Clinical Guideline
Aminoglycoside: Recommendations for Use, Dosing and Monitoring Clinical Guideline

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Policy developed by: South Australian expert Advisory Group on Antimicrobial Resistance (SAAGAR)
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Summary
The Aminoglycoside: Recommendations for Use, Dosing and Monitoring Clinical Guideline provides direction across the state for the safe and effective use of aminoglycoside antibiotics.

Keywords
Aminoglycoside, gentamicin, monitoring, dosing, therapy, recommend*, empirical, directed, ototoxicity, guideline, clinical, guideline, antibiotic, antimicrobial, Aminoglycoside: Recommendations for Use, Dosing and Monitoring Clinical Guideline

Policy history
Is this a new policy? N
Does this policy amend or update an existing policy? Y
Does this policy replace an existing policy? N
If so, which policies?
Aminoglycoside: recommendations for use, dosing and monitoring, May 2016 (Version 2)

Applies to
All Health Networks

Staff impact
All Clinical, Medical, Nursing, Allied Health, Emergency, Dental, Mental Health, Pathology

PDS reference
CG088

Version control and change history

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<th>Version</th>
<th>Date from</th>
<th>Date to</th>
<th>Amendment</th>
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<td>Updating references &amp; including appendices</td>
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Aminoglycosides: recommendations for use, dosing and monitoring in adult patients

May 2017
Disclaimer
This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability to the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for:

- discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion; this includes the use of interpreter services where necessary
- advising consumers of their choice and ensure informed consent is obtained
- providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct
- documenting all care in accordance with mandatory and local requirements.
Introduction

Aminoglycosides are bactericidal antibiotics used to treat infections caused by aerobic Gram-negative organisms. Gentamicin, amikacin and tobramycin are available for parenteral use in Australia. Gentamicin is the most commonly prescribed aminoglycoside in Australian hospitals.

Background

This guideline has been developed by the SA expert Advisory Group on Antimicrobial Resistance (SAAGAR) to assist prescribers to safely manage aminoglycoside therapy. Empiric short-term use of aminoglycoside antibiotics is potentially life-saving but prolonged or inappropriate use can cause harm. Empiric therapy with aminoglycosides should be limited to 72 hours. Therapeutic drug monitoring (TDM) is required if greater than 48 hours of therapy is anticipated. In such cases aminoglycoside blood levels must be checked to ensure adequate dosing and clearance. Monitoring of renal function is required. Audiometric and vestibular testing is recommended to monitor for cochlear and vestibular toxicity.

Definitions

AUC means: method based on Area-Under-the-Concentration curve
IBW means: patient’s ideal body weight
SAAGAR means: South Australian SA expert Advisory Group on Antimicrobial Resistance (SAAGAR)
TDM means: therapeutic drug monitoring

Standards

The following National Safety and Quality Health Service Standard (NSQHSS) standards apply:

**Standard 3 – Preventing & Controlling Healthcare Associated Infections**

- Criterion 3.14 – Developing, implementing and regularly reviewing the effectiveness of the antimicrobial stewardship system.

**Standard 4 – Medication Safety**

- Criterion 4.1 – Developing and implementing governance arrangements and organisational policies, procedures and/or protocols for medication safety, which are consistent with national and jurisdictional legislative requirements, policies and guidelines.

Principles of the standards

Standard 3 aims to prevent patients from acquiring preventable healthcare associated infections and effectively manage infections when they occur by using evidence-based strategies that are based on the risk to both patients and staff.

Standard 4 aims to ensure competent clinician safely prescribe, dispense and administer appropriate medicines to informed patients and carers.
Recommendations

**Empirical therapy**

Aminoglycosides are valuable first-line agents for empirical treatment of Gram-negative infections such as pyelonephritis and intra-abdominal infection.

Empirical therapy with aminoglycosides is recommended for a limited course only (one to three doses given at 0, 24 and 48 hours depending on renal function). TDM is not required for courses of less than 48 hours.

Aminoglycosides must be initiated at doses likely to have therapeutic benefit (see specific guidelines from *Therapeutic Guidelines: antibiotic* [1] in Appendix 1 and recommendations for dosing according to IBW in Appendix 2).

