THE NORTHERN HOSPITAL

GENTAMICIN

"The Decline of the Carthaginian Empire", oil on canvas, 1817,
Joseph Mallord William Turner, Tate Gallery London.

"Delenda est Carthago" - (Carthage must be destroyed)

Marcus Porcius Cato, 149 B.C

Cato was sent on an embassy to the Carthaginians and Masinissa the Numidian, who were at war with one another, to inquire into the grounds of their quarrel. Masinissa had been a friend of the Roman people from the first, and the Carthaginians had entered into treaty relations with Rome after the defeat which the elder Scipio had given them. The

treaty deprived them of their empire, and imposed a grievous money tribute upon them. Cato, however, found the city by no means in a poor and lowly state, as the Romans supposed, but rather teeming with vigorous fighting men, overflowing with enormous wealth, filled with arms of every sort and with military supplies, and not a little puffed up by all this.

He therefore thought it no time for the Romans to be ordering and arranging the affairs of Masinissa and the Numidians, but that unless they should repress a city which had always been their malignant foe, now that its power was so incredibly grown, they would be involved again in dangers as great as before. Accordingly, he returned with speed to Rome, and advised the Senate that the former calamitous defeats of the Carthaginians had diminished not so much their power as their foolhardiness, and were likely to render them in the end not weaker, but more expert in war; their present contest with Numidia was but a prelude to a contest with Rome, while peace and treaty were mere names with which to cover their postponement of war till a fit occasion offered.

In addition to this, it is said that Cato contrived to drop a Libyan fig in the Senate, as he shook out the folds of his toga, and then, as the senators admired its size and beauty, said that the country where it grew was only three days' sail from Rome. And in one thing he was even more savage, namely, in adding to his vote on any question whatsoever these words: "In my opinion, Carthage must be destroyed". Publius Scipio Nasica, on the contrary, when called upon for his vote, always ended his speech with this declaration: "In my opinion, Carthage must be spared".

He saw, probably, that the Roman people, in its wantonness, was already guilty of many excesses, in the pride of its prosperity, spurned the control of the Senate, and forcibly dragged the whole state with it, whithersoever its mad desires inclined it. He wished, therefore, that the fear of Carthage should abide, to curb the boldness of the multitude like a bridle, believing her not strong enough to conquer Rome, nor yet weak enough to be despised. But this was precisely what Cato dreaded, when the Roman people was inebriated and staggering with its power, to have a city which had always been great, and was now but sobered and chastened by its calamities, forever threatening them. Such external threats to their sovereignty ought to be done away with altogether, he thought, that they might be free to devise a cure for their domestic failings.

In this way Cato is said to have brought to pass the third and last war against Carthage.

Plutarch, The Life of Cato, the Elder, First Century A.D

Although he was 88 years old, such was Cato's standing and reputation in the Senate, he was among those chosen to go on a diplomatic mission to Carthage in 149 B.C. Carthage had just the year before paid off the last of its fifty year tribute to Rome, in consequence of losing the Second Punic War (218- 201 B.C). Carthage had been quiet for half a century, but now its rulers considered that debt discharged, and they no longer owed Rome allegiance, a concept totally at odds with Roman sensibilities, which said that once an enemy had been defeated it was forever. The concept of temporary truces was one that did not sit well with the Republic. Carthage had waged war on its North African neighbour, Numidia, which happened to also be an ally of Rome, from the days of

the Second Punic War. The Romans assumed a right to mediate between the two states, and so accordingly had sent their delegation, which the Carthaginians, reluctantly and coldly "greeted".

What Cato saw of Carthage deeply disturbed him. He was not concerned over its dispute with Numidia, so much as the unexpected size, wealth and power of the city. After half a century of seemingly placid subservience to Rome, Carthage had long since ceased to be seen as a threat. The terrifying stories of the attack on Italy by Hannibal were distant stories told by very old men, such as Cato himself, who as young man had fought against Hannibal during the Second War. His mind and memory were sharp despite his years, which were beyond all but a very few handful of others. When Cato spoke of Carthage, people listened with silent reverence. To Cato, it seemed that the Carthaginians had not been so humbled as most Romans suspected. They were arrogant, they were strong, and in their attack on Numidia had made it clear that they had lost none of their aggressiveness. The fifty year "truce" with Rome, had been, in his opinion, merely an opportunity for Carthage to rebuild, and now in the minds of the Carthaginians, that truce was over.

