

**Guidelines for the Management of
Neutropenic Sepsis**

Based on an original document prepared by:

**Moira Taylor, Consultant Microbiologist
Stepping Hill Hospital**

**Ken Mutton, Consultant Virologist
Christie Hospital & MRI**

**Edward Kaczmarski, Consultant Microbiologist
Christie Hospital & MRI**

**Revised by David Kaye Pharmacist Christie Hospital
Edward Kaczmarski
Ken Mutton
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Management of Febrile Neutropenic Patients

For patients under the care of Christie Hospital consultants (non-surgical oncology), all infective episodes need to be taken extremely seriously and treated urgently with antibiotics.

The patient may have been issued with an information card which will detail information about their chemotherapy regimen and the recommended antimicrobial regimen.

In the first instance the Christie Hospital advice line should be contacted on 0161-446-3658 for either advice (on how to manage the patient locally) or referral back to the centre. Failing this, contact the Christie/local microbiologist.

1.0 Introduction

Fifty to 60% of febrile neutropenic patients prove to have infections and 16-20% of those with a neutrophil count $<100/\text{mm}^3$ have a bacteraemia. Fever is commonly as a result of bacteraemia and usually due to Gram positive cocci (eg coagulase negative staphylococci, *Staphylococcus aureus*, viridans streptococci) or Gram negative bacilli (eg *Escherichia coli*, *Klebsiella spp*, *Pseudomonas aeruginosa* etc). Fungal infections tend to occur after patients have received broad-spectrum antibiotics and have had prolonged periods of neutropenia but may occur as primary infections.

Infections in neutropenic patients typically take 2-7 days to respond to antimicrobial therapy. Acute respiratory viral infections eg influenza or respiratory syncytial virus may be associated with severe illness in the immunocompromised host.

2.0 Definitions

2.1 Definition of fever:

- an oral or tympanic membrane temperature of 38°C or more maintained for one hour, or 38.3°C on one occasion

Fever may not be present in some infected neutropenic patients who are dehydrated, taking steroids or NSAIDs and the possibility of infection must be considered in any neutropenic patient who is unwell. Fever may also be a complication of transfusion, some drugs e.g cytarabine, and malignant disease e.g lymphoma, renal carcinoma.

2.2 Definition of neutropenia

Increased susceptibility to infection is likely when the neutrophil count falls below $1000/\text{mm}^3$ with escalating risk at $<500/\text{mm}^3$ and at $<100/\text{mm}^3$.

The risk of infection is greater the faster the rate of decline of the neutrophil count and the longer the duration of neutropenia especially if neutropenia lasts for > 10 days.

3.0 Clinical assessment of the neutropenic patient

Carry out a full history and examination **within one hour of presentation** ie assess as an emergency.

3.1 **History and examination**

Expected onset and anticipated duration of neutropenia may be estimated by establishing day of neutropenia in relationship to first day of the current cycle of chemotherapy.

It is useful to enquire whether:

- blood products have been administered within the previous 6-24 hours as this may account for a febrile episode.
- rigors are associated with use or flushing of a central venous line.

Patients with the following features should be assessed and treated with **utmost urgency**-

Shock, acute respiratory distress, DIC, multiple organ failure.

Sepsis is a systemic inflammatory response syndrome (SIRS) triggered by an infection. SIRS is defined as two or more of the following:

- Temperature >38 deg C or <36 deg C
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute or PaCO₂ <32mmHg and

Resuscitation guidelines are available at www.survivingsepsis.org

The resuscitation of a patient in severe sepsis or sepsis-induced hypoperfusion (hypotension or lactic acidosis) should begin as soon as the syndrome is recognised. Do not delay pending ICU admission.

Severe sepsis = sepsis with at least one organ failure or dysfunction.

Septic shock = severe sepsis with hypotension unresponsive to fluid resuscitation.

It is important to enquire and look for inflammation/infection at the following sites and sample as appropriate :-

- Mouth – teeth, gums, pharynx
- ENT problems esp involving sinuses
- Eyes including fundi
- Upper gastrointestinal symptoms
- Lung – cough, shortness of breath, sputum
- Perineum especially anal area (defer PR examination until antibiotics started)
- Diarrhoea – if present isolation precautions may be advisable – discuss with a member of the infection control team
- Skin lesions – (NB think about fungal, Pseudomonas, generalized herpes and varicella zoster infections)
- Look for genito-urinary infections or discharges. Consider the possibility of reactivation of genital herpes, fungal infection and necrotising fasciitis.
- Look at: vascular access sites especially central venous line insertion sites: bone marrow aspiration sites: nail margins: skin tunnels :surgical incision sites etc.