**Directed therapy**

Subsequent antimicrobial therapy should be guided by susceptibility results and, where possible, a switch to alternative therapy should be made. In general, a switch to third-generation cephalosporins (as an aminoglycoside substitute) should be avoided. If cultures are negative, β-lactamase inhibitor combinations (such as amoxicillin/clavulanic acid or piperacillin/tazobactam) can be used as they generate less selection pressure for multi-resistant organisms.

TDM is required if more than three doses are needed and should start on the FIRST DOSE of directed therapy.

An aminoglycoside dose prediction method based on Area-Under-the-Concentration curve (AUC) should be used. *Simple nomograms or trough concentration monitoring are no longer recommended, with the exception of frequent trough monitoring of low-dose aminoglycosides given in divided daily doses as synergistic treatment for conditions such as endocarditis.*

Consideration of ototoxicity (vestibular and cochlear) should be a routine part of clinical assessment and formal testing utilised according to clinical indications.

**Recommendations for SA public hospitals:**

> Practices of aminoglycoside prescribing and monitoring should regularly be reviewed and updated. The following information should be available to medical, nursing and pharmacy staff:

- methods of identifying patients who have been prescribed an aminoglycoside
- timing of aminoglycoside dosing
- support for aminoglycoside dosing and monitoring (protocol development and maintenance, pharmacy staffing, phlebotomy, pathology and audiology services).

> Strategies to eliminate unnecessarily long courses of aminoglycoside therapy should be in place:

- gentamicin usage as part of triple antibiotic therapy following gastrointestinal surgery should not continue for more than three days
- prescribing gentamicin within the variable dose section of the patient’s national inpatient medication chart for a maximum of three doses before specialist review (exception: 8-hourly dosing in endocarditis) OR automatic stop orders for aminoglycoside courses longer than three days, unless otherwise specified (an opt-out system)
- education of medical staff regarding ideal body weight-based dosing for short-course empiric therapy
- Infectious diseases/ clinical microbiologist and/or clinical pharmacist review / advice for patients on an aminoglycoside for more than three days.
 Therapeutic drug monitoring (TDM) is required if more than three doses are needed and should start on the FIRST DOSE of directed therapy:

- Use a computerised “Area-under-the-curve” (AUC) method for aminoglycoside dose prediction. Examples of computerised AUC methods for dose calculation include Aladdin, DoseMe, ID-ODS, SebaGen and ClinCalc. A workflow practice for TDM should be developed. This should include consideration of practical dosing and blood sampling strategies to support good patient care and accurate dose prediction.

- AUC estimates based on two serum concentrations collected within a single dosing interval are the most accurate method of TDM. Some available software programs can make AUC estimates based on a single level as well as two levels; single level estimates are generally less accurate than two-level methods but are more accurate than non-AUC methods.

- Where low-dose aminoglycosides are administered in divided doses for synergistic treatment for endocarditis, trough monitoring is the preferred aminoglycoside monitoring method (refer to Appendix 2 extracted from Therapeutic Guidelines: antibiotic [1] for specific target levels).

- Use of potential aminoglycoside substitutes, particularly third-generation cephalosporins, should be considered only when narrow-spectrum antibiotics are not an option.

- Regional and smaller hospitals should liaise with a tertiary referral centre to develop a system to manage patients requiring directed therapy with aminoglycosides. Options include remote clinical supervision (for example by engaging metropolitan drug information services to assist with TDM), access to clinical microbiologist / infectious disease specialist advice, or training and supervision of local staff.

- In regional and smaller hospitals, the availability of laboratory services which can provide timely aminoglycoside blood level results should be considered before commencing directed therapy. If delays in receiving timely results are likely to occur, a switch to alternative therapy should be made. In general, a switch to third-generation cephalosporins (as an aminoglycoside substitute) should be avoided (refer to Directed therapy). Alternatively, consider transferring the patient to a larger hospital with daily pathology services.

- Patient consent - patients and/or their guardians and carers should be informed of the potential toxicities of aminoglycoside therapy and documentation of this discussion should be recorded in the patient’s clinical notes. For patients likely to receive repeated courses such as those with cystic fibrosis, this need only occur with the initial course. Appendix 4 is an example of consumer information suitable for patients and/or carers.

