Clinical Guideline

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

Full Guideline

Update information
January 2020: After a surveillance review, we have updated recommendation 1.2.1.1 with a link to MHRA safety advice on the use of fluoroquinone antibiotics and a footnote on the UK marketing authorisation for their use.

This change can be seen in the short version of the guideline at: https://www.nice.org.uk/guidance/cg151

September 2012
Developed for NICE by the National Collaborating Centre for Cancer

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Foreword

This clinical guideline provides an overview of the prevention and empiric management of neutropenic sepsis in children, young people and adults with cancer. The clinical questions have focussed on areas of uncertainty and aimed to provide support to clinicians where there is a wide variation in practice.

The Guideline Development Group (GDG) are pleased that the guideline relates to the whole of the patient pathway with particular emphasis on issues of importance to patients, carers and their families and that the remit covers patients of all ages.

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.

The guideline development process involved close consultation with stakeholders, including patients, carers and many different professional groups and organisations. The GDG comprised a hugely informed and enthusiastic group of people whose dedication, sense of humour and thoughtfulness have inspired this guidance. The GDG would particularly acknowledge Janie Thomas who made a significant contribution to this guideline. Despite serious illness she shared her patient experience for the benefit of others with dedication and enthusiasm.

We hope that this guideline will improve the care of patients having treatment for cancer who are at risk of this potentially life-threatening complication.

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GDG Chair

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GDG Clinical Lead

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Key priorities for implementation

Definition of neutropenia and fever

- Diagnose neutropenic sepsis in patients having anticancer treatment whose neutrophil count is 0.5 x 109 per litre or lower and who have either:
  - a temperature higher than 38^{o}C **or**
  - other signs or symptoms consistent with clinically significant sepsis.

Information and support for patients and carers

- Provide patients having anticancer treatment and their carers with written and oral information, both before starting and throughout their anticancer treatment, on:
  - neutropenic sepsis
  - how and when to contact 24-hour specialist oncology advice
  - how and when to seek emergency care.

Investigations appropriate for clinical management and risk stratification

- 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 (see also recommendations in section 4.2.2).

Assessing the patient's risk of septic complications

- A healthcare professional with competence in managing complications of anticancer treatment should assess the patient's risk of septic complications within 24 hours of presentation to secondary or tertiary care, basing the risk assessment on presentation features and using a validated risk scoring system[1].

Reducing the risk of septic complications of anticancer treatment

- For adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours in whom significant neutropenia (neutrophil count 0.5 x 10^9 per litre or lower) is an anticipated consequence of chemotherapy, offer prophylaxis with a fluoroquinolone during the expected period of neutropenia only.

Timing of initial antibiotic treatment

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

Empiric intravenous antibiotic monotherapy or intravenous antibiotic dual therapy

- Offer beta lactam monotherapy with piperacillin with tazobactam[2] as initial empiric antibiotic therapy to patients with suspected neutropenic sepsis who need intravenous treatment unless there are patient-specific or local microbiological contraindications.

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

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[1] Examples of risk scoring systems includeThe 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

[2] At the time of publication (September 2012) piperacillin with tazobactam did not have a UK marketing authorisation for use in children aged under 2 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The child's parent or carer should provide informed consent, which should be documented. See the GMC's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

Inpatient versus outpatient management strategies

- Consider outpatient antibiotic therapy for 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.

Duration of inpatient care

- Offer discharge to patients having empiric antibiotic therapy for neutropenic sepsis only after:
  - the patient's risk of developing septic complications has been reassessed as low by a healthcare professional with competence in managing complications of anticancer treatment using a validated risk scoring system[3] **and**
  - 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.

[3]Examples of risk scoring systems include 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

Key research recommendations

- **A prospective national cohort study should be carried out to assess the incidence of suspected and proven neutropenic sepsis in patients having anticancer treatment**.

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.

- **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.**

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 the development of 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

- **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.**

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 overly-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.

- **Randomised studies should investigate primary prophylaxis of neutropenic sepsis in 2 populations: children and young people (aged under 18) having treatment for solid tumours or haematological malignancies, or stem cell transplantation; and adults (aged 18 and older) diagnosed with lymphoma. The studies should compare the effectiveness of fluoroquinolone antibiotics given alone, fluoroquinolone antibiotics given together with granulocyte-colony stimulating factor (G-CSF) preparations, and G-CSF preparations given alone. Outcome measures should include overall mortality, infectious episodes and adverse events. In addition, quality of life should be determined using quantitative**

and qualitative methods. The resulting data should be used to develop a cost-effectiveness analysis comparing these 3 forms of prophylaxis in children and young people having anticancer treatment, and in adults diagnosed with lymphoma.

