# Haematology neutropenic sepsis in adults

Nottingham University Hospitals NHS Trust

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| **Full Title of Guideline:** | **Guideline for the Management of Neutropenic Sepsis in Haematology** 1866 |
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| **Scope** ***(Target audience, state if Trust wide):*** | FY1/2, CT1/2 and Haematology ST3-ST7 doctors, pharmacists and nurses. |
| **Review date** ***(when this version goes out of date):*** | June 2026 |
| **Explicit definition of patient group to which it applies** ***(e.g. inclusion and exclusion criteria, diagnosis):*** | All adult haematology patients |
| **Changes from previous version** ***(not applicable if this is a new guideline, enter below if extensive):*** | Addition made to ensure consultant approval for use of Vancomycin and gentamicin due to nephrotoxicity risk<br><br>New section relating to actions if pseudomonas isolated<br><br>Updated screenshots for gentamicin prescribing on ePMA |
| **Summary of evidence base this guideline has been created from:** | Guidance reviewed with local Microbiological surveillance data. |
| ***This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date or outside of the Trust.*** | |

## Flow chart 1: Antibiotic prescribing for Neutropenic Sepsis in Haematology Patients

Suspected or confirmed neutropaenia **OR** Day 0 onwards of autograft/ allograft/**CAR-T therapy**

**PLUS**

Fever ≥38 **OR** clinical features of sepsis

**YES**

Take Blood cultures - peripherally plus cultures from any lines (e.g. PICC line, Hickman line)

IV antibiotics **WITHIN AN HOUR OF FEVER ONSET**

Take bloods including FBC, U+E and lactate.

**DO NOT WAIT FOR RESULTS BEFORE COMMENCING ANTIBIOTICS**

**In case of CAR-T / bispecific antibody therapy consider possibility of Cytokine Release Syndrome (CRS) and discuss with Haematology SPR**

**NON-ALLOGRAFT/ NON- CAR-T PATIENTS**

**NO/ MILD PENICILLIN ALLERGY:**

Meropenem 1g IV TDS

**SEVERE PENICILLIN ALLERGY:**

Ciprofloxacin PO 500mg BD (or if vomiting IV 400mg BD, or if High Risk SEPSIS give 1st dose as IV 400mg then convert to oral)

**PLUS** Vancomycin IV[#] - refer to dosing calculator and antibiotic website for dosing

**PLUS** Metronidazole IV 500mg TDS

**WITHIN 100 DAYS OF ALLOGRAFT /CAR-T OR ONGOING GUT GVHD**

**NO/MILD PENICILLIN ALLERGY:**

Ceftazidime 2g IV single dose followed by 1g IV TDS

**SEVERE PENICILLIN ALLERGY:**

Ciprofloxacin PO 500mg BD (or if vomiting IV 400mg BD, or if High Risk SEPSIS give 1st dose as IV 400mg then convert to oral)

**PLUS** Vancomycin IV[#] - refer to dosing calculator and antibiotic website for dosing

**PLUS** Metronidazole IV 500mg TDS

**IS NEUTROPENIA CONFIRMED OR IS THE PATIENT DAY 0 ONWARDS AUTOGRAFT/ALLOGRAFT/CAR-T *therapy?***

**AND HAVE U&Es BEEN CHECKED WITHIN 24 HOURS?**

**YES TO BOTH**

**GIVE SINGLE DOSE IV GENTAMICIN BASED ON RENAL FUNCTION**

**Check for AKI.** Refer to the gentamicin dosing calculator on the antibiotic website Continue once daily.

**PRE-DOSE LEVEL AND WAIT BEFORE EVERY DOSE**

**NO**

**Are there features of severe/ high risk sepsis, including hypotension (SBP <90mmHg) unresponsive to fluid resuscitation?**

**YES**

**ARRANGE HAEMATOLOGY ST ON CALL REVIEW.**

If clinically indicated, give IV Gentamicin. **Check for AKI.** Refer to the gentamicin dosing calculator on the antibiotic website. Continue once daily if neutropenia confirmed

**PRE-DOSE LEVEL AND WAIT BEFORE EVERY DOSE**

**NO**

**AWAIT FBC AND U&E BEFORE GIVING GENTAMICIN**

If neutropenia confirmed dose IV Gentamicin according to current renal function. **Check for AKI**. Refer to the calculator on the antibiotic website or gentamicin guideline or contact a pharmacist if unsure.

