Nottingham University Hospitals NHS
NHS Trust

Title of Guideline (must include the word "Guideline" (not protocol, policy, procedure etc)	**GUIDELINES FOR THE MANAGEMENT OF FEBRILE NEUTROPENIA IN ONCOLOGY PATIENTS**
Contact Name and Job Title (author)	Dr Vanessa Potter, Oncology Consultant Dr Stephen Holden Consultant Microbiologist
Division & Speciality	Cancer and associated specialties – Oncology & Radiotherapy
Date of submission	November 2015
Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis)	Adult and Teenage Oncology patients receiving cytotoxic chemotherapy under the care of an adult oncologist at City Campus, NUH.
Version	3
Changes from previous guideline	Updated flow chart to highlight to check for previous multi-resistant gram neg infection. Updated Teicoplanin dosing, highlighted prompt to consider *C.difficile* infection.
If this version supersedes another clinical guideline please be explicit about which guideline it replaces including version number	1538a
Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues? Evidence base: (1-5)	Local microbiological sensitivity surveillance Summary of product characteristics for individual medicines. Recommended best practice based on clinical experience of guideline developers. Manual for Cancer Services: Acute Oncology – Including metastatic spinal cord compression measures. Version 1. DH National Cancer Action Team. April 2011. Neutropenic Sepsis: prevention and management of neutropenic sepsis in cancer patients. NICE Guideline written September 2012.
Consultation Process	Oncology Directorate Members NUH Chemotherapy Strategy Group Members NUH antimicrobial guidelines committee
Target audience	All staff on oncology wards and SRU, chemotherapy clinic, the research team and pharmacy.
Ratified by:	NUH antibiotic guidelines committee
Review date:	January 2018

1	NICE Guidance, Royal College Guideline, SIGN
2a	meta analysis of randomised controlled trials
2b	at least one randomised controlled trial
3a	at least one well-designed controlled study without randomisation
3b	at least one other type of well-designed quasi-experimental study
4	well –designed non-experimental descriptive studies (ie comparative / correlation and case studies)
5	expert committee reports or opinions and / or clinical experiences of respected authorities
6	recommended best practise based on the clinical experience of the guideline developer

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.

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

Suspicion of Neutropenia defined as:
Chemotherapy within 4 weeks

Suspicion of Neutropenia and Fever

Fever defined as:
Temp >38.5°C on 1 occasion
or
Clinical signs of septicaemia
or
Temp >38.0°C on two occasions separated by 1 hour
or
Good history of fever detected by patient before admission

Temp 37-38°C repeat after 1 hour

Take Blood Cultures

Neutropenic sepsis can be fatal if not treated promptly, give antibiotics BEFORE blood results are obtained

Check Allergy Status, review previous microbiology for risk of multi-resistant gram negative infection and GIVE FIRST DOSE OF ANTIBIOTIC(S) IMMEDIATELY

Patient **NOT** allergic to penicillin:

- **Piperacillin/Tazobactam 4.5g IV TDS**
- **Plus** for patients who are known or previous MRSA positive: **IV vancomycin Plus a single dose of IV Gentamicin** if patient has severe sepsis or blood pressure fails to respond to initial fluid bolus. (Refer to antibiotic website for dosing)

Patient with **NON-SEVERE penicillin allergy (no anaphylaxis, angioedema or immediate onset urticaria) or on high dose methotrexate or risk of multi-resistant gram negative infection**

- **Meropenem 1g IV TDS**
- **Plus** for patients who are known or previous MRSA positive: **IV Vancomycin** (Refer to antibiotic website for dosing)

Patient with **SEVERE penicillin allergy**

- **If severe sepsis or unable to take orally: Ciprofloxacin 400mg IV BD**
- **Plus** for all patients: **IV Vancomycin** (Refer to antibiotic website for dosing)
- **Plus a single dose of IV Gentamicin** if patient has severe sepsis or blood pressure fails to respond to initial fluid bolus. (Refer to antibiotic website for dosing)

Please then contact Oncology SpR or Consultant on call to inform them of patient and for advice / further guidance

For further treatment, investigations and monitoring please see **Guidelines for the management of Febrile Neutropenia in Oncology Patients on the Clinical effectiveness intranet page or on the antibiotics website http://nuhnet/diagnostics_clinical_support/antibiotics**

March 2014, Review March 2016

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 THAT THE 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 allergies. You should also check for possible antibiotic allergies with the patient immediately prior to administration.
Subsequent management will depend on confirmation of neutropenia.

