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# CME Haematology

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## Neutropenic sepsis: management and complications

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### Background

Neutropenic sepsis (NS) is a common and predictable complication of bone marrow disorders and cytotoxic chemotherapy, with an estimated incidence of 70–100% during the neutropenic phase after intensive chemotherapy.[1] Patients with neutropenia are vulnerable to invasive infection, which can be rapidly overwhelming, causing septic shock and death. There is widespread recognition that NS, as with all forms of sepsis, is a medical emergency in which urgent administration of intravenous fluid and antibiotics have proven benefits on outcome.[2,3] Despite this, NS remains a major complication of cancer chemotherapy, with an associated mortality rate ranging from 2% to 21%.[4–6]

### Why does good management matter?

The National Institute for Health and Clinical Excellence (NICE) of the UK recently analysed official death statistics, demonstrating a doubling of the annual mortality rate from NS between 2001 to 2010, with a peak of 700 deaths in 2010.[7] Even after factoring in the increased numbers of cancer diagnoses over the same period, the proportion of deaths resulting from NS continues to rise, particularly in the 15–24-year age group. A key question for clinicians is whether, with better management, a proportion of these deaths could be avoided. Current data demonstrate marked regional inconsistencies in the immediate management of NS in the UK, with delayed administration of antibiotics in most patients, suggesting that there is considerable scope for improvement.[8]

### Initial assessment

The defining presenting features of sepsis are two or more of fever (>38°C) or hypothermia (<36°C), tachycardia (>90 beats per minute (bpm)) and tachypnoea (>20 bpm).[9] However, in many patients with neutropenia, particularly those taking steroids, the systemic inflammatory response to infection is attenuated, meaning that the diagnostic criteria for sepsis might not be fulfilled, and a clear focus of infection might not be found.[10] For this reason, there must be a high index of suspicion for infection in all patients undergoing chemotherapy who become unwell, even in the absence of fever.[1,7,10–12] The only evidence of NS might be a general deterioration in condition, or non-specific signs, such as confusion. The neutrophil count typically reaches its nadir approximately five to seven days after administration of chemotherapy, at which time patients are particularly susceptible to infection.[13]

In hospital, immediate assessment of the airway, breathing and circulation, with vigorous resuscitation where necessary, should be swiftly followed by history and examination, focusing on the skin, oropharynx, intravascular access sites and perineum in particular as possible sources of infection. A digital rectal examination should be avoided owing to the risk of causing translocation of gut flora through the rectal mucosa. Occult sources of infection are summarised in Box 1.[14] As well as bedside observations and initiation of appropriate monitoring, blood should be sampled for: full blood count, kidney and liver function tests, C-reactive protein and blood cultures.[7] All patients with a central access device should have paired cultures on admission from the line and periphery. Samples from skin lesions, diarrhoea, urine and other possible foci of infection, if appropriate, should also be taken for culture.

### Immediate treatment

#### *Urgent, empirical antibiotics*

Prompt administration of empirical antibiotics (and fluids) is vital. Delaying treatment until neutropenia is confirmed with a full blood count is dangerous and carries with it a significant risk of death.[3,15] The gold standard time of the international Surviving Sepsis Campaign of 1 h to antibiotic administration is now an integral part of most NS hospital protocols, which advocate empirical, broad-spectrum, intravenous antibiotics as soon as possible (within 1 h), plus intravenous crystalloid fluids.[2] Removal of central venous access devices as part of the initial empiric management of suspected NS is not recommended unless there is clear evidence of a line infection.

Antibiotic regimens vary regionally, but recent NICE guidance advocates initial empirical monotherapy for suspected NS with Tazocin™ (a combination of piperacillin and tazobactam) only.[7] Combination treatment with an additional aminoglycoside is not routinely recommended because this does not obviously improve efficacy, but is associated with an increased risk of renal toxicity.[7,16] Common bacterial pathogens in patients with NS are summarised in Box 2.[10]

**Box 1. Occult sources of infection in haematology patients.[14]**

- Empyema
- Endocarditis
- Intravenous catheter
- Meningitis
- Neutropaenic enterocolitis
- Osteomyelitis
- Perforated viscus
- Sinusitis
- Skin and/or soft tissue

### *Locating the source of infection*

Following initial treatment, further investigations to identify the underlying cause of the sepsis are recommended. All patients should have paired cultures on admission from a line and periphery. If the patient's initial bloods were taken from a central venous access device, further peripheral blood cultures are essential, and urinalysis and chest X-ray should be considered.