A full systems review should include a thorough history of overseas residence and travel, pets, hobbies, occupation, sexual history and potential environmental exposures to unusual organisms. Important overseas related organisms might include strongyloides and *Trypanosoma cruzi* (the agent of Chagas disease)

3.2 Investigations

- Full Blood Count (FBC)
- CRP (if routinely available as an urgent investigation)
- Urea and Electrolytes (U+Es)
- Liver Function Tests
- Coagulation screen
- Group and save
- Blood gases if hypoxic
- ECG if hypotensive
- Chest radiography
- Cultures of lesions - including culture for fungi –Biopsy specimens for fungal). or bacterial investigations MUST NOT be sent in formalin. Histology should also be considered (send in formalin or other fixative as after discussion with Pathology)
- Stool microscopy, culture and *C. difficile* toxin detection, cryptosporidium if diarrhoea - also consider whether virology would be useful- send faeces in clean plain container for electron microscopy. For gastroenteritis send samples for EM and PCR.
- Urinalysis and culture - if urinary symptoms present or patient catheterised
- Blood cultures - peripheral and also through iv catheter lumens (should consider taking blood through each lumen of line)
- Mycobacterial blood culture should be sent in special MBBact bottles if required.
- Respiratory secretions for rapid testing for viral antigens by immunofluorescence and/or PCR, e.g. nasal wash, NPA, BAL. Direct viral detection by PCR is the preferred method for diagnosing respiratory viral infections and can be done using NPA,BAL or if not available by throat swab.
- A clotted blood sample (7-10ml, plain tube) should be sent for viral serology and a convalescent sample sent 10-14 days later if appropriate)
- If varicella zoster or herpes simplex is being considered,
- Send a glass slide touched against an opened lesion and allowed to air dry, and transported in a slide carrier
- swabs for virus culture and PCR
- send serum (clotted blood) for IgG and IgM.

Also in VZ - remember infection control precautions are needed to protect both staff and other patients – discuss with a member of the infection control team.

- Patients who are not getting better or are at high risk of a fungal infection should be discussed with the radiologists regarding appropriateness of additional imaging

e.g. ultrasonography, CT (especially useful for diagnosis of pulmonary aspergillosis), MRI, radionuclide imaging.

If invasive fungal infection is being considered,

- Send EDTA blood for Aspergillus and Candida PCR
- Aspergillus galactomannan assay is particularly useful on clotted blood and CSF
- Culture and PCR on sputum, BAL and other material e.g. CSF, skin biopsy.

- If CMV is being considered e.g. after bone marrow transplantation:
 - Send EDTA blood-for CMV PCR.
 - Consider CMV PCR on BAL and GI biopsy

If Pneumocystis pneumonia is being considered:

Send bronchial washings (or if these are unobtainable sputum, or EDTA blood) for *Pneumocystis jirovecii* (PCP) PCR

- Bronchial washings should be routinely microscopically examined and cultured for bacteria, fungi, and mycobacteria.

3.3 Follow up assessment

- FBC daily
- U + Es, LFTs and coagulation at regular intervals depending on clinical features
- Serial CRPs or other acute phase reactants
- If fever persists, repeat blood cultures based on clinical assessment
- Repeat chest radiology as clinically indicated

4.0 Initial treatment

4.1 Who to treat

- All febrile patients with neutrophil counts $<500/\text{cm}^3$ and those whose counts are $<1000/\text{cm}^3$ but are falling rapidly.
- Afebrile patients with neutrophil counts $<500/\text{cm}^3$ should also be treated if they have symptoms compatible with infection.