Continue once daily

**PRE-DOSE LEVEL AND WAIT BEFORE EVERY DOSE**

**[#]If use of IV Vancomycin in combination with IV Gentamicin is required, this should be approved by a haematology consultant. IV Vancomycin plus IV gentamicin is highly nephrotoxic.**

# Guideline for the Management of Neutropenic Sepsis

**The criteria for treatment are outlined in the table below, patients should meet criteria 1 AND 2 or 3**

| **Criteria for Treatment**<br>**Criteria 1 AND 2 or 3** | | **Comments** |
|---|---|---|
| **1.** | **Presence of neutropenia i.e. neutrophils <1.0x $10^9$/L**<br>**OR**<br>**suspected neutropenia**<br>**OR**<br>**day 0 onwards of autograft or allograft** | **If patient admitted from home and history of recent chemotherapy within past 4 weeks treat as neutropenic sepsis without waiting for full blood count (FBC) result (if not neutropenic downgrade treatment later).**<br>**Some patients may be neutropenic due to their blood disorder without any prior exposure to chemotherapy.** |
| **2.** | **Presence of fever** | i.e. temperature ≥ 38ºC on one occasion<br>Or a clear history of pyrexia measured by patient prior to admission. If temperature is 37-38ºC, repeat after 1 hour to see if the above criteria for treatment are met. |
| **3.** | **Clinical signs of sepsis / obvious focus of infection** | i.e. tachycardia, low blood pressure, tachypnoea, chest signs, etc. |

**These patients need immediate assessment and initiation of treatment with broad spectrum antibiotics within 1 hour of being found to be septic (see NCEPOD recommendations).**

**Presentation of Septic Neutropenic Patients**

1. **In-Patients on Toghill / Fletcher / SRU**
    - Many in-patients will be neutropenic following chemotherapy. If sepsis is suspected **during normal working hours** the Haematology ST or CT1/2 doctors should be informed immediately and **IV antibiotics started WITHIN 1 HOUR. The PGD for first dose Meropenem should be used if appropriate.**
    - **Out of hours** the nursing staff should call the Hospital @ Night team and request urgent patient review so that **IV antibiotics are started within 1 hour. The PGD for first dose Meropenem should be used if appropriate.**

2. **Out-Patients Taken to ED at QMC**

    - Patients presenting themselves or via an ambulance to QMC ED should be assessed immediately by an experienced ED doctor and commenced on **IV antibiotics within 1 hour.**
    - The patient should be discussed with the Haematology ST on call.
    - The patient should be transferred once haemodynamically stable and after the first dose of antibiotics have been given, to a bed on Fletcher or Toghill if available or to Specialist Receiving Unit (SRU).
    - If the patient is too unwell for transfer they should be reviewed by the Haematology ST at QMC during working hours or the medical registrar on duty out of hours.

3. **Out-Patients Taken to SRU at City Campus**

    - Out-patients arriving directly to SRU should be seen and assessed immediately by the SRU junior doctor and **IV antibiotics started within 1 hour.**
    - The Haematology ST on call or covering outliers should be notified once assessment has been done.

4. **Patients Telephoning / Presenting to the Haematology DCU or Nurse Bleep holder**

    - Patients who telephone the Haematology Day Case Unit or the Nurse Bleep holder during the normal working day, with fever or other symptoms that might suggest sepsis should be asked either to attend either the Specialist Receiving Unit (SRU) or the Haematology Day Case Unit (DCU) for assessment.
    - On arrival at the DCU, patients should be immediately assessed and if sepsis suspected **IV antibiotics should be started within 1 hour** in the DCU.

Patients telephoning out of hours should be asked to attend SRU. The SRU doctor should assess the patient as soon as possible on arrival and **commence IV antibiotics within 1 hour.**

**<u>Assessment</u>**

**Take brief history, including details of recent treatment and chemotherapy drugs given. Check previous detection of antibiotic resistant Gram negative organisms from clinical specimens or surveillance cultures. Check for allergies to antibiotics. Clinical examination for signs of:**

1. Oropharyngeal infection
2. Chest infection or coryzal symptoms - including the possibility of SARS-CoV 2 infection or other respiratory viruses
3. Hickman line / PICC site infection
4. Perianal sepsis, but do NOT perform a digital examination
5. Typhlitis

