

Aminoglycosides: an update on indications, dosing and monitoring

SUMMARY

Aminoglycosides (gentamicin, tobramycin and amikacin) are highly effective parenteral drugs commonly used as initial empirical therapy of serious Gram-negative infections. They have rapid bactericidal activity and relatively low rates of resistance in Australia compared with other antibiotics used to manage Gram-negative infections.

Therapeutic Guidelines: Antibiotic was updated in March 2025 and provides new guidance on the role of aminoglycosides, optimised dosing, and drug selection. The guidelines now recommend that dosing in adults is based on lean body weight, and provide calculators to assist with dose calculations.

Therapeutic drug monitoring is required when aminoglycoside therapy is expected to continue beyond 48 hours; monitoring the area under the aminoglycoside concentration–time curve is recommended in adults.

Introduction

The aminoglycosides gentamicin, tobramycin and amikacin are highly effective drugs for treating Gram-negative infections. Because of concerns and controversies around their narrow therapeutic range, the need to screen for multiple toxicity risk factors, and challenges with individualised dosing and monitoring, some clinicians advocate for replacement of aminoglycosides in empirical therapy with alternatives such as carbapenems or broad-spectrum beta lactams. However, increased and widespread use of these alternative antibiotics is associated with risk of escalating antibiotic resistance.¹

In March 2025, *Therapeutic Guidelines: Antibiotic* (referred to as ‘the Antibiotic guidelines’ in this article) was updated.² The update considered Australian resistance data for aminoglycosides, antimicrobial stewardship principles, practical considerations, and advice on aminoglycoside use and breakpoints* from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI).

This article provides an update on the role of parenteral aminoglycosides in the treatment of infections and recommendations in the Antibiotic guidelines, and highlights important considerations for their safe and effective use.

Indications for aminoglycosides

Parenteral aminoglycosides are primarily used for short-term empirical therapy of serious infections suspected to have a Gram-negative source. They are often preferred to broad-spectrum beta lactams or carbapenems for initial empirical therapy (see ‘Advantages and disadvantages of aminoglycosides’, below). Aminoglycosides also have a role in directed therapy.

EUCAST and CLSI are the 2 leading international organisations that provide antimicrobial susceptibility testing and reporting guidelines for Australian microbiology laboratories. They recently reviewed the role of aminoglycosides by re-examining existing clinical data, preclinical data and collated minimum inhibitory concentration (MIC) distribution data, resulting in changes to their aminoglycoside breakpoints and dosing strategies. Both EUCAST and CLSI now recommend that aminoglycosides should be used in combination with another active therapy, such as an antimicrobial from another class with known susceptibility against the pathogen, or a source control procedure (e.g. surgery). The exception is infections originating in the urinary tract, where monotherapy with an aminoglycoside may be appropriate because aminoglycosides are concentrated in the urine and renal tissues.^{4,5}

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* Breakpoints define whether a microorganism is susceptible or resistant to an antimicrobial. All susceptibility testing methods rely on breakpoints, also known as interpretive criteria, so that results of susceptibility tests can be interpreted and reported to clinicians.³

In the Antibiotic guidelines,² for infections originating outside the urinary tract, aminoglycosides are usually recommended in combination with another antimicrobial or a source control procedure, but the other antimicrobial does not always have activity against Gram-negative bacteria. For example, an aminoglycoside is combined with amoxicillin or ampicillin for intra-abdominal infections; however, because resistance to amoxicillin and ampicillin in Enterobacterales is high (about 50%),⁶ the aminoglycoside may be the only active drug in up to half of all cases. The Antibiotic guidelines continue to recommend aminoglycosides for empirical therapy of serious Gram-negative infections without always including a second active therapy, because there has not been a signal that clinical failures are occurring and there is substantial clinical experience with their use. Recommended indications for aminoglycoside use are listed in Box 1.