Cato fled back to Rome in alarm to report on this situation, and to try to convince the Senate that Carthage was a real threat once again. In order to broach the subject, he casually let some figs fall from his toga when he got up to make a speech. When the senators asked where such magnificent specimens came from he told them from Carthage - and that they were still fresh as this city was only three days journey from Rome! He told them of the threat he believed Carthage to be, but initially the senators were skeptical, perhaps just attributing his ranting to the fears of an old man who remembered the last war. Cato persisted however in persuading his colleagues of the emerging threat, ending every single one his speeches from then on with the loud cry "Carthage must be destroyed!". Eventually he did convince the Senate, but he never knew this. He died just before Rome launched an invasion of the North African city.

The Romans were in for a shock. Expecting a quick and easy victory, they soon came to see that Cato had been correct in his assessment of Carthage's true strength. The Roman army was not what it had been in Cato's day - smaller, less experienced, not having been seriously tested for half a century, and not battle hardened. The early campaigns led to embarrassing setbacks, but the Romans were very quick learners. They could not take the city by direct storm and so settled down to a bitter siege - a siege that would take no less than three years to bring success. The final defeat of Carthage, was achieved, ironically, by Scipio Aemilianus whose relative included a certain senator by the name of Publius Scipio Nasica, who had countered every one of Cato's speeches with a catch cry of his own "In my opinion, Carthage must be spared"! Scipio Aemilianus was the grandson of the great Scipio Africanus who had finally defeated Hannibal in the Second War. This time there would be no reemergence. The entire city's population was taken into slavery and the it was systematically and completely destroyed. Legend had it that even the surrounding fields were salted so that nothing could grow in them again. Later Rome built a completely new city near the original site, that became the capital of its new North African province of Libya. As Scipio Aemilianus gazed upon the wreck of the once mighty city, he supposedly uttered a passage from the Iliad, that described the fall of Troy.

Polybius recorded that Scipio also wondered to himself if Rome was one day destined for the same fate of empire.

In the microbial world we have grand allies, but we also have fearful enemies. We have in the past defeated some of these enemies in battle, though this does not mean we have won the war against them. Indeed as wise Cato saw, in the Carthaginians, past defeats have merely ultimately bred an even greater threat! We hold some pathogens in check, yet they bide their time and await another opportunity, growing ever stronger as they do, whilst we grow ever more complaisant! Our adversaries now include the tribes of the CRE, VRE, MRSA amoung others. Gentamicin remains a reliable old weapon but a crude one with many drawbacks. We may still use it however against old adversaries when no better options exist. By use of the single daily dosing approach we may ensure a total "cidal" destruction, rather than a "static" holding one. By this complete killing action we may better "salt the fields" of our long -time enemies!

"The Course of Empire: Destruction," oil on canvass, Thomas Cole, 1836

GENTAMICIN

Introduction

Gentamicin is a **bactericidal aminoglycoside** antibiotic.

It is on the **World Health Organization's** List of Essential Medicines, a list of the most important medication needed in a basic health system.

It is recommended for the treatment of serious infections possibly caused by Gram-negative organisms primarily because of its rapid bactericidal activity and comparatively low levels of resistance in most community and hospital associated Gram-negative pathogens.

These properties make it a very useful **empirical** drug when rapid control of a serious infection is required.

However, gentamicin can have significant **ototoxic** and **nephrotoxic effects** and so many physicians are reluctant to use it.

Ototoxicity is less frequently but, unlike nephrotoxicity, is much less commonly reversible.

Prolonged therapy is an independent risk factor for nephrotoxicity. Conversely, short term therapy (three days or less) has a *very low* incidence of nephrotoxicity.