Data from studies of adults with leukaemia, stem cell transplantation and many solid tumours suggest that prophylaxis with fluoroquinolone antibiotics reduces the risk of neutropenic sepsis. However, the benefit of fluoroquinolone antibiotics in adults diagnosed with lymphoma is unclear. Children and young people having anticancer treatment are a distinct population and differ from adults in a number of ways, including the types of cancer they have, the anticancer treatment they are given, their reactions to fluoroquinolones and subcutaneous injections, and the ease with which they can adhere to daily medication. The effects of these differences are not known, but it is known that death rates from neutropenic sepsis are higher in children and young people than in adults. Studies of primary prophylaxis of neutropenic sepsis in children and young adults, and in adults with lymphoma, could be of great value in helping to reduce the risk of neutropenic sepsis in these 2 patient populations.

- **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.**

Moderately strong evidence was found 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 readmission 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.

List of all recommendations

Chapter 2 - Diagnosis of neutropenic sepsis

Definition of neutropenia and fever

- Diagnose neutropenic sepsis in patients having anticancer treatment whose neutrophil count is 0.5 x 10^9 per litre or lower and who have either:
  - a temperature higher than 38°C **or**
  - other signs or symptoms consistent with clinically significant sepsis.

Chapter 3 - Information, support and training

Information and support for patients and carers

Content of information and support

- Provide patients having anticancer treatment and their carers with written and oral information, both before starting and throughout their anticancer treatment, on:
  - neutropenic sepsis
  - how and when to contact 24-hour specialist oncology advice
  - how and when to seek emergency care.

Training for healthcare professionals

- Healthcare professionals and staff who come into contact with patients having anticancer treatment should be provided with training on neutropenic sepsis. The training should be tailored according to the type of contact.

Chapter 4 – Identification and assessment

Signs and symptoms that necessitate referral to secondary/tertiary care

- Suspect neutropenic sepsis in patients having anticancer treatment who become unwell.
- Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care.

Emergency assessment in secondary/tertiary care

Investigation appropriate for clinical management and risk stratification

- 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 (see also recommendations in section 4.2.2).

Further assessment

- After completing the initial clinical assessment (see recommendations in section 4.2.1), try to identify the underlying cause of the sepsis by carrying out:
  - additional peripheral blood culture in patients with a central venous access device if clinically feasible
  - urinalysis in all children aged under 5 years.
- Do not perform a chest X-ray unless clinically indicated.

Assessing the patient's risk of septic complications

- A healthcare professional with competence in managing complications of anticancer treatment should assess the patient's risk of septic complications within 24 hours of presentation to secondary or tertiary care, basing the risk assessment on presentation features and using a validated risk scoring system[4].

Chapter 5 – Reducing the risk of septic complications of anticancer treatment

Preventing the septic complications of anticancer treatment

- For adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours in whom significant neutropenia (neutrophil count 0.5 x 10^9 per litre or lower) is an anticipated consequence of chemotherapy, offer prophylaxis with a fluoroquinolone during the expected period of neutropenia only.
- Rates of antibiotic resistance and infection patterns should be monitored in treatment facilities where patients are having fluoroquinolones for the prophylaxis of neutropenic sepsis[5].
- Do not routinely offer granulocyte-colony stimulating factor (G-CSF) for the prevention of neutropenic sepsis in adults receiving chemotherapy unless they are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity.

Chapter 6 – Initial treatment

Timing of initial antibiotic treatment

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

Empiric intravenous antibiotic monotherapy or intravenous antibiotic dual therapy

- Offer beta lactam monotherapy with piperacillin with tazobactam[6] as initial empiric antibiotic therapy to patients with suspected neutropenic sepsis who need intravenous treatment unless there are patient-specific or local microbiological contraindications.
- Do not offer an aminoglycoside, either as monotherapy or in dual therapy, for the initial empiric treatment of suspected neutropenic sepsis unless there are patient-specific or local microbiological indications.

Empiric glycopeptide antibiotics in patients with central venous access devices

- Do not offer empiric glycopeptide antibiotics to patients with suspected neutropenic sepsis who have central venous access devices unless there are patient-specific or local microbiological indications.

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[4] Examples of risk scoring systems include 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

[5] For more information see the Department of Health's Updated guidance on the diagnosis and reporting of *Clostridium difficile* and guidance from the Health Protection Agency and the Department of Health on *Clostridium difficile* infection: how to deal with the problem.

[6] At the time of publication (September 2012) piperacillin with tazobactam did not have a UK marketing authorisation for use in children aged under 2 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The child's parent or carer should provide informed consent, which should be documented. See the GMC's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

Indications for removing central venous access devices

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

Inpatient versus outpatient management strategies

- Consider outpatient antibiotic therapy for 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.

Chapter 7 – Subsequent treatment

Changing the initial empiric treatment in unresponsive fever

- For patients with confirmed neutropenic sepsis and a high risk of developing septic complications, a healthcare professional with competence in managing complications of anticancer treatment should daily:
  - review the patient's clinical status
  - reassess the patient's risk of septic complications using a validated risk scoring system[7]
- Do not switch initial empiric antibiotics in patients with unresponsive fever unless there is clinical deterioration or a microbiological indication.

