Guidelines: Synergistic Gentamicin for Endocarditis in non-pregnant adults ≥16 years old

Background

There is a lack of published evidence on optimal synergistic dosing of gentamicin in endocarditis but several NHS boards have developed weight-based dosing guidance with some including reduced dosing in renal impairment. An audit project in NHS GG&C examined data from patients receiving synergistic gentamicin and pharmacokinetic analysis was used to develop dosing guidance based on weight and renal function aimed at achieving the recommended peak and trough levels.

The guidance does not apply to gentamicin use in the following:

- patients treated in Renal units or receiving haemodialysis or haemofiltration
- major burns
- ascites
- age < 16 years
- cystic fibrosis

Contra-indications and cautions

- Contra-indications to gentamicin therapy – hypersensitivity, myasthenia gravis
- Cautions to gentamicin therapy:
  - Patients with decompensated liver disease - aminoglycosides are associated with an increased risk of renal failure.
  - Concurrent administration of neurotoxic and / or nephrotoxic agents increases the risk of gentamicin toxicity. Review therapy and consider amending or withholding nephrotoxic drugs during gentamicin treatment. Avoid co-administration with the following:
    - neuromuscular blockers
    - other potentially nephrotoxic (e.g. NSAIDs and ACE Inhibitors) or ototoxic drugs
    - potent diuretics
    - other aminoglycosides

    This list is not exhaustive – consult the Summary of Product Characteristics (eSPC) for a full list (www.medicines.org.uk)
  - Chronic Kidney Disease (CKD) Stage 4 or more, known or suspected acute kidney injury in the previous 48 hours (≥ 50% increase in baseline serum creatinine or oliguria > 6 hours). If gentamicin is clinically indicated, give one dose as per guidance and check with microbiology or an infection specialist before giving a second dose.

Treatment of endocarditis

- Synergistic gentamicin is recommended for treatment of enterococcal and some streptococcal species (depending on penicillin MIC). It is recommended by the British Society of Antimicrobial Chemotherapy for the empiric treatment of prosthetic valve endocarditis (PVE) and PVE associated with staphylococci.
- All patients with suspected or proven endocarditis should be discussed with an infection specialist and cardiology. All blood cultures with significant isolates, including those in keeping with infective endocarditis, are communicated to clinical teams by a consultant microbiologist, who will give treatment recommendations based on susceptibility information and patient factors.

Dosage guidelines

- These guidelines aim to produce a 1 hour post dose "peak" concentration of 3-5 mg/L and an end of dosage interval "trough" concentration of <1 mg/L. The dose amount and dosage interval are based on estimated creatinine clearance (see Box 1) and **actual** body weight.
- **Doses should be administered by IV bolus injection over 3-5 minutes.**

Box 1: Estimation of creatinine clearance (CrCl)

The following 'Cockcroft Gault' equation can be used to estimate creatinine clearance (CrCl)

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 1.23 \text{ (male) OR } \times 1.04 \text{ (female)}}{\text{serum creatinine (micromol/L)}}$$

Cautions:

- Use actual body weight or maximum body weight whichever is lower. For maximum body weight table see https://www.sapg.scot/media/4471/maximum-body-weight-table.pdf
- In patients with low creatinine (< 60 micromol/L), use 60 micromol/L.
- Note: Use of estimated glomerular filtration rate (eGFR) is not recommended.

Gentamicin: Synergistic Dosage Guidelines

	Patient Actual Body Weight				
Creatinine Clearance* (DO NOT use eGFR)	**<45 kg**	**45-65 kg**	**66-85 kg**	**86-110 kg**	**>110 kg**
<25 ml/min	40 mg	60 mg	80 mg	100 mg	120 mg
	Take a sample after 24 hours. Do not give a further dose until the concentration is <1 mg/L				
25-44 ml/min	40 mg 24 hourly	60 mg 24 hourly	80 mg 24 hourly	100 mg 24 hourly	120 mg 24 hourly
>44 ml/min	40 mg 12 hourly	60 mg 12 hourly	80 mg 12 hourly	100 mg 12 hourly	120 mg 12 hourly

***If creatinine is not known: give 1mg/kg gentamicin (maximum 120mg) and seek advice from pharmacy **(DO NOT use eGFR**: creatinine clearance **must** be calculated).

