Prevention and management of neutropenic sepsis in patients with cancer: summary of NICE guidance

Robert Phillips consultant paediatric oncologist, Barry Hancock emeritus professor of oncology, John Graham director consultant in clinical oncology, Nathan Bromham senior researcher, Huajie Jin health economist, Sabine Berendse information specialist

1Leeds General Infirmary, Leeds LS1 3EX, UK; 2University of Sheffield, Weston Park Hospital, Sheffield S10 2SJ, UK; 3National Collaborating Centre for Cancer, Cardiff CF10 3AF, UK; 4Taunton and Somerset NHS Foundation Trust, Taunton TA1 5DA, UK

This is one of a series of BMJ summaries of new guidelines based on the best available evidence: they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Neutropenic sepsis is a potentially fatal complication of treatment for cancer, with mortality rates of 2-21%. An investigation by the National Confidential Enquiry into Patient Outcome and Death and a follow-up report by the National Chemotherapy Advisory Group highlighted problems in the management of neutropenic sepsis in adults receiving chemotherapy. The problems included inadequate management of neutropenic sepsis leading to avoidable deaths, and the lack of systems for urgent assessment and of policies at organisation level for dealing with neutropenic sepsis. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the prevention and management of neutropenic sepsis in patients of any age with cancer.

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group’s experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets.

Information and support for patients and carers

- Provide patients having anticancer treatment and their carers with written and verbal information, before starting and throughout their cancer treatment, on:
  - Neutropenic sepsis
  - How and when to access 24 hour specialist oncology advice
  - How and when to seek emergency care.

[Based on the experience and opinion of the Guideline Development Group (GDG)]

Training for healthcare professionals

- Provide training on the identification and management of neutropenic sepsis to all healthcare professionals likely to be involved in the management of patients having cancer treatment. [Based on the experience and opinion of the GDG]

Reducing the risk of septic complications of anticancer treatment

- For adult patients (aged ≥18 years) with acute leukaemias, stem cell transplants, or solid tumours in whom clinically significant neutropenia (neutrophil count ≤0.5 x 10⁹/L) is an expected consequence of chemotherapy, offer prophylaxis with a fluoroquinolone only during the expected period of neutropenia. The lack of data for children and young people and for patients with lymphomas, makes it impossible currently to recommend the use or avoidance of a fluoroquinolone during periods of neutropenia. [Based on moderate to high quality evidence from systematic reviews and meta-analyses of randomised controlled trials]

- Centres where patients are receiving fluoroquinolones for antibiotic prophylaxis of neutropenic sepsis should monitor rates of antibiotic resistance. [Based on the experience and opinion of the GDG]
• Do not routinely offer granulocyte colony stimulating factor
  to prevent neutropenic sepsis in adults having
  chemotherapy unless they are receiving this as an integral
  part of the chemotherapy regimen or to maintain dose
  intensity. [Based on high quality evidence from systematic
  reviews and meta-analyses of randomised controlled trials
  and de novo economic analysis]

Outside these indications, the role of granulocyte colony
stimulating factor in the treatment of patients with cancer is
highly controversial. An economic analysis undertaken
specifically for the guideline showed that the use of granulocyte
colony stimulating factor when given solely to prevent
neutropenic sepsis was highly unlikely to be cost effective.

Referral guidance
• Suspect neutropenic sepsis if patients having cancer
treatment become unexpectedly or seriously unwell.
• Refer patients with suspected neutropenic sepsis
  immediately for assessment at their appropriate local
  hospital.
[Both points are based on the experience and opinion of the
GDG]

Emergency treatment and assessment
Suspected neutropenic sepsis is an acute medical emergency.
• Start immediate empirical antibiotic treatment. [Based on
the experience and opinion of the GDG] The current
National Cancer Action Team’s guidance and measures
for cancer services suggest that treatment should be started
within one hour.7
• Use monotherapy (the combination pipercillin with
tazobactam) as initial empirical antibiotic treatment, and
do not prescribe additional aminoglycoside(s), unless there
are patient specific or local microbiological indications,
such as a high rate of resistance to pipercillin with
tazobactam. [Based on high quality evidence from
systematic reviews and meta-analyses of randomised
controlled trials]
• Do a full clinical assessment of patients, including:
  – History and examination
  – Full blood count, and kidney and liver function tests
    (including albumin)
  – C reactive protein, lactate and blood culture
  – Additional peripheral blood culture, if possible, in
    patients with a central venous access device to improve
    the detection rates for bacteraemia
  – Urinalysis in all children aged ≤5 years.
[Based on low quality evidence from observational studies
and the experience and opinion of the GDG]
• Do not do chest radiography unless clinically indicated.
[Based on low to moderate quality evidence from
observational studies]
• Do not prescribe empiric glycopeptide antibiotics to
patients with neutropenic sepsis and a central venous access
device. [Based on very low or low quality evidence from
systematic reviews of randomised controlled trials]
• Do not remove the central venous access device as
  empirical management. However, it may require removal
  if it is suspected to be the focus of uncontrolled infection.
[Based on very low or low quality evidence from
observational studies]

