GUIDELINES FOR THE MANAGEMENT OF FEBRILE NEUTROPENIA IN ONCOLOGY PATIENTS

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Ratified by	• Nottingham Antibiotic Guidelines Committee
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Evidence base	• Local microbiological sensitivity surveillance • Summary of product characteristics for individual medicines. • Recommended best practice based on clinical experience of guideline developers.
Changes from previous guideline	• Layout of guidelines re-formatted (v4.0) • Addition of summary flowchart (v4.0) • Addition of guidelines for the use of oral antibiotics following initial IV therapy (v.4.0) • Change to generic Piperacillin/Tazobactam from Tazocin® (v.4.1)
Inclusion criteria	• Adult Oncology patients with confirmed or suspected febrile neutropenia
Distribution	• Oncology medical staff • Oncology wards • Oncology chemotherapy clinic • Oncology research team • Pharmacy • Admissions unit. City Campus, Nottingham University Hospitals NHS Trust • Antibiotic website: http://nuhweb/antibiotics • Clinical Effectiveness Department intranet page
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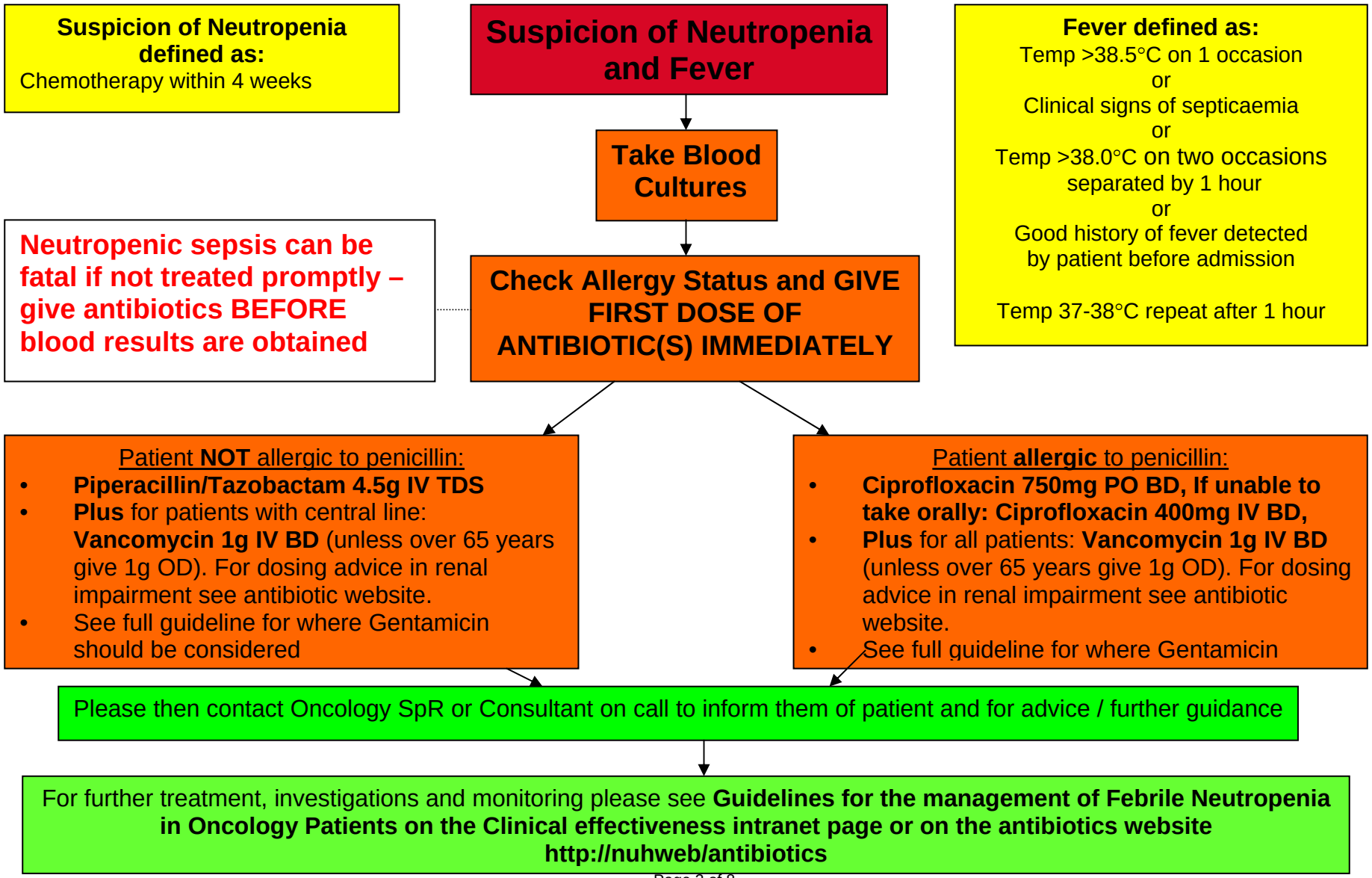
This guideline has been registered with the Trust.
Clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague.
Caution is advised when using guidelines after a review date.