Advantages and disadvantages of aminoglycosides

There are many advantages of using aminoglycosides (Box 2). Compared with other classes of antibiotics with activity against Gram-negative pathogens (e.g. broad-spectrum cephalosporins, carbapenems),

aminoglycosides are active against a greater percentage of Enterobacterales (e.g. *Escherichia coli*), and retain activity against most extended-spectrum beta-lactamase (ESBL)-producing strains.^{6,7} Use of aminoglycosides also minimises the need to use antibiotics on the World Health Organization watch list (e.g. piperacillin+tazobactam, ceftriaxone, cefotaxime, meropenem), which have a broader spectrum of activity, are more likely to promote antimicrobial resistance and are associated with a higher incidence of *Clostridioides difficile* infection.¹

Aminoglycoside toxicity is well recognised (Box 2). Nephrotoxicity occurs in 10 to 25% of patients, although this is dependent on the cumulative dosage and is rare when treatment is limited to less than 72 hours.^{8,9} Importantly, nephrotoxicity is generally reversible.⁸ Vestibular and auditory toxicities are unpredictable, may occur soon after starting aminoglycosides or weeks after treatment has stopped, and can persist after treatment. Rare cases of sudden idiosyncratic deafness have been reported. Irreversible auditory and vestibular toxicities are more often linked to extended courses of therapy. However, serious toxicity can occur following minimal exposure in patients with genetic susceptibility, although this is rare.⁸

Box 1 Recommended indications for aminoglycoside use²

Empirical therapy

- Short-term empirical therapy of serious infections suspected to have a Gram-negative source (e.g. intra-abdominal infections, urinary tract infections, sepsis of unknown source)

Initial directed therapy, pending results of susceptibility tests

- Confirmed Gram-negative infections where resistance to other empirical antimicrobials is suspected
- As part of combination therapy for *Pseudomonas aeruginosa* infections

Directed therapy

- Confirmed Gram-negative infections that are resistant to antibiotics more appropriate for longer term use
- As part of combination therapy for brucellosis, nocardiosis and nontuberculous mycobacterial infections
- Synergistic therapy (with another antimicrobial) for streptococcal, enterococcal and Bartonella endocarditis (see Box 2)

Box 2 Advantages and disadvantages of aminoglycosides²

Advantages

- Aminoglycosides are bactericidal and associated with rapid control of Gram-negative infections.
- Most community- and healthcare-associated [NB1] Gram-negative pathogens are susceptible to aminoglycosides.
- Aminoglycosides have a 'postantibiotic effect' (where bacterial killing continues for many hours after plasma concentration is undetectable) that allows for effective once-daily therapy.
- When combined with cell-wall-active drugs (e.g. beta lactams, glycopeptides), aminoglycosides are synergistic for enterococcal and streptococcal infections.
- Aminoglycosides rarely cause hypersensitivity reactions.
- Aminoglycosides are rarely associated with *Clostridioides difficile* infection.

Disadvantages

- Aminoglycosides cause nephrotoxicity, usually associated with prolonged treatment courses (longer than 5 to 7 days) and pre-existing kidney impairment. Nephrotoxicity is generally reversible.
- Aminoglycosides cause vestibular and, less commonly, auditory toxicity, mostly associated with prolonged treatment courses. Vestibular and auditory toxicities are generally irreversible.

Adapted with permission from: Principles of aminoglycoside use [published 2025 Mar]. In: *Therapeutic Guidelines*. Melbourne: Therapeutic Guidelines Limited; accessed 2025 Mar 11. <https://www.tg.org.au>

NB1: Healthcare-associated pathogens, also known as nosocomial pathogens, are microorganisms acquired in healthcare settings, while community-associated pathogens are those acquired in the community. Examples of Gram-negative healthcare-associated pathogens include carbapenemase-producing Enterobacterales, and *Pseudomonas aeruginosa*, often associated with prolonged hospital stays or invasive procedures.