Switching from intravenous to oral antibiotic treatment

- Switch from intravenous to oral antibiotic therapy after 48 hours of treatment in patients whose risk of developing septic complications has been reassessed as low by a healthcare professional with competence in managing complications of anticancer treatment using a validated risk scoring system[7].

Duration of inpatient care

- Offer discharge to patients having empiric antibiotic therapy for neutropenic sepsis only after:
  - the patient's risk of developing septic complications has been reassessed as low by a healthcare professional with competence in managing complications of anticancer treatment using a validated risk scoring system[7] **and**
  - 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.

Duration of empiric antibiotic treatment

- Continue inpatient empiric antibiotic therapy in all patients who have unresponsive fever unless an alternative cause of fever is likely.
- Discontinue empiric antibiotic therapy in patients whose neutropenic sepsis has responded to treatment, irrespective of neutrophil count.

[7] Examples of risk scoring systems include 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

Methodology

Introduction

What is a Clinical Guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – and these can include prevention and self-care through to primary and secondary care and on to more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

In 2009 when this topic was commissioned, clinical guidelines for the NHS in England, Wales and Northern Ireland were produced in response to a request from the Department of Health (DH). Before deciding whether to refer a particular topic to the National Institute for Health and Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of four National Collaborating Centres (NCCs) to produce a guideline. The Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups. The National Collaborating Centre for Cancer (NCC-C) was referred the topic of the prevention and management of neutropenic sepsis in cancer patients in October 2009 as part of NICE's twenty-third wave work programme. However, the guideline development process began officially in September 2010 when sufficient capacity became available at the NCC-C.

Who is the Guideline Intended For?

This guideline does not include recommendations covering every detail of the prevention and management of neutropenic sepsis in cancer patients. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing Clinical Evidence Based Questions'.

This guideline is relevant to all healthcare professionals who come into contact with patients with neutropenic sepsis or suspected of having neutropenic sepsis, as well as to the patients themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance and commissioning in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

The Remit of the Guideline

Guideline topics selected by the Department of Health identify the main areas to be covered by the guideline in a specific remit. The following remit for this guideline was received as part of NICE's twenty-third wave programme of work:

- *'To produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients.'*

Involvement of Stakeholders

Key to the development of all NICE guidance is the involvement of relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2009). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the guideline on prevention and management of neutropenic sepsis in cancer patients can be found in Appendix E.2.

The Guideline Development Process – Who Develops the Guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2009, 2012) A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG) (Appendix E.1), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline
- forming the GDG
- developing clinical questions
- identifying the health economic priorities
- developing the review protocol
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

The Scope

The remit was translated into a scope document by the Guideline Development Group (GDG) Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2009). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit set by the DH
- inform professionals and the public about the expected content of the guideline.
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategy

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The list of key clinical issues were discussed and revised before the formal consultation process. Further details of the discussion at the stakeholder workshop can be found on the NICE website (www.nice.org.uk).

The scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the 'NICE guidelines manual' (NICE 2009). The full scope is shown in Appendix D. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations, NICE staff and the NICE Guideline Review Panel (GRP)[8]. Further information about the GRP can also be found on the NICE website. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the GRP, signed off by NICE and posted on the NICE website.

The Guideline Development Group (GDG)

The neutropenic sepsis GDG was recruited in line with the 'NICE guidelines manual' (NICE 2009). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were interviewed before being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Details of the adverts were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (Appendix E.2). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (Appendix E.1).

Guideline Development Group Meetings

Eleven GDG meetings were held between 21st September 2010 and 18th May 2012. During each GDG meeting (held over either one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Members

Individuals with direct experience of neutropenic sepsis gave an important user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

[8] As from 1st January 2012, the Guideline Review Panel (GRP) will be no longer be part of the NICE guideline development process (NICE 2012)

Developing Clinical Evidence-Based Questions

Background

Clinical guidelines should be aimed at improving clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope the GDG formulated a clinical question. For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: P - the population (the population under study, I -, the interventions (what is being done), C - the comparisons (other main treatment options), O - the outcomes (the measures of how effective the interventions have been). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

The final list of clinical questions can be found in the scope (Appendix E).

Review of Clinical Literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder (now NHS Evidence), National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews (CDSR), Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), DH Data, Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Developing the review protocol

For each clinical question, the information specialist and researcher (with input from other technical team and GDG members) prepared a review protocol. This protocol explains how the review was to be carried out (Table A) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in the full evidence review.

Table A Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GDG.
Objectives	Short description; for example 'To estimate the effects and cost effectiveness of…' or 'To estimate the diagnostic accuracy of…'.
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.)
The review strategy	The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1985 onwards
- Psychinfo 1806 onwards
- Web of Science [specifically Science Citation Index Expanded]
- (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards]
- Biomed Central 1997 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 8–10 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, November 2011 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review.

