Guideline for the use of amikacin for drug resistant tuberculosis and nontuberculous mycobacterial infections in Queensland

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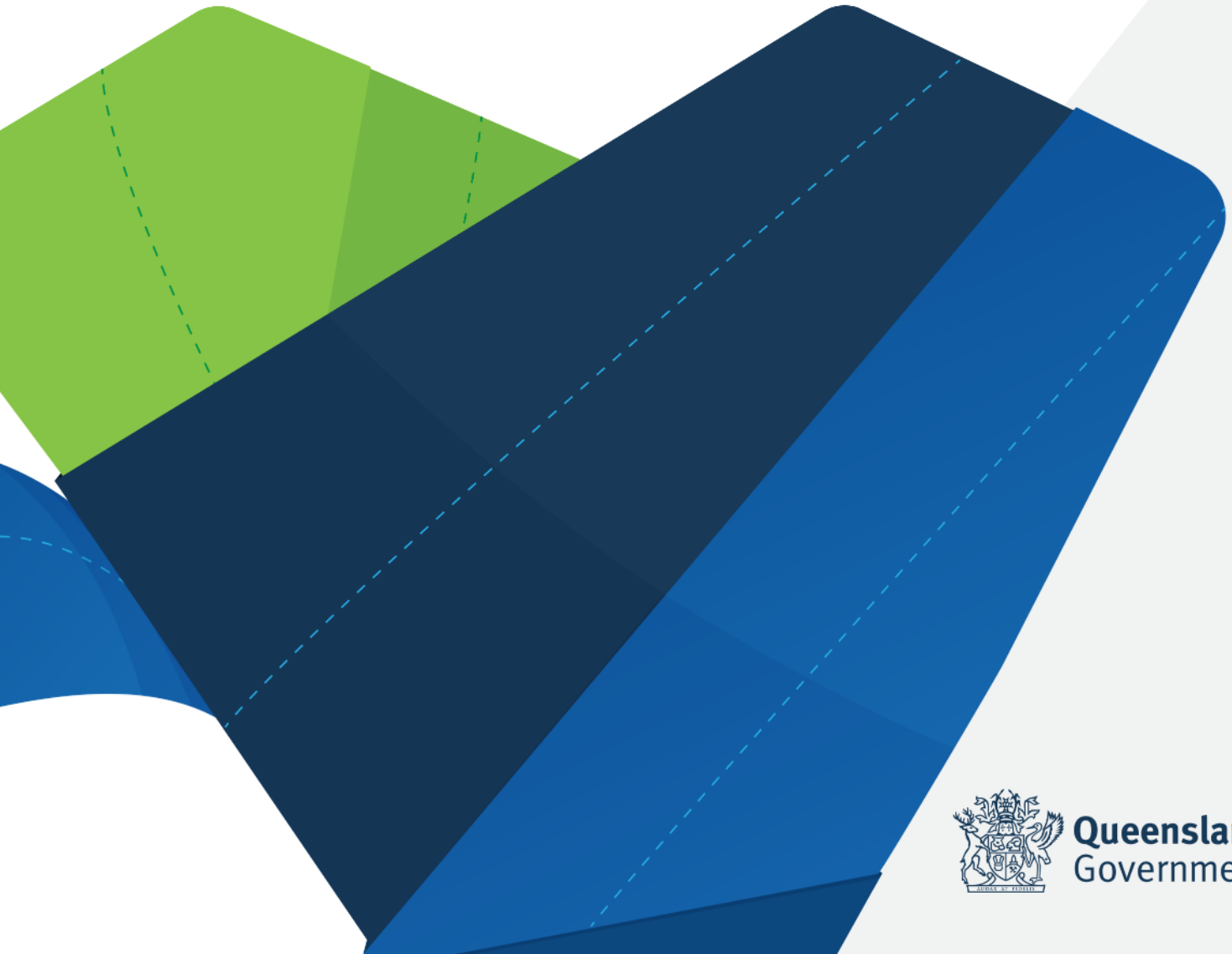