Monitoring of plasma concentrations has been recommended to guide safe and effective dosing, but will not prevent the rare occurrence of **sudden idiosyncratic deafness** and is probably not necessary in short term use (three days or less). [1]

There is growing awareness amoung physicians of aminoglycoside-related toxicity, leading some clinicians to argue that aminoglycosides should be used rarely and replaced by other less toxic but generally more broad-spectrum antibiotics (e.g. carbapenems, broad-spectrum cephalosporins).

Given the rapid emergence however of resistance to other classes of antibiotics, and the increase in rates of *Clostridium difficile* infection, concerns about aminoglycoside toxicity should be balanced against the known advantages of aminoglycosides. [2]

Advantages of aminoglycosides: [2]

These include:

1. Rapid bactericidal activity associated with rapid control of Gram-negative infections.

2. Generally low rates of resistance among community associated and healthcare associated Gram negative pathogens

3. A "post-antibiotic effect" whereby bacterial killing continues for many hours after plasma concentration is undetectable.

    - This allows for effective once daily therapy with reduced rates of toxicity

4. Synergistic killing when combined with cell wall active drugs (e.g. beta lactams, glycopeptides) for enterococcal and streptococcal infections.

5. Low rate of drug hypersensitivity reactions

6. Low associated rate of *C. difficile* infection

7. Low cost of drug

Disadvantages of aminoglycosides: [2]

1. Nephrotoxicity:

    - This is generally reversible.

    - It is usually associated with:

        - ♥ **Prolonged** treatment courses (**i.e longer than 5 - 7 days**)

        - ♥ **Pre-existing** renal impairment.

2. Vestibular and, less commonly, auditory toxicity:

    - This is generally irreversible.

    - Again it is mostly associated with prolonged treatment courses

3. Some recently identified Enterobacteriaceae strains (CRE) exhibit resistance to multiple drug classes, sometimes including the aminoglycosides

Gentamicin remains a valuable antibiotic for the short term empiric treatment of patients with suspected serious infections from gram negative organisms.

If therapy is extended beyond 48 hours, close monitoring of plasma levels will be required.

Empirical versus Directed Therapy [1]

Empirical Therapy (< 48 hours):

The primary indication for aminoglycosides is short term empirical therapy for presumed serious gram negative infections pending the outcome of investigations.

Dosing in **empirical therapy** should not continue beyond **48 hours** (i.e a maximum of three empirical doses at 0, 24 and 48 hours); given the "post-antibiotic effect" of aminoglycosides, this effectively provides 72 hours of therapy.

For patients with renal impairment (CrCl less than 40 mL/min), a single dose of aminoglycoside, with no subsequent doses, can be life-saving and is generally safe.

Monitoring of the aminoglycoside plasma concentration is **not** required in most patients, because **empirical treatment** is of short duration.

However, consider monitoring if the patient's renal function is changing rapidly or substantially (e.g. critically ill patients with severe sepsis, suspected acute renal failure) or in patients with altered pharmacokinetics

If possible, replace an aminoglycoside with a safer antibacterial when sensitivity data are available.

Directed Therapy (> 48 hours):

Aminoglycoside therapy **beyond 48 hours** is indicated for directed therapy in only a few circumstances.

These include:

- Infections when resistance to other less toxic antibiotics has been confirmed, or is suspected
- Initial combination therapy with other antibiotics (e.g. a broad-spectrum penicillin or cephalosporin, a carbapenem) for *Pseudomonas aeruginosa* infections until susceptibility to alternative antibiotics is known
- In combination with other antibiotics for brucellosis and mycobacterial infections.

History

Streptomycin was discovered in 1943, by Albert Israel Schatz (1920-2005).

This was the first aminoglycoside antibiotic to be discovered, and was the first effective treatment for tuberculosis.

Gentamicin was first isolated from *Micromonospora purpurea* a species of Gram-positive bacteria widely present in the environment (water and soil).

Chemistry

Aminoglycosides contain as a portion of their molecule an amino-modified glycoside sugar.

