Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients

NICE guideline

Draft for consultation, February 2012

If you wish to comment on this version of the guideline, please be aware that all the supporting information and evidence is contained in the full version.

Contents

Introduction

Neutropenic sepsis is a potentially fatal complication of anti-cancer treatment (particularly chemotherapy). Mortality rates ranging between 2 and 21% have been reported in adults. Aggressive use of inpatient intravenous antibiotic therapy has reduced morbidity and mortality rates, and intensive care management is now needed in fewer than 5% of cases in England.

Systemic therapies to treat cancer can suppress the ability of bone marrow to respond to infection. This is particularly the case with systemic chemotherapy, although radiotherapy can also cause such suppression.

Chemotherapy is most commonly given in a day-case or outpatient setting so most episodes of obvious sepsis, and fever in a person with potential sepsis, present in the community. People receiving chemotherapy and their carers need to be told about the risk of neutropenic sepsis and the warning signs and symptoms. Neutropenic sepsis is a medical emergency that requires immediate hospital investigation and treatment.

A report by the National Confidential Enquiry into Patient Outcome and Death ('Systemic anti-cancer therapy: for better for worse?' [2008]) and a follow-up report by the National Chemotherapy Advisory Group ('Chemotherapy services in England: ensuring quality and safety' [2010]) highlighted problems in the management of neutropenic sepsis in adults receiving chemotherapy. These included inadequate management of neutropenic fever leading to avoidable deaths and the need for systems for urgent assessment and organisation-level policies for dealing with neutropenic fever. These reports also highlighted variation in the provision of information on the treatment of side effects and on access to 24-hour telephone advice.

There is national variation in the use of primary and secondary prophylaxis, risk stratification in episodes of neutropenic sepsis, oral or intravenous antibiotics, bone marrow growth factors, and inpatient or outpatient management policies.

This guideline aims to improve outcomes by providing evidence-based recommendations on the prevention, identification and management of this life-threatening complication of cancer treatment.

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Patient-centred care

This guideline offers best practice advice on the care of patients with neutropenic sepsis resulting from anti-cancer treatment.

Treatment and care should take into account patients' needs and preferences. People with neutropenic sepsis resulting from anti-cancer treatment should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent and the code of practice that accompanies the Mental Capacity Act. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

If the patient is under 16, healthcare professionals should follow the guidelines in the Department of Health's 'Seeking consent: working with children'.

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in the Department of Health's 'Transition: getting it right for young people'.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with neutropenic sepsis resulting

from anti-cancer treatment. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

Key priorities for implementation

The following recommendations have been identified as priorities for implementation.

Information, support and training

Information and support for patients and carers

- Provide patients having anti-cancer treatment and their carers with written and verbal information, both before starting and throughout their anti-cancer treatment, on:
  - neutropenic sepsis
  - how and when to contact 24-hour specialist oncology advice
  - how and when to seek emergency care. **[1.1.1.1]**

Reducing the risk of septic complications of anti-cancer treatment

- Offer prophylaxis with a quinolone during the expected period of neutropenia to all adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours. **[1.2.1.1]**

Managing suspected neutropenic sepsis in secondary and tertiary care

Emergency treatment and assessment

- Treat suspected neutropenic sepsis as an acute medical emergency and offer empiric antibiotic therapy immediately. **[1.4.1.1]**

- Include in the initial clinical assessment of patients with suspected neutropenic sepsis:
  - history and examination
  - full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate and blood culture. **[1.4.1.2]**

Starting antibiotic therapy

All patients

- Offer beta lactam monotherapy with piperacillin-tazobactam as initial empiric antibiotic therapy for suspected neutropenic sepsis unless there are local microbiological contraindications. **[1.4.3.1]**
- Do not offer an aminoglycoside, either as monotherapy or in dual therapy, for the initial empiric treatment of suspected neutropenic sepsis unless there are local microbiological indications. **[1.4.3.2**]

