Management of the patient with neutropenic sepsis

Introduction

Neutropenic sepsis is defined as sepsis in any patient with a neutrophil count of $<1.0x10^9$/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 $<1.0x10^9$/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). Diagnosis and investigation of the patient with neutropenic sepsis was described in the previous issue of *BJHM* (73(6), 2012, p. C89). The current article focuses on the management 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.

Management

Initial management

The most important intervention in neutropenic sepsis is rapid diagnosis followed by prompt and appropriate treatment. This includes appropriate antibiotics, fluid resuscitation and correction of any abnormalities found on investigations. It is essential that any suspected case of neutropenic sepsis is discussed with a senior doctor at an early stage (a specialist registrar as a minimum, especially if adverse features are present according to *Figures 1* and *2*). Low-risk patients are all those patients not in the high-risk categories, although if there is doubt, treat as a high-risk patient. Prompt involvement of intensive care specialists is also important, depending on the clinical condition of the patient.

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 (high efficiency particulate air) filtered air. However, for patients with shorter duration and less profound neutropenia less guidance exists and local hospital policies should be followed.

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 ($<4\times10^9$ cells/litre or $>12\times10^9$ 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 or serum lactate >4 mmol/dl
Septicaemia is sepsis that has an infection in the bloodstream itself	

Antibiotic therapy

Infections are most commonly caused by Gram-positive cocci (e.g. coagulase negative staphylococci, *Staphylococcus aureus*, viridans streptococci) or Gram-negative bacilli (e.g. *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*). High-risk patients (*Figure 2*) should be treated urgently according to individual hospital guidelines for antibiotic prescribing in neutropenic sepsis. These are generally found on hospital intranets and in accident and emergency departments.

Most guidelines suggest treatment with duo-therapy including an antipseudomonal penicillin (e.g. Tazocin) plus an agent to cover Gram-negative sepsis such as gentamicin. However, gentamicin is nephrotoxic, so should be avoided in those with renal impairment, those at high risk of renal failure (e.g. myeloma patients) or those receiving other nephrotoxic treatments. Guidelines for treating such patients vary from hospital to hospital therefore local advice should be sought from a microbiologist (or from local guidelines) in these situations (likewise in the event of a patient with a penicillin or other relevant drug allergy). Levels also need to be monitored according to guidelines in the British National Formulary.

Additional antibiotic cover should be considered if the patient has severe mucositis or there is evidence of intravenous catheter-related infection (e.g. if there are signs of inflammation around the catheter insertion point or along the track). In these situations antibiotics should provide cover against Gram-negative and staphylococcal organisms respectively, and will depend on local guidelines but may include teicoplanin or vancomycin particularly if meticillin-resistant *S. aureus* or penicillin-resistant pneumococci are likely (e.g. if the patient has suffered these infections in the past). If there is any evidence of a subcutaneous tunnel or peri-port infection, septic emboli, hypotension associated with catheter use or a non-patent catheter, removal of the intravenous line should be seriously considered and immediate discussion with a specialist registrar or consultant is suggested.

Most guidelines for treatment of low-risk patients with neutropenia (i.e. any patients other than those listed in *Figure 2*) suggest intravenous ciprofloxacin and co-amoxiclav (although some hospital guidelines do not include ciprofloxacin to reduce resistance and *C. difficile* infection rates). Oral antibiotics may be substituted for intravenous antibiotics at the discretion of the clinician.

Aciclovir should be considered if patients have lesions caused by herpes simplex or varicella zoster if they are neutropenic and febrile, even if it is thought that the lesions are not contributing to the sepsis. If a lower respiratory tract infection is suspected, particularly if influenza is being considered, antiviral therapy (oseltamivir or zanamivir) should be started as soon as possible once a nasopharyngeal or other appropriate aspirates have been taken for a viral screen. Cover for atypical organisms should also be considered if a respiratory focus is suspected. Consideration should also be given to the possibility of cytomegalovirus if patients have pneumonitis, gastrointestinal or CNS symptoms especially if the patient has received a bone marrow transplant. Early advice from a haematology or microbiology registrar should be sought.

The role of granulocyte-colony stimulating factor to help neutrophil recovery in patients with neutropenic sepsis remains controversial and granulocyte-colony stimulating factor should only be prescribed after discussion with a senior doctor. Although use of granulocyte-colony stimulating factor reduces the time to neutrophil recovery and the length of hospitalization, overall mortality appears not to be influenced although individual factors will need to be taken into account (e.g. the chemotherapy regimen being used, the predicted duration of neutropenia, an individual's previous neutrophil response to chemotherapy, and the patient's clinical state) (Clark et al, 2005; Aapro et al, 2011).

In patients with severe sepsis, or requiring additional support as a result of organ failure, growth factor support is recommended as reduced time to neutrophil recovery may reduce organ damage and increase survival. Controversially, there are also reports of respiratory deterioration with acute respiratory distress syndrome during granulocyte-colony stimulating factor-induced neutropenia recovery (Azoulay et al, 2002).

Figure 2. High-risk patients with neutropenia (Haji-Michael et al, 2010).