Gentamicin sulfate is a mixture of the sulfates of antimicrobial substances produced by *Micromonospora purpurea.*

Classification

The aminoglycosides include three principle groups:

Streptomyces derived antibiotics (the "mycins"):

1. **Tobramycin:**
    - This is marginally more active *in vitro* than gentamicin against *P. aeruginosa* but not against other aerobic Gram-negative bacteria.
    - It is inactivated by a similar range of bacterial enzymes as gentamicin.
2. **Streptomycin**
3. **Paromomycin**
4. **Neomycin**
    - This is severely nephrotoxic and ototoxic when used systemically.
    - It is available in Australia as a combination **topical** preparation.
    - Topical use can induce sensitization.
5. **Framycetin** (or neomycin B):
    - This is used topically for superficial eye and ear infections.
    - Short-term use has not been associated with ototoxicity.

Micromonospora derived antibiotics (the "micins"):

Gentamicin:

- This is active against a broad range of Gram-negative bacteria, including *Pseudomonas aeruginosa.*
- Approximately 95% (or more) of aerobic Gram-negative isolates remain susceptible to gentamicin, so it is the aminoglycoside of choice.

Semisynthetic aminoglycoside antibiotics:

Amikacin:

- This is more resistant to enzymatic inactivation than gentamicin or tobramycin, so it should be reserved for treating infections **resistant to other aminoglycosides**.

Preparation

Gentamicin Sulfate:

Ampoules:

- 10 mg/mL, 1 mL
- 40 mg/mL, 2 mL

Mechanism of Action

The aminoglycosides inhibit bacterial protein synthesis by irreversibly binding to the 30S ribosomal subunit.

They have a concentration dependent bactericidal effect.

Pharmacodynamics

Gentamicin is active against a broad range of Gram-negative bacteria, including *Pseudomonas aeruginosa.*

Approximately 95% (or more) of aerobic Gram-negative isolates *remain susceptible* to gentamicin, so it is the current **aminoglycoside of choice.**

Note that, as for all antibiotics, the prevalence of bacterial resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

The Post Antibiotic Effect: [6]

The use of higher-dose, extended interval (i.e., once-daily) aminoglycoside regimens to optimize bacterial killing is justified by a general pharmacodynamic principle of aminoglycosides, namely concentration-dependent killing, and by the partial attribution of the toxicity of aminoglycosides to prolonged serum concentrations.

Clinical studies have shown at least equal effectiveness and no greater toxicity when compared with traditional regimens.

A dose of 5–7 mg/kg of gentamicin, tobramycin, or netilmicin, with at least a 24 hour dosing interval should be employed and a similar regimen can be applied to amikacin dosing.

The "post-antibiotic effect" of gentamicin allows for bacterial killing that continues **for many hours after plasma concentration is undetectable.**

Pharmacokinetics

Absorption:

- Gentamicin in administered **IV** or **IM**.

  The IV route is preferred.

  Gentamicin is rapidly absorbed after IM injection and peak serum levels are usually achieved within 30 - 90 minutes and are measurable for 6 - 8 hours.

Distribution:

- Aminoglycosides are **hydrophilic** drugs that are preferentially distributed into **lean** tissue, (as opposed to fatty tissue).

- Gentamicin is widely distributed into body fluid including ascitic, pericardial, pleural, synovial and abscess fluids.

- Concentration in bile is low.

Metabolism and excretion:

- Gentamicin is excreted *almost entirely* by **renal glomerular filtration**, hence the half-life of the drug is prolonged in the presence of renal failure.

  Adjustments in the dose and frequency of administration of gentamicin are necessary to allow for the degree of renal failure

- The serum half life of gentamicin is approximately 2-3 hours in adults with normal renal function.

  It is significantly prolonged in patients with impaired renal function and in premature or newborn infants

Indications

These include: [3]

1. Empirical treatment for < 48 hours:

   - For serious Gram-negative infections

2. Directed therapy for > 48 hours:

- Serious systemic enterococcal infections (with beta lactams or vancomycin)
- Serious infections due to sensitive organisms that are resistant to other antibacterials
- Brucellosis

3. Surgical prophylaxis
4. *P. aeruginosa* infections, including cystic fibrosis, bronchiectasis (inhalation)
5. Some eye infections.