**Recommendations for risk assessment and clinical monitoring for nephrotoxicity and ototoxicity.**

- SAAGAR recommends reducing the risk of aminoglycoside toxicity by adopting the above monitoring and dosing guidelines. Limiting empiric therapy to 72 hours is the most important intervention.

- Aminoglycoside use should be restricted to appropriate clinical indications. Appendix 5 outlines possible indications for directed therapy [2, 3].

- Avoid use as directed therapy in patients with risk factors for toxicity including pre-existing renal impairment, advanced age, hearing impairment, pre-existing ear conditions (e.g. tinnitus), balance issues, previous exposure to aminoglycosides or a family history (first-degree relative) of auditory toxicity caused by an aminoglycoside.

- If therapy continues beyond 72 hours, check creatinine and calculate creatinine clearance at least twice each week OR daily if renal function is unstable or there is concomitant use of nephrotoxic agents.
Patients on prolonged aminoglycoside therapy should be monitored for ototoxicity by audiometric and vestibular testing. SAAGAR notes that high-frequency audiometric testing is not widely available and that formal vestibular testing may not be available at all sites, but arrangements should be made for referral for specialist testing if therapy is continued. Bedside evaluation tests may be helpful for detecting vestibular toxicity [4]. Refer to Appendix 6.

Appendices

Appendix 1 - Empiric therapy dosing guidelines
Appendix 2 - Initial adult gentamicin dose recommendations
Appendix 3 - Dosing guidelines for multiple daily dosing
Appendix 4 - Example consumer fact sheet: Aminoglycosides (gentamicin, tobramycin, amikacin)
Appendix 5 - Indications for directed therapy with parenteral aminoglycosides
Appendix 6 – Possible beside tests of vestibular function and results if patient has bilateral vestibular hypofunction

References

Appendix 1 – Empiric therapy dosing guidelines from Therapeutic Guidelines: Antibiotic, Version 15
(reprinted with permission)

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### Empirical aminoglycoside dosage for the treatment of infection in adults

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>more than 60 mL/min</td>
<td>gentamicin or tobramycin [6] [7]</td>
<td>4 to 5 mg/kg</td>
<td>16 to 20 mg/kg</td>
</tr>
<tr>
<td></td>
<td>amikacin [8] [9]</td>
<td>40 to 60 mL/min</td>
<td>4 to 5 mg/kg</td>
</tr>
<tr>
<td>less than 40 mL/min</td>
<td></td>
<td></td>
<td>4 mg/kg</td>
</tr>
</tbody>
</table>

1. Use the Cockcroft-Gault formula or [online calculator](https://example.com) to estimate CrCl. If serum creatinine is less than 60 micromol/L, use a value of 60 micromol/L in the Cockcroft-Gault formula or online calculator.

2. The CrCl dosing bands are based on the consensus view of the Antibiotic Expert Groups, because clinical evident is lacking.

3. If actual body weight is more than 20% over the ideal body weight, use ideal body weight to calculate the dose. For morbidly obese patients, seek expert advice.

4. In some patient groups (severe sepsis or septic shock, renal replacement therapy, severe burns, cystic fibrosis, pregnancy, ascites, morbid obesity) the pharmacokinetics of aminoglycosides may be altered and the doses in the table may not achieve the target area under the concentration-time curve. Consider monitoring the aminoglycoside plasma concentration from the first dose to optimise dosing.

5. Pharmacokinetics studies suggest a higher dose (gentamicin or tobramycin 7 mg/kg daily; amikacin 28 mg/kg daily) is appropriate for some critically ill patients with severe sepsis or septic shock (see critically ill adults with severe sepsis for further information).

6. Most clinical studies of once-daily aminoglycoside (gentamicin, tobramycin, netilmicin) therapy have suggested that a dose of 4 to 5 mg/kg is effective and associated with limited toxicity.

7. Round dose to the nearest multiple of 40 mg.

8. For amikacin dosing in patients with nocardial brain abscess (see nocardiosis), and in resistant Mycobacterium avium complex (see resistant organisms and severe disease).

9. Round dose to the nearest multiple of 125mg.

10. The single dose for patients with CrCl less than 40 mL/min is bases on the consensus view of the Antibiotic Expert Groups, because clinical evidence is lacking.