Summary of Guidelines for the Immediate Management of Suspected or Confirmed Febrile Neutropenia in Oncology Patients



PATIENTS WITH SUSPECTED NEUTROPENIC SEPSIS MUST BE ASSESSED, CULTURES TAKEN AND ANTIBIOTIC THERAPY STARTED WITHIN ONE HOUR OF ADMISSION (or suspicion of fever if already an inpatient).
TREATMENT MUST THEREFORE BE STARTED BEFORE BLOOD RESULTS ARE KNOWN.
A BRIEF HISTORY ONLY CAN BE TAKEN TO ESTABLISH PATIENT FULFILS CRITERIA FOR TREATMENT BEFORE COMMENCING ANTIBIOTICS (a full history can be completed after first dose of antibiotics have been given).
BLOOD CULTURES SHOULD BE TAKEN BEFORE ANTIBIOTICS ARE STARTED.

1. CRITERIA FOR TREATMENT

Any patient where there is reasonable suspicion of neutropenia i.e. chemotherapy within the previous 4 weeks and demonstrable fever OR good history of fever detected by patient before admission should be treated with broad spectrum antibiotics according to this guideline.
The patient should be carrying a card to confirm chemotherapy and any antibiotic sensitivities. You should also check for possible antibiotic sensitivities with the patient immediately prior to administration.
Subsequent management will depend on confirmation of neutropenia.

Definition of neutropenia

Neutrophils < 1.0 x 10^9/L

Definition of fever

Temperature >38.0°C on two occasions separated by one hour or
Temperature >38.5°C on one occasion or clinical signs of septicaemia.
If temperature 37-38°C repeat after one hour to see if the above criteria for treatment are met.
A clear history of pyrexia measured by patient prior to admission is sufficient evidence.

2. CLINICAL ASSESSMENT FOR PRESENCE OF SIGNS LOCALISING INFECTION

Oro-pharyngeal infection
Signs of chest infection
Coryzal symptoms
Central / peripheral line infection
Diarrhoea, abdominal pain
UTI

Screening Investigations

FBC, U&Es, LFTs
Peripheral blood cultures and central line blood cultures (if patients have a line, please state on the blood culture request form which type of line is present).
Chest X-ray
MSSU and urinalysis
If symptomatic, stool cultures (for MC&S and CDT)
If sore mouth, 2 swabs - one for candida, one for viral (in viral transport medium)
If coryzal symptoms, consider nasopharyngeal aspirates.
Sputum sample
Blood gases if indicated

3. TREATMENT

Initiate antibiotic treatment IMMEDIATELY with:

- **Piperacillin/Tazobactam 4.5g IV TDS**. Piperacillin/Tazobactam dose should be reduced in renal impairment (see antibiotic website http://nuhweb/antibiotics). (for penicillin allergic patients see ** below)
- For patients with **central** lines (including PICC lines) add **Vancomycin 1g IV BD**, unless the patient is over 65 years, when 1g OD should be used
  [See further information regarding dosing, renal impairment and monitoring – page 7]
- If allergy/contraindications to vancomycin, give teicoplanin 400mg IV every 12 hours for 3 doses, then 400mg IV daily until day 4. For dosing in renal impairment see antibiotic website.