Contra-indications/precautions [2]

Contraindications:

Aminoglycosides should **not** be used in patients with:

1. A history of vestibular or auditory toxicity caused by an aminoglycoside
2. A history of serious hypersensitivity reaction to an aminoglycoside (rare)
3. Myasthenia gravis.

Precautions:

Aminoglycosides should generally be avoided, unless the infection is **serious/ life-threatening**, in the following situations:

1. Pre-existing significant auditory impairment (hearing loss or tinnitus)
2. Pre-existing vestibular condition (dizziness, vertigo or balance problems)
3. A family history (first-degree relative) of auditory toxicity caused by an aminoglycoside.
4. Chronic renal impairment (creatinine clearance less than 40 mL/min) or rapidly deteriorating renal function:
    - Impairment increases risk of toxicity due to higher plasma concentrations (aminoglycosides are predominantly renally cleared).
5. Advanced age (e.g. 80 years or older), depending on calculated renal function.
6. Avoid concomitant use of other nephrotoxic / ototoxic agents:

For example:

- **Cisplatin**, **other aminoglycosides**, **polymyxin antibiotics** and **vancomycin.**

- The concurrent use of gentamicin with potent diuretics, such as **frusemide**, should be avoided, since certain diuretics by themselves may cause ototoxicity.

  In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering the antibiotic concentration in serum and tissue.

7. Children

- Decrease dose in neonates; half-life is prolonged.

Pregnancy

Gentamicin is a category D drug with regard to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

It may be given on specialist advice for severe or life-threatening infections for which safer drugs are inappropriate.

Breast feeding:

Safe to use in pregnancy.

Adverse Effects

These include:

1. Nephrotoxicity: [2]

   Usually presents as gradually worsening non-oliguric renal failure with increasing serum creatinine and proteinuria, but may present as acute tubular necrosis. [3]

   Aminoglycoside induced nephrotoxicity is generally reversible.

   Risk factors include:

   - Prolonged treatment courses (longer than 5 to 7 days)

- Pre-existing renal impairment.
- Dehydration
- High plasma concentrations,
- Concomitant treatment with other nephrotoxic drugs.

Before starting an aminoglycoside, the serum creatinine should be measured and creatinine clearance calculated

If therapy is ongoing, assess renal function 2 to 3 times each week, or more frequently if renal function is unstable.

2. Ototoxicity:

Ototoxicity may be manifested by both vestibular and auditory ototoxicity.

This can manifest as tinnitus, vertigo, nystagmus and/ or hearing impairment/ deafness

Aminoglycoside induced vestibular and auditory toxicity can persist after stopping aminoglycoside therapy and is not predicted by plasma concentrations.

Sudden idiosyncratic deafness (which has a genetic basis) occurs rarely. [2]. Auditory changes are generally irreversible, usually bilateral and may be partial or total.

The risk factors for ototoxicity include: [3]

- Length of treatment
- High plasma concentrations
- Repeated courses.
- Pre-existing tinnitus, vertigo, hearing impairment, an abnormal audiogram
- Concomitant treatment with other ototoxic drugs.
- Genetic predisposition:
    - ♥ Those with the **mitochondrial DNA mutation A1555G** are highly likely to become deaf if treated with an aminoglycoside; consider screening patients for this mutation if they have a maternal relative whose deafness results from this.

For prolonged courses of aminoglycosides (longer than 5 days), formal vestibular function testing and high-frequency audiometric testing should be considered, if available. [2]

In patients receiving gentamicin for endocarditis, baseline audiometry should be recorded at the initiation of therapy and repeated periodically if therapy extends beyond 14 days. [2]

If vestibular or auditory toxicity is noted, stop the aminoglycoside and seek expert advice

3. Allergic reactions:

- Significant reactions/ anaphylaxis is **rare.**
- Cross allergenicity among aminoglycosides has been documented.

4. Neuromuscular blockade:

Gentamicin can have some curare like effects on neuromuscular transmission.

