



**Hull and East Yorkshire Hospital NHS Trust  
Queen's centre for Oncology and Haematology  
Castle Hill Hospital**

**GUIDELINES FOR THE  
PREVENTION AND  
MANAGEMENT OF  
INFECTION IN ADULT  
NEUTROPENIC  
PATIENTS**

**2018**

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# **GUIDELINES FOR THE PREVENTION AND MANAGEMENT OF INFECTION IN ADULT NEUTROPENIC PATIENTS**

## **1 INTRODUCTION**

Most infectious processes in the patient with neutropenia evolve with minimal clinical expression. Hence, the probability of infection should be considered when an otherwise unexplained change in the patient's clinical status takes place. Infection in a neutropenic patient can progress rapidly and is a life-threatening event. Prompt management of the patient is therefore critical. The prophylactic use of antimicrobial agents to reduce the risk of septic complications is recommended for patients at the highest risk.

## **2 PURPOSE**

This guideline has been written in order to comply with the NICE guidance, CG 151 on the prevention and management of neutropenic sepsis in cancer patients.

## **3 SCOPE**

This protocol is specifically aimed at haematology and oncology patients who became neutropenic following cancer chemotherapy. However, it may be applicable for other haematology patients and also non-haematology/oncology patients who develop neutropenia for other reasons. Where possible such patients should be discussed with a consultant haematologist. Antibiotic management should be discussed with a Microbiologist or the Infection Consultant on call if out of hours when the neutropenic regime is being considered for non haematology/oncology patients.

## **4 DUTIES**

All healthcare practitioners (nurses, doctors and pharmacists) within the Trust involved in the process of managing neutropenic patients should be familiar with and adhere to these guidelines.

## **5 CONTENT**

### **Severity of Neutropenia**

Moderate	0.5 – 1.0 x 10 <sup>9</sup> /l
Severe	Less than 0.5 x 10 <sup>9</sup> /l
Do not act on total WBC – always use the absolute neutrophil count	

In general the risk of infection increases with the severity and duration of neutropenia.

### **Signs of Infection in Neutropenic Patients**

Any one of:

Pyrexia > 38<sup>0</sup>C on a single reading

Pyrexia > 37.5<sup>0</sup>C on two readings over 1-2 hours

Rigor or other signs of fever (cold, sweating, shivering)

Any signs of infection (sore throat, cough, urinary symptoms, skin lesions, diarrhoea)

Unexplained abdominal pain

Unexplained hypotension

Unexplained tachycardia

Any unexplained clinical deterioration, even in the absence of fever

Please note that focal signs of infection may be present or absent

### **Assessment and Investigation**

Patients must be admitted immediately and urgently assessed (history and examination) by clinical staff with experience of handling neutropenic patients.

They should assess the patient's risk of septic complications, basing the risk assessment on presentation features and using a validated risk scoring system, Multinational Association of Supportive Care in Cancer (MASCC).

The oncology or haematology team responsible for the patient should be made aware as soon as possible that the patient has been admitted for suspected neutropenia.

Any patient suspected of being neutropenic should be considered to be severely neutropenic until blood count is known. Antibiotic treatment (see Treatment of Neutropenic Patients) should be started as soon as possible, aiming for a **door-to-needle time of less than one hour**. Waiting for results before initiating antibiotics could result in rapid deterioration in the patient's condition.

Initial and ongoing clinical assessment should include

- Temperature
- Pulse
- Blood pressure
- Respiration rate
- Oxygen saturation
- Fluid balance (input and output charting)

Initial Investigations

- Full blood count
- Biochemical profile
- C-reactive protein
- Peripheral blood cultures (irrespective of temperature)
- Blood cultures from venous access device including each lumen if applicable
- Lactate (if signs of ongoing clinical deterioration)

Further Investigations

- Chest X-ray if there are respiratory symptoms
- Sputum specimen if productive with request for atypical pneumonia screen
- Urinalysis and urine sample for culture
- Bacterial and viral pharyngeal swabs
- Swabs from potential sites of infection (ears, nose, skin lesion, venous access device exit site)
- Stool sample for culture and *Clostridium difficile* testing if diarrhoea is present

Venous access devices must be assessed for signs of infection as the use of these devices increase the risk of infection.

