out	
University Health Network	Abbott	PETINIA

CEDIA cloned enzyme donor immunoassay; EMIT enzyme multiplied immunoassay technique; KIMS kinetic interaction of microparticle in solution; PETINIA particle enhanced turbidimetric inhibition immunoassay.

Tobramycin

Hospital	Vendor	Assay Principle
Halton Healthcare	Referred out	
Headwaters Healthcare Centre	Referred out	
Humber River Hospital	Referred out	
Joseph Brant Hospital	Referred out	
Lakeridge Health	Siemens	PETINIA
Mackenzie Health	Referred out	
Markham Stouffville Hospital	Referred out	
Michael Garron Hospital	Referred out	
North York General Hospital	Referred out	
Scarborough Health Network	Beckman	EMIT
Sinai Health	Referred out	
St. Michael's Hospital, Unity Health	Roche	EIA
St. Joseph's Health Centre, Unity Health	Roche	EIA
Sunnybrook Health Sciences Centre	Roche	EIA
The Centre for Addiction and Mental Health	Referred out	
The Hospital for Sick Children	Roche	EIA
Trillium Health Partners	Siemens	PETINIA
William Osler Health System	Referred out	
Women's College Hospital	Referred out	
University Health Network	Abbott	PETINIA

EIA enzyme immunoassay; EMIT enzyme multiplied immunoassay technique; PETINIA particle enhanced turbidimetric inhibition immunoassay.

Vancomycin

Hospital	Vendor	Assay Principle
Halton Healthcare	Abbott	PETINIA
Headwaters Healthcare Centre	Beckman	PETINIA
Humber River Hospital	Beckman	EMIT
Joseph Brant Hospital	Siemens	PETINIA
Lakeridge Health	Siemens	PETINIA
Mackenzie Health	Beckman	EMIT
Markham Stouffville Hospital	Beckman	EMIT
Michael Garron Hospital	Roche	KIMS
North York General Hospital	Roche	KIMS
Scarborough Health Network	Beckman	EMIT
Sinai Health	Roche	KIMS
St. Michael's Hospital, Unity Health	Roche	KIMS
St. Joseph's Health Centre, Unity Health	Beckman	EMIT
Sunnybrook Health Sciences Centre	Roche	KIMS
The Centre for Addiction and Mental Health	Referred out	
The Hospital for Sick Children	Roche	KIMS
Trillium Health Partners	Siemens	PETINIA
William Osler Health System	Siemens	PETINIA
Women's College Hospital	Referred out	
University Health Network	Abbott	PETINIA

EMIT enzyme multiplied immunoassay technique; KIMS kinetic interaction of microparticle in solution; PETINIA particle enhanced turbidimetric inhibition immunoassay.

Voriconazole

Hospital	Vendor	Assay Principle
Halton Healthcare	Referred out	
Headwaters Healthcare Centre	Referred out	
Humber River Hospital	Referred out	
Joseph Brant Hospital	Referred out	
Lakeridge Health	Referred out	
Mackenzie Health	Referred out	
Markham Stouffville Hospital	Referred out	
Michael Garron Hospital	Referred out	
North York General Hospital	Referred out	
Scarborough Health Network	Referred out	
Sinai Health	Referred out	
St. Michael's Hospital, Unity Health	Referred out	
St. Joseph's Health Centre, Unity Health	Referred out	
Sunnybrook Health Sciences Centre	Referred out	
The Centre for Addiction and Mental Health	Referred out	
The Hospital for Sick Children	Lab Developed Test	LC-MS/MS
Trillium Health Partners	Referred out	
William Osler Health System	Referred out	
Women's College Hospital	Referred out	
University Health Network	Abbott (third party reagent)	Homogenous Enzyme Immunoassay

LC-MS/MS liquid chromatography tandem mass spectrometry.

Acknowledgments

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