- Aminoglycosides should therefore be used cautiously in patients with neuromuscular disorders such as myasthenia gravis or parkinsonism. In such cases, gentamicin may aggravate muscle weakness.
- The possibility of prolonged or secondary apnoea should be considered if the drug is administered to anaesthetised patients who are concurrently receiving neuromuscular blocking agents such as suxamethonium (succinylcholine), tubocurarine or decamethonium.

  This also applies to patients who are receiving massive transfusions of citrated blood.

  If neuromuscular blockade occurs, it may be reversed by the administration of **IV calcium salts**

Dosing

Single daily dosing versus multiple (or synergistic) daily dosing:

The "post-antibiotic effect" of gentamicin allows for bacterial killing that continues for many hours after plasma concentration is undetectable. This allows for effective **once daily dosing** (**i.e 24 hourly**) with **reduced rates of toxicity**

When given in combination with some cell wall active drugs (e.g. penicillins, glycopeptides), aminoglycosides provide useful **synergistic killing** of some difficult to treat pathogens (e.g. enterococci, viridans streptococci), provided the pathogen does not have high level resistance to the aminoglycoside. In these situations **multiple daily** (**or**

synergistic) **dosing** is used. This is **8 hourly or 12 hourly** regimes (at *roughly* 80 mg per dose for adults with normal renal function).

Dosing per Kilogram:

Aminoglycosides are hydrophilic drugs that are preferentially distributed into lean tissue, so **lean body weight** is the most accurate weight measurement for calculating aminoglycoside doses.

However, the calculation of lean body weight is relatively complicated, so for practicality, **ideal body** weight is often used. [2]

Empirical therapy (< 48 hours):

In general terms: [1,3]

The *initial dose* is based on the patient's age and weight, then the *dose interval* for either one or two further doses (or none at all) is determined by the patient's renal function. [1]

For example, a patient with normal renal function would receive a maximum of three empirical doses at 0, 24 and 48 hours.

As dosing with gentamicin will not continue beyond 48 hours, monitoring of plasma concentrations is not required.

Susceptibility results should be used to guide ongoing therapy. **If possible, replace an aminoglycoside with a safer antibacterial when sensitivity data are available.**

If susceptibility results are not available by 72 hours and empirical intravenous therapy is still required, the gentamicin containing regimen should be ceased and an alternative regimen used.

For critically ill patients: [2]

Pharmacokinetic/pharmacodynamic modeling studies predict that an initial gentamicin dose of **7 mg/kg daily** is required to achieve the target area under the concentration–time curve (AUC) in **critically ill** patients with severe sepsis or septic shock (usually those requiring intensive care support), due to an increased volume of drug distribution and enhanced renal drug clearance.

Higher doses also ensure that pathogens with a relatively high minimum inhibitory concentration (MIC) to gentamicin (e.g. *Pseudomonas aeruginosa*) are adequately treated.

Modeling predictions require assumptions regarding a number of key patient physiological parameters, so the relevance of this recommendation needs to be carefully considered in each patient.

Clinical experience suggests an initial gentamicin dose of 7 mg/kg is unlikely to cause toxicity in appropriately selected patients.

In patients with known or likely pre-existing renal impairment (such as patients with advanced age, e.g. older than 80 years, a lower gentamicin dose should be used

However, **prompt** antibiotic initiation in critically ill patients confers a significant survival benefit, so **do not** delay gentamicin administration to ascertain renal function. Consider monitoring from the first dose, particularly if the patient's renal function is not known.

The **Australian Medicine's Handbook** suggests the following:

Adult: [3]

Use the higher dose for young adults and the lower dose for the elderly:

Cr Cl > 60 mL/minute:	IM / IV	**5 - 7 mg/kg once daily.**
Cr Cl 30 - 60 mL/minute:	IM / IV	**4 - 5 mg/kg once daily.**
Cr Cl < 30 mL/minute:	IM/IV	**4 mg/kg** once daily, and seek expert advice.