## Investigations

**Full set of observations / EWS score / oxygen saturations (**assess for high risk sepsis**)** - if present arrange for senior medical review within 1 hour and proceed to full sepsis six bundle**).**

**Take immediate peripheral blood cultures and Hickman line / PICC line blood cultures (if available).**

**Check FBC for degree of neutropenia (but do not wait for result before starting treatment).**

**Check U&E (as need creatinine result to dose aminoglycosides, ensure check for AKI) and lactate.**

**Arrange MSU.**

**Arrange stool culture if loose stools present.**

**Arrange CXR (immediate if there are chest signs or symptoms, or the following morning if there are none and it is past midnight).**

**Ask nurses to take swabs from Hickman line site and mouth.**

**Obtain weight – for dosing of aminoglycoside**

**If CXR/imaging raises the possibility of PCP send serum for β-D-glucan and a viral throat swab and induced sputum (if possible) for PCP PCR.**

**Arrange nose and throat swabs if there are coryzal symptoms for respiratory virus PCRs including SARS-CoV2.**

**If prescribing IV Gentamicin or IV vancomycin, fluid balance should be activated on nerve centre**

**If prescribing IV Gentamicin ensure patient is counselled and given patient information leaflet 'Hearing and balance problems with antibiotics'**

## Treatment

Start fluid resuscitation and IV antibiotics WITHIN 1 HOUR – write first dose up as once only dose if necessary to be given immediately. Ensure nursing staff are informed of the prescription.

**(All doses assume normal renal / hepatic function – check antibiotic website for dose if abnormal)**

**For ALL PATIENTS WITH SUSPECTED NEUTROPENIA: Initiate treatment immediately (DO NOT WAIT FOR X-RAY OR FBC RESULTS)**

**PLEASE NOTE THAT PATIENTS WHO HAVE UNDERGONE AN ALLOGENEIC STEM CELL TRANSPLANT WITHIN THE PREVIOUS 100 DAYS, CAR-T cell therapy *OR* HAVE EVIDENCE OF ONGOING GVHD OF THE G.I. TRACT SHOULD RECEIVE A DIFFERENT ANTIBIOTIC COMBINATION THAN THE GENERALITY OF CLINICAL HAEMATOLOGY PATIENTS TO MITIGATE AGAINST DISRUPTION TO THE GUT MICROBIOME AND HENCE TO REDUCE THE RISK OF SEVERE GUT GVHD**

**If neutropenia not confirmed and renal function has not been checked for >24 hours, e.g. patients newly admitted to SRU, do not give Gentamicin until U&E results are back UNLESS patient is hypotensive/unwell in which case discuss with haem ST/consultant. ENSURE check trends in previous renal function. Other antibiotics, e.g. meropenem, ceftazidime, should be given immediately without waiting for renal function results.**

| | Non-allograft / non-CAR-T patients | Allograft patients/ CAR-T cell therapy (up to 100 days) plus patients with ongoing gut GVHD |
|---|---|---|
| **No/mild penicillin allergy** | **Meropenem** 1g IV TDS<br><br>PLUS<br><br>**If confirmed neutropenia AND U&E checked within 24 hours**<br><br>**Gentamicin*** IV once daily. Use gentamicin dosing calculator for dosing or refer to antibiotic website. See Appendix A.<br><br>Dose reductions are required in AKI and CKD and levels should be monitored (see antibiotic website).<br><br>If no U&E result from the last 24 hours, but there are features of severe/high risk sepsis:<br><br>Arrange haematology ST review and if clinically indicated give a single dose of Gentamicin IV, based on most recent renal function (Ensure check if AKI- dose reduction required in AKI and CKD) and continue once daily if neutropenia confirmed.<br><br>If no features of severe/high risk sepsis, await FBC and U+Es before giving gentamicin. See flow chart on page 2. | **Ceftazidime** 2g IV single dose followed by 1g IV TDS<br><br>PLUS<br><br>**If confirmed neutropenia AND U&E checked within 24 hours**<br><br>**Gentamicin*** IV once daily. Use gentamicin dosing calculator for dosing or refer to antibiotic website. See Appendix A.<br><br>Dose reductions are required in AKI and CKD and levels should be monitored (see antibiotic website).<br><br>If no U&E result from the last 24 hours, but there are features of severe/high risk sepsis:<br><br>Arrange haematology ST review and if clinically indicated give a single dose of Gentamicin IV, based on most recent renal function (Ensure check if AKI- dose reduction required in AKI and CKD) and continue once daily if neutropenia confirmed.<br><br>If no features of severe/high risk sepsis, await FBC and U+Es before giving gentamicin. See flow chart on page 2. |
| | If there are strong signs of a Gram positive infection (e.g. a red and inflamed Hickman exit site/tunnel infection, severe mucositis), consider adding **Vancomycin** IV – use vancomycin dosing calculator or refer to antibiotic website for dosing. If AKI dose reductions or use of alternative agents may be required refer to antibiotic website. Consultant approval is required if IV vancomycin plus IV Gentamicin is prescribed due to the high risk of nephrotoxicity. | |