Alternatives to aminoglycosides

In patients who have relevant contraindications and precautions that preclude aminoglycoside use, broad-spectrum beta lactams such as piperacillin+tazobactam, amoxicillin+clavulanate, ceftriaxone and cefotaxime may be used, with choice between these beta lactams depending on the indication and target pathogens. A beta-lactam-based regimen can be used as initial therapy for patients in whom empirical intravenous therapy is likely to continue for 72 hours or longer (except in patients with sepsis or septic shock). This pragmatic approach avoids the need to switch to a beta lactam from an aminoglycoside at 72 hours, since empirical aminoglycoside dosing should not continue beyond 48 hours (i.e. a maximum of 3 doses at 0, 24 and 48 hours). However, if the likely duration of intravenous therapy is not known, or the patient has sepsis or septic shock, it is preferable to start with an aminoglycoside regimen and not delay administration of antibiotics to make this determination.

Carbapenems, such as meropenem, are broad-spectrum antibacterial drugs with activity against many strains of Gram-negative bacteria that are resistant to other drug classes. However, because widespread use is linked to an increasing prevalence of multidrug-resistant (MDR) bacteria, carbapenems should be reserved. For example, the Antibiotic guidelines recommend a tiered approach to empirical therapy for sepsis and septic shock from a urinary tract source in adults, to minimise the use of carbapenems.² For urosepsis (without septic shock), monotherapy with either an aminoglycoside or ceftriaxone is recommended. For septic shock from a urinary tract source, the combination of an aminoglycoside and ceftriaxone is recommended to broaden the spectrum of empirical therapy to include adequate activity against ESBL-producing strains and *Streptococcus agalactiae* (group B streptococcus, which is important for pregnant patients), while providing adequate coverage for most cases of diagnostic uncertainty. In contrast, meropenem is reserved for sepsis or septic shock from a urinary tract source in patients at risk of infection with MDR Gram-negative bacteria (e.g. recent stay in hospital or a long-term care facility either with a known outbreak of MDR Gram-negative bacteria, or in a country with a high prevalence of MDR Gram-negative bacteria).

Choosing an aminoglycoside

When used for empirical therapy of **serious Gram-negative infections**, the choice of aminoglycoside is influenced by the likely expected pathogens for the infection, local antibiograms, the availability of different aminoglycosides, and any applicable local, state or national guidelines. Gentamicin and tobramycin are most commonly used, and usually in

combination with other antibiotics. Amikacin has a broader spectrum than gentamicin and tobramycin, and is reserved for treatment of organisms in which resistance to gentamicin and tobramycin is intrinsic, confirmed or suspected.

For infections suspected or known to be caused by **Enterobacterales** (e.g. *E. coli*, *Klebsiella pneumoniae*), either gentamicin or tobramycin can be used. The prevalence of MDR Enterobacterales is increasing worldwide, particularly ESBL-producing strains. Data from 2022 show that the proportion of ESBL-producers among *E. coli* blood culture isolates varied significantly across Australia, from 6% in Tasmania to 25% in the Northern Territory.⁷ Around 70% of Australian ESBL-producing *E. coli* isolates are gentamicin susceptible;¹⁰ however, resistance rates to individual aminoglycosides are variable, and the choice of aminoglycoside should be informed by the local antibiogram. Amikacin may retain activity against Enterobacterales that have aminoglycoside-modifying enzymes conferring resistance to gentamicin and tobramycin,¹¹ therefore, amikacin may be preferred in areas where ESBL-producing Enterobacterales and carbapenemase-producing Enterobacterales are more prevalent. Notably, because both EUCAST and CLSI recommend that gentamicin and tobramycin should only be used in combination with another active therapy for infections originating outside the urinary tract, microbiology laboratories using these clinical breakpoints may not be reporting gentamicin and tobramycin susceptibilities for non-urinary tract infections.

For infections suspected or known to be caused by ***Pseudomonas aeruginosa***, tobramycin is preferred to gentamicin. International data show that tobramycin has twofold lower MICs and, given they have similar pharmacokinetic and pharmacodynamic profiles and dosing, this may confer an advantage for its use over gentamicin. Amikacin also appears to have more activity against *P. aeruginosa* than gentamicin, after accounting for the higher recommended dose. Based on this, EUCAST and CLSI both removed gentamicin breakpoints for *P. aeruginosa*;^{4,5,12} therefore, microbiology laboratories using these clinical breakpoints may not be reporting gentamicin susceptibilities for *P. aeruginosa*.