4.2 Definitions of High and Low Risk Patients with Neutropenia

4.2.1 High risk patients

- 1) Those who are already inpatients when fever and neutropenia develop
- 2) Outpatients who need acute hospital care for problems in addition to the fever and neutropenia
- 3) Outpatients with uncontrolled cancer (e.g. acute leukaemia not in remission, those with tumours progressing during anticancer therapy)
- 4) Patients on immunosuppressive agents e.g. cyclosporin A, steroids
- 5) Patients with specific foci of infection e.g. intravascular catheter infection, tunnel infection, new pulmonary infiltrate
- 6) Presence of any of the following features abdominal pain, nausea and vomiting, diarrhoea
neurological or mental changes
allogeneic BMTs or autologous BMT
pregnancy
HIV
recent treatment with antibiotics (within previous 72 hours)
renal failure (creatinine clearance $<30\text{ml}/\text{min}$)
hepatic failure
respiratory insufficiency
haemodynamic instability
inability to take oral medications
- 7) Neutropenia likely to last for more than 10 days
- 8) Recent fludarabine treatment
- 9) Phase I or II clinical trial patients (inform investigator)

4.2.2 Low risk patients

All those not in the above categories

If in doubt, treat as high risk patient

4.3 Empirical treatment of high risk patients - suitable iv antibiotic regimens

NB. All antimicrobial doses are approximate and may need to be altered according to patient's clinical condition, weight and renal function etc.

Monotherapy

There is a growing body of evidence suggesting in patients with solid tumours monotherapy with a carbapenem is as effective as duotherapy and has a better safety profile.

It is especially useful if renal impairment is present or in patients receiving nephrotoxic drugs.

Monotherapy should NOT be used in patients showing evidence of septic shock or if a Pseudomonas infection is likely

- **Meropenem monotherapy**

Meropenem 1gm tds is the preferred carbapenem.

In patients with renal impairment (creatinine clearance less than 50 ml/min) dose adjustment is required (see SPC).

Duotherapy

- Antipseudomonal penicillin (eg Tazocin 4.5g tds - qds) **plus** gentamicin*

OR

- Meropenem **plus** gentamicin*

In the event of specific concern about methicillin resistant or coagulase-negative staphylococcal sepsis, vancomycin can be given pending susceptibility testing results.

*Gentamicin (3-5mg/kg) may be given as a single daily dose depending on clinical condition and renal function. Monitoring of levels should be performed after the first dose and then at least every 3 to 4 days (more frequently if there is evidence of renal impairment) according to local protocols

For *Stenotrophomonas maltophilia* consider using Cotrimoxazole (1.44gm (three 480mg tablets) PO BD) or Timentin.

Only consider including a glycopeptide (e.g. vancomycin) as first line treatment if:

- IV catheter related infection e.g. signs of inflammation around the catheter insertion point or along catheter track
- MRSA or penicillin resistant pneumococci are likely
- Patient has severe mucositis

Antibiotics should be given through each lumen of an involved IV catheter on a rotational basis if there is an infection of a multi-lumen catheter

If the patient is poorly or deteriorating or if there is no improvement within 24 - 48 hours contact the relevant oncologist, haematologist or microbiologist (for Christie Hospital patients via switchboard 0161-446-3000).

4.4 **Treatment of low risk patient – iv or oral antibiotic regimens**

IV regimen		oral regimen
Ciprofloxacin	400mg bd	750mg bd
plus		
Co-amoxiclav	1.2G tds	625mg tds

Oral antibiotics may be substituted for iv antibiotics at the discretion of the clinician in low risk patients with fever and neutropenia.

Other antibiotic options:

levofloxacin (NB this may be less effective in Pseudomonas infections) clindamycin (if Gram positives and anaerobes are likely to be responsible e.g. cellulitis, fasciitis)

Neutropenic patients with fever should be managed in hospital but may be treated as an outpatient, at the discretion of the responsible clinician.

If low risk hospitalised patients are stable at day 3 of antibiotic therapy, consider discharge home to continue oral antibiotics as an option if :

- patient is mentally competent,
- lives near the hospital (within an hour),
- has someone at home all the time,
- has access to transport and a telephone and
- home conditions are deemed satisfactory.

5. **Reassess at 48 hours**

If afebrile at 48 hours

No cause found

Low risk – consider change to oral antibiotics if not already on them

High risk – discontinue aminoglycoside at 48 hrs if on duotherapy

Cause found

Continue on appropriate antibiotics based on susceptibility test results

Persistent fever at 48 hours

Reassess daily with repeat of history taking and clinical examination and repeat laboratory investigations and radiology as clinically appropriate.

No change ie remains febrile “but well”

Continue antibiotics - consider stopping aminoglycoside at 48 hours if cultures negative and no focus evident.