| **Non-allograft patients and Allograft patients (up to 100 days) plus patients with ongoing GVHD or patients with CAR-T cell therapy up to 100 days** | |
|---|---|
| **Severe penicillin allergy (anaphylaxis, angioedema, immediate onset urticaria)** | **Ciprofloxacin** PO 500mg BD (or if vomiting IV 400mg BD or if High Risk SEPSIS give 1st dose as IV 400mg then convert to oral)<br><br>**PLUS**<br><br>**Vancomycin**[a] IV - Use vancomycin dosing calculator available on the website or refer to antibiotic website for dosing.<br><br>**PLUS**<br><br>Metronidazole[c] IV 500mg TDS<br><br>**PLUS**<br><br>**If confirmed neutropenia AND U&E checked within 24 hours**<br><br>**Gentamicin**[b] **IV once daily** (Consultant haematologist approval required as this combination is highly nephrotoxic.) Use gentamicin dosing calculator for dosing or refer to antibiotic website. See Appendix A. Dose reductions are required in AKI and CKD and levels should be monitored (see antibiotic website).<br><br>If no U&E result from the last 24 hours, but there are features of severe/high risk sepsis:<br><br>Arrange haematology ST review and if clinically indicated give a single dose of Gentamicin IV, based on most recent renal function and continue once daily if neutropenia confirmed.<br><br>If no features of severe/high risk red sepsis, await FBC and U+Es before giving gentamicin. See flow chart on page 2 |

[a] If allergy/contraindication to Vancomycin, substitute **Teicoplanin** 12 mg/kg IV every 12 hours for 3 doses and then 12 mg/kg ONCE daily thereafter (requires dose reduction in renal impairment, see antibiotic website). NB there are case reports within the literature of cross sensitivity between vancomycin **and** teicoplanin which is thought to be due to their structural similarities. Those patients with a severe allergy to vancomycin should be discussed with microbiology. If there is a history of Vancomycin Infusion Reaction (an infusion related reaction) then consider using the alternative teicoplanin.

[b] **Multi- resistant Pseudomonas** If there have been recent multi-resistant Pseudomonas isolates, there may have been a switch from Gentamicin to Amikacin (15 mg/kg/day in 2 divided doses) as the first line aminoglycoside. Please check current policy, haematology consultants will inform ward prescribers when informed by microbiology.

[c] Metronidazole to be given because the Ciprofloxacin/Vancomycin/Gentamicin combination will not cover anaerobes, e.g. clostridium. Review metronidazole at 48 hours and stop unless blood cultures indicate it needs to be continued.

## Carbapenem resistant enterobacteriaceae (CRE)

If the patient is identified as CRE positive via surveillance screening or a clinical specimen, additional or alternative antibiotics to those listed in the treatment table below will be required.

**If no up-to-date antibiotic plan or advice from Microbiology is already in place for this admission, cases should be discussed on an individual basis with Microbiology.**

## Review of antibiotics with blood results

If the blood results show that the patient is not actually neutropenic then the antibiotics should be reviewed to those appropriate for the infection being treated as per NUH antibiotic guidelines.

## Review antibiotics at 48 Hours

1. If the temperature has settled and there are no positive isolates of Gram negative bacteria – STOP gentamicin at 48 hours and continue Meropenem (non allograft patients) or ceftazidime (allograft patients) for a total 5 day course.
2. If the patient is penicillin allergic and receiving metronidazole stop this at 48 hours unless blood cultures have isolated an anaerobe which requires ongoing metronidazole.
3. If the patient's temperature lyses and there are no signs of complicated infection and there is a positive culture result with an oral alternative antibiotic, then an IV to oral switch may be possible after 48 hours if the patient has the oral route available. Give 5 days total treatment.
4. If blood cultures are positive then review antibiotics and change as per microbiology advice. Consider switching to narrow spectrum agent if sensitive organism cultured.
5. If Pseudomonas species cultured, please check sensitivities. Preferred agents for treating Pseudomonas species would be Ceftazidime IV 2g TDS or Piperacillin tazobactam (Tazocin) IV 4.5g QDS. If the patient remains clinically unwell, please discuss with microbiology regarding the addition of a second agent (possible options are aminoglycoside e.g. Amikacin/Tobramycin or Ciprofloxacin, or Colistin dependent on sensitivities and any contraindications to use). Higher dosing regimes will be required, refer to antibiotic website.