Prescribing

Prescribe synergistic gentamicin doses on HEPMA – select option 'Gentamicin Synergistic (ENDOCARDITIS) and add dose and frequency. The (pink) 'NON-PREGNANT ADULT ≥16 years old PARENTERAL SYNERGISTIC (usually in endocarditis) GENTAMICIN: MONITORING CHART' can be used to record dose and sample times to facilitate the correct interpretation of gentamicin concentration results (this is **NOT** a prescribing chart and is only to be used for documenting gentamicin levels - synergistic gentamicin doses and frequency must be prescribed and charted on HEPMA).

Monitoring

1. Take a blood sample in an orange lithium heparin tube for gentamicin analysis one hour after the first gentamicin bolus injection has been administered (labelled as a "peak" sample). At the first dose, the concentration may not yet be at steady state, and any repeat peak concentration measurements may be higher than the first.
2. Take a second sample for gentamicin analysis at the end of the first dosage interval (labelled as a "trough" sample) then give the next dose. **Do NOT delay giving the second gentamicin dose while waiting for the trough concentration to be reported, unless there are concerns over deteriorating renal function.**
   - If the gentamicin peak concentration is within the range of 3-5 mg/L and the gentamicin trough is <1 mg/L, continue the present dosage regimen (dose amount and dose frequency).
   - Record the **exact** time of gentamicin doses and sample times on the sample request form.
   - A record of the synergistic gentamicin sample times and results should be documented on the (pink) "NON-PREGNANT Adult ≥16 years old PARENTERAL SYNERGISTIC (usually in endocarditis) GENTAMICIN: MONITORING CHART".(appendix 1)
3. Seek advice from pharmacy if you are unsure how to interpret the results or if the concentrations are not within the ranges above.
4. If the gentamicin trough concentration is ≥1 mg/L and a further dose has already been administered, re-check the trough and await the result before re-dosing. **Do NOT give a further dose until the gentamicin concentration is <1 mg/L.**
5. If the prescribed dose amount/dose frequency is altered ensure this is updated on HEPMA.
6. Monitor the patient's creatinine daily. If renal function is stable, check the gentamicin "trough" and "peak" concentrations every 2 days. If renal function deteriorates, or if the concentrations measured are not within the target range, check the levels daily and discuss the dose regimen with pharmacy.

Gentamicin duration

Synergistic Gentamicin therapy is most commonly given for 2 weeks except in the case of enterococcal infective endocarditis (IE) when it may be given for up to 6 weeks (microbiology or infectious diseases should be consulted on the duration of synergistic gentamicin). The addition of synergistic gentamicin in staphylococcal **native valve** IE is no longer recommended as it increases renal toxicity without evidence of additional benefit.

NHS Ayrshire and Arran have produced a Gentamicin patient information leaflet (see Appendix 2 or AthenA) which can be used to ensure patients understand the length of treatment.

Toxicity

Gentamicin can cause nephrotoxicity and ototoxicity (cochlear and vestibular). The risk of gentamicin toxicity increases with increasing duration of therapy.

Nephrotoxicity

- Monitor creatinine daily. Seek advice from pharmacy if renal function is unstable (e.g. a change in creatinine of >15-20%).
- Be alert for and react to any signs of renal toxicity e.g. increasing creatinine, decreased urine output/oliguria.
- Discuss the ongoing need for gentamicin with microbiology/ID if the patient has signs of worsening renal function.

Ototoxicity

- Gentamicin-induced ototoxicity occurs independently of drug concentration.
- Toxicity is associated with prolonged gentamicin use (usually >7 days) and is secondary to accumulation of drug within the inner ear.
- Ototoxicity is suggested by any of the following: new tinnitus, dizziness, poor balance, hearing loss, oscillating vision.
- Patients prescribed gentamicin should be advised to report signs of ototoxicity (see below regarding the Patient Information Leaflet which should be issued to the patient). They should be asked about any signs and symptoms of ototoxicity regularly and this should be documented in the case notes.
- If gentamicin continues for >7 days the patient should be referred to audiology for ongoing audiometry testing.
- If ototoxicity is suspected **STOP** gentamicin treatment and refer to microbiology/ID for advice on ongoing therapy.

Bibliography

1. NHS Greater Glasgow and Clyde Guidelines: Synergistic Gentamicin for Endocarditis in Adults (GGC Version 3 published 30/11/19). Accessed online April 2021.
2. Gould, K et al.(2012) Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy *Journal of Antimicrobial Chemotherapy* 67: 269-289 Accessed online 5th May 2021

Appendix 1: Synergistic gentamicin - monitoring chart (link)

Appendix 2: Intravenous Gentamicin Patient Information Leaflet (link)