Features that may suggest infection:

- Inflamed exit site/tunnel
- Pyrexia/rigors post flushing
- Previous history of line infection
- Other soft tissue infection

Things to avoid

- Urinary catheterisation should not be performed (unless clinically indicated)
- Vaginal or rectal examinations and suppositories and enemas are contraindicated in neutropenic patients.
- Venous access devices must not be removed without discussion with the treating consultant.

### **Treatment of Neutropenic Patients**

Intravenous fluids, antibiotic therapy and all prescribed medical treatment must be commenced immediately without waiting for results from investigations, aiming for a **door-to-needle time of less than one hour**. Diuretics and anti-hypertensive medications should be reviewed during this episode.

Check the patient's records (notes and electronic annotations) for alerts such as previous infection with *Clostridium difficile* or multidrug resistant organisms.

The antibiotic guidance below is recommended for initial management of neutropenic patients.

### **Human Granulocyte Stimulating Factors (GCSF) for the treatment of neutropenic sepsis**

GCSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, GCSF should be considered in patients with febrile neutropenia who are at high risk of infection-associated complications or who have prognostic factors that are predictive of poor clinical outcomes.

High risk features include expected prolonged (more than 10 days) and profound neutropenia (less than  $0.1 \times 10^9/L$ ), age more than 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection or hospitalization at the time of fever development.

***GCSF should only be used following discussion with a consultant haematologist or oncologist.***

Indication	Suggested antibiotic	Information
First-line	Piperacillin/Tazobactam IV 4.5g 8 hourly	Dose reduction in moderate to severe renal impairment (12 hourly if creatinine clearance < 20ml/min)
If penicillin allergic	Teicoplanin IV (see Information for dosing) and Aztreonam 2g IV 8 hourly	Teicoplanin: 6mg/kg IV 12 hourly for 3 doses then 24 hourly. Therapeutic drug monitoring is only required if the treatment length will be more than 2 weeks; See trust Guidelines on the Prescribing of Glycopeptides Antibiotics in Adults for more detailed information: <a href="http://intranet/antibiotic/heyhguidelines.asp">http://intranet/antibiotic/heyhguidelines.asp</a> .
If known to be colonised by extended spectrum B-lactamase producing organisms (ESBLs) or Piperacillin/Tazobactam resistant organisms	Meropenem 1g IV 8 hourly	Routine addition of aminoglycosides has been found to be associated with increased adverse events and of no significant benefit.
If known or considered to be at risk of colonisation with Carbapenemase producing gram negative bacteria (CPE)	<b>Please discuss with a Consultant Microbiologist or the Infection Consultant on call out of hours</b>	

<p>Consider additional antibiotics if:</p> <p>Patient with severe sepsis or rapidly deteriorating or known to be colonised by resistant Gram negative organisms</p> <p>Patient has evident bowel signs/symptoms, pelvic/gynaecological disease or sinus disease</p> <p>Patient known to be colonised by or has a past history of infection with MRSA or penicillin resistant pneumococci</p> <p>Clear evidence of intravascular catheter associated sepsis</p> <p>Patient has signs or symptoms of lower respiratory tract infection</p>	<p>Gentamicin 5mg/kg IV once daily</p> <p>Metronidazole 500mg IV 8 hourly</p> <p>Teicoplanin IV (see Information above for dosing)</p> <p>Teicoplanin IV (see Information above for dosing)</p> <p>Clarithromycin 500mg oral 12 hourly</p>	<p>Should be avoided in patients with renal impairment.</p> <p>Dose frequency should be adjusted according to drug serum levels measured within 6-14 hours after the first dose (Using the Nomogram Chart). See trust Guidelines on the Prescribing of Aminoglycoside Antibiotics in Adults for more detailed information:  <a href="http://intranet/antibiotic/heyhguidelines.asp">http://intranet/antibiotic/heyhguidelines.asp</a>.</p> <p>Macrolide antibiotics can inhibit hepatic metabolism of other drugs – this can be a particular problem with those drugs with a narrow therapeutic index, e.g. warfarin, theophylline, cyclosporin etc. Dose adjustment and careful monitoring may be necessary.</p> <p>Dose adjustment needed in those with moderate to severe renal impairment.</p>
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**Antibiotic therapy should always be critically reviewed after 48 hours.**

Usually the antibiotic regimen is not altered for 48 hours irrespective of the patient's temperature, unless the clinical state of the patient is deteriorating.