Definition of neutropenic sepsis in patients receiving anticancer treatment:
Neutrophils $\leq 1.0 \times 10^9$/L

Temperature >38.0°C on two occasions separated by one hour or
Temperature >38.5°C on one occasion
Or other signs or symptoms consistent with clinically significant sepsis.

If temperature 37-38°C repeat after one hour to see if the above criteria for treatment are met.
Note: 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- if recent antibiotic therapy consider *C. difficile* infection
UTI

Screening Investigations
FBC, U&Es, LFTs, lactate
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
MSU 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 viral throat swab or nasopharyngeal aspirate.
Sputum sample
Blood gases if indicated

3. TREATMENT

Initiate antibiotic treatment IMMEDIATELY with:

Piperacillin/Tazobactam 4.5g IV TDS (for penicillin allergic patients or patients receiving treatment with high-dose methotrexate see ** below).

If at risk of Multi resistant gram negative infection then give **Meropenem IV 1g TDS** (for severe penicillin allergic patients discuss with microbiology).

For patients who are known/previous MRSA positive add **Vancomycin IV.** Refer to antibiotic website for dosing or use vancomycin dosing calculator available on the antibiotic website and monitor levels.

If allergy/contraindications to vancomycin, substitute Teicoplanin 12 mg/kg IV every 12 hours for 3 doses, then refer to antibiotic website for maintenance dosing ONCE daily thereafter (dose reduction required in renal impairment – see antibiotic website).

NB There are reports of cross sensitivity between vancomycin and teicoplanin, those with a severe allergy to vancomycin should be discussed with microbiology. A history of "red man syndrome" (an infusion related reaction which occurs on rapid infusion, typically consisting of severe hypotension, wheezing dyspnoea, urticaria, pruritis, flushing of the upper body) is not a contraindication to using teicoplanin.

If the patient has severe sepsis or blood pressure fails to respond to initial fluid bolus, give a single dose of **Gentamicin IV 5mg/kg (max 500mg)**. Dose should be reduced in renal impairment, a gentamicin calculator is available on the antibiotic website.

****Severe Penicillin Allergy (anaphylaxis, angioedema, immediate onset urticaria):**

Ciprofloxacin 400mg IV BD if severe sepsis or unable to take **oral ciprofloxacin 750mg BD.** If the patient has received quinolone prophylaxis (ciprofloxacin or levofloxacin) discuss the patient with microbiology.

PLUS

IV Vancomycin. Refer to antibiotic website for dosing or use the vancomycin dosing calculator available on the antibiotic website and monitor levels.

If the patient has severe sepsis or blood pressure fails to respond to initial fluid bolus, give a single dose of **Gentamicin IV 5mg/kg (max 500mg)**. Dose should be reduced in renal impairment, a gentamicin calculator is available on the antibiotic website.

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.

If on review the patient is NOT neutropenic, review whether an infective cause is likely. If a probable focus of infection is identified treat as per the relevant NUH guideline. If there is no identifiable focus and the patient is not severely septic then consider stopping antibiotics.

At 48 hours the protocol can be rationalised:

If blood cultures are positive, a medical microbiologist will telephone with the result and offer management advice. Other microbiology results should also be reviewed (e.g. any urine, respiratory or swab samples)

If at 48 hours, cultures have shown no growth but the patient's condition has not improved on first line antibiotics, try to determine a likely source or another cause of fever e.g. underlying disease. Discuss with a specialist oncology registrar or consultant who may wish to seek further advice from microbiology. The empiric antimicrobial regime should not usually be changed in patients with unresponsive fever unless there is clinical deterioration or a microbiological indication.

If there is no response to treatment beyond 48-72 hours:

These cases should be discussed with an experienced oncology specialist trainee or a consultant before contacting microbiology for further advice. Non-response to treatment may be due to a number of factors including:

- Non-infective cause for pyrexia deterioration e.g. underlying disease, reaction to medication.
- Multi-resistant bacteria: Review previous microbiology results, assess risk factors for multi-resistant organisms (see above) and discuss with microbiology where appropriate.
- Ongoing focus requiring attention e.g. line infection requiring line removal.
- Invasive fungal infection (IFI): This is rare in patients receiving chemotherapy for solid organ malignancy but is more likely in those with prolonged neutropenia (>10 days), prolonged high-dose corticosteroid therapy (> 3weeks) and use of certain other T-cell immunosuppressants e.g. ciclosporin. **Discuss with seniors +/- a medical microbiologist if anti-fungal treatment is being considered**
- Other atypical infections: These may include agents of atypical pneumonia e.g. *Legionella* spp. *Pneumocystis* pneumonia (PCP), disseminated viral infections and other less common problems.