Confirming the diagnosis
• Diagnose neutropenic sepsis in every patient whose
  temperature is >38°C and neutrophil count <0.5 × 10⁹/L.
[Based on low quality evidence from observational studies]

Assessing the patient’s risk of septic complications
• An oncology specialist should assess every patient’s risk
  of septic complications within 24 hours, using a validated
  risk scoring tool. [Based on moderate quality evidence from
  systematic reviews of observational studies]
No clear evidence describes the superiority of one system over
another. The box describes two commonly used systems: the
Multinational Association for Supportive Care in Cancer
(MASCC) score (for adults) and a modified Alexander rule (for
children and young people).5,7

Patients at low risk of septic complications
• Consider treating patients at low risk of developing septic
  complications with outpatient antibiotic treatment, if
  clinically appropriate and their domestic circumstances
  will allow them to return to hospital promptly if a problem
develops. [Based on moderate quality evidence from
systematic reviews]

Patients at high risk of septic complications
• Review and repeat the risk assessment daily while the
  patient is an inpatient, using the validated risk scoring tool.
[Based on the experience and opinion of the GDG]
• Switch from intravenous to oral antibiotic treatment after
  48 hours in patients who are reassessed as being at low risk
of septic complications, and discharge them home if
clinically appropriate and domestic circumstances allow.
[Based on low to moderate quality evidence from
randomised trials]
• Discontinue empirical antibiotic treatment in patients who
  have clinically responded to treatment—for example, by
  defervescence and an absence of signs of infection,
  irrespective of neutrophil count. [Based on low quality
  evidence from observational studies]
• Continue inpatient empirical antibiotic treatment in patients
  who have unresponsive fever unless an alternative cause
  of fever is likely. [Based on the experience and opinion of
  the GDG]
• Do not change primary empirical antibiotics in patients
  with unresponsive fever unless there is clinical deterioration
  or a specific microbiological indication. [Based on low
  quality evidence from randomised trials]

Overcoming barriers
Teenagers and young adults with cancer seem to be twice as
likely to die of neutropenic sepsis as other age groups,4 and the
Guideline Development Group urges those who care for these
patients to emphasise to them the life threatening nature of this
condition. The recommendation not to use granulocyte colony
stimulating factor to prevent episodes of neutropenia challenges
conventional practice; however, granulocyte colony stimulating
factor may be an integral part of the chemotherapy regimen or used to maintain dose intensity in some patients having chemotherapy with proved survival advantage. Clinicians may need to explain clearly their decisions to use granulocyte colony stimulating factor to healthcare commissioners. Effective monitoring and hospital-wide asepsis should mitigate potential problems such as antibiotic resistance patterns and *Clostridium difficile* from the increased use of prophylactic fluoroquinolone antibiotics; the GDG concluded from the available evidence that the potential disadvantage from this was outweighed by the reduction in mortality from neutropenic sepsis. Delivering care outside hospital to patients at low risk of septic complications will need careful implementation of early, risk stratified discharge together with informed community support to enable this to happen safely and improve the experience of patients.

The members of the Guideline Development Group were Barry W Hancock, Robert Phillips, Wendy King, Barbara Anne Crosse, Mark Holland, Catherine Oakley, Rosemary A Barnes, Anne Higgins, Peter Jenkins, Anton Kruger, Paul D Wallman, Jeannette Hawkins, Helen Clayson, Miranda Holmes, Anne Davidson, Janie Thomas, Nicola Harris, Rachel Drew. The members of the guideline team at the National Collaborating Centre for Cancer were John Graham, Andrew Champion, Angela Bennett, Lianne Gwillim, Nathan Bromham, Karen Francis, Mia Schmidt-Hansen, Catrin Lewis, Sabine Berendse, Stephanie Arnold Huajie Jin, Alec Miners, and Timothy Simmons. The members of the NICE project team were Sharon Summers-Ma, Claire Turner, Anthony Gildea, Judith Thornton, Jasdeep Hayre, and Judy McBride.

Contributors: All authors contributed to the conception and drafting of this article and revising it critically. They have all approved this version. RP and BH are the guarantors of this article.

Competing interests: All authors have completed the ICJME uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; JG, NB, HJ, and SB were all employed by the National Collaborating Centre for Cancer, which was commissioned and funded by NICE to produce this guideline; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.