## Review antibiotics at 48-72 hours

If there are no positive bacterial isolates and no response to antibiotics at >48-72 hours, fungal infection should be considered. Risk factors for fungal infection include prolonged severe neutropenia, current/recent corticosteroid therapy, T cell depleting agents (e.g. ATG, Campath, Fludarabine, Bendamustine) ) then:

1. Discuss with haematology consultant or ST +/- micro.
2. Refer to anti-fungal guideline.
3. Request high resolution CT chest.
4. Send blood for beta D glucan and galactomannan.
5. If starting AmBisome (liposomal Amphotericin B), it is usual to stop the aminoglycoside to preserve renal function - if in doubt discuss with the ST.

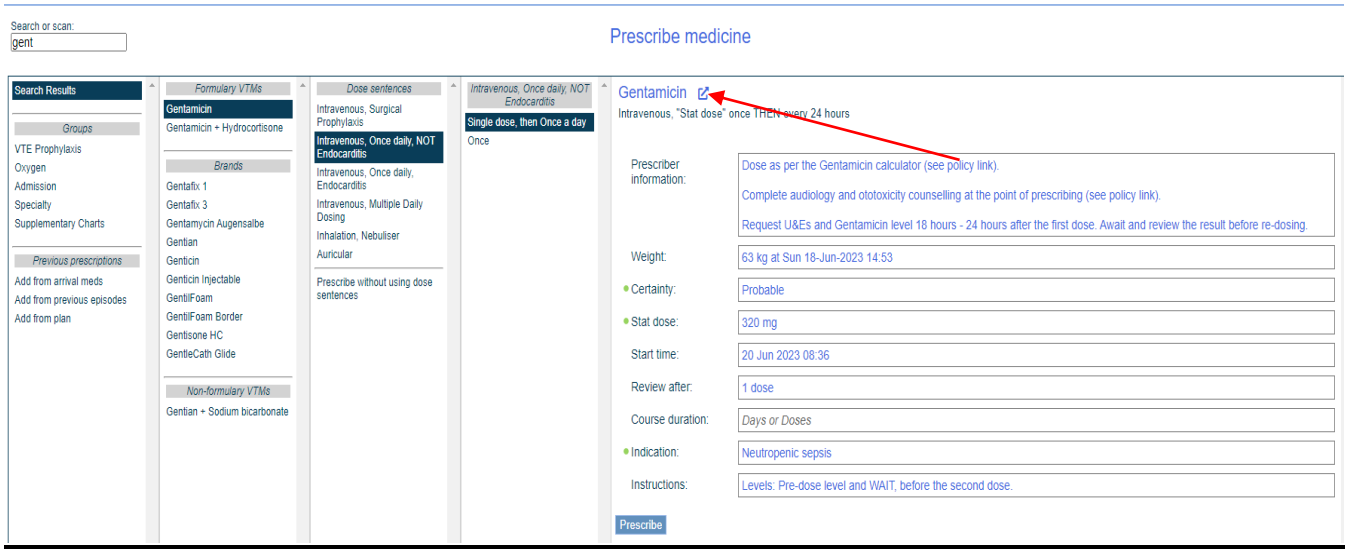
**Appendix A**

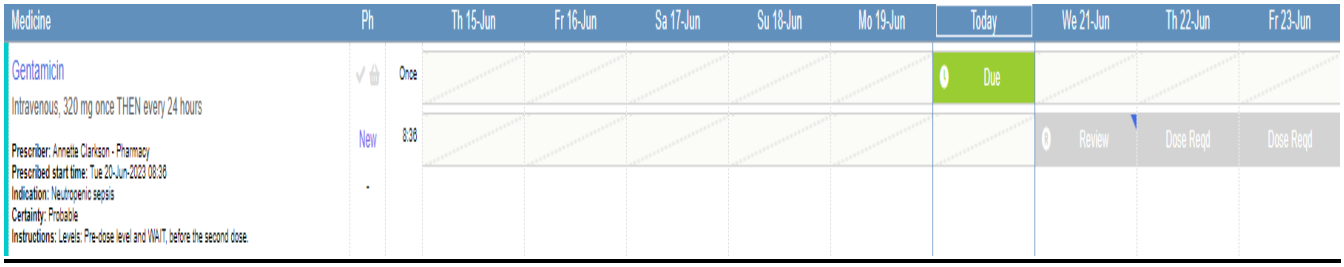
**Gentamicin prescribing**

- Gentamicin is nephrotoxic. Dose reductions are required in acute and chronic renal failure, ensure use the gentamicin dosing calculator or refer to the antibiotic website for dosing. Links can also be accessed via the gentamicin prescribing dose sentences on ePMA. Anuric and oliguric (<500ml/day) patients can be assumed to have a CrCl < 10ml/min.
- If the patient is obese – defined as **more than 120% of their ideal body weight** (IBW) – a dose correction is required. It is recommended that in these cases the dosing calculator available on the antibiotic website is used.
- Ensure fluid balance chart is activated on Nervecentre
- Ensure patient is counselled on ototoxicity and vestibular toxicity risks of gentamicin and given the patient information leaflet 'Hearing and balance problems with antibiotics' (Link to the leaflet can be found via the gentamicin dose sentence on ePMA.)

Below is an example prescription. On ePMA, ensure prescribe using the 'dose sentence for Intravenous ONCE daily NOT endocarditis. A 'hard review' should be set on the prescription on ePMA. **The default, is level and wait for all doses.**

Dose reductions are required in AKI and CKD and levels should be monitored (see antibiotic website).




Where it states 'review', this is to indicate pre dose levels are required. To indicate when further levels are required, click on the date the dose is due and select hard review. In the reason box add 'Pre dose level and wait'. It is required that the dose needs to be set each day, though you can set for a number of days at a time if appropriate.

Refer to the Quick reference guide for prescribing antimicrobials on ePMA.

