

Neutropenic sepsis

Definition of neutropenic sepsis

- Neutrophils $< 1 \times 10^9 / L$ {cid.oxfordjournals.org/content/52/4/e56.full}
This is the most widely used criterion, though some guidelines recommend $< 0.5 \times 10^9 / L$ {<http://www.nice.org.uk/guidance/cg151/chapter/1-recommendations#>}
AND any of
- Temperature $> 38^\circ C$ OR
- Signs or symptoms indicating infection (see below) OR
- Raised C-reactive protein ($> 80 \text{mg/L}$)

Bad prognostic features in neutropenic sepsis

- Degree of neutropenia (< 0.5 is worse)
- Duration of neutropenia (> 7 days is worse)
- Cause (chemotherapy also causes functional impairment of residual neutrophils)
- Older age
- Poor functional status
- Obesity
- Bone marrow infiltration by malignancy

Pathophysiology of neutropenic sepsis

- Chemotherapy both suppresses production of white blood cells, and damages mucosa in the gut, increasing translocation of bacteria
- Patients on chemotherapy often have indwelling venous lines
- In the absence of neutrophils, normal signs of a reaction to infection (e.g. airspace consolidation) do not develop
- 20% have a bacterial aetiology found, but no focal source of infection
- 30% have a focal infection
- 50% no aetiology is established.
- (Note: Most cases of neutropenic sepsis arise following chemotherapy, but there are other causes of neutropenia [see questions], and some do not increase the risk of neutropenic sepsis)

History of neutropenic sepsis

- Presenting complaint
 - Incidental fever at home
 - Generally unwell / fevers / rigors / malaise
 - May be focal symptoms e.g. productive cough, rash, dysuria, diarrhoea, jaundice, abdominal pain
- History of presenting complaint
 - Cancer diagnosis (acute leukaemia particularly high risk; chronic bone marrow failure e.g. MDS, aplastic anaemia also high risk)
 - Last chemotherapy - when and what (haematopoietic stem cell transplant recipients are at particularly high risk until engraftment)
 - Duration of symptoms
 - Other chemotherapy side effects: mucositis, diarrhoea, hepatitis, confusion
- Past medical history
 - Other causes of neutropenia

- Organ failure
- Medications
 - Clozapine, sulfasalazine, and antithyroid drugs (carbimazole and propylthiouracil) can cause agranulocytosis.
 - Was G-CSF (granulocyte colony stimulating factor) given following chemotherapy?
- Allergies
 - Penicillin allergy severely restricts treatment options for neutropenic sepsis

Examination findings in neutropenic sepsis

- Signs of sepsis
 - Temperature, tachycardia, tachypnoea (SIRS criteria)
 - Hypotension (septic shock if fails to respond to fluid bolus of 500ml 0.9% saline or similar)
- Hydration status (mucous membranes, skin turgor, capillary refill)
- Sources of sepsis
 - **ENT:** Oral mucositis / inflamed tonsils / inflamed or bulging tympanic membrane / paranasal sinus tenderness
 - **Neurological:** Neck stiffness / photophobia
 - **Respiratory:** Dullness on percussion / bronchial breathing / crepitations / wheeze
 - **Cardiac:** New heart murmur
 - **Abdominal:** Abdominal pain / guarding
 - **Musculoskeletal:** New rash (check everywhere) / inflamed joints / new spinal tenderness
 - **Lines:** Cellulitis / pus from indwelling intravenous catheters (PICC / Hickman lines)

Initial management of neutropenic sepsis

- The two vital priorities are blood cultures (both from peripheral veins and any indwelling lines), and broad spectrum antibiotics. Both are very important, but if blood cultures cannot be taken promptly then antibiotics should not be delayed.
- **ABCDE approach**
 - Including good venous access and fluid challenges
 - Oxygen if sats <94%
- **Initial investigations**
 - Cultures
 - Blood cultures (peripheral and line), urine culture, stool if diarrhoea
 - Other fluids (pus, sputum, pleural fluid, ascites, CSF, synovial fluid) as relevant for microbiology
 - Relevant viral serology if clinical suspicion
 - Bloods
 - FBC, U+E, LFT, C-reactive protein (or ESR), clotting, bone profile
 - Blood film
 - Group and screen
 - ABG/VBG (for immediate results including lactate)
 - ECG for baseline
 - Imaging
 - Chest X-ray if indicated
 - Further imaging as dictated by history and examination to identify a source
- **Broad spectrum antibiotics - follow local guidelines if available**
 - Piperacillin/tazobactam (Tazocin® 4.5g IV every 6 hours)
{<http://www.nice.org.uk/guidance/cg151/chapter/1-recommendations#>}
 - Alternative empirical strategies: meropenem 1g every 8 hours; or imipenem-cilastatin 500mg every 6 hours; or cefepime 2g every 8 hours

