Neutropenic Patients and Neutropenic Regimes

Neutropenia means a low neutrophil count. The normal range for neutrophils is $2.5-7.5 \times 10^9/L$. Moderate neutropenia is defined as a neutrophil count of $0.5-1.0 \times 10^9/L$. Severe neutropenia is a count of $<0.5 \times 10^9/L$.

As the neutrophil count falls, especially once neutrophils are $<1 \times 10^9/L$, a patient becomes immunocompromised and at risk of serious infections which may be fatal.

When faced with a patient with neutropenia it is important to answer the following questions:

- What is the underlying cause of neutropenia?
- What is the cause of neutropenic sepsis if present?

Neutropenic patients can therefore be divided into three clinical groups:

- Otherwise well patients with neutropenia. These patients may be known to be neutropenic previously or presenting de novo and require investigation to look for an underlying diagnosis.
- (Previously) immunocompetent patients, now presenting with neutropenia and compromised, requiring urgent treatment.
- (Known) immunocompromised patients presenting with neutropenia and compromised, requiring urgent treatment.

Incidental neutropenia

Neutropenia is a common finding on routine FBC. Patients may have recurrent infections, autoimmune diseases, a previously diagnosed haematological disease or solid tumour indicating an obvious disease-related state. However, when the finding is unexpected, thorough consideration of possible underlying causes is the first step. [1]

Congenital

- Rare disorders of neutrophil production (present from birth) - eg, Kostmann's syndrome, X-linked agammaglobulinaemia, Shwachman-Diamond syndrome, Chédiak-Higashi syndrome, myelokathexis and cyclical neutropenia.
- Ethnic variation - particularly in patients of African descent.
- Cyclical neutropenia in children (rare - recurring episodes of severe neutropenia accompanied by malaise, fever, adenopathy, anorexia and ulceration of mucous membranes).

Acquired

- Decreased or ineffective neutrophil production:
  - Bone marrow infiltration with malignancy.
  - Aplastic anaemia.
  - Vitamin B12 or folate or iron deficiency.
  - Chemotherapy - cytotoxics and immunosuppressants. [2]
  - Exposure to chemical agents - eg, benzene, organophosphate.
  - Radiotherapy.
  - Drugs - eg, phenytoin, chloramphenicol, alcohol (abuse).
  - Autoimmune neutropenia.
  - Infections - eg, infectious mononucleosis, hepatitis B or C, human immunodeficiency virus, cytomegalovirus infection, typhoid.
- Accelerated neutrophil turnover in the blood:
  - Felty's syndrome (rheumatoid arthritis, splenomegaly, and granulocytopenia).
  - Hypersplenism.
  - Malaria and acute bacterial infections.
- Changes in shifts of cells from the circulating to the marginal blood pools:
  - Dengue fever, measles and viral infections.
- Unclear or combination of mechanisms:
  - Toxoplasmosis, malaria, kala-azar.
  - Treatment with a wide variety of analgesics, anti-inflammatories, anticonvulsants, antibiotics, antihistamines, diuretics, hypoglycaemics and antidepressants.
  - Thyroid dysfunction.
  - Autoimmune neutropenia.

An initial approach may therefore include history, examination and blood tests, guided by clinical suspicion. Initial additional tests (if not already tested) may reasonably include U&Es, serum folate, vitamin B12, iron and ferritin, serum liver enzymes, serum proteins, antinuclear and anti-DNA antibodies and rheumatoid factor and TFTs.
Many of the cases will be transient, or will resolve when the underlying cause is treated or removed. Approximately 34% of cases will be chronic and idiopathic.\(^1\) There is currently no evidence to support prophylactic antibiotics for asymptomatic patients with idiopathic neutropenia.

**Febrile neutropenia**

Febrile neutropenia is defined as an oral temperature ≥38.5°C or two consecutive readings of ≥38.0°C for two hours and an absolute neutrophil count ≤0.5 x 10^9/L, or expected to fall below 0.5 x 10^9/L.\(^2\) Successful management depends on early recognition. Patients should be educated to monitor their symptoms (including body temperature) and be given clear written instructions on when and how to contact the appropriate service in the event of concerns.

**Initial assessment**

- **History to include:**\(^3\)
  - Whether the patient belongs to a high-risk group - eg, active neoplastic disease, a recent course of chemotherapy, immunosuppressant therapy (eg, azathioprine, steroids) or immunosuppressive illnesses such as HIV.
  - Chronic kidney disease.
  - Include duration since last chemotherapy cycle if applicable.
  - Any recent blood products.
  - Any intravascular devices - eg, cannulae, central lines, urinary catheter.
  - Checking past microbiology results for history of resistant organisms.

- **Examination:**
  - Cardiac and respiratory systems (and resuscitate where necessary). NB: signs and symptoms of infection in neutropenic patients can be minimal.
  - General examination: pyrexia, stigmata of infective endocarditis, lymphadenopathy, skin rashes.
  - Potential foci of infection:
    - Ear, mouth and nose examination.
    - Fundoscopy.
    - Gastrointestinal tract (avoid digital rectal examination until antibiotics have been given).
    - Respiratory system.
    - Genitourinary tract.
    - Neurological - eg, neck stiffness.

