Assessment of the patient with neutropenic sepsis

Introduction

Neutropenic sepsis is defined as sepsis in any patient with a neutrophil count of $<1.0 \times 10^9$/litre. Sepsis is the leading cause of mortality in neutropenic patients with mortality rates up to 21%. Although most patients will have neutropenia secondary to chemotherapy, occasionally other causes will also present. Therefore, it is essential to consider whether a septic patient may also be neutropenic and may be at high risk of complications. Patients with febrile neutropenia (an oral or tympanic membrane temperature of 38°C or more maintained for 1 hour, or 38.5°C on one occasion, in any patient with a neutrophil count of $<1.0 \times 10^9$/litre) are at high risk of developing neutropenic sepsis (for further definitions see *Figure 1*).

The National Confidential Enquiry into Patient Outcome and Death (2008) identified several inadequacies in the management of febrile neutropenia (leading to neutropenic sepsis) in the UK. Key relevant failures included failure to make the diagnosis, a lack of awareness that patients without a fever may still have neutropenic sepsis, delayed admission, delayed resuscitation, delayed prescription and administration of antibiotics, failure to adhere to local antibiotics policy, and lack of early assessment by senior staff. Therefore, the National Chemotherapy Advisory Group (2009) published recommendations for robust systems to be put in place to admit and manage patients with febrile neutropenia with the aim of improving safety and outcome. This is important because most patients with febrile neutropenia respond well to empirical therapy and do not develop major complications, yet those that become unwell can develop critical illness very rapidly (National Chemotherapy Advisory Group, 2009).

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In addition to the National Chemotherapy Advisory Group recommendations, guidelines include those published by the international Surviving Sepsis Campaign (Dellinger et al, 2008) as well as those published by Haji-Michael et al (2010). The National Institute for Health and Clinical Excellence is currently producing a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients (due for publication in 2012). This article focuses on the identification and diagnosis of neutropenic sepsis and provides both an educational and practical guide for all junior trainees, for use in combination with local policies, to improve the management of neutropenic sepsis. A second article looks at the management of these patients.

Pathophysiology of sepsis

Figure 1 shows definitions of the various sepsis syndromes according to the Surviving Sepsis Campaign (Dellinger et al, 2008). The syndrome of septic shock occurs when high levels of cytokine and secondary mediators, released in response to bacterial, fungal or viral antigens, result in systemic vasodilation (hypotension), diminished myocardial contractility, widespread endothelial injury and activation, causing systemic leukocyte adhesion and diffuse alveolar capillary damage in the lung, in addition to activation of the coagulation system, culminating in disseminated intravascular coagulation. The hypoperfusion resulting from the combined effects of widespread vasodilation, myocardial pump failure and disseminated intravascular coagulation causes multiorgan system failure that affects the liver, kidneys and CNS, among others.

Neutrophils play an essential role in responding to infection. Their main function is to respond to effector chemokine signals to enter sites of infection where they phagocytose bacteria, releasing bacteriostatic and bacteriocidal agents. These actions lead to the formation of pus,

Figure 1. Definitions of sepsis syndromes (Dellinger et al, 2008).

Sepsis is a systemic inflammatory response syndrome that is characterized by widespread tissue injury often caused by severe infection

Systemic inflammatory response syndrome is defined as two or more of the following by the American College of Chest Physicians and the Society of Critical Care:	Temperature >38°C or <36°C
	Heart rate >90 beats per minute
	Respiratory rate >20 breaths per minute or $PaCO_2$ <32 mmHg
	White blood cell count <4000 cells/mm^3 or >12 000 cells/mm^3 (<4×10^9 cells/litre or >12×10^9 cells/litre), or greater than 10% band forms (immature white blood cells). In the context of known neutropenia, this point cannot be used to identify the presence of systemic inflammatory response syndrome or sepsis
Severe sepsis is defined as sepsis with new signs of organ dysfunction or a decrease in organ perfusion evidenced by:	Lactic acidosis
	Oliguria (<30 ml/h or <0.5 ml/kg/h)
	Hypotension (<90 mmHg or decrease of >40 mmHg)
	Alteration of mental status
Septic shock is defined as:	Severe sepsis and
	Persistent hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <60 mmHg, or a reduction of 40 mmHg in systolic blood pressure from baseline) despite adequate fluid substitution (typically upwards of 6 litres or 40 ml/kg of crystalloid replacement) and
	Exclusion of other reasons for hypotension (such as cardiogenic shock)
	Signs of systemic hypoperfusion may be either end-organ dysfunction (*Table 3* gives further details) or serum lactate >4 mmol/dl

Septicaemia is sepsis that has an infection in the bloodstream itself

inflammation, heat and swelling of infected tissue. It is therefore easy to understand why neutropenic patients are at high risk of infection by bacteria and it is important to realize that so-called 'classic' local signs of infection may not be present.