If deteriorating

- Rotate antibiotics eg piperacillin/tazobactam (Tazocin) to meropenem
- Consider adding in a glycopeptide eg vancomycin if there is evidence of a line infection or mucositis.

Antibiotics should be given through each lumen of an involved iv catheter on a rotational basis if there is an infection of a multi-lumen catheter

6. **If still febrile at day 4-6**

Consider adding in antifungal treatment (especially if likely to remain neutropenic, clinically unstable, worsening radiology, laboratory investigations) and review antibiotics as at 48 hours.

Repeat CXR - if pulmonary symptoms / infiltrates are present consider bronchoscopy and BAL along with high resolution CT scan chest. Start intravenous itraconazole if patient is not on an azole for prophylaxis. If already on an azole introduce caspofungin or lipid associated amphotericin (Abelcet 5mg/kg or Ambisome 3mg per kg). For Christie Haematology patients contact the Attending Consultant Haematologist for advice.

If positive BAL for fungi, or Aspergillus PCR or galactomannan assay is positive, consider voriconazole for proven aspergillus or posaconazole /Ambisome (5mg/kg or higher) for proven zygomycete infection eg.mucor.

NB. Experienced oncologists/microbiologists may choose to prescribe doses that fall **outside** the manufacturers license (please consult BNF or respective SPC and see note on page 11).

7. Duration of antibiotics

• **Patients with neutrophil count greater than/equal to 500/mm³**

- stop antibiotics if patient has been afebrile for 3 days if:

- a) cultures indicate organism eradicated
- b) all sites of infection have resolved
- c) patient free of signs and symptoms
- d) falling acute phase reactants eg CRP

• **Patients with neutrophil count less than 500/mm³**

- low risk and above factors a) to d) met, stop antibiotics when patient has been afebrile for 5-7 days

- high risk (eg if patient has mucositis, ulcers, bleeding points, iv-catheter site infection present or if invasive procedures or ablative chemotherapy pending) continue antibiotics so that patient receives at least 10 days treatment in total or until neutrophils >500/mm³

Patients who have antibiotics stopped while they are still neutropenic should be monitored closely for signs of infection and fever and if these occur intravenous antibiotics should be started again

Patients who remain febrile after their neutrophil counts have returned to 500/mm³ should be assessed for the presence of fungal infections (consider evaluation of liver and spleen by ultrasonography for hepatosplenic candidiasis, CT, or MRI scans, serum for galactomannan, EDTA blood for candida and aspergillus PCR, and PCR for viral infections).

8. Common modifications to initial empirical treatment in neutropenic patients

Bacteraemia

1) *Pre-antibiotic cultures yield:*

- Gram-positive isolate other than methicillin-sensitive *Staphylococcus aureus*— add a glycopeptide (eg vancomycin 1g bd (check levels and use lower dose if renal impairment) if patient has not responded satisfactorily pending full identification and sensitivities. Teicoplanin may be considered for out-patient requiring once daily administration
- Gram-negative isolate – if stable continue current regimen – if unstable consider adding an aminoglycoside especially if *Pseudomonas* is likely

2) *Organism isolated while on antibiotics*

Is an abscess present that needs draining? Is there evidence of endocarditis?

- Gram-positive isolate – consider adding a glycopeptide if not already on one; if already on a glycopeptide review antibiotic sensitivity as the organism might be a VRE or GISA (glycopeptide insensitive *Staph aureus*). If glycopeptide resistant use linezolid 600mg bd iv or orally or alternatively (if MRSA, GISA or glycopeptide resistant *Enterococcus faecium*) consider quinupristin/dalfopristin (Synercid) 7.5mg/kg tds into a central vein) or daptomycin. Note that daptomycin must not be used if there is evidence of pneumonia.
- o **These decisions should be made after discussion with a microbiologist.**
- Gram-negative isolate – change to a new combination regime based on sensitivity test results

Head, ear, eye, nose and throat

Gingivitis – add metronidazole (500mg tds iv)

Vesicular or ulcerative lesions – consider HSV and VZ. Add aciclovir 5mg/kg tds iv for herpes simplex, 10mg/kg tds iv for VZ infection. For early lesions if not widespread or haemorrhagic consider oral aciclovir 400 mg five times a day for HSV, 800 mg five times a day for VZ, or valaciclovir 500mg bd for HSV, 1g tds for VZ.