5. WHEN TO SWITCH FROM IV TO ORAL ANTIBIOTICS

Review the need for any ongoing antibiotic therapy

Switch from intravenous to oral antibiotic therapy after 48 hours of treatment in patients whose risk of developing septic complications is considered low. (As assessed by an oncology registrar or consultant using one of the below validated risk scoring systems)

Examples of risk scoring systems include The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients (Journal of Clinical Oncology 2000; 18: 3038–51]) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

If a source of infection has been identified in these patients, prescribe the appropriate oral antibiotic (consult microbiology if in doubt).

If the source of infection has NOT been identified the following oral antibiotics can be considered:

- **Ciprofloxacin 500mg PO BD** – if high risk of pseudomonas or patient profoundly neutropenic
- **Co-amoxiclav 625mg PO TDS** – if low risk of pseudomonas and neutrophils recovering (**Levofloxacin 500mg PO OD** should be used in patients with a penicillin allergy)
- If known *C.difficile* carriage (PCR positive) review the need for continuing antibiotics

The quinolones (levofloxacin and ciprofloxacin) can increase selection for *C.difficile* infection and MRSA colonisation/infection. Therefore for all patients with previous MRSA/*C.difficile,* microbiology approval must be sought to approve quinolone use.

6. REVIEW THE NEED FOR ANTIBIOTICS

Empiric antibiotic therapy should be continued in all patients who have unresponsive fever unless an alternative cause of fever is likely.

Discontinue antibiotic therapy in patients whose neutropenic sepsis has responded to treatment, irrespective of neutrophil count. Evidence of response to treatment may include:

- Ayprexial for >24 hours
- Stable haemodynamic parameters
- No clinical evidence of an ongoing focus of infection
- Negative blood cultures after therapy

7. OTHER MEDICATION WHICH MAY BE REQUIRED IN NEUTROPENIC SEPSIS

<u>Respiratory tract infections</u>
Patients in whom the likely source of sepsis is the lower respiratory tract (LRTI) may be infected with an atypical respiratory pathogen not covered by the standard treatment.

Unless a quinolone (e.g. ciprofloxacin or levofloxacin) is being given, clarithromycin should be added to the antibiotic regime for patients with evidence of LRTI.

Mouth ulceration

If severe mouth ulceration, consider adding:

For oral candidiasis: Fluconazole PO 100mg daily.

For simple mucocutaneous herpes simplex infection: Aciclovir PO 400mg 5 x daily.

Suspected abdominal sepsis

Add in **Metronidazole 500mg IV TDS** if patient prescribed ciprofloxacin and vancomycin, metronidazole is not required if the patient is prescribed Piperacillin/Tazobactam or meropenem. If suspect *C. difficile* infection, send a stool sample and treat patient as per the *C. difficile* treatment guidelines.

Rectal medication

Neutropenic 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’.

Equality Impact Assessment Report

1. Name of Policy or Service
Response to external best practice policy

2. Responsible Manager
Annette Clarkson (Acting Lead pharmacist antimicrobials and infection control)

3. Name of person Completing EIA
Annette Clarkson

4. Date EIA Completed
09/11/2015

5. Description and Aims of Policy/Service

The guideline has been written to detail how to manage adult oncology patients admitted where a diagnosis of neutropenic sepsis is suspected.

6. Brief Summary of Research and Relevant Data
There is no research or relevant data at the present time.

7. Methods and Outcome of Consultation
Consultations have been carried out with the following:

Oncology directorate meeting
Antibiotic guidelines committee

Comments from the above consultations have been received and incorporated where appropriate.

8. Results of Initial Screening or Full Equality Impact Assessment:

Equality Group	Assessment of Impact
Age	No Impact Identified
Gender	No Impact Identified
Race	No Impact Identified
Sexual Orientation	No Impact Identified
Religion or belief	No Impact Identified
Disability	No Impact Identified
Dignity and Human Rights	No Impact Identified
Working Patterns	No Impact Identified
Social Deprivation	No Impact Identified

9. Decisions and/or Recommendations (including supporting rationale)

From the information contained in the procedure, and following the initial screening, it is my decision that a full assessment is not required at the present time.

10. Equality Action Plan (if required)

N/A

11. Monitoring and Review Arrangements

Review January 2018