Critical Appraisal

From the literature search results database, one researcher scanned the titles and abstracts of every article for each question and full publications were ordered for any studies considered relevant or if there was insufficient information from the title and abstract to inform a decision. When the papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data on the type of population, intervention, comparator and outcomes (PICO) were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using a modification of GRADE (NICE 2009; http://gradeworking group.org/). Where possible this included meta-analysis and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each topic outcome was examined for the quality elements defined in Table B and subsequently graded using the quality levels listed in Table C. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

Table B Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator or outcomes between the available evidence and the clinical question.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the minimal important difference.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table C Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2009). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

For non-interventional questions, for example the questions regarding diagnostic test accuracy, a narrative summary of the quality of the evidence was given.

Needs Assessment

As part of the guideline development process the NCC-C invited a specialist registrar, with the support of the GDG, to undertake a needs assessment (Appendix E.3). The needs assessment aims to describe the burden of disease and current service provision for patients with neutropenic sepsis in England and Wales, which informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

Incorporating Health Economics Evidence

The aim of providing economic input into the development of the guideline was to inform the GDG of potential economic issues relating to the prevention and management of neutropenic sepsis. Health economics is about improving the health of the population through the efficient use of resources. In addition to assessing clinical effectiveness, it is important to investigate whether health services are being used in a cost effective manner in order to maximise health gain from available resources.

Prioritising topics for economic analysis

After the clinical questions had been defined, and with the help of the health economist, the GDG discussed and agreed which of the clinical questions were potential priorities for economic analysis. These economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2009):

- the overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- the current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty
- the feasibility of building an economic model

For each topic, a review of the economic literature was conducted. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics filter.

For systematic searches of published economic evidence, the following databases were included:

- Medline
- Embase
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment (HTA)
- Health Economic Evaluations Database (HEED)

Methods for reviewing and appraising economic evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies or 'cost of illness' studies are generally excluded from the reviews (NICE, 2009).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE, 2009, Appendix H). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the Guideline. There are two parts to the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table D).

Table D: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness.
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness.
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration.

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table E).

Table E: Methodological quality

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness.
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness.
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the GRADE table for clinical evidence.

If high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised as described above. However, it is often the case that published economic studies may not be directly relevant to the specific clinical question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, for priority topics, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GDG, the health economist investigated the feasibility of developing an economic model. In the development of the analysis, the following general principles were adhered to:

- the GDG subgroup was consulted during the construction and interpretation of the analysis
- the analysis was based on the best available clinical evidence from the systematic review
- assumptions were reported fully and transparently
- uncertainty was explored through sensitivity analysis
- costs were calculated from a health services perspective
- outcomes were reported in terms of quality-adjusted life years

Linking to NICE technology appraisals

There are no published technology appraisals (TA) relevant to this guideline.

Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying LETR statement.

LETR (Linking Evidence to Recommendations) statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:

- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost-effectiveness of an intervention
- the quality of the evidence (see GRADE)
- the degree of consensus within the GDG
- other considerations – for example equalities issues

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed. To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Consultation and Validation of the Guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (Appendix E.2) had one opportunity to comment on the draft guideline which was posted on the NICE website between 16 February 2012 and 28 March 2012 in line with NICE methodology (NICE 2009).

The pre-publication process

An embargoed pre-publication of the guideline was released to registered stakeholders to allow them to see how their comments have contributed to the development of the guideline and to give them time to prepare for publication. (NICE 2012).

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other Versions of the Guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three other versions of the neutropenic sepsis guideline which are available from the NICE website:

- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- NICE Pathways, which is an online tool for health and social care professionals that brings together all related NICE guidance and associated products in a set of interactive topic-based diagrams.
- 'Understanding NICE Guidance' ('UNG'), which describes the guideline using non-technical language. It is written chiefly for people having anticancer treatment but may also be useful for their families and carers.

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before November 2011 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Three years after publication of the guideline, NICE will commission a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline. Additional health economic advice and support for this guideline was provided by the London School of Hygiene and Tropical Medicine and funded by the National Collaborating Centre for Cancer.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