Sinus tenderness or nasal ulcerative lesions – suspect fungal infection eg aspergillus or zygomycetes such as mucor.

Gastrointestinal

Retrosternal symptoms – consider endoscopy – likely organisms include candida (add fluconazole 100 - 400mg daily) or HSV (add aciclovir). In severely immunocompromised patients CMV should be considered and could be diagnosed by PCR on gastric secretions or biopsy.

Acute abdominal pain – seek surgical advice – add metronidazole.

Perianal lesions – add metronidazole – consider surgery when not neutropenic. If HSV reactivation a possibility add aciclovir.

Diarrhoea – consider *Clostridium difficile* – add metronidazole (if possible 400mg tds orally for 10 days – if unable to swallow 500mg tds iv) – if *C. difficile* is isolated and diarrhoea is not settling on metronidazole consider vancomycin 125mg qds orally for 10 days (the injection can be used as an oral solution).

Irinotecan-associated diarrhoea should be treated early and aggressively.

As soon as the first liquid stool occurs patient must increase oral fluid intake and start (high-dose) loperamide.

It occurs at a median time of 5 days. If diarrhoea persists more than 24 hours after starting oral fluid and loperamide (4mg first dose, then 2mg 2-hourly until 12 hours after last liquid stool - max 48 hrs due to risk of paralytic ileus) start ciprofloxacin 500mg bd.

Admit to hospital if:

- Diarrhoea is associated with fever
- Grade 3 or 4 diarrhoea (requiring iv fluids)
- Diarrhoea persists > 48hrs

Respiratory

A new focal lesion in a patient recovering from neutropenia may be evidence of returning normal inflammatory response.

A new focal lesion in a patient remaining neutropenic – consider– if possible take bronchial washings (BAL) and culture, aspergillus PCR – consider CT scan – consider starting antifungal.

A new interstitial pneumonitis - consider BAL or other respiratory tract samples for PCP PCR, aspergillus PCR and viral PCRs .If unable to collect BAL specimen the above PCRs may be done on other respiratory secretions and on EDTA blood (noting that blood may have lower sensitivity).Consider empirical (high dose) trimethoprim-sulphamethoxazole (120mg/kg daily - see BNF). Continually reassess until a diagnosis is confirmed.

For respiratory problems consider CMV, mycobacteria especially TB, *Pneumocystis jirovecii*, respiratory viruses such as RSV, influenza, parainfluenza, adenovirus and atypical bacteria Such as mycoplasma or Chlamydia.

In severely immuno-compromised patients chest and /or upper abdominal pain may indicate invasive aspergillosis. Discuss appropriate investigations with radiologist and send serum (clotted blood) for aspergillus galactomannan testing, and EDTA-anticoagulated blood and respiratory tract samples for aspergillus PCR.

Central nervous system infections

Consider infectious causes immediately when patients present with fever and headache or other neurological symptoms such as depressed conscious level, confusion and cranial nerve lesions. Initiate appropriate investigations and empiric antibiotic cover as soon as possible. In some instances steroids would be indicated at time of antibiotic administration.

Consider urgent CT scan if there is evidence of raised intracranial pressure and/or focal neurology and then perform lumbar puncture if indicated. CSF should be sent for cell count, biochemistry, cytology, bacterial staining, antigens and culture, PCR for meningococci and pneumococci. Always send CSF to virology for HSV, enteroviruses and VZV PCR and consider requesting CMV, EBV, HHV-6 /7.

If subacute presentation arrange MR scan and send CSF for Toxoplasma PCR, JC polyomavirus PCR and EBV if solitary space occupying lesion present. Toxoplasma PCR should also be done on EDTA blood. If yeast infection is suspected do Indian ink staining on CSF and request cryptococcal antigen detection on serum and CSF, as well as yeast culture. If aspergillus is suspected send CSF for galactomannan and PCR.

Initial therapy for meningitis/encephalitis should be Cefotaxime 2g qds and consider adding aciclovir 10mg/kg tds iv.

If Listeria is a concern add high dose Ampicillin 2g 4hourly iv. Consider Vancomycin +/- rifampicin if pneumococcal penicillin resistance suspected.

Consider steroids if pneumococcal or TB infection is considered a strong possibility. Discussion with microbiologist or ID physician is advised.

Amend antibiotics, add antifungals or antivirals on the basis of laboratory results.