Patients with neutropenia are considered high risk if any of the following apply (if none of below apply, consider the patient low risk):	
Those who are inpatients when fever and neutropenia develop	
Those requiring admission for medical problems in addition to neutropenia and fever	
Uncontrolled malignancy (e.g. progression of disease despite previous therapy, acute leukaemia not in remission)	
Immunosuppressive therapy (e.g. steroids, ciclosporin)	
Specific foci of infection (e.g. intravascular catheter infection, tunnel infection, new pulmonary infiltrates)	
Presence of any of the following:	Abdominal pain, nausea and vomiting
	Neurological or mental changes
	Allogeneic bone marrow transplants or autologous bone marrow transplants
	Pregnancy
	HIV
	Antibiotics within 72 hours
	Renal failure (creatinine clearance <30 ml/min)
	Hepatic failure
	Respiratory insufficiency
	Haemodynamic instability
	Inability to take oral medications
Neutropenia likely to last >10 days	
Recent fludarabine treatment	
Phase I or phase II clinical trial patients	

Subsequent management

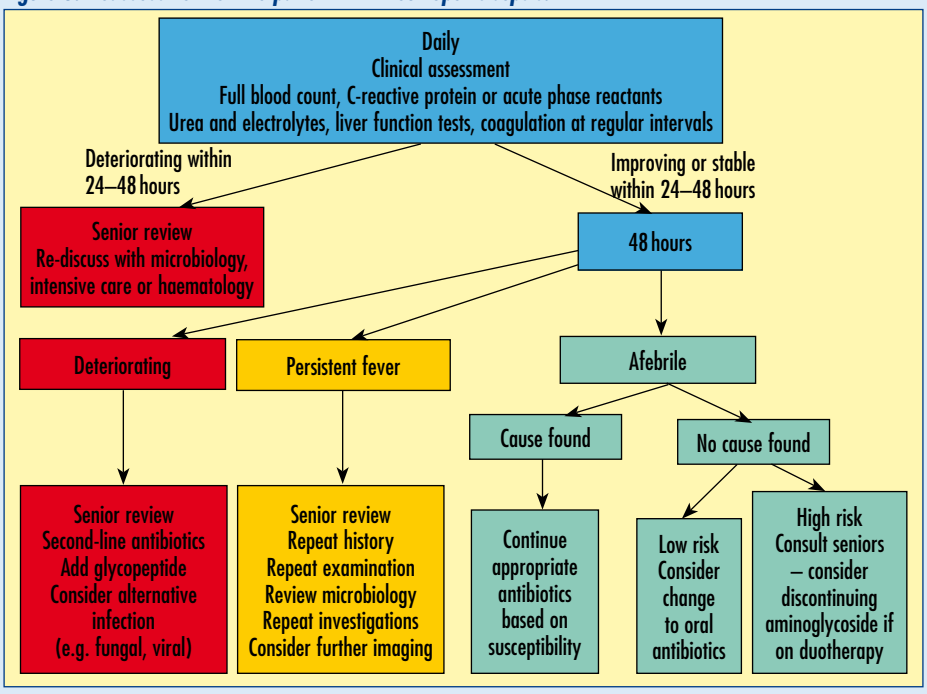
Regular re-assessment of a neutropenic patient is essential. Follow-up assessment and actions needed in the event of further deterioration are detailed in *Figure 3*. Once culture and other test results become available modifications can be made to initial empirical treatment but all changes should be discussed with microbiology. Recommendations for stopping antibiotics in patients with resolved neutropenic sepsis depend on a number of criteria although decisions about continuing therapy should be made after consultation with a senior. Guidelines state that antibiotics can be stopped in patients with neutrophil counts $\geq 0.5 \times 10^9$/litre if the patient has been apyrexial for 3 days and if the following criteria are met (Haji-Michael et al, 2010):

- Cultures are negative at the onset or indicate that the organism has been eradicated
- All sites of infection have resolved
- Patient is free of signs and symptoms
- Levels of acute phase reactants, e.g. C-reactive protein, are falling.

If the patient's neutrophil count remains less than 0.5×10^9/litre but he/she is low risk and meets the above criteria, antibiotics can be stopped when the patient has been apyrexial for 5–7 days. If the patient's neutrophil count remains $<0.5 \times 10^9$/litre and the patient is high risk antibiotics should be continued so that the patient receives at least 10 days treatment in total or until neutrophils are 0.5×10^9/litre. Any patient who remains neutropenic but whose antibiotics have been stopped should be closely monitored for signs of infection and fever. If these occur, intravenous antibiotics should be re-started.

The decision to stop any medication likely to be causing neutropenia should be made in consultation with senior colleagues. Generally, if the neutropenia is not too severe ($>0.5 \times 10^9$/litre), and the medication is essential, it may be continued with close monitoring. However, if the neutrophil count drops to 0.5×10^9/litre or signs of sepsis develop, the medication should be discontinued immediately.

Figure 3. Reassessment of the patient with neutropenic sepsis.



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.
- Neutropenic sepsis must be 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.
- Local policies for management of neutropenic sepsis must be consulted when treating these patients.
- The most important intervention in neutropenic sepsis is rapid diagnosis followed by prompt and appropriate treatment.
- If neutropenic sepsis is suspected intravenous antibiotics should be administered immediately.
- Involvement of senior clinicians at an early stage is essential.

Conclusions

Neutropenic sepsis is a serious, potentially life-threatening condition. This review has highlighted key information needed to help junior doctors to promptly start correct treatment and to involve seniors early in the care of the patient with aim of reducing the door to needle time for administration of appropriate antibiotic therapy. 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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