- **Investigations:**\(^3\)
  - FBC (current neutrophil level).
  - Two sets of blood cultures from a peripheral vein, and any indwelling venous catheters.
  - Other investigations to consider in a neutropenic septic patient:
    - Blood film, D-dimer and fibrinogen testing (to look for disseminated intravascular coagulation).
    - U&E, creatinine.
    - LFTs.
    - CRP and ESR.
    - Coagulation screen.
    - CXR.
    - Serology or polymerase chain reaction for viruses - eg, cytomegalovirus.
    - More specialised investigations such as bronchoscopy and CT scans.

- Sputum, urine, skin swabs and stool specimens where clinically indicated.

**Management**

See also the separate **Sepsis (Septicaemia)** article.

The most widely used instrument is the Multinational Association for Supportive Care in Cancer (MASCC) index.\(^4, 5\) It uses the following characteristics:

- **Burden of illness:**
  - No, or mild symptoms - 5 points.
  - Moderate symptoms - 3 points.
  - Severe symptoms - 0 points.

- **Absence of hypotension (systolic blood pressure ≥90 mm Hg) - 5 points.**
- **Absence of chronic obstructive pulmonary disease - 4 points.**
- **Presence of solid tumour/lymphoma with no previous fungal infection - 4 points.**
- **No dehydration - 3 points.**
- **Outpatient status (at onset of fever) - 3 points.**
- **Age ≤60 years - 2 points.**

Low-risk cases are those scoring ≥21.
Oral antibacterial therapy can be used safely in some low-risk febrile neutropenia patients although its use in the UK is still low. These are patients who are haemodynamically stable, who do not have acute leukaemia or evidence of organ failure, and who do not have pneumonia, an indwelling venous catheter or severe soft tissue infection.

Quinolone with amoxicillin plus clavulanic acid is the preferred choice given the rise in Gram-positive febrile neutropenia episodes. Oral quinolone therapy should not be used in patients who have taken a quinolone antibacterial as prophylaxis.

The National Institute for Health and Care Excellence (NICE) recommends that all patients who require intravenous treatment be commenced on beta-lactam monotherapy with piperacillin and tazobactam. Aminoglycosides should NOT be used for initial empirical therapy, unless there are specific patient or local related reasons.

Coverage for meticillin-resistant *Staphylococcus aureus* (MRSA) or resistant Gram-negative bacteria may be required. If pneumonia is diagnosed, antibiotic cover must be extended to treat atypical organisms such as *Legionella* spp. and *Mycoplasma* spp. by adding a macrolide antibiotic.
Granulocyte colony-stimulating factor

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) is given subcutaneously and stimulates the production of neutrophils in the bone marrow. rhG-CSF may reduce the duration of chemotherapy-induced neutropenia and thereby reduce the incidence of associated sepsis. There is currently no evidence of improved overall survival.

In some cases (but not routinely), rhG-CSF is used prophylactically - eg, following chemotherapy. rhG-CSF can also be given to help counteract an infection, along with antibiotics.

Filgrastim (unglycosylated rhG-CSF) and lenograstim (glycosylated rhG-CSF) have similar actions but do not have any clear-cut routine indications. In congenital neutropenia filgrastim usually increases the neutrophil count with an appropriate clinical response. Pegfilgrastim is a derivative of filgrastim, with a more prolonged duration of activity. Lipegfilgrastim is also a derivative of filgrastim.

Follow-up

- The frequency of this should be determined by severity but may be required every 2-4 hours in cases needing resuscitation.
- Daily assessment of fever trends, bone marrow and renal function is indicated until the patient is afebrile and neutrophil count is ≥0.5 x 10^9/L.
- If the patient is afebrile and the neutrophil count is ≥0.5 x 10^9/L at 48 hours, low-risk patients with no obvious cause found can be changed to oral antibiotics. High-risk patients with no cause found can have their aminoglycoside discontinued. When a cause has been found they should continue on appropriate specific therapy.
- If the neutrophil count is normal, the patient is asymptomatic and has been afebrile for 48 hours and blood cultures are negative, antibacterials can be discontinued. If the neutrophil count is still low, but the patient has not had complications and has been afebrile for 5-7 days, antibacterials can be discontinued. In some high-risk cases (acute leukaemia and following high-dose chemotherapy) antibiotics are often continued for up to 10 days, or until the neutrophil count is normal.
- Careful consideration may be required (and appropriate microbiological advice sought) regarding future prophylaxis.

Prognosis

Mortality from febrile neutropenia has reduced but remains significant. Aggressive use of inpatient intravenous antibiotics has reduced the need for intensive care management to fewer than 5% of cases in England. Overall mortality rates are approximately 5% in patients with solid tumours but may be as high as 11% in some haematological malignancies. The serious medical complication rate in those with a MASCC risk score of ≥21 is estimated to be 6% and mortality just 1%.

Prognosis is worst in patients with proven bacteraemia, with mortality rates of 18% in Gram-negative and 5% in Gram-positive bacteraemia.

Prevention

Adult patients (aged over 18 years) with acute leukaemias, stem cell transplants or solid tumours, who undergo chemotherapy which is likely to cause a period of significant neutropenia (ie neutrophil count 0.5 x 10^9 or lower), should be offered prophylaxis with a fluoroquinolone. This should be taken only during the period of neutropenia.

Further reading & references

- Neutropenic sepsis: prevention and management in people with cancer; NICE Clinical Guideline (September 2012)
- Management of febrile neutropenia: ESMO Clinical Practice Guidelines; European Society for Medical Oncology (2010)
- Neutropenic sepsis: prevention and management in people with cancer; NICE Clinical Guideline (September 2012)
- British National Formulary (BNF); NICE Evidence Services (UK access only)

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