Clinical assessment of the neutropenic patient

A full history and examination must be carried out on any patient at risk of neutropenia presenting with potential symptoms of sepsis. Basic observations should be performed immediately on presentation of the patient to the hospital, GP or nurse to detect signs of sepsis and patients must be assessed within 1 hour and treated as an emergency. If any signs of sepsis are detected (as detailed in *Figure 1* and *Table 1*) resuscitation measures should be commenced urgently. In practise history-taking, examination and initial investigations should be performed simultaneously.

History

The patient history should focus on the following areas:

Determine the likelihood and cause of neutropenia

The main causes of neutropenia are shown in *Table 2*. It is estimated that 75% of neutropenia is caused by drugs and most data on the management of neutropenic sepsis have involved cancer patients treated with chemotherapeutic agents. Neutropenia following cytotoxic therapy commonly manifests between 1 and 2 weeks after exposure to the drug and the effect varies according to the dose and duration of exposure. It is therefore essential to obtain a detailed drug history, including the administration dates and doses for each drug. This can usually be obtained from the written information given to all patients prescribed cytotoxic drugs. Electronic notes and clinic letters are also invaluable but hard copies of the patient's notes should be requested as soon as possible after the patient presents in an emergency setting.

If the neutropenia is not drug-related, determining the age at onset helps with the differential diagnosis. A family history of frequent or unusual infections, or sudden death may indicate inherited disorders.

Determine the predicted duration and severity of neutropenia

The main risk factors for developing neutropenic sepsis are the severity and duration of neutropenia (Bodey et al, 1966; Elting et al, 1997), and the time until the first dose of antibiotics is administered for neutropenic fever (Krell and Jones, 2009). Increased susceptibility to infection is likely when the neutrophil count falls below 1.0×10^9/litre with escalating risk at $<0.5 \times 10^9$/litre and $<0.1 \times 10^9$/litre. 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 it lasts for >10 days. Incidence also varies according to pre-treatment of the patient with other chemotherapy and his/her other comorbidities. Although bone marrow recovery usually occurs within days of stopping a particular medication, it may take several weeks. Records of past full blood counts will help to establish the chronicity of the neutropenia.

Determine if a fever is or has been present

The incidence of febrile episodes (core temperature >38.3°C) after intensive myelosuppressive chemotherapy for haematological malignancy is 70–100% dependent on intensity of therapy (Martin et al, 2003; Danai et al, 2006; Moerer and Quintel, 2009). Approximately 40% of these patients developed severe sepsis and septic shock.

Although the incidence of sepsis in non-oncology-related neutropenia is less clearly defined it is likely to be significantly lower because it involves less intensive chemotherapy regimens. However, it is important to recognize that neutropenic patients may not develop a temperature despite being septic, especially if concurrently taking antipyretics, steroids or other immunosuppressant drugs. Patients receive chemotherapy are counselled

Table 1. Examples of end organ dysfunction caused by sepsis

End organ	Dysfunction	Symptoms
Lung	Acute lung injury	Shortness of breath, cough
	Acute respiratory distress syndrome	Hypoxia on blood gas
Brain	Encephalopathy	Confusion, agitation, coma
Kidney	Acute renal failure	Oliguria, anuria, volume overload
	Electrolyte abnormalities	Arrhythmias
Liver	Coagulopathy	Bruising, delayed blood clotting
Heart	Heart failure	Shortness of breath, orthopnoea, fluid overload

Table 2. Common causes of neutropenia

Cause	Example
Infection	Viral (human immunodeficiency virus, Epstein–Barr virus)
	Bacterial (tuberculosis)
	Parasitic (malaria)
Iatrogenic	Radiation
	Drugs, e.g. cytotoxic chemotherapy, antiepileptics, antipsychotics, procainamide, antithyroid drugs, e.g. sulfasalazine, chloramphenicol
	Toxins, e.g. benzenes, insecticides, heavy metals
Diseases of the bone marrow	Aplastic anaemia, myelofibrosis
Neoplasia	Leukaemias, myelodysplastic syndromes
	Metastases
Autoimmune and inflammatory disorders	Autoimmune neutropenia
	Systemic lupus erythematosus
	Associated with other diseases, e.g. Felty's syndrome
Congenital disorders	Bone marrow dysfunction
	Disorders of production of neutrophils, e.g. Kostmann syndrome
	Cyclic neutropenia
Others	Hypersplenism
	Metabolic deficiency, e.g. vitamin B_{12}, folate and copper
	Racial neutropenia in Afro-caribbeans

about home monitoring of their temperature and the importance of contacting the oncology service early for urgent medical assessment in the event of feeling unwell and may be able to produce readings documented at home.