Confirming a diagnosis of neutropenic sepsis

- Diagnose neutropenic sepsis in patients with a temperature higher than 38^{o}C and a neutrophil count lower than 0.5 × 10^{9}/litre. **[1.4.4.1]**

Managing confirmed neutropenic sepsis

Assessing the patient's risk of septic complications

- A member of the oncology team should assess the patient's risk of septic complications as soon as possible and within 48 hours of presentation to secondary or tertiary care, basing the risk assessment on presentation features and using a validated risk scoring system[1]. **[1.5.1.1]**

Patients at low risk of septic complications

- Offer outpatient antibiotic therapy to patients with confirmed neutropenic sepsis and a low risk of developing septic complications, taking into account the patient's social and clinical circumstances and discussing with them the need to return to hospital promptly if a problem develops. **[1.5.2.1]**

[1] Validated risk scoring systems include the Multinational Association for Supportive Care in Cancer (MASCC) risk index for adults (aged 18 years and over) (Klastersky J, Paesmans M, Rubenstein EB et al. [2000] The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients [Journal of Clinical Oncology 18: 3038–51]) and the modified Alexander rule for children (aged under 18) (Dommett R, Geary J, Freeman S et al. [2009] Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting [European Journal of Cancer 45: 2843–9]).

Patients at high risk of septic complications

- Discharge patients having empiric antibiotic therapy for neutropenic sepsis whose risk of developing septic complications has been re-assessed as low by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment using a validated risk scoring system[2]. **[1.5.3.4]**

[2] Validated risk scoring systems include the Multinational Association for Supportive Care in Cancer (MASCC) risk index for adults (aged 18 years and over) (Klastersky J, Paesmans M, Rubenstein EB et al. [2000] The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients [Journal of Clinical Oncology 18: 3038–51]) and the modified Alexander rule for children (aged under 18) (Dommett R, Geary J, Freeman S et al. [2009] Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting [European Journal of Cancer 45: 2843–9]).

Guidance

The following guidance is based on the best available evidence. The full guideline [hyperlink to be added for final publication] gives details of the methods and the evidence used to develop the guidance.

The recommendations in this guideline were developed after discussion of the relevance of the evidence to children, young people and adults with cancer. The recommendations are intended for use in patients of any age. Where age-limited or disease-specific recommendations are made they are clearly indicated as such.

1.1 Information, support and training

1.1.1 Information and support for patients and carers

1.1.1.1 Provide patients having anti-cancer treatment and their carers with written and verbal information, both before starting and throughout their anti-cancer treatment, on:

- neutropenic sepsis
- how and when to contact 24-hour specialist oncology advice
- how and when to seek emergency care.

1.1.2 Training for healthcare professionals

1.1.2.1 Provide training on identifying and managing neutropenic sepsis to healthcare professionals who come into contact with patients on anti-cancer treatment.

1.2 Reducing the risk of septic complications of anti-cancer treatment

1.2.1.1 Offer prophylaxis with a quinolone during the expected period of neutropenia to all adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours.

1.3 When to refer patients in the community for suspected neutropenic sepsis

1.3.1.1 Suspect neutropenic sepsis in patients having anti-cancer treatment who become unwell.

1.3.1.2 Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care.

1.4 Managing suspected neutropenic sepsis in secondary and tertiary care

1.4.1 Emergency treatment and assessment

1.4.1.1 Treat suspected neutropenic sepsis as an acute medical emergency and offer empiric antibiotic therapy immediately.

1.4.1.2 Include in the initial clinical assessment of patients with suspected neutropenic sepsis:

- history and examination
- full blood count, kidney and liver function tests (including albumin), C-reactive protein, lactate and blood culture.

1.4.2 Further assessment

1.4.2.1 After completing the initial clinical assessment identify the underlying cause of the sepsis by carrying out:

- peripheral blood culture in patients with a central venous access device if clinically feasible
- urinalysis in all children aged 5 years and younger.