For directed therapy of most **nontuberculous mycobacterial infections**, amikacin is used because it retains activity, whereas gentamicin and tobramycin have no activity.

For synergistic treatment of Gram-positive infective endocarditis (e.g. streptococcal or enterococcal endocarditis), gentamicin is preferred because other aminoglycosides have less evidence and clinical experience is lacking.

Dosing of aminoglycosides

The recommended doses of aminoglycosides for empirical therapy in the Antibiotic guidelines are 7 mg/kg for gentamicin and tobramycin, and 30 mg/kg for amikacin (with appropriate dose adjustments for adults with kidney impairment who do not have septic shock or require intensive care support).² Whether using the peak concentration (C_{max}) or the area under the concentration–time curve (AUC) as the target, using a starting gentamicin dose of 7 mg/kg achieves the required target in 85% or more of adults, for pathogens with an MIC of up to 2 mg/L.¹³

For children greater than 1 month old, a dose of 7 mg/kg is also recommended for gentamicin and tobramycin, and 20 mg/kg for amikacin.² For neonates, initial dosing of aminoglycosides varies according to gestational and chronological age. These starting doses should be followed by therapeutic drug monitoring for dosage adjustment, if indicated (see ‘Plasma concentration monitoring’, below).

Although it is known that aminoglycosides are concentrated in the urinary tract, there is insufficient evidence to recommend using lower doses of aminoglycosides for urinary tract infections.

Patients with altered pharmacokinetics (e.g. critically ill patients with sepsis or septic shock, patients with augmented renal clearance or undergoing dialysis) may require modified dosages.

These aminoglycoside dosages are not suitable for synergistic therapy (e.g. for streptococcal or enterococcal endocarditis, *Bartonella* infections) or for directed therapy of nontuberculous mycobacterial infections, brucellosis or nocardiosis.

Weight metric in adults

The aminoglycoside dosage in adults depends on the patient’s kidney function and the drug’s volume of distribution, which are related to body weight. Aminoglycosides are hydrophilic drugs that are preferentially distributed into lean tissue, so lean body weight (LBW) is the most accurate weight descriptor for calculating aminoglycoside doses. In a large study, LBW performed better than total body weight and ideal body weight in estimating gentamicin volume of distribution across all patients, including underweight patients and those with obesity.¹⁴

Previously, actual body weight was recommended for dose calculations in patients without obesity, and adjusted body weight in those with obesity. The Antibiotic guidelines now recommend aminoglycoside dosing based on LBW in adults.² The guidelines also now include calculators for initial doses of gentamicin, tobramycin and amikacin using parameters of height, actual body weight, age, sex and serum

creatinine. However, expert advice (e.g. from an infectious diseases physician or pharmacist) is required for aminoglycoside dosing in adults with obesity with a body mass index (BMI) of 35 kg/m² or more. The calculators are not appropriate for dosing of aminoglycosides for synergistic therapy or directed therapy.

When calculating the aminoglycoside dose in adults, kidney function should be calculated using the Cockcroft–Gault formula. Ideal body weight should be used for patients of normal weight (BMI between 18.5 and 24.9 kg/m²), whereas actual body weight should be used for patients who are underweight (BMI 18.5 kg/m² or below). In patients who are overweight (BMI of 25 kg/m² or more), adjusted body weight (using adjusted body weight factor of 0.4) is preferred.¹⁵

Weight metric in children

In children, while fat-free mass is the most accurate weight descriptor for calculating aminoglycoside doses,¹⁶ for practicality, the Antibiotic guidelines recommend that actual body weight can be used for dose calculations in children without obesity. Children with obesity require individualised dosing, using either adjusted body weight or fat-free mass.

Monitoring of aminoglycosides

Clinical monitoring

Because aminoglycosides are associated with nephrotoxicity, and vestibular and auditory toxicity, clinical monitoring for these is required for all patients treated with aminoglycoside therapy (Box 3). The aminoglycoside should be discontinued if nephrotoxicity is suspected or vestibular or auditory toxicity is detected.

