Drug Guideline: Amikacin

Summary:
Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin. It acts by inhibiting protein synthesis of susceptible bacteria. Amikacin is used for short term treatment of serious infections caused by micro-organisms that are resistant to other aminoglycosides.

Approved by: Medical Director
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Replaces Existing Drug Guideline: Amikacin_2012

1. Introduction contains:
The risk addressed by this policy:

Patient Safety

The Aims / Expected Outcome of this policy:

Amikacin will be administered safely and appropriately without any adverse side effects.

Related Standards or Legislation

- NSQHS Standard 1 Governance
- National Standard 4 Medication Safety

Related Policies

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2. Policy Statement:
- All care provided within Liverpool Hospital will be in accordance with infection control, manual handling and minimisation and management of aggression guidelines.
- Medications are to be prescribed and signed by a medical officer/authorised nurse practitioner (NP) unless required during an emergency.
- All drugs administered during an emergency (under the direction of a medical officer/authorised nurse practitioner) are to be documented during the event, then prescribed and signed following the event.
Medications are to be given at the time prescribed (as close to the time as is possible when multiple drugs require ‘same time’ administration and, when the nurse is caring for more than one patient, recognition is given to a possible short delay to administration – antibiotics and other lifesaving drugs are to be prioritised) and are to be signed by the administering nurse.

Parenteral medication prescriptions and the drug are to be checked with a second registered or endorsed enrolled nurse prior to administration. The “rights of drug administration” must be followed: right: patient, drug, dose, route, administration, time, reason for the drug, documentation, education and evaluation/outcome.

Adverse drug reactions are to be documented and reported to a medical officer.

Medication errors are to be reported using the hospital electronic reporting system: IIMS.

Guidelines are for adult patients unless otherwise stated.

Amikacin may be administered via a peripheral cannula or central line.

Amikacin must always be administered via a dedicated lumen and never “piggybacked” with other drugs or fluids. Where multiple infusions are required, administer with other compatible drugs, via a three-way tap.

If administered peripherally the infusion must be diluted appropriately as it may cause pain and inflammation at the site.

Amikacin must be administered by infusion pump.

Amikacin infusions must not be administered via the drug infusion port on a haemodialysis circuit.

Patient’s renal function should be closely monitored.

3. Principles / Guidelines

Amikacin is a semisynthetic aminoglycoside broad spectrum antibiotic derived from kanamycin. It acts by inhibiting protein synthesis of susceptible bacteria.

Amikacin’s structure has been altered to reduce enzymatic deactivation, thus reducing bacterial resistance. Many Gram negative organisms resistant to gentamicin and tobramycin in vitro are sensitive to amikacin.

Amikacin must be reserved for treating infections due to micro-organisms that are resistant to other aminoglycosides. Eg: Multiresistant Acinetobacter species.

Primary indication is as short-term empirical therapy up to 3 doses with no further doses given beyond 48 hours. Monitoring of amikacin levels is not required unless amikacin is given beyond 48 hours.

There are only few circumstances in which directed therapy is indicated, these include but are not restricted to:

Infections when resistance to other safer antimicrobials has been shown (eg multiresistant Acinetobacter baumannii)

Infections in patients intolerant of other antimicrobial alternatives

Monitoring of aminoglycoside plasma concentrations is recommended in these patients and should commence on the first dose of directed therapy.

• Previous hypersensitivity reaction to an aminoglycoside.
• Previous vestibular or auditory toxicity due to an aminoglycoside

Precautions

Unless there is no appropriate safer alternative, and in the absence of streptococcal or enterococcal endocarditis, aminoglycosides should be avoided if treatment extends more than 48
Consider giving an alternative antibiotic to amikacin in patients with the following:

- Pre-existing significant sensorineural hearing problems.
- Pre-existing vestibular problems (including dizziness, vertigo or tinnitus)
- Family history of a first degree relative with aminoglycoside attributed neurotoxicity
- Pre-existing renal damage (baseline creatinine clearance <40mL/min).
- Patients with neuromuscular disorders (Myasthenia Gravis or Parkinson’s disease) as muscle weakness may be aggravated due to the curare like effect on the neuromuscular junction.
- Chronic liver disease and severe cholestasis (serum bilirubin > 90 micromol/L)
- Pregnancy - because of their chemical similarity, aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus. It should also be noted that therapeutic blood levels in the mother do not equate with safety for the fetus. Gentamicin has been used frequently for severe sepsis in pregnancy but is classed as a category D drug (see eTGA) therefore its use should be avoided if alternatives are available.
- Lactation - compatible but may cause diarrhoea in the infant