## Gentamicin monitoring

A pre-dose, level is required **18-24 hours** after the first dose. This should be sent in a gold top serum separator tube to clinical pathology. It is **not** necessary to do a post-dose (or peak) level for once daily dosing.

**DUE TO THE FREQUENT USE OF CONCURRENT NEPHROTOXIC DRUGS IN HAEMATOLOGY PATIENTS, THE DEFAULT POSITION IS THAT A PRE-DOSE LEVEL SHOULD BE TAKEN DAILY AND THE RESULTS REVIEWED BEFORE AUTHORISING ADMINISTRATION OF THE NEXT DOSE.**

If however there is clinical concern about waiting for the level result due to a patient being hypotensive/unwell, a level can be taken and the gentamicin given before the level comes back after discussion with the haem ST/consultant.

Refer to the full text Gentamicin guideline, or antibiotic website for further information.

## Checklist for monitoring of gentamicin

The clinical team caring for the patient are responsible for ensuring that these tasks are assigned to the most appropriate staff member, suggestions as to the most appropriate personnel have been made. See table below

| Task | Person responsible |
|---|---|
| Blood tests requested for U&E and gentamicin levels | Prescriber currently caring for patient |
| Taking the blood tests and ensuring samples sent to laboratory | Nursing staff to ensure levels have been taken by phlebotomy or the Drs, any request forms that have not been actioned (e.g. patient refused or unable to obtain blood sample) should be highlighted to the prescriber caring for the patient |
| Checking that U&E and gentamicin levels have been ordered or taken as per guidance | Prescriber and pharmacist caring for patient. |
| Checking and interpreting the gentamicin level results and taking appropriate action | Prescriber caring for patient and pharmacist |
| Fluid balance monitoring via e-fluid balance on nervecentre<br><br>Fluid balance monitoring recorded with documentation of urine output | Prescriber and nurse to electronically mandate for a fluid balance to be started.<br><br>Nurse and HCAs caring for the patient |
| Counselling patient on the risks of ototoxicity and vestibular toxicity and provision of a patient information leaflet where greater than a single dose is planned | Prescriber and pharmacist caring for patient. |
| Arranging audiometry monitoring and genetic testing for mitochondrial mutations where required as per full text gentamicin guideline, see section 3 | Prescriber caring for patient |