Child: [3]

1 month - 10 years:	IM / IV	**7.5 mg/kg (maximum 320 mg) once daily.**
>10 years:	IM/IV	**6–7 mg/kg (maximum 560 mg) once daily.**

Add the required dose to 100ml of compatible IV fluid and administer over 30 minutes. [5]

Smaller doses are used in **non-critically** ill patients - **see below and latest Antibiotic Therapeutic Guidelines.**

Directed therapy (> 48 hours):

In general terms: [1]

If a susceptible Gram-negative organism is identified, gentamicin should only be continued if the patient has one of the following indications for **directed therapy**:

- Infections when resistance to other safer antimicrobials has been shown
- Combination therapy for serious *Pseudomonas aeruginosa* infections and brucellosis

- Low doses as synergistic treatment for streptococcal and enterococcal endocarditis.

The first dose of directed therapy is based on the patient's age and weight, as for empirical therapy, monitoring will then guide subsequent dosing.

Monitoring: [2]

Monitoring for once daily dosing > 48 hours:

Monitoring the aminoglycoside plasma concentration is mandatory from the *first dose* of *directed therapy* or if *therapy is planned for longer than 48 hours.*

The aims of monitoring the aminoglycoside plasma concentration are to ensure adequacy of dosing and to avoid excessive drug exposure, which can be associated with nephrotoxicity, and occasionally vestibular and auditory toxicity.

Treatment for > 48 hours: measure **drug concentration** and monitor **serum creatinine** every 3 - 5 days in clinically stable patients. [3]

Obtain these results daily if the clinical state (especially renal function) is unstable - or consider the use of an alternative agent.

Computerised methods can be successfully used for gentamicin monitoring. They estimate the **24-hour area under the curve (AUC)** of concentration against time and recommend dose adjustment to achieve the target AUC. These methods are the most sophisticated as they automatically adjust for significant individual variation in volume of distribution and elimination. The timing of the blood sample will depend on the specific program used.

The older **nomograms** that were used for plasma concentration monitoring are now discouraged. These graphical methods had significant limitations as they were based on population pharmacokinetics and had only been validated in adult patients with normal renal function.

The approach to monitoring the aminoglycoside concentration depends on the dosing regimen used i.e single daily dosing or multiple daily dosing.

Examples of on-line computerised AUC methods that are freely available include:

- **Aladdin:**
  - ♥ www.asainc.net.au/aladdin
- **TCI-Works:**
  - ♥ http://www.tciworks.info/

Note that **trough** plasma concentrations cannot be used to monitor **once-daily** (or less frequent) dosing in adults because they are often below the laboratory detection limit and correlate poorly with overall exposure.

If monitoring is required and AUC methods are not available, seek expert advice

Monitoring for multiple (synergistic) daily dosing:

The **AUC** approach to monitoring aminoglycoside plasma concentrations is not required for **multiple-daily (i.e 8-hourly or 12-hourly)** dosing regimens.

Instead, the **trough (pre-dose) 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.

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, consideration should be given to stopping gentamicin - seek expert advice

Additional monitoring in long term therapy: [3]

- Monitor for cochlear toxicity with pure tone audiometry testing (high tone range) every 1–2 weeks during prolonged treatment, e.g. osteomyelitis and endocarditis

- Monitor *clinically* for vestibular toxicity (e.g. ask about dizziness, tinnitus, confusion and oscillopsia).

*Dosing for **non**-critically ill patients:*

Adult: [2]

Use the higher dose for young adults and the lower dose for the elderly:

Cr Cl > 60 mL/minute:

- **IM / IV 4 - 5 mg/kg once daily 3 doses (at 0, 24 and 48 hours)**

Cr Cl 40 - 60 mL/minute:

- **IM / IV 4 - 5 mg/kg 36 hourly 2 doses (at 0 and 36 hours)**

Cr Cl < 40 mL/minute:

- **IM/IV 4 mg/kg single dose, then seek expert advice for subsequent dosing or selection of alternative drug**