- Specific resistance patterns may be an indication for adding cover for MRSA (vancomycin, teicoplanin or linezolid); Vancomycin-resistant enterococci (linezolid or daptomycin); or Extended spectrum beta lactamase *E. coli* (meropenem)
- Specific presenting features may be an indication for additional antibiotics [a macrolide or quinolone if pneumonia due to an atypical organism is suspected; vancomycin for suspected central line infection; gentamicin for suspected Gram negative septic shock; specific therapy for *C. difficile* if diarrhoea and abdominal signs are present]
- If there is a history of immediate hypersensitivity to penicillin or other beta-lactams, they should be avoided in initial empirical therapy. Suitable combination regimens include ciprofloxacin plus clindamycin, *or* aztreonam plus vancomycin.
- Many centres use fluoroquinolones (e.g. ciprofloxacin, levofloxacin) as antibacterial prophylaxis in neutropenic patients. Such patients should not be treated for neutropenic sepsis with a regimen that includes a fluoroquinolone.
- Supportive care
 - Oral or iv maintenance fluids
 - Antiemetics
 - Nutrition support
 - Topical agents for mucositis (benzylamine and chlorhexidine mouthwashes)
 - Transfusion if needed
- Indwelling central venous lines should not routinely be removed as part of initial management

Further management of neutropenic sepsis

- Repeat blood cultures should be taken with each temperature spike (if no organism has grown)
- Antifungals - follow local guidelines if available
 - Empirical antifungals should be considered in high risk patients [Neutrophils < 0.5 for >7 days] in whom fever persists for >4 days without a cause.
 - If antifungal therapy is instigated, investigations for fungal infection should include a CT thorax for moulds, and laboratory tests as per local availability (may include galactomannan antigen, beta-glucan or PCR-based tests)
 - If there is no new pulmonary infiltrate, then *Candida* is more likely than *Aspergillus*, so use caspofungin 70mg IV loading dose, thereafter 50mg iv once daily
 - If there is a new pulmonary infiltrate, or the patient was receiving anti-candida prophylaxis (usually fluconazole) start voriconazole IV 6mg/kg every 12 hours for two doses, thereafter 4mg/kg every 12 hours; or liposomal amphotericin B IV 3mg/kg once daily
 - *Pneumocystis jirovecii* can cause pneumocystis pneumonia (PCP) in the context of chronic immunosuppression. If suspected a broncho-alveolar lavage (BAL) should be performed, and treatment with high dose co-trimoxazole (120mg/kg daily in divided doses) started if positive.
- Granulocyte-colony stimulating factor should not routinely be used in neutropenic sepsis. It reduces length of stay but has no other effect on outcomes. It may be used in high risk patients with expected length of neutropenia >7 days. The usual dose of filgrastim is 30 million units (300 microgram) SC once daily.
- Central venous lines should not be routinely removed. They should be removed in cases of bacteraemia due to *S. aureus*, *P. aeruginosa* or fungal infection. In these instances antibiotics should be continued for at least two weeks after line removal.

Common questions about neutropenic sepsis

- What is the definition of neutropenic sepsis
 - Neutrophils < $1 \times 10^9 / L$ is the most widely used criterion (though some guidelines recommend < $0.5 \times 10^9 / L$)

- AND any of
 - Temperature > 38°C OR
 - Signs or symptoms indicating infection OR
 - Raised C-reactive protein (>80mg/L)
- What can be done to prevent neutropenic sepsis?
 - G-CSF can be used following chemotherapy regimens with a high risk of prolonged neutropenia
 - Antibiotic prophylaxis with a fluoroquinolone reduces febrile episodes and mortality {<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170789/>}
 - Antifungal prophylaxis with fluconazole 50mg PO once daily.
 - Antiviral prophylaxis with aciclovir 200mg PO three times daily.
- What are the causes of neutropenia?
 - Congenital
 - Benign ethnic neutropenia; cyclical neutropenia; Chediak-Higashi
 - Failure of production leading to pancytopenia
 - Myelosuppressive chemotherapy or irradiation is overwhelmingly the most common.
 - Others include infiltration of bone marrow by cancer; vitamin B12 or folate deficiency; myelodysplastic syndrome; aplastic anaemia
 - Increased consumption
 - Post-infectious
 - Idiosyncratic drug reactions (e.g. carbimazole; clozapine; co-trimoxazole; penicillin)
 - Autoimmune disease e.g. SLE; autoimmune neutropenia (antibody-mediated neutrophil destruction)
 - Paroxysmal nocturnal haemoglobinuria
 - Haemophagocytic syndrome
- How do you investigate neutropenic sepsis?
 - Cultures
 - Blood cultures (peripheral and line), urine culture, stool if diarrhoea
 - Other fluids (pus, sputum, pleural fluid, ascites, CSF, synovial fluid) as relevant for microbiology
 - Relevant viral serology if clinical suspicion
 - Bloods
 - FBC, U+E, LFT, C-reactive protein or ESR, coagulation, calcium, lactate, glucose
 - Blood film
 - Group and screen
 - ABG/VBG
 - ECG
 - Imaging
 - CXR if indicated
 - Further imaging as dictated by history and examination to identify a source
- When should lines be removed in neutropenic sepsis?
 - Central venous lines should not be routinely removed.
 - They should be removed in cases of bacteraemia due to *S. aureus*, *P. aeruginosa* or fungal infection.
- What is the myeloid reconstitution syndrome?
 - As the neutrophil count recovers, some patients develop worsening symptoms and signs of focal infection as a pyogenic reaction occurs at the site of (previously unlocalised) infection
- What is typhlitis?
 - Also known as necrotising enterocolitis, it is inflammation of the bowel in the context of neutropenia that is not due to a particular pathogen. It should be managed as neutropenic sepsis initially, though if perforation occurs surgery is required. Other causes of colitis should be ruled out (norovirus, *C. difficile*, cytomegalovirus, ischaemia)

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