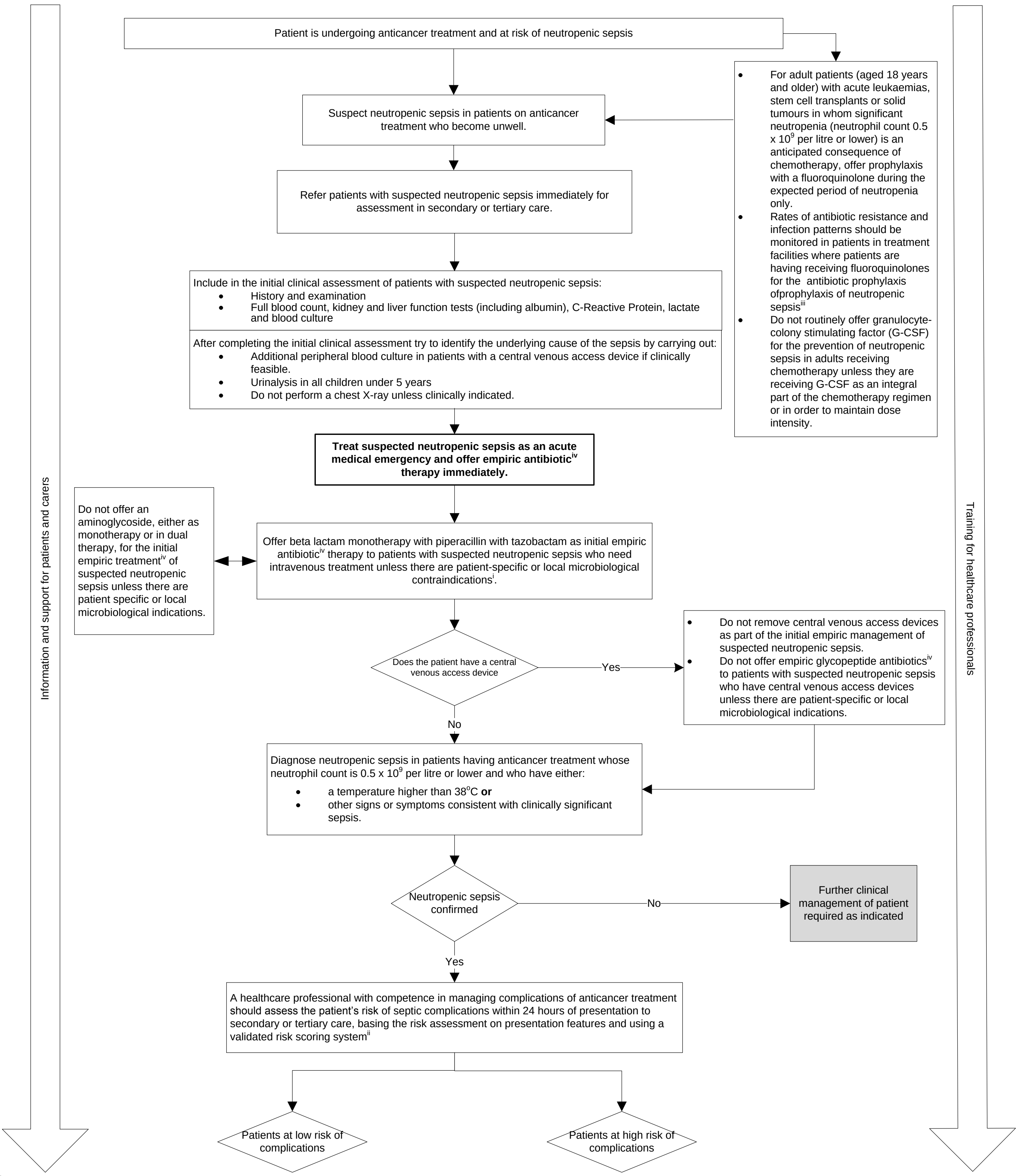
References

Briggs, A., Claxton K, Sculpher M, Decision Modelling for Health Economic Evaluation. 2006, Oxford: Oxford University Press.

National Institute for Health and Clinical Excellence (2009) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidelinesmanual