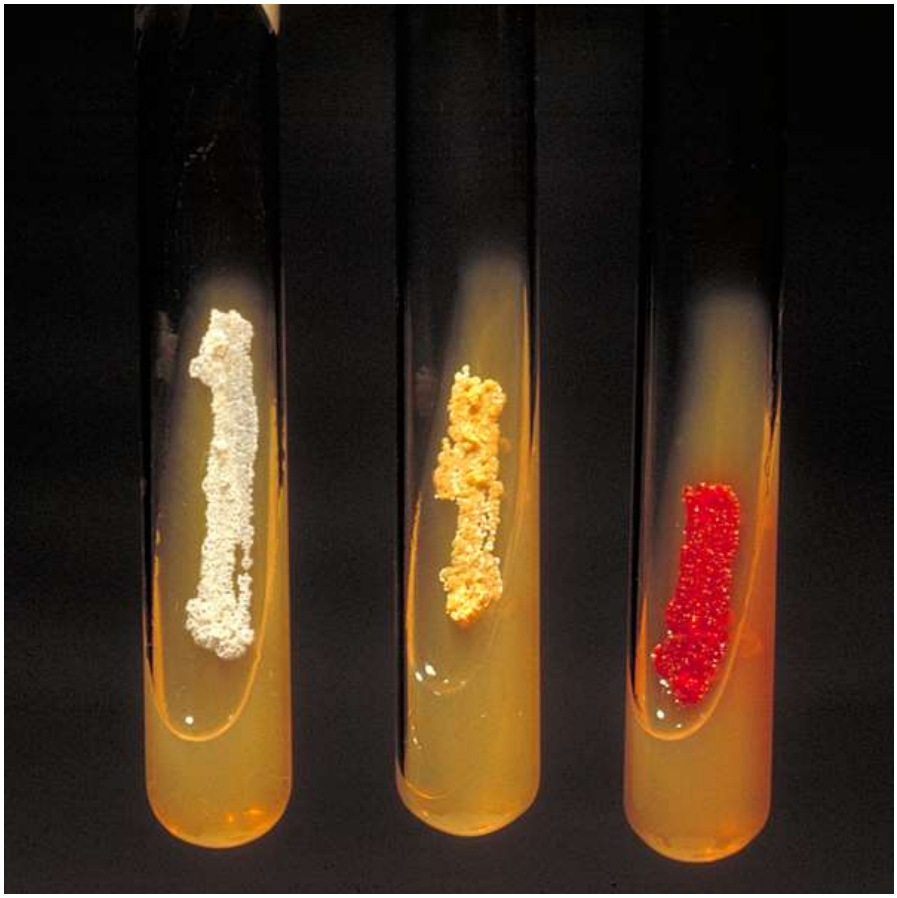
Add the required dose to 100ml of compatible IV fluid and administer over 30 minutes. [5]

Child/ neonates:

- **See latest Antibiotic Therapeutic Guidelines.**

Appendix 1

Nomenclature: "micin" versus "mycin"



Slant cultures demonstrating variations in colony appearance between aerobic Actinomycetes organisms. White colonies indicate Actinomadura madurae, yellow colonies indicate Nocardia asteroides, and ***red colonies*** *indicate* ***Micromonospora species****. (CDC Public Health Image Library).*

Micromonospora *is a genus of bacteria of the family Micromonosporaceae. They are gram-positive, spore-forming, generally aerobic, and form a branched mycelium; they occur as saprotrophic forms in soil and water.*

Various species of ***Micromonospora*** *are sources of aminoglycoside antibiotics, which spellings often ending with "****micin****" e.g.* ***Gentamicin.***

*This is to distinguish certain other aminoglycosides whose names end with "****mycin****" that come from very different organisms, e.g. neomycin and streptomycin, which are produced by* ***Streptomyces species.***

Taxonomy of Micromonospora purpurea:

Kingdom: Bacteria

Phylum: Actinobacteria

Order: Actinomycetales

Family: Micromonosporaceae

Genus: *Micromonospora*

Species: ***Micromonospora purpurea:***

This his is the species that produces the antibiotic ***gentamicin.***

References

1. Robert FW Moulds at al. Gentamicin: a great way to start. Aust Prescr 2010; 33:134 - 5.

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