**Significant Interactions**

1. Ethacrynic acid, frusemide and other potent diuretics, due to the risk of ototoxicity or aminoglycoside toxicity.
2. Avoid concurrent use with other neurotoxic and/or nephrotoxic antibiotics, including other aminoglycosides, polymyxin B, colistin, cisplatin, vancomycin, amphotericin, clindamycin, sulphamethoxazole and cephalosporins.
3. Avoid concurrent use with neuromuscular blocking agents, e.g. suxamethonium, halogenated hydrocarbon inhalation, anaesthetics, opioid analgesics, massive transfusions with citrated anticoagulated blood. Neuromuscular blockade may be enhanced, resulting in skeletal muscle weakness and respiratory depression or paralysis (treatment with anticholinesterase agents or calcium salts may help reverse the blockade).
4. Amikacin is inactivated by solutions containing penicillins. For this reason, amikacin and penicillins should not be combined in IV injections/infusions.
5. The inactivation of some aminoglycosides by penicillins has been reported in vivo, especially in patients with renal failure who maintain a higher level of the penicillin for a longer period of time compared to patients with normal renal function. Therefore, when amikacin and penicillins are used together in patients with renal failure, the time of administration of each drug should be staggered so that several hours separate each infusion.

**Adverse Effects**

1. Increased serum transaminases (ALT, AST), increased serum bilirubin, hepatomegaly, and hepatic necrosis.
2. Nephrotoxicity – decreased creatinine clearance.
3. Ototoxicity – auditory and vestibular changes, tinnitus, vertigo, dizziness, nystagmus, hearing loss which can be permanent, usually manifested by diminution of high-tone acuity.

*Note*: Factors which may increase the risk of toxicity include excessive dosage, dehydration and previous exposure to ototoxic drugs.

**Presentation**

Vials (clear, colourless, sterile solution), 500 mg (500,000 IU)/2 mL
Administration Guidelines
The required dose will depend on the volume of distribution and renal clearance, which are related to lean (or ideal) body weight (Table 1), doses are quoted in terms of mg/kg.

The dosage administration will be for:
- Initial dosing for both Empirical and Directed Therapy (Table 2).
- Subsequent dosing for empirical therapy (Table 3).

Table 1: Ideal Body Weight

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Inches</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>155</td>
<td>61</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>160</td>
<td>63</td>
<td>53</td>
<td>57</td>
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<td>165</td>
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<td>210</td>
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<td>98</td>
<td>102</td>
</tr>
<tr>
<td>215</td>
<td>85</td>
<td>102</td>
<td>107</td>
</tr>
</tbody>
</table>

Ideal weight for male = 50 kg + 0.9 kg/each cm over 152 cm (2.3 kg/each inch over 5 feet)
Ideal weight for female = 45.5 kg + 0.9 kg/each cm over 152 cm (2.3 kg/each inch over 5 feet)

Table 2: Initial Dosing for Empirical and Directed Therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>Initial Dose (For subsequent dosing refer to Table 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to 29 years</td>
<td>24mg/kg up to 2.25g</td>
</tr>
<tr>
<td>30 to 60 years</td>
<td>20mg/kg up to 2g</td>
</tr>
<tr>
<td>More than 60 years</td>
<td>16mg/kg up to 1.5g</td>
</tr>
<tr>
<td>*10 years or more with severe sepsis</td>
<td>28mg/kg up to 2.5g</td>
</tr>
</tbody>
</table>

*Patients with severe sepsis have higher volumes of distribution and therefore require a higher mg/kg dose.
Empirical Therapy – Subsequent Dosing (Maximum no. of doses = 3 over 48 hours)

The dosing interval for subsequent empirical dosing is based on the patient's renal function since elimination of aminoglycosides is by renal excretion. Monitoring of amikacin plasma concentrations is not required with empirical therapy not exceeding 48 hours.