Genitourinary infections

The possibility of sexually transmitted diseases should be considered and excluded by microscopy, culture and PCR. Genital HSV infection will require aciclovir orally 800mg five times daily or aciclovir 10mg/kg tds iv.

If infection in the female genital tract is considered a possibility consider adding metronidazole or clindamicin.

9. Removal of intravenous lines

This should be considered if there is a subcutaneous tunnel or periport infection, septic emboli, hypotension associated with catheter use, or a non-patent catheter.

Specific infections that often require line removal include *Candida spp* and other fungi, *P. aeruginosa*, *Corynebacterium jeikeium*, *Stenotrophomonas maltophilia*, *Bacillus spp* and *Acinetobacter spp*. Single isolates require confirmation with a repeat blood culture.

S. aureus and persistent coagulase negative staphylococcal infections may also necessitate line removal.

Where line removal is not possible Alcohol 70% injection may be used to lock lines. Absolute alcohol injection may be diluted to 70% with Water for Injection and used to lock an infected lumen for up to 7 days.

THE FOLLOWING SECTION RELATES MAINLY TO PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES

10. Allogeneic Bone Marrow Transplant patients.

The advice of a Christie haematologist should always be sought.

11. Use of antiviral drugs

Patients with lesions due to herpes simplex or varicella zoster should be treated with aciclovir if they are neutropenic and febrile even if it is thought the lesions are not contributing to the sepsis (HSV 5mg/kg tds iv for at least 5 days, for genital herpes reactivation use 10mg/kg tds); VZV - 10mg/kg tds iv for 10 days).

Consideration should be given to the possibility of CMV if patients have pneumonitis, gastrointestinal or CNS symptoms especially if they have had a bone marrow transplant .

These patients should have an EDTA blood sample collected together with bronchoalveolar lavage, faeces, and biopsy (as appropriate clinically) sent for CMV PCR.

Discuss the appropriate use of ganciclovir or foscarnet with a Virologist.

If CMV infection is proven, monitor response to therapy with twice weekly PCR on EDTA blood. If CMV viral load does not appear to be reducing with ganciclovir discuss resistance testing with a Consultant Virologist.

In patients with recurrent CMV, long term ganciclovir or other maintenance antiviral therapy may be indicated for example cidofovir, valganciclovir. In CMV pneumonitis, hyperimmune globulin should be used in addition to ganciclovir or foscarnet.

If a lower respiratory tract infection is suspected send nasal washings or nasopharyngeal aspirate for rapid virus antigen detection, respiratory secretions or nose and throat swab for respiratory virus PCR and blood for antibody testing. Respiratory syncytial virus and parainfluenza virus may require nebulised ribavirin. Influenza A and Influenza B require treatment with oseltamivir (oral) or zanamivir (inhaled) as soon as possible. In influenza pneumonia in a patient who cannot tolerate these preparations consider intravenous ribavirin.

12. Infection control

Patients with profound and protracted neutropenia after ablative chemotherapy and bone marrow transplants should be nursed in a specialized unit with protective isolation, positive pressure ventilation and HEPA filtered air.

However for patients with shorter duration and less profound neutropenia little guidance exists.

The following seems reasonable:

The single most important factor should be good general hygiene ie staff members should wash their hands carefully with antiseptic liquid soap BEFORE and after contact with patients who are neutropenic. Application of alcohol hand rub is useful for visibly clean hands before patient contact.

Aprons should be worn for all nursing procedures and gloves should be worn where contact with body fluids or wounds is going to occur as for normal contact procedures.

If possible nurse in a single room with en-suite facilities in a building that is well maintained ie the room should be structurally sound with no cracks or defect in floors, ceilings, window fittings etc and should be well decorated ie paint or wallpaper should not be peeling off. Perforated ceiling tiles should be replaced with non-perforated ones. (If neutropenic patients are to be admitted on a regular basis consideration should be given to identifying and maintaining such rooms to a suitable standard ready for use).

Consider sealing the windows or transferring elsewhere if building work is being carried out nearby especially if likely to be neutropenic for >10 days.

The room should be free from clutter that may collect dust eg venetian blinds with horizontal slats should be replaced with unslatted window blinds.

Moist reservoirs eg leaking taps, humidifiers, flower vases should be excluded from areas housing neutropenia patients. The environment should be kept dry. Showers should be regularly maintained, kept dry between usage and if not used on a daily basis, should be run through by ward staff before patient use.