If screening cultures produce positive results or there is clinical suspicion of a particular organism then the antibiotic regimen should be adjusted.

**Ongoing Assessment of Patient**

Medical / nursing staff should maintain a high level of surveillance for infection, watching closely for any signs and symptoms. Many patients with profound neutropenia do not have localising signs of infection, however, as neutrophils return these symptoms/signs may develop, prompt administration of prescribed intravenous fluids and antibiotics is essential.

1. Nursing staff must ensure TPR and BP are recorded every hour for 4 hours then if stable every 4 hours around the clock.

**Septic Shock May Occur Rapidly**

Inform on-call doctor immediately if patient shows any signs of going into shock. Accept continuing pyrexia only if the patients condition is stable and satisfactory.

2. A strict record of fluid intake and output must be maintained. Urine output must be totalled every 4 hours and if less than 200mls, reported to the medical staff.

3. To prevent renal failure the doctor on call must be alerted to any deterioration immediately, the situation needs to be remedied with aggressive intravenous fluid replacement and inotropic agents if there is not an adequate response to fluid therapy after discussion with the on-call haematologist or oncologist.

4. Transfers to Intensive Care Unit may be necessary following consultation with treating Consultant and ICU Consultant.

5. Patients with neutropenic sepsis can occasionally appear to have an acute abdomen and the surgical team should only be involved after discussion with the treating consultant.

6. Monitor full blood count and biochemical profile daily. Depending on the chemotherapy regime coagulation screening may also be required.

See Appendix 1 for additional assessments.

**Duration of Antibiotic Therapy in Patients Responding to Treatment**

Antibiotics should be continued until afebrile for 48 hours. If there is a focus of infection identified the duration of antibiotic therapy is guided by the resolution of signs and symptoms.

- If blood cultures negative and no focus of infection complete 5 days of therapy
- If blood cultures positive continue antibiotics for 7 days UNLESS deep seated focus of infection suspected/found e.g. endocarditis or a specific organism is isolated which requires a longer duration of treatment.
- *Staphylococcus aureus* bacteraemia requires a minimum of 2 weeks IV therapy



- If deep seated infection suspected/found please discuss ongoing management with a Microbiologist or Infection Team Consultant on call if advice required out of hours.

### **Management of Patients Failing to Respond to Treatment**

Antibiotics should be reviewed if there is no clinical response after 48 hours. The review of a patient's treatment should take into account any microbiology results and sensitivities and should consider the risk of catheter infection and atypical organisms including fungi.

The current second line antibiotic regimen is:  
Meropenem 1g intravenous 8 hourly

If fevers persist for more than 96 hours, refractory to broad spectrum antibacterial treatment, antifungal treatment should be started and appropriate imaging (high resolution chest CT +/- CT sinuses if upper respiratory tract symptoms) done.

See trust Guideline on Management of Systematic Fungal Infection in Immunocompromised Patients on the intranet site:  
<http://intranet/antibiotic/heyhguidelines.asp>.

### **Discharge of Patients**

Patients should not be discharged without agreement of supervising oncologist or haematologist. Patients should not be discharged before completing their duration of antibiotics (as advised above).

Medical Staff should decide when clinical signs indicate the patient is no longer at risk from neutropenic sepsis i.e. the neutrophil count is  $0.5 - 1.0 \times 10^9/l$ , intravenous antibiotic regimens are completed and the patient has been afebrile for >24 hours.

### **Management of Low Risk Neutropenic Sepsis**

Although febrile neutropenia is a potentially life threatening complication of systemic anti-cancer therapy a proportion of patients are at a lower risk for significant medical complications. These patients have the potential to be de-escalated from intravenous to oral therapy and then discharged early.