### *Confirming the diagnosis and/or risk assessment*

Precise definitions of NS vary, but most protocols require two criteria to be met: a neutrophil count of $\leqslant 0.5 \times 10^9$/l and either a fever of $\geqslant 38.0$°C or other signs and symptoms consistent with clinically significant sepsis.[8] Once NS has been confirmed and initial management instigated, a haematology or oncology specialist will risk-stratify the patient to determine whether they might be suitable for outpatient treatment. Various clinical risk prediction systems exist, the most commonly used and widely validated of which is the Multinational Association for Supportive Care in Cancer (MASCC) index (Table 1).[17] Certain low-risk patients, defined as those with a high probability of fever resolution without the development of serious complications, might be suitable for outpatient treatment with oral antibiotics.[7] Most experts consider high-risk patients to be those with anticipated prolonged (more than seven days) hospital stay, profound neutropenia ($<0.1 \times 10^9$/l), and/or significant medical comorbidities, including hypotension, pneumonia and new-onset abdominal pain.[10] Risk stratification is complex and non-specialists should treat all patients as high risk and prescribe intravenous antibiotics, unless advised otherwise.

### *Immediate complications and management of neutropaenic sepsis*

Severe sepsis (in which signs of organ dysfunction or hypoperfusion complicate sepsis) and septic shock (in which hypotension persists despite adequate fluid resuscitation), frequently and sometimes devastatingly complicate the prognosis of patients with NS.[15] Cardiovascular insufficiency in patients with NS – as indicated by refractory hypotension or signs of inadequate oxygen delivery to end organs, such as confusion and oliguria –mandates early involvement of the critical care team, because these patients are likely to require advanced monitoring and cardiorespiratory support. The mortality from severe sepsis in patients with haematological malignancies has been estimated at 36%, using data from disease registries in the USA.[18]

The key to successful initial resuscitation in severe sepsis in all patients, neutropaenic or otherwise, is the rapid correction of hypovolaemia and restoration of oxygen delivery, using an immediate challenge of a compound sodium lactate solution, such as Hartmann's, with response measured by blood pressure, heart rate, urine output and, if available, central venous pressure (CVP).[14] Given that goal-directed therapy, titrated to the CVP among other parameters, has proven benefits on outcome, urgent central venous catheter placement is recommended.[19] Single and multi-organ failure are common, with examples including acute respiratory distress syndrome, acute kidney injury, congestive cardiac failure and disseminated intravascular coagulation. Their management is beyond the scope of this paper, but all are likely to require an intensive care environment.

## Key points

- **Neutropenic sepsis is a medical emergency in which broad-spectrum antibiotics must be given without delay**
- **In total, 75% of hospital patients do not receive their antibiotics within the 1 h target door-to-needle time**
- **The typical presenting features of sepsis can be blunted or absent in patients with neutropenia, meaning that a high index of suspicion is essential in all patients taking anticancer treatment**
- **Patients with neutropenia are at high risk of severe sepsis and septic shock, with a mortality of >36%**
- **Early input must be sought from the critical care team, particularly when patients are hypotensive**

**KEY WORDS: neutropaenic sepsis, broad-spectrum antibiotics, severe sepsis, septic shock**

## Subsequent management

### *Review at 48 h*

In patients with uncomplicated NS managed in a standard inpatient setting, daily review and reassessment of risk, using a validated tool such as the MASCC index, are essential.[7] If, at 48 h, the patient is afebrile or reassessed as being at low risk of septic complications, switching from intravenous to oral antibiotics might be appropriate. Alternatively, if the patient is taking dual therapy, the aminoglycoside can be discontinued at this point. Discharge home might be possible, provided clinical and domestic circumstances allow.

If fever persists at 48 h, or the patient's condition deteriorates, full reassessment is necessary, and fungal or atypical infection should be suspected. Primary empirical antibiotics should not be changed at this point unless there is a clinical deterioration or a specific microbiological indication.[7,10] In the event of deterioration, antibacterial therapy should be rotated or cover broadened, as per local policy.

### *Management post-48 h*

If fever persists beyond four to six days, investigations for fungal infection should be instigated; usually a high-resolution CT scan of chest in the first instance. Such patients should also be assessed by an infectious diseases physician or clinical microbiologist, and empirical antifungals considered.[10] Commonly used antifungals, which must provide Aspergillus cover, include caspofungin, voriconazole and liposomal amphotericin B (AmBisome™).

Overall duration of antibiotics is variable but, in general, if a patient has been afebrile for five to seven days and has had no complications, discontinuing antibiotics is often appropriate, even if the neutrophil count remains below $0.5 \times 10^9$/l.