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Aminoglycoside clinical guideline, Version 2.1 (May 2017)
### Appendix 2 – Initial adult gentamicin dose recommendations
(adapted from Central Adelaide LHN Aminoglycosides – Dosing and Monitoring Guidelines for Adult Patients, July 2015)

<table>
<thead>
<tr>
<th>MALE</th>
<th>FEMALE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height (cm)</strong></td>
<td><strong>Height (feet/inches)</strong></td>
</tr>
<tr>
<td>152-154</td>
<td>4’9”-5’0”</td>
</tr>
<tr>
<td>155-163</td>
<td>5’1”-5’4”</td>
</tr>
<tr>
<td>164-172</td>
<td>5’5”-5’7”</td>
</tr>
<tr>
<td>173-180</td>
<td>5’8”-5’11”</td>
</tr>
<tr>
<td>181-189</td>
<td>6’0”-6’2”</td>
</tr>
<tr>
<td>190-198</td>
<td>6’3”-6’6”</td>
</tr>
<tr>
<td>199-207</td>
<td>6’7”-6’11”</td>
</tr>
<tr>
<td>208-216</td>
<td>7’0”-7’1”</td>
</tr>
</tbody>
</table>

*Use Actual Body Weight if less than patient’s Ideal Body Weight (IBW). If patient is obese (BMI > 30) consider dosing based on Adjusted Body Weight. Adjusted Body Weight = IBW + 0.4(Actual Body Weight – IBW).

^Gentamicin 5mg/kg (based on IBW) given as a single daily dose.
1. The AUC approach to monitoring aminoglycoside plasma concentrations is not required for multiple-daily (8-hourly or 12-hourly) dosing regimens. Instead, the trough (predose) concentration should be measured to ensure the gentamicin concentration is detectable but not elevated. Aim for a trough concentration of 0.5 to 1 mg/L to minimise toxicity. In patients with impaired renal function, it may be necessary to change from 8-hourly to 12-hourly dosing to maintain the trough concentration in this range.

2. Measure the trough concentration at least twice weekly if renal function is normal and stable. If renal function is changing rapidly or substantially (e.g., critically ill patients with severe sepsis, suspected acute renal failure), monitoring should be more frequent (in some cases daily). If renal function is deteriorating substantially, stop gentamicin and seek expert advice.
Appendix 4: Example Consumer Fact Sheet

Aminoglycosides
(Gentamicin, tobramycin & amikacin)

You have been prescribed an antibiotic that is part of a group of antibiotics called aminoglycosides. Aminoglycosides work by stopping bacteria from growing and by killing them. They are usually used to treat serious infections for which other medicines may not work. This includes infections in:

> your chest (including your lungs)
> your urinary tract (kidneys or bladder)
> your heart (sometimes called endocarditis)
> your blood (sometimes called bacteraemia or septicaemia).

Aminoglycosides can treat other types of infection not mentioned here.

Your doctor will be able to tell you about the infection that you are being treated for.

This medicine will be given to you as an injection into a muscle or into a vein.

Side-effects

Like all medicines, aminoglycosides can cause some side-effects. If they occur, most are likely to be minor or temporary. However, some can be serious, but are not very common. Do not be alarmed as you may not experience any side-effects.

One of the more serious side-effects aminoglycosides can sometimes cause is damage to the ear or hearing loss. It can occur at any time during your treatment with an aminoglycoside but is more likely to happen when you are treated with it for a long time. Your doctor will monitor your progress; this may involve some blood and hearing tests.

Tell your doctor immediately if you notice any of the following symptoms:

> hearing problems
> ringing in the ears
> dizziness
> problems with balance.

If you want to know more about the possible side-effects of aminoglycosides ask your doctor or pharmacist.

The information contained within this publication does not constitute medical advice, and is for general information only. Readers should always seek independent, professional advice where appropriate.