### **Identifying low risk neutropenic patients**

A number of different scoring systems have been developed and validated to identify neutropenic septic patients with a low risk of complications. Of the scoring systems currently in use the Multinational Association of Supportive Care in Cancer (MASCC) is the most widely validated and accepted system with a sensitivity (at a MASCC score < 21) for the prediction of serious medical complications ranging between 40% and 80% and a specificity ranging between 59% and 95% (Klastersky et al, 2000).

The MASCC score should be calculated for all neutropenic patients using the characteristics shown in the table below. The maximum theoretical score is 26 as only one weighting for 'Burden of Illness' may be included.

In keeping with the NICE guideline (CG151 Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients) and acute oncology best practice all patients should be assessed within 24 hours by consultant medical staff. Any patient with a MASCC score  $\geq 21$  should be considered for oral antibiotics and outpatient management after confirmation of ALL of the following features:

- (1) Patient does not live alone
- (2) Carer (or caregiver) available 24 hours a day

- (3) Lives less than 30 minutes distance from hospital
- (4) Able to take oral antibiotics
- (5) Able to call bleep 500 if needed
- (6) Agree to take over own care at home

		Yes	No	Score
Does the patient have a solid tumour or lymphoma (except Burkitts)?		4	0	
Is the patient dehydrated or requiring IV fluids?		0	3	
Is the systolic BP <90 mmHg?		0	5	
How sick is the patient now? (select one)	No or mild symptoms (events barely noticeable, not interfering with performance or functioning)	5	0	
	Moderate symptoms (patient uncomfortable or events influence performance of daily activities)	3	0	
	Severe symptoms (severe discomfort and/or performance of daily activities limited)	0	0	
Is the patient <60 years old		2	0	
Does the patient have COPD?		0	4	
Did the patient develop febrile neutropenia while an inpatient?		0	3	
Total MASCC score:				

Score  $\geq$  21 = low risk: assess whether patient can be managed as outpatient with oral abx  
 Score < 21 = high risk: treat as inpatient with iv antibiotics

### Antibiotic selection

Patients with no recorded penicillin allergies should be treated with Ciprofloxacin 750mg oral 12 hourly and Co-amoxiclav 625mg oral 8 hourly.

Patients with a recorded penicillin allergy should receive Ciprofloxacin 500mg oral 12 hourly and Clindamycin 450mg oral 6 hourly.

Patients taking prophylactic Ciprofloxacin following NICE guidance CG151 should NOT be treated using this policy without discussion with a consultant microbiologist.

### Prophylaxis

In an effort to reduce the risk of septic complications of anticancer treatment current NICE guidance (CG 151) recommends the use of prophylaxis with a fluoroquinolone during the expected period of neutropenia in **patients with acute leukaemias, stem cell transplants or solid tumours in whom significant neutropenia (neutrophil count  $\leq 0.5 \times 10^9/L$ ) is anticipated.**

In this patient population it is anticipated that the neutropenic period following chemotherapy would be at least 2 weeks in duration. It is advised that the patient should commence Ciprofloxacin 500mg oral 12 hourly as prophylaxis and continue this therapy as long as the neutrophil count is  $\leq 0.5 \times 10^9/L$ .

This recommendation should include patients receiving active treatment ONLY and not those patients being managed with best supportive care.

***In the event of persistent diarrhoea this therapy should be reviewed.***

### **GCSF for Primary Prophylaxis**

Primary prophylaxis with GCSF could be considered in patients with solid tumours with the first cycle of chemotherapy and continued through subsequent cycles of chemotherapy. Its use is advised in patients being treated with curative intent who have an approximately 20% or higher risk for febrile neutropenia and have one or more of the following factors:

- (1) Bone marrow involvement by the tumour
- (2) Recent surgery and/or open wound
- (3) Liver dysfunction [bilirubin > 34 micromoles per litre]
- (4) Renal dysfunction [creatinine clearance less than 50]
- (5) Age more than 65 years receiving full chemotherapy dose intensity
- (6) Prior chemotherapy or radiation therapy