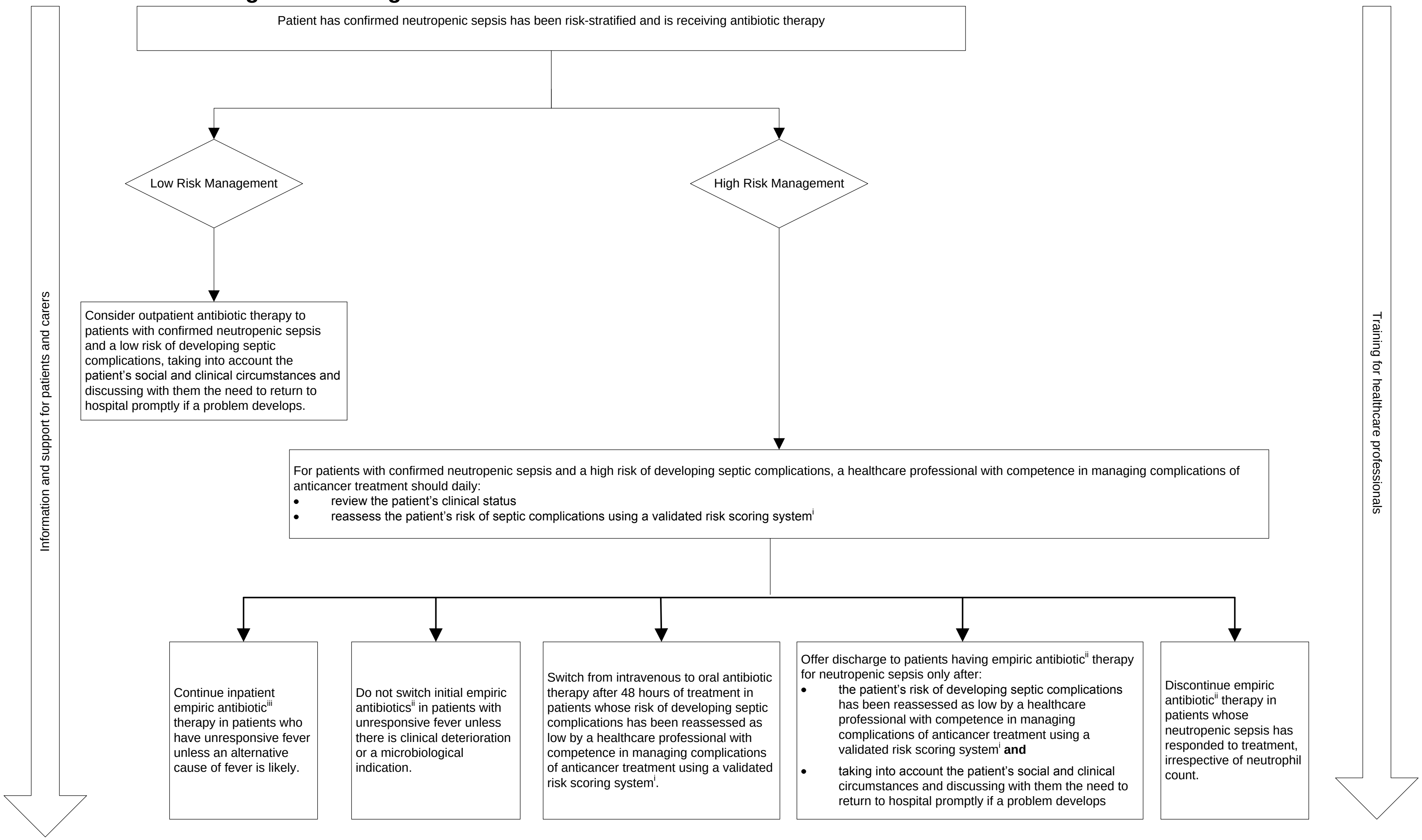
National Institute for Health and Clinical Excellence (2012) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidelinesmanual

Algorithm: Summary of recommendations



[i] At the time of publication (September 2012) piperacillin with tazobactam did not have a UK marketing authorisation for use in children aged under 2 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The child's parent or carer should provide informed consent, which should be documented. See the GMC's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.
[ii] Examples of risk scoring systems includeThe 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).
[iii] For more information see the Department of Health's Updated guidance on the diagnosis and reporting of *Clostridium difficile* and guidance from the Health Protection Agency and the Department of Health on *Clostridium difficile* infection: how to deal with the problem..
[iv] An empiric antibiotic is given to a person before a specific microorganism or source of the potential infection is known. It is usually a broad-spectrum antibiotic and the treatment may change if the microorganism or source is confirmed.

Overview of low and high risk management



[i] Examples of risk scoring systems include 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

[ii] An empiric antibiotic is given to a person before a specific microorganism or source of the potential infection is known. It is usually a broad-spectrum antibiotic and the treatment may change if the microorganism or source is confirmed.

1 Epidemiology and service provision of neutropenic sepsis in England and Wales

This chapter provides a summary of the needs assessment that was carried out to inform development of this guideline and includes current information available regarding the epidemiology of neutropenic sepsis and existing service provision across England and Wales. The full needs assessment report can be found as a supplementary document accompanying the guideline.

1.1 Introduction

The purpose of this guideline is to ensure prompt and effective management of cancer patients presenting with neutropenic sepsis, as well as advising on prevention and diagnosis of this important complication of anticancer treatments. It is a significant cause of mortality and morbidity and causes delays and dose reductions to planned treatment. The greatest risk of neutropenic sepsis is with cytotoxic chemotherapy. The Guideline Development Group (GDG) recognises the importance of distinguishing uncomplicated neutropenic fever from neutropenia with severe sepsis and shock, and indeed septic shock can occur without fever. In clinical practice the terms febrile neutropenia and neutropenic sepsis are used interchangeably in this patient group and recommendations within this guideline use the term "neutropenic sepsis" to indicate the full range of severity of illness.

The neutrophils or granulocytes form part of the innate immune system. Normally they constitute 60-70% of the total leukocyte count. They circulate in the blood and are found inactive in the bone marrow. Neutrophils respond early to signals reporting injury or infection, migrating to the affected area. They have a role in both directly killing non-host cells such as bacteria by phagocytosis and chemical damage via degranulation, and activating other parts of the immune system, for example T cells (Nathan, 2006, Witko-Sarsat, *et al.,* 2000). They have a circulating life span of between 8 hours and 5 days (Pillay, *et al.,* 2010), and take approximately six days to enter circulation from the bone marrow (Dancey, *et al.,* 1976).