Plasma concentration monitoring

Many health services have their own guidelines and protocols for therapeutic drug monitoring of aminoglycosides, which should be followed. Monitoring aminoglycoside plasma concentrations is generally not required for therapy that will be stopped within 48 hours (i.e. after 3 doses). However, consider monitoring from the first dose if kidney function is changing rapidly or substantially, or in patients with altered pharmacokinetics (e.g. patients with obesity). Plasma concentration monitoring is recommended from the first dose if therapy is expected to continue for more than 48 hours.²

For **once-daily or less frequent dosing of aminoglycosides**, AUC monitoring is preferred to trough concentration monitoring in adults because it more accurately predicts efficacy and toxicity.^{17–19} A target AUC of between 80 and 100 mg.hr/L is recommended for gentamicin and tobramycin

Box 3 Recommended clinical monitoring for aminoglycoside toxicity²

Nephrotoxicity

- Assess kidney function before starting an aminoglycoside, unless immediate empirical treatment is required in critically ill patients.
- During therapy, monitor kidney function 2 to 3 times weekly, or more frequently if renal function is unstable or drug accumulation is suspected. Decreasing dosage requirements (based on therapeutic drug monitoring) may be an early indicator of kidney impairment.

Vestibular and auditory toxicity

- Advise patients to report balance or hearing issues, even post-treatment.
- Regularly assess for gait ataxia and imbalance, oscillopsia and blurred vision during head movement, and hearing loss. Spontaneous vertigo is not a feature.
- To monitor vestibular function, compare visual acuity at rest and during passive sinusoidal head rotation at 2 Hz. A loss of more than 2 lines suggests hypofunction.
- For courses longer than 5 days, consider formal testing of vestibular function and high-frequency audiometry. For prolonged therapy (greater than 14 days), baseline and periodic audiometry is recommended.

when used for empirical therapy of Gram-negative organisms. Targets for directed therapy should be based on the MIC of the pathogen.

Several methods are available for AUC monitoring.²⁰ Model-informed precision dosing using Bayesian dosing software is preferred because it can account for significant individual variation in aminoglycoside pharmacokinetics; some software can also adjust for uncertainty in sampling and the assay method. Manual calculation methods, using pharmacokinetic equations such as the trapezoidal rule,²¹ or using a spreadsheet,²² are less advanced alternatives.

At least 2 aminoglycoside plasma concentrations are required if using a manual calculation method, usually measured 30 minutes after the infusion has finished, and 6 to 8 hours after the dose. In contrast, if using Bayesian dosing software, next-dose predictions can be made with a single concentration, taken any time after the first dose is administered. In children, the requirement for repeat sampling, and the limited availability of appropriate paediatric Bayesian dosing software, are limitations to the use of AUC monitoring.

Trough plasma concentrations are poorly correlated with overall exposure and are unsuitable to monitor

efficacy, but they can indicate aminoglycoside accumulation and be used to minimise toxicity. Trough plasma concentrations are used in some paediatric centres where AUC monitoring is not available.

Measure the concentration immediately before the next dose, aiming for less than 1 mg/L for gentamicin or tobramycin, or less than 4 mg/L for amikacin.²

If efficacy monitoring is required and AUC methods are not available, gentamicin peak concentrations (taken immediately after the infusion has ended) can be used, aiming for a C_{max}/MIC ratio of 7 to 10.² Target peak concentrations for tobramycin and amikacin have not been established.

For **multiple-daily dosing for synergistic therapy**, trough concentration monitoring is recommended, aiming for less than 1 mg/L.² Measure the trough concentration twice weekly, or more frequently if kidney function is changing rapidly or substantially.

Conclusion

Aminoglycosides remain an important option for empirical therapy of serious Gram-negative infections due to their rapid bactericidal action, effectiveness against resistant pathogens, and postantibiotic effect. Individualised dosing and monitoring are critical for their safe and effective use. Optimal use of aminoglycosides can help preserve the utility of other antibiotics for managing serious Gram-negative infections. ◀

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