***Patients with breast cancer receiving FEC-T chemotherapy in neoadjuvant or adjuvant settings should receive primary prophylaxis with G-CSF for all the planned 6 cycles (starting from the first cycle).***

## **6 PROCESS FOR MONITORING COMPLIANCE**

The effectiveness of the policy will be audited by:

- Medical team who will undertake regular monitoring of the door-to-needle time for assessment and initiation of appropriate antibiotic therapy in patients at risk of neutropenic sepsis.
- Ongoing surveillance which will be undertaken by the Infection Prevention and Control Team in order to monitor infection patterns and rates of antibiotic (Ciprofloxacin) resistance with the introduction of Ciprofloxacin prophylaxis.

## **7 REFERENCES**

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- Adult antibiotic formulary:<http://intranet/guidelines/guidelines/259.pdf>
- Guidelines on the Prescribing of Glycopeptides Antibiotics in Adults for more detailed information: <http://intranet/antibiotic/heyhguidelines.asp>.
- Guidelines on the Prescribing of Aminoglycoside Antibiotics in Adults for more detailed information: <http://intranet/antibiotic/heyhguidelines.asp>
- Guideline on Management of Systematic Fungal Infection in Immunocompromised Patients on the intranet site: <http://intranet/antibiotic/heyhguidelines.asp>
- Infection control policies <http://intranet/infectioncontrol/policies.asp>
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## 8 APPENDICES

- Appendix 1 - Additional Assessments
- Appendix 2 – General Guidelines for In-Patient Care

**Additional Assessments**

Site	Information
Intravenous site	Assess daily for infection
Mouth and throat	Use a recognised oral assessment guide
Skin	Assess daily for breakdown, lesions and rashes. Assess wounds for infection.
Central nervous system	Monitor for changes in behaviour, headache, level of consciousness and orientation.
Genito-urinary function	Frequency, dysuria, haematuria Assess female patients for vaginal candidiasis if symptomatic. Patients should avoid the use of tampons.
Peri-anal region	Assess for infection if symptomatic

### General Guidelines for In-Patient Care

1. Patients will be cared for in an environment that minimises the risk of infection from other patients, hospital staff and visitors, preferably in a single en-suite room
2. Protected isolation must be clearly indicated by appropriate signage and protective isolation measures taken in accordance with Infection Control Policy.
3. Educate patient and relatives about the need to restrict visitors who have transmissible illnesses e.g. bacterial infections, herpes, colds, influenza, chickenpox, shingles or measles. Patients must also avoid contact with people who have been recently vaccinated with live or attenuated virus vaccines because of the risk of disseminated disease.
4. Careful hand washing is the single most important action for the health professional, patient, the patient's family and visitors, in preventing cross infection. (Johnson et al 2000)
5. Fresh flower, plants should not be placed in the patients room as pathogens could flourish in stagnant water. Denture mugs and soap dishes should also be removed. (Otto 1997)
6. Food may be a source of infection and dietary restrictions may be necessary (Johnson et al 2000). Offer advice about choice of food available. Offer cooked foods only avoiding unprepared fresh fruit, raw vegetable, raw eggs and garnishes. Relatives must be informed of food restrictions when bringing food into the ward.
7. Sterile water or filtered tap water is recommended for immunocompromised patients. Ice making equipment could also be a source of infection therefore ice should not be offered. (Dept. of Environment 1998).
8. Face cloths should be avoided and disposable wipes should be provided.
9. Sanitary towels should be used instead of tampons.
10. Patients must be encouraged to wash/shower twice daily (if the shower is used, it must be cleaned and disinfected before and after use).
11. Washbowls must be cleaned with hot and soapy water and dried thoroughly.
12. Patients may travel to x-ray etc in a wheelchair but the department need to be informed to minimise waiting and avoid patient contact.
13. The rooms should be cleaned daily and all surfaces damp dusted.
14. See infection control policies (<http://intranet/infectioncontrol/policies.asp>) aimed at ensuring a higher standard of cleaning in areas where neutropenic patients are being managed.