1.4.2.2 Do not perform a chest X-ray unless clinically indicated.

1.4.3 Starting antibiotic therapy

All patients

1.4.3.1 Offer beta lactam monotherapy with piperacillin-tazobactam as initial empiric antibiotic therapy for suspected neutropenic sepsis unless there are local microbiological contraindications.

1.4.3.2 Do not offer an aminoglycoside, either as monotherapy or in dual therapy, for the initial empiric treatment of suspected neutropenic sepsis unless there are local microbiological indications.

Empiric glycopeptide antibiotics in patients with central venous access devices

1.4.3.3 Do not offer empiric glycopeptide antibiotics to patients with suspected neutropenic sepsis who have central venous access devices.

1.4.3.4 Do not remove central venous access devices as part of the initial empiric management of suspected neutropenic sepsis.

1.4.4 Confirming a diagnosis of neutropenic sepsis

1.4.4.1 Diagnose neutropenic sepsis in patients with a temperature higher than 38^{o}C and a neutrophil count lower than 0.5×10^{9}/litre.

1.5 Managing confirmed neutropenic sepsis

1.5.1 Assessing the patient's risk of septic complications

1.5.1.1 A member of the oncology team should assess the patient's risk of septic complications as soon as possible and within 48 hours of presentation to secondary or tertiary care, basing the risk assessment on presentation features and using a validated risk scoring system[3].

1.5.2 Patients at low risk of septic complications

1.5.2.1 Offer outpatient antibiotic therapy to patients with confirmed neutropenic sepsis and a low risk of developing septic complications, taking into account the patient's social and clinical circumstances and discussing with them the need to return to hospital promptly if a problem develops.

1.5.3 Patients at high risk of septic complications

1.5.3.1 For patients with confirmed neutropenic sepsis, a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment should daily:

- review the patient's clinical status
- re-assess the patient's risk of septic complications ,using a validated risk scoring system[2].

[3] Validated risk scoring systems include the Multinational Association for Supportive Care in Cancer (MASCC) risk index for adults (aged 18 years and over) (Klastersky J, Paesmans M, Rubenstein EB et al. [2000] The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients [Journal of Clinical Oncology 18: 3038–51] and the modified Alexander rule for children (aged under 18) (Dommett R, Geary J, Freeman S et al. [2009] Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting [European Journal of Cancer 45: 2843–9]).

1.5.3.2 Do not switch primary empiric antibiotics in patients with unresponsive fever unless there is clinical deterioration or a microbiological indication.

1.5.3.3 Switch from intravenous to oral antibiotic therapy after 48 hours of treatment in patients whose risk of developing septic complications has been re-assessed as low by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment using a validated risk scoring system[4].

1.5.3.4 Discharge patients having empiric antibiotic therapy for neutropenic sepsis whose risk of developing septic complications has been re-assessed as low by a healthcare professional with recognised professional competence in managing complications of anti-cancer treatment using a validated risk scoring system[4].

1.5.4 Duration of empiric antibiotic treatment

1.5.4.1 Continue inpatient empiric antibiotic therapy in patients who have unresponsive fever unless an alternative cause of fever is likely.

1.5.4.2 Discontinue empiric antibiotic therapy in patients whose neutropenic sepsis has responded to treatment, irrespective of neutrophil count.

[4] Validated risk scoring systems include the Multinational Association for Supportive Care in Cancer (MASCC) risk index for adults (aged 18 years and over) (Klastersky J, Paesmans M, Rubenstein EB et al. [2000] The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients [Journal of Clinical Oncology 18: 3038–51] and the modified Alexander rule for children (aged under 18) (Dommett R, Geary J, Freeman S et al. [2009] Successful introduction and audit of a step-down oral antibiotic strategy for low risk paediatric febrile neutropaenia in a UK, multicentre, shared care setting [European Journal of Cancer 45: 2843–9]).

2 Notes on the scope of the guidance

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover. The scope of this guideline is available here.