Cytotoxic anticancer chemotherapy is designed to kill neoplastic stem cells by damaging the DNA irreparably. The mechanism behind this damage varies according to the chemotherapy drug. The more rapidly dividing normal cells such as hair follicles, mucosal linings and bone marrow cells can also be affected, causing the well documented toxicities of alopecia, mucositis and bone marrow suppression leading to neutropenia, anaemia and thrombocytopenia. For the majority of chemotherapy regimens, the neutrophil count falls to its lowest level approximately 5-7 days after administration of chemotherapy (Holmes, 2002), and can take up to 2-4 weeks to recover, although for some drugs and regimens, these timescales are considerably different. There is a tendency for neutropenic sepsis to occur more commonly in the first two cycles of treatment (Lyman and Delgado, 2003). While novel biological agents generally have a lower rate of neutropenia than cytotoxic chemotherapy, such problems can still occur.

When neutropenic, the patient is vulnerable to invasive infection (Bhatt and Saleem, 2004) which can potentially cause overwhelming sepsis and death. Deterioration can be very rapid, sometimes without an obvious focus for infection. Reported mortality for untreated neutropenic sepsis ranges from 2 to 21% (Herbst, *et al.,* 2009). Neutropenic sepsis is therefore considered a medical emergency, and as with severe sepsis and septic shock from any cause, there is widespread agreement that early administration of broad spectrum antibiotics and management of shock is key to successful treatment (Rivers, *et al.,* 2001). There is almost no universal agreement about the details of many aspects of the care of a patient with neutropenic sepsis, although there are many common themes (Phillips, *et al.,* 2007).

There are various strategies for preventing neutropenic sepsis. Primary prophylaxis aims to prevent first episodes of neutropenic sepsis, and secondary prophylaxis is a strategy used to prevent subsequent episodes. Granulocyte colony stimulating factors (GCSF), antibiotics, and alterations to the cytotoxic regimen are the main prophylactic strategies.

Recently neutropenic sepsis has been highlighted as an area of clinical priority in the UK, initially by a publication from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD 2008) then by a subsequent report from the National Chemotherapy Advisory Group (NCAG, 2009).

In 2008, NCEPOD published "For better or for worse? A review of the care of patients who died within 30 days of receiving anticancer therapy" (NCEPOD, 2008). This report looked at the deaths of patients within 30 days of chemotherapy, and highlighted aspects of care which could be improved. Recommendations covered the development of appropriate clinical care pathways and local policies, staff training and timely availability of antibiotics. A specific recommendation was made for antibiotics to be given within 30 minutes of presentation to patients with suspected neutropenic sepsis and shock.

Following the NCEPOD report, (NCEPOD, 2008) NCAG published "Chemotherapy Services in England: Ensuring quality and safety" (NCAG, 2009). The aim of the report was "to bring about a step change in the quality and safety of chemotherapy services in England, taking account of the concerns from peer review and from NCEPOD". Key recommendations made included, the introduction of acute oncology provision, appropriate patient education and access to emergency advice and healthcare. A "door to needle" time of one hour was recommended for antibiotics to be administered in cases of suspected neutropenic sepsis.

Current practice concerning the management of neutropenic sepsis has also been influenced by many other international recommendations, guidelines and studies.

The Surviving Sepsis Campaign (Dellinger, *et al.,* 2008) has produced international guidelines for the management of severe sepsis, including severe neutropenic sepsis. It recommends early investigations such as blood cultures and serum lactate, early administration of antibiotics (within 30 minutes), and goal directed resuscitation.

A number of risk scores which have influenced some current guidelines have come into use over the past few years. These include scores to identify those patients at both high and low risk of severe sepsis.

The Modified Early Warning Score (MEWS) (Subbe, *et al.,* 2001) has been validated to identify seriously unwell adult patients within general medical wards rather than those with neutropenic sepsis, but it and similar scoring systems are in widespread use.

There are several specific risk scores for neutropenic sepsis which have the aim of identifying those patients at low risk of developing severe sepsis, meaning that less aggressive treatment than has been "traditional" may be appropriate. These cover both adults (Klastersky, *et al.,* 2000) and children (Alexander, *et al.,* 2002).

The details surrounding the treatment and prevention of neutropenic sepsis in published literature vary greatly. There is also no universally agreed definition of "neutropenia" and "sepsis" in this context amongst published literature (Clarke, *et al.,* 2011).

1.2 The epidemiology of neutropenic sepsis in England and Wales

1.2.1 Incidence of neutropenic sepsis

The incidence of neutropenic sepsis in England and Wales is difficult to determine with any degree of certainty, because of variations in definition of neutropenic sepsis and lack of a consistent code used on NHS clinical coding databases.