**Box 2. Common bacterial pathogens in neutropaenic sepsis.[10]**

**Gram-positive pathogens**

Coagulase-negative *staphylococci*

*Staphylococcus aureus* (including methicillin-resistant strains)

*Enterococcus species* (including vancomycin-resistant strains)

Viridans group *streptococci*

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

**Gram-negative pathogens**

*Escherichia coli*

*Klebsiella* spp.

*Enterobacter* spp.

*Pseudomonas aeruginosa*

spp. = species.

**Table 1. Multinational Association for Supportive Care in Cancer scoring index for risk-stratifying patients with neutropaenic sepsis.[17]**

| Characteristic | Score |
|---|---|
| Burden of illness | |
| No or mild symptoms | 5 |
| Moderate symptoms | 3 |
| Severe symptoms | 0 |
| No hypotension (systolic blood pressure >90 mmHg) | 5 |
| No chronic obstructive pulmonary disease | 4 |
| Solid tumour or no previous fungal infection | 4 |
| No dehydration | 3 |
| Outpatient at onset of fever | 3 |
| Age <60 years | 2 |

Score range 0–26: score ⩾21 indicates low risk; <21 indicates high risk.

### *Adjunctive therapies*

Steroids, intravenous immunoglobulin and activated protein C have all be used as adjuncts in patients with severe sepsis or shocked patients with neutropenia, but none improve outcomes unequivocally, or are recommended in the new NICE guidance on NS.[7,14] Clinical guidelines from the European Society for Medical Oncology do advise the use of granulocyte colony-stimulating factor (G-CSF) in certain, high-risk patients with NS, for example, those with confirmed bacteraemia, hypotension, pneumonia and more than seven days of fever.[20]

## Conclusions

NS is a medical emergency requiring immediate evaluation and treatment with empirical, broad-spectrum antibiotics, without waiting for a full blood count. New national NICE guidance provides a standardised care protocol for use throughout the UK for the first time.

## References


1 Penack O, Buchheidt D, Christopeit M *et al.* Management of sepsis in neutropenic patients: guidelines from the infectious diseases working party of the German Society of Hematology and Oncology. *Ann Oncol* 2010; doi: 10.1093/annonc/mdq442.

2 Dellinger RP, Levy MM, Carlet JM *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008;36:296–327.

3 Gaieski DF, Mikkelsen ME, Band RA *et al.* Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. *Crit Care Med* 2010;38:1045–53.

4 Herbst C, Naumann F, Kruse EB *et al.* Prophylactic antibiotics or G-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy. *Cochrane Database Syst Rev* 2009:CD007107.

5 Smith TJ, Khatcheressian J, Lyman GH *et al.* 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;24:3187–205.

6 Kuderer NM, Dale DC, Crawford J *et al.* Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006;106:2258–66.

7 National Institute for Clinical Excellence and the National Collaborating Centre for Cancer. *Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients.* Cardiff: NCC-C, 2012. www.nice.org.uk/nicemedia/live/13905/60864/60864.pdf [Accessed 28 February 2013].

8 Clarke RT, Warnick J, Stretton K, Littlewood TJ. Improving the immediate management of neutropenic sepsis in the UK: lessons from a national audit. *Br J Haematol* 2011;153:773–9.

9 Bone RC, Balk RA, Cerra FB *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992;101:1644–55.

10 Freifeld AG, Bow EJ, Sepkowitz KA *et al.* Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2011;52:e56–93.

11 de Naurois J, Novitzky-Basso I, Gill MJ *et al.* Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol* 2010;21:v252–v56.

12 National Comprehensive Cancer Network. *NCCN clinical practice guidelines in oncology. Prevention and treatment of cancer-related infections.* Version 1.2012.NCCN: Fort Washington, 2012. www.nccn.org/professionals/physician_gls/pdf/infections.pdf [Accessed 28 February 2013].

13 Holmes FA, Jones SE, O'Shaughnessy J *et al.* Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. *Ann Oncol* 2002;13:903–9.

14 Cohen J, Drage S. How I manage haematology patients with septic shock. *Br J Haematol* 2011;152:380–91.

15 Kumar A, Roberts D, Wood KE *et al.* Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;34:1589–96.

16 Paul M, Soares-Weiser K, Grozinsky S, Leibovici L. Beta-lactam versus beta-lactam–aminoglycoside combination therapy in cancer patients with neutropaenia. *Cochrane Database Syst Rev* 2003:CD003038.

17 Klastersky J, Paesmans M, Rubenstein EB *et al.* The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000;18:3038–51.

18 Williams MD, Braun LA, Cooper LM *et al.* Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care* 2004;8:R291–8.

19 Rivers E, Nguyen B, Havstad S *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.

20 Crawford J, Caserta C, Roila F, Group ObotEGW. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. *Annals of Oncology* 2010;21:v248–51.


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