Groups that are covered

- Children, young people and adults with cancer (haematological and solid tumour malignancies) receiving anti-cancer treatment.
- No subgroups needing special consideration have been identified.

Groups that are not covered

- Children, young people and adults with neutropenia or neutropenic sepsis not caused by anti-cancer treatment.

How this guideline was developed

NICE commissioned the National Collaborating Centre for Cancer to develop this guideline. The Centre established a Guideline Development Group (see appendix A), which reviewed the evidence and developed the recommendations.

There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available.

3 Implementation

NICE has developed tools to help organisations implement this guidance.

Note: these details will apply when the guideline is published.

4 Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

4.1 Service provision for neutropenic sepsis in patients with cancer

A prospective national cohort study to assess the incidence of suspected and proven neutropenic sepsis in patients having anti-cancer treatment.

Why this is important

The incidence of suspected neutropenic sepsis in England and Wales is difficult to determine. A national cohort study of patients referred for suspected neutropenic sepsis including diagnoses and clinical outcomes should be undertaken to improve service planning and delivery. Such a study may also generate hypotheses concerning more and less efficient methods of delivering services for neutropenic sepsis, which could then be formally tested.

4.2 Patient support and information

A descriptive study involving patients who have had neutropenic sepsis and their carers to be undertaken to find out what types of support and information patients and carers were given, which of these they found helpful or unhelpful, and whether they think additional or different types of support or information are needed.

Why this is important

There is a lack of research on the experience of patients who have had neutropenic sepsis and their carers. Better knowledge of the support and information patients and carers are given, how helpful they find it and how they think it could be improved will allow us to develop different approaches to providing information and support and test these in practice. This research could improve the experience of patients, and potentially their clinical outcomes. It may also highlight important inequities and suggest ways of addressing them.

4.3 Signs and symptoms that predict neutropenic sepsis in the community

A prospective study should be carried out to determine which signs and symptoms experienced by patients in the community predict neutropenic sepsis and the outcomes of these episodes.

Why this is important

The initial decision to refer to secondary or tertiary care for investigation for suspected neutropenic sepsis is an important step that has both risks and benefits. An over-inclusive approach will inconvenience many patients and carers, expose patients to unnecessary invasive testing and increase resource use by the health service. Referral criteria that are too narrow will delay the emergency treatment of infection and may lead to death, increased need for intensive or critical care facilities, and reduced overall quality of life for patients with cancer and their carers. The current research base in this area is weak and largely extrapolated from selected populations in hospitals. A clearer, quantitative understanding of how the features of neutropenic sepsis appear in patients may lead to more accurate referral criteria for suspected neutropenic sepsis.

4.4 Reducing the risk of complications of anti-cancer treatment in children and young people

Randomised studies should be undertaken to investigate the cost effectiveness of primary prophylaxis of neutropenic sepsis with antibiotics and/or granulocyte colony-stimulating factor (GCSF) preparations in children and young people having treatment for solid tumours or haematological malignancies, or stem cell transplantation.

Why this is important

Data from adult studies suggest that antibiotic prophylaxis with quinolone antibiotics protects against neutropenic sepsis and death. In children and young people the infecting agents in neutropenic sepsis are often different from the agents that infect adults. Children and young people also differ in the types of malignancies and anti-cancer treatments they have. Adverse

reactions to treatment with quinolones and subcutaneous injections are also different in children and young people, and they are thought to have greater difficulty adhering to daily medication. The effect of each of these differences is unclear, but it is known that children and young people have higher death rates from neutropenic sepsis than adults. Formal randomised studies comparing management strategies using GCSF, quinolone antibiotics, or GCSF plus quinolone antibiotics are needed. The studies should measure overall mortality, infectious episodes, quality of life and adverse events, and use qualitative methods to investigate the experiences of children and young people having anti-cancer treatment.