- **Gentamicin** should be given to the following:
  - patients who are shocked (systolic BP <100)
  - patients who do not respond to Piperacillin/Tazobactam alone for 48 hours, or who deteriorate after initial assessment.
  - **Gentamicin IV 5mg/kg/day (max 500mg)** unless renal impairment where Crcl <40ml/min when the dose should be reduced. Give as a single dose in 100ml sodium chloride 0.9% intravenously over 30 minutes. Round the dose up or down to the nearest 40mg increment e.g. 320mg or 360mg.

  [See further information regarding dosing, renal impairment and monitoring – page 8]

****Penicillin Allergic Patients:**
Patients who are allergic to penicillins should receive:

- **Ciprofloxacin 400mg IV BD** (instead of Piperacillin/Tazobactam or **ciprofloxacin 750mg PO BD** if the patient is able to take oral medication.
  PLUS
- **Vancomycin 1g IV BD**, or 1g OD if over 65 years (whether or not a central line is in situ)
- Gentamicin if shocked - see above for dosing etc

If the patient has received quinolone prophylaxis, ciprofloxacin will not be appropriate – contact Microbiology for advice.

4. ASSESSMENT at 24-48 hours

The registrar or consultant should review the patient within 24 hours of admission (this also applies at weekends).

Check FBC and U & Es daily. Assess daily for signs of localised infection and bleeding. Repeat blood cultures if temperature spikes.

At 48 hours the protocol can be rationalised:
If any cultures show growth, add in the appropriate antibiotic, as advised by Microbiology.

If blood cultures are negative and Gram positive sepsis e.g. cellulitis, line infection is unlikely, vancomycin can be stopped (need to check with laboratory that the blood cultures are definitely negative).

Consider adding Gentamicin if patient is still pyrexial, and not already receiving this.

Take advice from Microbiology on second line antibiotics if cultures have shown no growth but the patient's condition has not improved on first line antibiotics and gentamicin.

5. WHEN TO STOP IV ANTIBIOTICS:

IV antibiotics can be stopped when the neutrophil count is >0.5 x 10^9/L and rising **AND** the patient is apyrexial for at least 24 hours.

In other patients who are apyrexial, if a source of infection has been identified, prescribe the appropriate oral antibiotic.

If no organisms have been isolated, and the patient is apyrexial, when the neutrophil count has recovered oral antibiotics are not usually necessary.

If the neutrophil count has not fully recovered but the patient is apyrexial and well oral antibiotics may be used:

- Ciprofloxacin 500mg BD PO – if high risk of pseudomonas or patient profoundly neutropenic
- Co-amoxiclav 625mg TDS PO – if low risk of pseudomonas and neutrophils recovering (Levofloxacin 500mg OD PO should be used in patients with a penicillin allergy)

Treatment duration should be for 7 days in total, taking into account duration of IV treatment.

If the patient is still pyrexial, contact Microbiology for advice - it may be appropriate to continue IV therapy with alternative antibiotics, or a suitable oral preparation may be recommended.

6. OTHER MEDICATION WHICH MAY BE REQUIRED IN NEUTROPENIC SEPSIS:

<u>Mouth ulceration</u>
If severe mouth ulceration, consider adding:
For fungal infections - Use fluconazole 100mg daily oral.
For herpes simplex infection - Use aciclovir 400mg 5 x daily oral (if IV necessary, see BNF for doses)

<u>Suspected abdominal sepsis</u>
Add in Metronidazole 500mg IV TDS if patient prescribed ciprofloxacin and vancomycin, metronidazole is not required if the patient is prescribed Piperacillin/Tazobactam
(If patient has diarrhoea, wait for microbiology results before starting metronidazole.)

<u>Rectal medication</u>
Neutropaenic patients should not be examined or receive medicines rectally, because of the risk of inducing bacteraemia through damage to the bowel wall. This includes the use of suppositories and enemas for constipation.

Haematological support

Sepsis can prolong chemotherapy-induced pancytopenia. Patients may require blood or platelet transfusions.