Cite this as: BMJ 2012;345:e5368

Related links

**bmj.com/archive**

Previous articles in this series

- Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance (2012;345:e4947)
- Risk assessment of fragility fractures: summary of NICE guidance (2012;345:e3698)
- Risk identification and interventions to prevent type 2 diabetes in adults at high risk: summary of NICE guidance (2012;345:e4624)
- Management of an acute painful sickle cell episode in hospital: summary of NICE guidance (2012;344:e4063)
Further information on the guidance

There are many local, regional, national, and international guidelines on the management of neutropenic sepsis, and great variation in practice in the United Kingdom. Few of these guidelines focus on the management of neutropenic sepsis in the NHS setting, and none has explicitly examined the cost effectiveness of their recommendations. This NICE guideline was developed to reduce unwarranted variation in service provision and bring into practice the most cost effective approaches to prevention and management of neutropenic sepsis. The recommendations were developed after discussion of the relevance of the evidence to children, young people, and adults and are intended for use in patients of any age with cancer. Where the guideline gives age limited or disease specific recommendations these are clearly indicated as such.

Methods

This guidance was developed by the National Collaborating Centre for Cancer using methods from NICE’s standard processes (www.nice.org.uk/guidelinesmanual). The guidance review involved literature searches to identify relevant evidence, with critical appraisal of the quality of the identified evidence. A multidisciplinary team (the Guideline Development Group (GDG)) of service users, carers, and healthcare professionals was established to review the evidence and develop the subsequent recommendations. The healthcare professionals in this team included medical and clinical oncologists, haematologists, a microbiologist, an emergency medicine physician, paediatricians, an adult acute medicine physician, and chemotherapy, paediatric, community, and haematology specialist nurses. The guidance then went through an external consultation with stakeholders. The GDG considered the stakeholders’ comments, reanalysed the data where necessary, and modified the guidance as appropriate.

NICE has produced three different versions of the guidance: a full version; a summary version known as the “NICE guidance”; and a version for people using NHS services, their families and carers, and the public. All these versions are available from the NICE website. Updates of the guidance will be produced as part of NICE’s guideline development programme.

Cost effectiveness analysis of the use of colony stimulating factors (particularly granulocyte colony stimulating factor) and antibiotics as prophylaxis in patients at risk of neutropenic sepsis

As neutropenic sepsis affects many patients and the use of colony stimulating factors and antibiotics carries potentially substantial differences in cost, the GDG had serious concerns about cost effectiveness. It conducted a systematic review of previous economic models, but all studies were deemed to be at most only partially applicable to the guideline and to have very serious or potentially serious limitations. Accordingly, the group constructed a de novo model, which examined the cost effectiveness of the use of fluoroquinolone antibiotics, colony stimulating factors, both, or neither, in the prevention of neutropenic sepsis for adults (age >18 years) with cancer who were being treated as outpatients and whose chemotherapy regimens did not include granulocyte colony stimulating factor (G-CSF).

Findings of the base-case economic analysis

At the NICE “willingness to pay” threshold of £20 000 ($25 000; $31 000) per quality adjusted life year:

- For patients with a solid tumour who can take fluoroquinolone, primary prophylaxis with fluoroquinolone is the most cost effective prophylactic strategy
- For patients with a solid tumour who cannot take fluoroquinolone, no prophylaxis is the most cost effective strategy
- For patients with non-Hodgkin lymphoma or Hodgkin lymphoma, no prophylaxis is the most cost effective strategy.

All the results in the analysis were robust to both structural sensitivity analysis and probabilistic sensitivity analysis.

To test the health economic model the following scenarios were explored: 100% risk of neutropenic sepsis; 90% drug discount; five days of G-CSF per cycle; reduced daily dose of G-CSF. The one way sensitivity analysis showed that the model was robust to all scenarios, except if the effectiveness of fluoroquinolones versus nothing or placebo was reduced to a relative risk of 0.79 and if the cost of pegylated G-CSF was discounted to £179.50 or less per dose when pegylated G-CSF became cost effective.

Future research

The guideline recommends research to:

- Assess the benefits and disadvantages of different types of support, and information about neutropenic sepsis, for patients and their relatives
- Determine the value of symptoms and signs in patients in the community predicting neutropenic sepsis and its outcome
- Evaluate the effectiveness of very early (within 24 hours) discharge from hospital with oral antibiotics for patients with neutropenic sepsis
- Investigate the cost effectiveness of prophylaxis of neutropenic sepsis with antibiotics and/or granulocyte colony stimulating factor preparations in children and young people, and in adults with lymphoma, receiving cancer treatment
- Determine the incidence of suspected and proved neutropenic sepsis in a prospective national cohort study