Queensland Government

Introduction

Although recent updates by the World Health Organization (WHO) for the treatment of multidrug resistant tuberculosis (MDR-TB) recommend prioritising the use of oral agents such as bedaquiline, fluoroquinolones, linezolid, clofazimine and cycloserine, there remains a role for the inclusion of the second line injectable, amikacin. A recent WHO technical report calls for further research on the value of injectable agents for the treatment of MDR-TB.[1] The role of injectable agents has further diminished with WHO rapid communication December 2019 recommending the preference for bedaquiline instead of amikacin (or other injectables) for the shorter MDR-TB regimen. Nonetheless, amikacin maintains a role as a potential component of the shorter MDR-TB regimen and as part of the longer MDR-TB regimen where preferred oral agents cannot be used.[2] The isolate must demonstrate amikacin susceptibility and be administered where adequate monitoring for toxicity is available. There is likely modest benefit from amikacin which can be attributed to a sterilising effect and weak in vitro bactericidal properties.

Injectables can be omitted altogether in children with mild forms of disease and drug resistant tuberculosis (DR-TB). Kanamycin and capreomycin are no longer recommended by the WHO for the treatment of MDR-TB given demonstrated increase in treatment failure and relapse. Increasing interest in inhaled therapy with amikacin for TB and utility for some nontuberculous mycobacterial infections (NTM) is acknowledged but not covered by this guideline.

In Queensland, amikacin, a semi-synthetic aminoglycoside derived from kanamycin remains the preferred injectable agent for DR-TB as, in addition to aligning with current WHO guidance, amikacin serum levels can be readily measured and unlike kanamycin and capreomycin, is TGA registered for use in Australia. When an injectable aminoglycoside is required to treat NTM infection, amikacin is generally used except for *M. chelonae* when tobramycin is the aminoglycoside of choice. Amikacin is a core drug in the treatment of *M. abscessus*, an often difficult to treat organism.

The following guidelines should be read in conjunction with the Adult Statewide Guidelines on Aminoglycoside Usage and the CHQ Paediatric Aminoglycoside therapeutic drug monitoring guidelines.

Pharmacokinetic/pharmacodynamic (PK/PD) considerations

Amikacin is a water-soluble aminoglycoside with linear pharmacokinetics and requires parenteral administration. Intravenous administration is usual and intramuscular injection almost never used in Australia.

PK/PD modelling studies with the hollow fibre model indicate optimal bacterial killing (EC90) is predicted by the Cmax/MIC ratio (Figure 1) at the site of infection with a ratio of 10 being optimal.[3] For pulmonary tuberculosis, the concentration of amikacin in lung tissue can be difficult to predict and the methodology to measure the minimum inhibitory

concentration (MIC) is yet to be standardised. Although MICs for MDR-TB are not routinely performed and will vary according to laboratory method used (MGIT vs 7H10 agar vs Lowenstein-Jensen media), these tend to be significantly lower than those for NTM organisms (e.g. *M. abscessus*). The Queensland Mycobacterium Reference Lab uses the MGIT system for M. tuberculosis drug susceptibility testing where the critical concentration is 1.0 mg/L which is equivalent to an epidemiological cut off value (E_{coff}). Susceptible strains would be expected to have an MIC of 1.0 mg/L or less. For nontuberculous mycobacteria, MIC is measured by broth microdilution methodology.

In general, a peak serum concentration (Cmax) of 40 to 50 mg/L is likely most efficacious for TB (see Therapeutic Drug Monitoring (TDM) page 6).

Toxicity is a major concern for aminoglycosides with oto/vestibular and nephrotoxicity most notable. While nephrotoxicity is (usually) completely or mostly reversible, eighth cranial nerve toxicity is often permanent. Study of MDR-TB adult patients has correlated ototoxicity with cumulative dose of amikacin with a cumulative area under the curve (AUC) of 87,232 mg*h/L giving a 10% risk of ototoxicity. Toxic level AUC typically occurs after 6 months duration of daily administered therapy and is highest ≥ 12 months.[4] Evidence for saturable aminoglycoside uptake in renal tubule cells and the inner ear suggest that higher peaks do not necessarily equate to greater toxicity, rather the duration of saturation.