Determine risk factors for increased incidence of sepsis

Uys et al (2007) identified malnourishment as an independent risk factor for the development of complications during febrile neutropenic episodes in cancer patients. The incidence of neutropenic sepsis increases with pre-treatment of the patient with other chemotherapy and the overall performance status. Other risk factors include insertion of central venous catheters and use of invasive diagnostic procedures. Oncology patients are further at risk of invasive tumour growth breaching mucosal barriers or of retention of secretions caused by tumour obstruction facilitating growth of pathogenic organisms. Chemotherapy may also increase the risk of sepsis by disrupting skin and mucosal barriers.

Identify potential sources and sites of infection

A careful systems enquiry will help to identify potential sources of any infection since the classic signs of infection seen on examination may be absent in neutropenic patients. Haji-Michael et al (2010) state that 50–60% of febrile neutropenic patients are proven to have infections with cultures. Typical pathogens causing sepsis in neutropenic patients are listed by their occurrence in each organ in *Table 3*. Often infections in the context of neutropenia are from an endogenous rather than an exo-genous source. As stated above in-dwelling central venous catheters such as Hickman or peripherally inserted central catheter lines are a common potential source of sepsis as are other in-dwelling lines such as urinary catheters, drain sites and surgical sites.

It is important to consider taking a detailed social history including pets, hobbies, occupation, travel history, sexual history and potential environmental exposures to unusual organisms to help to identify atypical organisms as possible sources for unusual infections according to the clinical scenario. This is particularly relevant if patients do not improve and no other source is found. Fungal infections tend to occur after patients have received broad-spectrum antibiotics and have had prolonged periods of neutropenia, although they can occur as primary infections. Risk factors include recent building work and occupational exposure, as well as prior lung disease.

Patients may have had repeated episodes of neutropenic sepsis and history of previous drug sensitivities is important, particularly whether patients have a history of meticillin-resistant *Staphylococcus aureus* and other drug-resistant pathogens. Ask about drug allergies. Early discussion of the case with senior doctors, the infection control team and microbiology is mandatory.

Physical examination

During the physical examination of a patient with neutropenia focus on finding signs of an infection (in addition to re-assessing the severity of any sepsis). The severity of sepsis can be determined using *Figure 1* and *Table 1*. *Figure 2* highlights important points to include in the examination. Frequent measurement of temperature, blood pressure, heart rate, respiratory rates, oxygen saturations and urine output are essential. It is important to be vigilant for 'cold' sepsis where features of sepsis are present at temperatures of <36°C. Digital rectal examination should not be performed before the administration of antibiotics because of the risk of seeding faecal flora. Consider the need for contact and isolation precautions, including the need to protect both staff and other patients from pathogens (e.g. meticillin-resistant *S. aureus*, *Clostridium difficile*, varicella zoster).

Investigations

Baseline investigations should include a full blood count, urea and electrolytes, liver function tests, coagulation screen,

Table 3. Typical pathogens during neutropenic sepsis

Origin	Frequent pathogens
Lung	*Pseudomonas aeruginosa*, pneumococci, alpha-haemolytic streptococci, *Acinetobacter* spp.
Abdomen	*Escherichia coli*, *Pseudomonas aeruginosa*, *Clostridium* spp., *Enterococcus* spp., *Klebsiella* spp.
Urogenital	*Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*
Soft tissue	*Staphylococcus aureus*, alpha-haemolytic streptococci
Central venous catheter	Coagulase-negative staphylococci, Corynebacteriae, *Propionibacterium* spp., *Candida albicans*, *Candida tropicalis*

From Penack et al (2007)

Figure 2. Important examination points.