G-CSF is not shown to reduce the duration of fever or antibiotic use and is not routinely indicated for use in established febrile neutropenia, nor is it licensed for this indication. However, use may be appropriate for established neutropenic sepsis with **at least two factors predictive of poor clinical outcome,** such as neutrophil count less than 0.1 x 10^9/L with fever for more than 10 days, uncontrolled primary disease, pneumonia, hypotension, multi-organ dysfunction or invasive fungal infection. The benefit of GCSF in these situations has not been proven to affect survival, but does reduce hospital stay. Consult 'Guidelines for the use of G-CSF in the department of clinical oncology'.

VANCOMYCIN DOSING AND MONITORING

Serum monitoring of pre-dose levels is essential to ensure therapeutic levels are achieved without renal toxicity.

The normal dose is 1g BD infused over 2 hours.

If mild renal impairment or age >65 years, frequency reduced to 1g OD.

For moderate or severe renal impairment please see separate guidance "Antibiotic doses for adults with renal impairment" available on the antibiotic website at: http://nuhweb/antibiotics

Monitoring of vancomycin levels

- A **pre-dose** sample (gold top serum separator tubes (preferred) or red top tube sent to microbiology) should be taken **before** the **third** or **fourth** dose. Recommended pre-dose levels for deep seated infection – bone/joint/pneumonia/endocarditis are 10-15mg/L, with other infections levels of 5-15mg/L are acceptable.
- Give time of last dose and time sample taken, details of dose and latest creatinine on the sample request form (without which the result cannot be interpreted)
- The dose **can be given** after the pre-dose level is taken if the serum creatinine is stable with good urine output
- It is not necessary to do a post dose level
- Try and time the dose so it is convenient for levels
- Results will be available on the results reporting system on the day that the sample is received.

GENTAMICIN DOSING AND MONITORING

Baseline U&Es must be taken on admission and these results should then be used to calculate creatinine clearance using the Cockcroft-Gault equation (a calculator is available on the antibiotic website: http:nuhweb/antibiotics, please note that this is particularly important in the elderly where the CrCl may be reduced even where the creatinine is within normal limits).

If possible ensure prescribed at a time, which is most convenient for levels to be monitored- e.g. 10am

Many elderly patients have a Crcl below 50ml/min, which, because of reduced muscle mass, may not be indicated by a raised creatinine level. It is therefore especially prudent to calculate the Crcl as outlined below for this patient group**.**

Anuric and oliguric (<500ml/day) patients can be assumed to have a CrCl < 10ml/min (severe renal impairment)

ONCE DAILY GENTAMICIN DOSING IN ESTABLISHED RENAL IMPAIRMENT

Crcl 10-40ml/min	Crcl <10 (severe)
3mg/kg *(max 300mg)* Check levels 18-24 hours after first dose. Redose only when levels <1mg/L	**2 mg/kg *(max 200mg)*** Redose according to levels Close monitoring of blood levels recommended and dose adjustment as necessary

Monitoring of Gentamicin levels

- Take a trough level only (gold top serum separator tubes (preferred) or red top), 18-24 hours after the **first** dose (should be <1mg/ml).
- Give time of last dose and time taken, details of dose and latest creatinine on the sample request form (without which results cannot be interpreted).
- **For a result to be returned the same day, samples must be at path lab reception before 3.30pm on weekdays and before 10am on weekends.**
- In a patient **<65 years**, if the **serum creatinine is normal with good urine output give the second dose** without waiting for the result.
- In a patient **>65 years old** or with **abnormal renal function**, **await the result before giving a second dose** and obtain advice from the medical microbiologist if the pre dose is level is >1.0 mg/L
- When the first dose of gentamicin has been given in the evening/night, the level should be taken by 3.00pm the following day if this falls within the 18-hour window, and sent for analysis immediately. If this is not possible the doctor must decide whether the second dose of gentamicin is given before the level is known. As a general guide, for patients over 65 years or with impaired renal function, the level and dose may be delayed until the next morning

Renal function should be checked at least three times a week and levels should be checked twice weekly or as advised by microbiology during a treatment course.
If renal function deteriorates then renal function should be checked daily and levels closely monitored.
All patients who are prescribed more than a single dose of Gentamicin should have a fluid balance chart completed and urine output should be closely monitored.