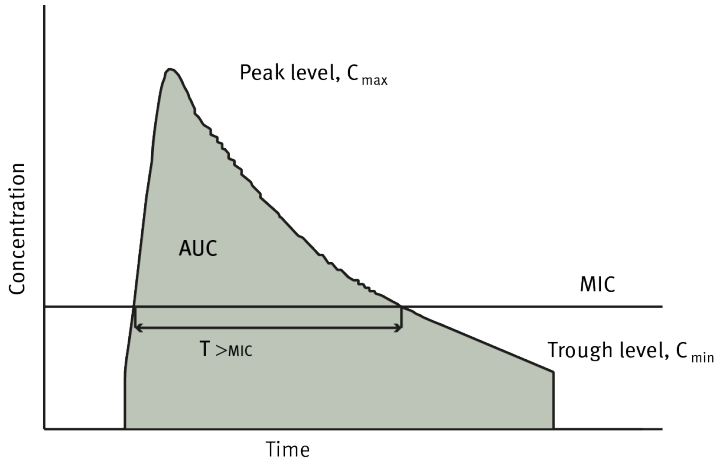

Figure 1 AUC, area under the concentration-time curve: Cmin, minimum concentration: Cmax, maximum concentration: MIC minimum inhibitory concentration: T>MIC, time during which the drug blood concentration is above the MIC [1]

Modelling studies indicate that thrice weekly dosing of amikacin at 25 mg/kg (adults) would deliver better Cmax/MIC outcomes with less total dose accumulation than daily dosed amikacin at 15 mg/kg. For this reason, the WHO technical report on PK/PD issues for drugs used to treat DR-TB has recently concluded "when given three times a week at 25 mg/kg body weight as part of a longer MDR-TB regimen, second-line injectable agents – amikacin and kanamycin – are likely to be more effective and less toxic".[1] Daily dosing at 15 mg/kg should be utilised when prescribed for the WHO endorsed short course regimen. In general, size and frequency of dosing is less likely contributive to toxicity but rather total cumulative dose and cumulative AUC. Lower doses for longer periods may indeed result in increased toxicity. Pre-existing renal impairment and advanced patient age are both important risk factors for aminoglycoside toxicity.

Summary of dosing recommendations

Adults

Amikacin dose should be calculated according to body weight; Ideal Body Weight (IBW) or actual body weight (whichever is less). Where actual body weight is greater than 20% above ideal, adjusted body weight (AdjBW) should be used. Further details regarding body weight calculations are outlined in the Statewide aminoglycoside guidelines.

Ideal body weight can be calculated with an online tool AMH – Adult IBW Calculator or according to the following formula: IBW for male = 50 kg + 0.9 kg/each cm over 152 cm; IBW for female = 45.5 kg + 0.9 kg/each cm over 152 cm.

Similarly refer to the Statewide guideline for contraindications to and precautions for aminoglycoside therapy.

To date, there are no randomised control trials (RCT) on intermittent vs daily dosing or the utilisation of therapeutic drug monitoring (TDM) targeting organism minimum inhibitory concentration (MIC) to help guide treatment and monitoring for toxicity. Further guidance on accurate dosing, frequency and monitoring/targets is required. Accepting these caveats, the recommended dosing for amikacin for MDR-TB is:

- 15 mg/kg/day for short course MDR-TB therapy.
- Thrice weekly therapy at 25 mg/kg/day should be considered for longer course (20 months) MDR-TB regimens and should be favoured where there are relative contraindications to amikacin use or early signs of nephrotoxicity on a daily regimen.

If renal impairment is present, dose frequency should be adjusted: if estimated glomerular filtration rate (eGFR) is 40 to 60 ml/min, then daily dose should be adjusted to every 36 hours or convert to thrice weekly dosing. If eGFR is less than 40 ml/min, expert advice from the TB Expert Advisory Group (TEAG) should be sought. At extremes of body weight, eGFR should be modified as explained in the statewide guideline for aminoglycoside use.

Duration: For short course MDR-TB therapy the duration of aminoglycoside is 4 to 6 months, with the longer duration based on positive cultures at month 4. For conventional long course therapy, the duration of amikacin is 6 to 7 months which may be modified depending on patient response.[2]

For children: Amikacin dose is based on ideal body weight (IBW). To estimate IBW in children, utilise paediatric growth charts appropriate for age and gender—available online at Child Growth Charts. The % Modified Schwartz formula is used to calculate Paediatric Creatinine Clearance (CrCl):

CrCl (mL/min/1.73 m2) = [36.5 x height (cm)] / Creatinine (micromol/L) = _____ mL/min/1.73 m2

The Modified Schwartz formula is not validated to be used in children <1 year of age. Cap CrCl at maximum of 120 mL/min/1.73 m2.