Creatinine Clearance (CrCl) needs to be calculated to estimate the patient's renal function. It is used to estimate the glomerular filtration rate. The modified Cockcroft-Gault Formula is the most widely recommended method for calculating CrCl.

The creatinine measurement used for the creatinine clearance estimate should be obtained as recently as possible (within 12 to 24 hrs). This might still overestimate renal function in acute renal failure.

Cockcroft-Gault Formula:

\[
\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{ideal weight (kg)}}{0.814 \times \text{serum creatinine (micromol/L)}}
\]

Adult females: Multiply the above equation by 0.85

Eg: A 75-year-old woman is admitted with multiresistant Acinetobacter sternal wound infection and severe renal impairment. She weighs 54 kg and her serum creatinine is 470 micromol/L. Using the modified Cockcroft-Gault formula:

\[
\text{CrCl} = \frac{(140 - 75) \times 54}{0.814 \times 470} \times 0.85 = 7.8 \text{ mL/min}
\]

Table 3: Subsequent dosing for empirical therapy

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Dosing Interval</th>
<th>Maximum no. of empirical doses</th>
<th>Timing of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>First dose</td>
</tr>
<tr>
<td>Greater than 60</td>
<td>24 hours</td>
<td>3</td>
<td>0 hrs</td>
</tr>
<tr>
<td>40 to 60</td>
<td>36 hours</td>
<td>2</td>
<td>0 hrs</td>
</tr>
<tr>
<td>30 to 40</td>
<td>48 hours</td>
<td>2</td>
<td>0 hrs</td>
</tr>
<tr>
<td>Less than 30</td>
<td>Give initial dose and then seek expert advice from microbiology and ICU staff specialist for subsequent dosing</td>
<td></td>
<td></td>
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</tbody>
</table>

The creatinine measurement used for the creatinine clearance estimate should be obtained as recently as possible (within 12 to 24 hrs).

Monitoring and Dosage Adjustment

Aminoglycosides such as amikacin have predominantly concentration dependent killing. Consequently, trough level monitoring to avoid toxicity is used in the absence of computerized methods.

- Trough level monitoring is not indicated if amikacin treatment does not extend beyond 48 hours unless renal function is unstable.
- Monitoring should commence on the first dose of directed therapy to guide subsequent dosing.
- Trough levels should be collected immediately before the prescribed dose is given.
- Do not wait for the trough level result before giving the prescribed dose (the trough level is used to adjust the subsequent dose).
• Adjust amikacin dose aiming for a target trough range of <2.0 mg/L.
• Because aminoglycosides have predominantly concentration dependent killing, switch to another drug class, increase the dosage interval above 24 hourly or seek specialist advice if trough amikacin level >2.0 mg/L at a dose of 750mg daily IV (as opposed to reducing the dose further).

Clinical Considerations
• Routine monitoring of aminoglycoside plasma concentrations is recommended for all patients receiving directed therapy. The aim is to delay the onset of nephrotoxicity and reduce the risk of vestibular as well as auditory ototoxicity. While nephrotoxicity is usually reversible, ototoxicity is much less commonly reversible.
• Monitor renal function. Serum creatinine should be checked, and creatinine clearance calculated before commencing an aminoglycoside. Daily serum creatinine, urea and nitrogen should also be checked.
• Once-daily dosing for creatinine clearance (CrCl) above 20 mL/min.
• Use a single dose of an aminoglycoside as initial therapy for presumptive Gram-negative infection in patients with renal failure. Treatment in this group may be best continued with nonaminoglycoside antimicrobials. If an aminoglycoside is strongly indicated, careful monitoring and care not to underdose need to be the principles guiding dose and frequency determination.

Dose and administration for Dialysis.
• Intermittent hemodialysis: the dose should be given post treatment. Dose adjustment is the same as for patients with impaired renal function.

4. Performance Measures
All incidents are documented using the hospital electronic reporting system: IIMS and managed appropriately by the NUM and staff as directed.

5. References / Links

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Reviewers: ICU Director, ICU Staff Specialists, ICU – NM, NUM, ICU – CNE, ICU – CNS, Pharmacist.
Endorsed by: Prof. Michael Parr, ICU Director