4.5 Switching from inpatient intravenous to outpatient oral antibiotic therapy in patients with neutropenic sepsis

A randomised controlled trial should be undertaken to evaluate the clinical and cost effectiveness of stopping intravenous antibiotic therapy or switching to oral therapy within the first 24 hours of treatment in patients with neutropenic sepsis who are having treatment with intravenous antibiotics. The outcomes to be measured are overtreatment, death, need for critical care, length of hospital stay, duration of fever and quality of life.

Why this is important

The Guideline Development Group found moderately strong evidence to support the use of outpatient therapies for patients with neutropenic sepsis who are at low risk of severe infection. These studies switched from inpatient to outpatient treatment at a variety of time points. A meta-regression undertaken by the Guideline Development Group suggested that very early (before 24 hours) discharge is associated with a greater risk of re-admission and need to change treatments, but the evidence was sparse. If a short period of hospital admission was found to be safe and effective for selected patients with neutropenic sepsis, it could provide considerable improvements in their quality of life and reduce the resource burden on hospitals.

5 Other versions of this guideline

5.1 Full guideline

The full guideline, 'Neutropenic sepsis: prevention and management of neutropenic sepsis in cancer patients' contains details of the methods and evidence used to develop the guideline. It is published by the National Collaborating Centre for Cancer, and is available from our website. Note: these details will apply to the published full guideline.

5.2 NICE pathway

The recommendations from this guideline have been incorporated into a NICE pathway. Note: these details will apply when the guideline is published.

5.3 'Understanding NICE guidance'

A summary for patients and carers ('Understanding NICE guidance') is available.

We encourage NHS and voluntary sector organisations to use text from this booklet in their own information about neutropenic sepsis.

6 Related NICE guidance

Published

- Colorectal cancer. NICE clinical guideline 131 (2011).
- Ovarian cancer. NICE clinical guideline 122 (2011).
- Lung cancer (update). NICE clinical guideline 121 (2011).
- Metastatic malignant disease of unknown primary origin NICE clinical guideline 104 (2010).
- Advanced breast cancer. NICE clinical guideline 81 (2009).
- Early and locally advanced breast cancer. NICE clinical guideline 80 (2009).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Prostate cancer. NICE clinical guideline 58 (2008).
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007).

- Improving outcomes for people with brain and other CNS tumours. NICE cancer service guidance (2006).
- Improving outcomes for people with sarcoma. NICE cancer service guidance (2006).
- Improving outcomes for people with skin tumours including melanoma. NICE cancer service guidance (2006).
- Improving outcomes in children and young people with cancer. NICE cancer service guidance (2005).
- Improving outcomes in colorectal cancers. NICE cancer service guidance (2004).
- Improving outcomes in head and neck cancers. NICE cancer service guidance (2004).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).
- Improving outcomes in haematological cancers. NICE cancer service guidance (2003).
- Improving outcomes in breast cancer. NICE cancer service guidance (2002).
- Improving outcomes in urological cancers. NICE cancer service guidance (2002).
- Improving outcomes in upper gastro-intestinal cancers. Service guidance (2001).
- Improving outcomes in gynaecological cancers. Service guidance (1999).
- Improving outcomes in lung cancer. Service guidance (1998).

Under development

NICE is developing the following guidance (details available from the NICE website):

- Familial breast cancer (update). NICE clinical guideline. Publication expected April 2013.
- Prostate cancer (update). NICE clinical guideline. Publication date to be confirmed.

- Referral for suspected cancer (update). NICE clinical guideline. Publication date to be confirmed.
- Bladder cancer. NICE clinical guideline. Publication date to be confirmed.

7 Updating the guideline

NICE clinical guidelines are updated so that recommendations take into account important new information. New evidence is checked 3 years after publication, and healthcare professionals and patients are asked for their views; we use this information to decide whether all or part of a guideline needs updating. If important new evidence is published at other times, we may decide to do a more rapid update of some recommendations. Please see our website for information about updating the guideline.

Appendix: The Guideline Development Group, National Collaborating Centre and NICE project team

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