Before the patient is admitted, the room should be well cleaned and the mattress on the bed should be checked to make sure that covers are intact.

Horizontal surfaces, equipment and furniture in the room should be damp dusted on a daily basis.

Encourage patient to eat freshly cooked, thoroughly heated meals. Neutropenic patients should avoid salads, soft boiled and lightly cooked eggs, unpeelable fresh fruit, raw vegetables, pate and unpasteurised dairy foods (esp soft cheeses) while neutropenic. They should also avoid additives like pepper and herbs that may contain Aspergillus and other fungi unless these are added during cooking.

The use of ice from ice making machines for consumption or use in clinical situations should be reviewed and appropriateness assessed.

Smoking (of any substances) should be avoided because of the risk of Aspergillus and other fungal infection.

Visitors should not enter patient's rooms if they have a viral upper or lower respiratory tract infection. Equally patients should not be admitted to a main ward where viral respiratory tract infections are a problem among patients or staff.

Any equipment shared between patients must be appropriately decontaminated and cleaned before use on the next patient.

Laundry should be changed daily

13. The role of prophylactic antimicrobials and other agents

Prophylactic antibiotics, antivirals and antifungals are not necessary for all neutropenic patients but have a part to play in management of some conditions especially haematological malignancies. These will need prescribing on a case by case basis following discussion with the Haematologist and Microbiologist/Virologist.

Passive immunization with specific immunoglobulins may be useful in selected patients eg varicella zoster immune globulin(ZIG) may be used for prophylaxis after contact with VZ in the nonthrombocytopenic patient. However when intramuscular

injections cannot be given IV IG or antiviral prophylaxis should be considered. These cases should be discussed with a Consultant Virologist and Haematologist.

GCSF or other colony stimulating factors should only be considered after discussion with a Haematologist or Consultant Oncologist.

14. **Summary: Empirical treatment of a febrile neutropenic**
NB. All antimicrobial doses are approximate and may need to be altered according to patient's clinical condition, weight and renal function etc.

Monotherapy

- Meropenem monotherapy (see below) 1gm tds

Reduce dose for creatinine clearance under 50ml/min.

Duotherapy

- Antipseudomonal penicillin (eg Tazocin 4.5g tds - qds) **plus** gentamicin*

OR

- Meropenem 1g tds **plus** gentamicin*

In the event of specific concern about staphylococcal sepsis, vancomycin can be given pending susceptibility testing results.

*Gentamicin (3-5mg/kg) may be given as a single daily dose depending on clinical condition and renal function. Monitoring of levels should be performed after the first dose and then at least every 3 to 4 days (more frequently if there is evidence of renal impairment) according to local protocols

For *Stenotrophomonas maltophilia* consider using Co-trimoxazole (1.44gm (three 480mg tablets) PO BD) or Timentin

Only consider including a glycopeptide (e.g. vancomycin) as first line treatment if:

- IV catheter related infection e.g. signs of inflammation around the catheter insertion point or along catheter track
- MRSA or penicillin resistant pneumococci are likely
- Patient has severe mucositis

Antibiotics should be given through each lumen of an involved IV catheter on a rotational basis if there is an infection of a multi-lumen catheter

If the patient is poorly or deteriorating or if there is no improvement within 24 - 48 hours contact the relevant oncologist, haematologist or microbiologist (for Christie Hospital patients via switchboard 0161-446-3000).

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Intravenous Vancomycin dosing

Normal dose for adults 1g bd over 100minutes.

For patients over 70 the dose is 750mg bd

For patients weighing less than 55kg the dose is 750mg bd.

For creatinine clearance less than 50ml/min see table below

Measure a trough level immediately before the 3rd or 4th dose. Give this dose and adjust subsequent doses according to the levels. The target trough level is 5 to 15mg/l.

Microbiology may advise aiming for higher trough levels of up to 20mg/l/

DOSING IN RENAL IMPAIRMENT.

Use 1gm or 750mg if under 55kg (approximately 15mg/kg)

CrCl ml/min (may be estimated)	Frequency of dosing	Monitoring
20-50ml/min	Once daily	Check trough level before 2 nd dose
10-20ml/min	Every 48 hours	Check trough level before 2 nd dose
Under 10 ml/min	Every 3 to 7 days	Check level after 3-5 days. Repeat dose once level is below 12 mg/l