Table 1 Dosing in children

	Tuberculosis	Nontuberculosis Mycobacterial (NTM) pulmonary infections
Infants, children and adolescents up to 12 years of age	22.5 mg/kg IV once daily (Maximum 1000 mg/day initial dose)	30 mg/kg IV once daily (Maximum 1250 mg/day initial dose)
Adolescents >12 years of age	15 mg/kg IV once daily (Maximum 1000 mg/day initial dose)	15 mg/kg IV once daily (Maximum 1250 mg/day initial dose)
Infusion duration	Dilute dose to maximum concentration of 10 mg/mL and infuse dose over 30 minutes. Document the infusion start and finish time, if the IV line was primed with drug or sodium chloride 0.9% and the mode of administration (burette/syringe driver). This information is required to perform TDM calculation.	

Therapeutic Drug Monitoring (TDM)

TDM recommendations given in this document are based on route of administration being intravenous.

Timing of sample

Cmax: There is currently limited and variable data on the ideal desired Cmax values for both MDR and NTM pulmonary infections. Where available, software utilising Bayesian principles can be used to calculate dosage based on a timed post dose level (x - y hrs post dose), otherwise manually plot on semi-logarithmic paper and extrapolate back to time = 0 and use this as the Cmax level. Alternatively, plasma samples can be taken at two different times (often 2 and 6 hours post dose) with Cmax calculation and dose adjustments completed either using Bayesian software, pharmacy AUC calculators or manual plotting on semi-logarithmic paper with extrapolation back to time = 0.

Where software support is not available, Cmax is estimated from post infusion peak blood level. The peak level (not to be confused with Cmax level) should be taken at the end or just after the infusion. This post infusion peak level can guide the clinician in appreciating their proximity to actual Cmax. However, Cmax should always be calculated when possible. The exact timing and optimal frequency of samples for estimating a Cmax has not been established. Commonly a blood sample is taken 30 minutes post end of infusion, though this strategy may be less practical in the outpatient setting (e.g. Hospital in the Home).

Trough level: Collect sample up to 1 hour before next dose.

Collection tube: Blood sample serum tube (gold top) or lithium heparin (green top).

TDM for MDR-TB

Serum levels for amikacin are readily available. In clinical studies, ototoxicity was not correlated with amikacin trough or peak levels but more so, with total cumulative dose. However, persistently high trough levels will lead to critical AUC toxicity targets being achieved sooner thus increasing total drug exposure.

In general, for MDR-TB a Cmax serum concentration of 40 to 50 mg/L is likely sufficient where the strain is reported as susceptible to amikacin, with no clear evidence to date that higher levels result in greater bactericidal rates.[5]

Target level

Cmax: 40 to 50 mg/L MDR-TB (peak)

Trough (30 minutes pre-dose): <2 mg/L (ideally <1 mg/L or undetectable)

TDM for nontuberculous mycobacteria (NTM)

Given higher MICs for NTM than TB (e.g. median MIC 16 mg/L for *M. abscessus*) it is appropriate to aim for higher peaks acknowledging that it may not be possible to safely achieve a Cmax/MIC of 10 at site of infection in these patients.

Although there is a lack of RCTs on the efficacy of intermittent vs daily dosing, prospective studies comparing thrice weekly dosing (25 mg/kg) vs daily dosing (15 mg/kg) in both MDR-TB and NTM patients demonstrates equivalent safety with thrice weekly dosing, with the benefit of less total drug exposure and ease of administration. Cmax values at 25 mg/kg ranged from 54 to 98 mg/L.[6] Monitoring of trough serum amikacin levels is prudent clinical practice.

Target Level

Cmax: 65 to 80 mg/L for NTM Pulmonary Infections

- Recommendations may vary in specialised patient groups Cmax of 80 to 100 mg/L is recommended by the Queensland Children's Hospital for children with cystic fibrosis (CF).