Skin examination focusing on rashes (including herpes simplex and reactivation of varicella zoster), ulcers or abscesses (beware of petechial rashes and ecchymoses indicating possible disseminated intravascular coagulation)

Carefully examine the oral mucosa and pharynx for aphthous ulcers, thrush or periodontal disease

Ear, nose and throat examination being vigilant for sinus infections

Examine all central venous catheter lines, catheters and port sites for signs of infection (redness, heat, exudates, pain)

Lymphadenopathy can be an indication of a disseminated infection or, possibly, malignancy

Respiratory examination may reveal infections which are usually bacterial or fungal pneumonias

Cardiovascular examination may reveal signs of infective endocarditis (often secondary to central venous catheter line infections)

Abdominal examination for signs of peritonism or pain

Genital and peri-rectal examination for mucous membrane abnormalities, rashes, abscesses and lymphadenopathy. Consider the possibility of reactivation of genital herpes, fungal infection and necrotizing fasciitis. It is not advised to perform digital rectal examinations on neutropenic patients until after antibiotics have been started because of the risk of dissemination of faecal flora

C-reactive protein, group and save, cultures of all potential pathogenic sites including blood cultures (both peripheral and also from all intravenous catheter lumens), chest radiography, urinalysis and culture, in addition to any other relevant investigations (e.g. nasopharyngeal aspiration, throat swabs). Blood gases, electrocardiograms, stool and sputum cultures should also be sent if the patient is hypoxic, hypotensive, having diarrhoea, or coughing with productive sputum respectively. Additional potential tests (including how to take samples) are shown in *Table 4*. A raised lactate level should immediately prompt discussion with seniors and/or intensive care staff given its significance as an early marker of reduced organ perfusion and severe sepsis.

Appropriate additional imaging (e.g. ultrasound, computed tomography, magnetic resonance imaging, radionuclide imaging) for patients who are not improving or are at high risk of fungal infections should be discussed with a radiologist.

Conclusions

Neutropenic sepsis is a serious, potentially life-threatening condition. This article has highlighted key information needed to help junior doctors to confidently make the diagnosis and to order appropriate investigations. In conjunction with a second article (which details the management of neutropenic sepsis) the current article aims to reduce the door to needle time for treatment of patients with neutropenic sepsis to improve outcomes. All hospitals are expected to produce local guidelines for the management of neutropenic sepsis and these should be used in conjunction with the advice given in this review. **BJHM**

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Table 4. Additional laboratory investigations for neutropenic patients including appropriate sampling. Discussion with microbiology or seniors is advised before sampling

Sample required	Appropriate sampling
Mycobacterium	Send in special MBBact bottles (may need to obtain from microbiology)
Respiratory virus antigens	Send respiratory secretions (throat swab, nasal wash, nasopharyngeal aspirate, bronchoalveolar lavage) for rapid antigen testing with immunofluorescence and/or polymerase chain reaction (polymerase chain reaction is the preferred method)
Viral serology	Send a clotted blood sample (7–10 ml) in plain (red-top) tube, plus a convalescent sample 10–14 days later if appropriate
Varicella zoster	Send swabs touched against an open lesion, or a glass slide touched against an opened lesion and allowed to air dry, and transport in a slide carrier
Herpes simplex	Send swabs touched against an open lesion, or a glass slide touched against an opened lesion and allowed to air dry, and transport in a slide carrier
IgG or IgM	Send serum (clotted blood, red-top tube)
Invasive fungal infection	Send EDTA blood (purple-top tube) for Aspergillus and Candida polymerase chain reaction; Aspergillus galactomannan assay is particularly useful on clotted blood in red-top tube, and CSF) Also send sputum, bronchoalveolar lavage, CSF or skin biopsy for fungal culture and polymerase chain reaction
Cytomegalovirus	Relevant particularly after bone marrow transplantation. Send EDTA blood (purple-top tube) for cytomegalovirus polymerase chain reaction
Pneumocystis pneumonia (*Pneumocystis jirovecii)*	Send bronchial washings (or if these are unobtainable sputum, or EDTA blood – purple-top tube) for polymerase chain reaction

KEY POINTS

- Neutropenic sepsis is defined as sepsis in any patient with a neutrophil count of $<1.0 \times 10^9$/litre.
- Sepsis is the major cause of mortality in patients with neutropenia.
- Any patient with potential neutropenic sepsis must be assessed and managed as an emergency.
- The National Confidential Enquiry into Patient Outcome and Death has highlighted inadequacies in the management of febrile neutropenia (leading to neutropenic sepsis) in the UK.
- Assessment of the patient with patient with neutropenic sepsis aims to quickly identify the severity and likely source of sepsis to guide further management.
- Senior support and advice should be sought at an early stage.
- Local policies for management of neutropenic sepsis must be consulted when treating these patients.