For more information

Infection Control Service
Communicable Disease Control Branch
11 Hindmarsh Square, Adelaide 5000
Telephone: 1300 232 272
www.sahealth.sa.gov.au/antimicrobials
Appendix 5 - Indications for directed therapy with parenteral aminoglycosides
(Adapted with permission from Jackson et al 2013 and Avent et al 2011)

<table>
<thead>
<tr>
<th>Aminoglycoside agent</th>
<th>Established indications</th>
<th>Routine use not suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin</td>
<td>Brucellosis</td>
<td>S.aureus bacteraemia and endocarditis</td>
</tr>
<tr>
<td></td>
<td>Infective endocarditis‡ (pathogen): <em>Enterococcus</em> spp., <em>Streptococcus</em> spp. and <em>Bartonella</em> spp.</td>
<td>Therapy where less toxic alternatives are available</td>
</tr>
<tr>
<td></td>
<td>Enteric organism bacteraemia: <em>Campylobacter</em> spp. and <em>Yersinia</em> spp.</td>
<td>Gram negative infections with endogenous resistance including <em>Stenotrophomonas maltophilia</em> and <em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td></td>
<td>Treatment of biological warfare agents: pneumonic plague and tularaemia</td>
<td>Routine use prior to urinary catheter insertion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intra-abdominal infection for &gt; three days</td>
</tr>
<tr>
<td>tobramycin</td>
<td><em>Pseudomonas aeruginosa</em> infection in cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>amikacin</td>
<td>Highly drug-resistant Gram-negative organisms, for example, metallo β-lactamase producing bacteria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Central nervous system <em>Nocardia</em> spp. infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mycobacterial infection including <em>M. tuberculosis</em>, <em>M. abscessus</em>, <em>M. avium complex</em>§</td>
<td></td>
</tr>
</tbody>
</table>

‡ Synergistic use
§ in the setting of drug-resistant tuberculosis
Appendix 6 - Possible bedside tests of vestibular function and results if patient has bilateral vestibular hypofunction
(Adapted with permission from Rogers, 2011)

<table>
<thead>
<tr>
<th>Test</th>
<th>Aim of evaluation</th>
<th>Results if vestibular toxicity present</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspection for nystagmus</td>
<td>Establish presence and grade of spontaneous and/or gaze nystagmus.</td>
<td>No nystagmus will be evident as loss of VOR input is usually symmetrical.</td>
<td>&gt; Requires experienced clinician.</td>
</tr>
<tr>
<td>Head thrust test</td>
<td>Establish if VOR input is present and normal.</td>
<td>Will have saccades in both directions.</td>
<td>&gt; Need appropriate training.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; Should be a routine test.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; Sensitivity of 84–100% if bilateral vestibular hypofunction.</td>
</tr>
<tr>
<td>Dynamic visual acuity test</td>
<td>Establish if patient has early oscillopsia.</td>
<td>Will have decline in vision when head is moving.</td>
<td>&gt; Snellen chart or similar required.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; Should be a routine test.</td>
</tr>
<tr>
<td>Standard Romberg</td>
<td>Tests vestibulospinal reflexes.</td>
<td>Positive with falls when acute.</td>
<td>&gt; May become negative if loss is compensated for.</td>
</tr>
<tr>
<td>Sharpened Romberg (tandem position)</td>
<td>Attempts to be more of a test of vestibular function by reduction of proprioceptive cues.</td>
<td>Cannot assume position when acute.</td>
<td>&gt; May be possible with eyes open if compensated, not with eyes closed.</td>
</tr>
<tr>
<td>Gait (including heel-toe walk)</td>
<td>Identify ataxia and gait abnormalities.</td>
<td>Wide based, slow, may need assistance when acute. Inability to heel-toe walk with eyes open</td>
<td>&gt; Even when compensated may have a shortened step length.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; History of any previous gait abnormalities must be taken into account</td>
</tr>
<tr>
<td>Falls and fall risk</td>
<td></td>
<td>Patient at great risk of falling.</td>
<td>&gt; Remains greater in all age groups even when compensated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; May need assistive device or may result in decreased activities.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt; History of any falls risk must be taken into account.</td>
</tr>
<tr>
<td>Bedside caloric test</td>
<td>Establish function of lateral semicircular canal.</td>
<td>Reduced response bilaterally.</td>
<td>&gt; Reliability enhanced if clinician is experienced.</td>
</tr>
</tbody>
</table>

VOR = Vestibulo-ocular reflex