Trough (30 minutes pre-dose): <2 mg/L (ideally <1 mg/L or undetectable)

Frequency of TDM

Take initial blood samples day 1 of therapy. Repeat sampling every 48 hours until target Cmax has been achieved. Cmax calculations can be repeated weekly or more often if there is a significant change in clinical state. It may not be necessary to continue Cmax calculations if target levels are consistently achieved and clinical status is stable. Repeat trough levels are recommended at least once weekly, after dose adjustment and more frequently if renal function deteriorating.

Monitoring for toxicity

Renal function (urea, creatinine, eGFR) and electrolytes (especially potassium and magnesium) should be checked prior to starting amikacin and then twice weekly or more frequently if renal function is deteriorating.

Weekly monitoring may be appropriate when clinical (including renal function) stability is apparent.

Baseline hearing should be checked with audiology prior or near commencing treatment and then ideally, weekly. It is acknowledged that in many settings weekly audiometry will not be feasible. WHO recommends testing at least monthly as a guide to minimum requirements. A bedside check or more formal studies (e.g. mono-thermal caloric test) for vestibular toxicity should be performed weekly. Refer to the statewide guideline for detailed recommendations of toxicity monitoring.

As aminoglycoside toxicity may emerge after cessation of the drug, periodic monitoring should be performed at least until 3 months post cessation of amikacin and prior to reintroduction of aminoglycosides for mycobacterial disease or other indication where clinically appropriate.

References

1. World Health Organization. Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2018 (WHO/CDS/TB/2018.6)

2. World Health Organization. WHO Consolidated Guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019 (WHO/CDS/TB/2019.7)

3. Srivastava S, Modongo C, Siyambalapitiyage Dona CW, Pasipanodya JG, Deshpande D, Gumbo T. Amikacin Optimal Exposure Targets in the Hollow-Fiber System Model of Tuberculosis. Antimicrob Agents Chemother. 2016 Oct;60(10):5922–7.

4. Modongo C, Pasipanodya JG, Zetola NM, Williams SM, Sirugo G, Gumbo T. Amikacin Concentrations Predictive of Ototoxicity in Multidrug-Resistant Tuberculosis Patients. Antimicrob Agents Chemother. 2015;59(10):6337–6343.

5. Juréen P, Ängeby K, Sturegård E, Chryssanthou E, C. G. Giske, J. Werngren, M. Nordvall, A. Johansson, G. Kahlmeter, S. Hoffner, T. Schön. J Clinical Micro. 2010;48(5):1853-1858.

6. Peloquin C. The Role of Therapeutic Drug Monitoring in Mycobacterial Infections. Microbiol Spectrum. 2017;5(1):TNM17-0029-2016.

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Therapeutic Guidelines Ltd. eTG Calculators. Melbourne; Vic: Therapeutic Guidelines Ltd; 2019.

World Health Organization. Technical report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. World Health Organization; 2018 (WHO/CDS/TB/2018.5)

Links

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Adult Statewide Guidelines on Aminoglycoside Usage
https://www.health.qld.gov.au/__data/assets/pdf_file/0019/713323/aminoglycoside-guidelines.pdf

CHQ Paediatric Aminoglycoside therapeutic drug monitoring guidelines
https://www.childrens.health.qld.gov.au/wp-content/uploads/PDF/ams/paed-tobramycin-gentamicin-therapeutic-drug-monitoring.pdf

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Statewide aminoglycoside guidelines
https://www.health.qld.gov.au/__data/assets/pdf_file/0019/713323/aminoglycoside-guidelines.pdf

AMH – Adult IBW Calculator

https://amhonline.amh.net.au/calculators/adultidealweight?menu=banner

Statewide guideline for contraindications to and precautions for aminoglycoside therapy
https://www.health.qld.gov.au/__data/assets/pdf_file/0019/713323/aminoglycoside-guidelines.pdf

Child Growth Charts
https://www.rch.org.au/childgrowth/Growth_Charts/

Document approval details

Document custodian

Director, Communicable Diseases Branch

Approving group

Tuberculosis Expert Advisory Group

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Version Control

Version	Date	Date of next revision	Comments
Version 1.0	March 2021	March 2022	New document