Local audits and service reviews have addressed the subject of neutropenic sepsis and assessed the impact of the condition on individual hospitals, cancer networks and regions. These have not been nationally coordinated, used different methodologies/criteria for diagnosing neutropenic sepsis and covered differing clinical environments - from a single ward to an entire cancer network; nevertheless they do provide useful baseline information on the burden of the condition on healthcare (Table 1.1).

Table 1.1 Summary of audits and reviews of rates of neutropenic sepsis

Time period	Number of cases	Audit description	Source
05/2007 – 08/2007	71 admissions in 64 patients	Audit of all patients admitted with neutropenic sepsis to the seven hospitals of the South West London Cancer Network (population 1.4 million)	Okera, at al., 2011
2 months	29 patients	Single institution audit at John Radcliffe Hospital, Oxford of patients admitted either to A&E or haematology.	Richardson, *et al.,* 2009
1 year (2008)	128 episodes in 119 patients	Single institution service improvement audit for an adult haematology department (no solid tumours) of episodes of neutropenic sepsis on the haematology ward.	Van Vliet, *et al.,* 2011
1 year (1/4/04 to 31/3/05)	762 episodes in 368 patients	4 Paediatric Oncology Centres (averaging 74.7 episodes each) and 43 Paediatric Oncology Shared Care Units (averaging 13.5 episodes each) in London	Dommett, *et al.,* 2009
1/1/2009 to 31/3/2009	32 episodes	3 hospitals of the North Wales Cancer Network	North Wales Cancer Network Audit of neutropenic sepsis in chemotherapy patients from North Wales
6 months	22 patients admitted through A&E	Mainly haematology patients in an adult cancer unit/haemato-oncology unit.	Submitted from survey
January 2008 to April 2009	42 episodes	Audit of a North-London general hospital with a cancer unit and adult haemato-oncology unit using coding for neutropenia to select cases	Submitted from survey
08/2010 to 10/2010	33 patients	Haematology and oncology unit in East London – two other audits from this hospital displayed similar results	Submitted from survey
03/2011 to 06/2011 inclusive	92 cases in 84 patients	Admissions to a Yorkshire Cancer centre for cancers treated there or in nearby cancer units (including some lymphoma but no other haemato-oncology)	Submitted from survey

These surveys show that busier specialist units admit over 20 patients a month with neutropenic sepsis, while the burden on general hospitals is considerably less, approximately three patients per month. These rates will vary hugely depending on population size, tumour types treated locally, chemotherapy regimens used and local demographics.

Consideration should be given to performing a national prospective audit to capture all incidences of neutropenic sepsis and identify the burden of disease in the UK.

1.2.2 Mortality from neutropenic sepsis

The most important adverse outcome from an episode of neutropenic sepsis is the death of the patient. As part of this report, a study has been undertaken to assess the reported death rates from neutropenic sepsis over the past 10 years.

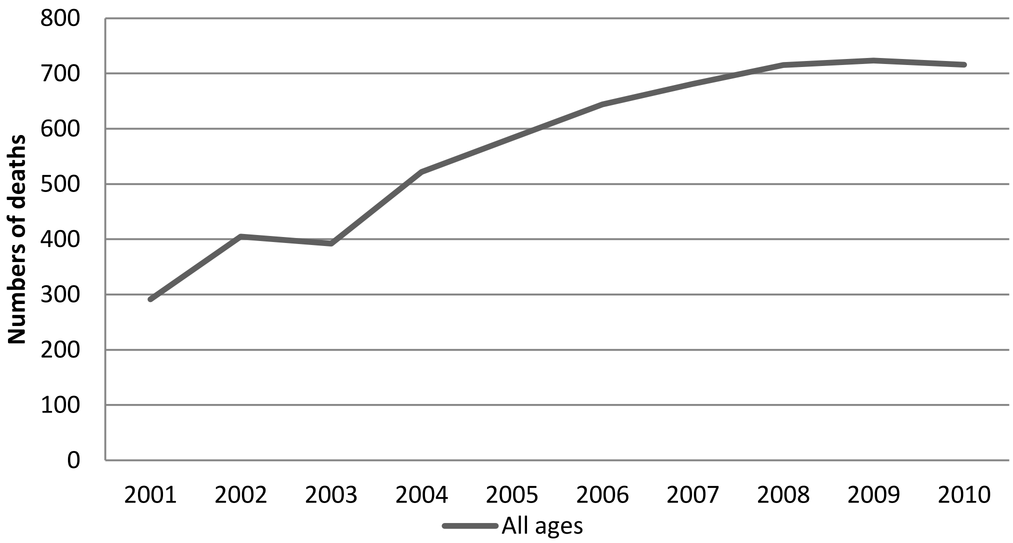
Methods

On the death of a patient, information from the Medical Certificate of Cause of Death is coded and recorded by the Office of National Statistics (ONS). A search of the ONS database between 2001 and 2010 was undertaken to identify patients (paediatric and adult) coded as having died with an underlying cancer diagnosis where both an infection and neutropenia were also reported on the death certificate. This means that “neutropenic sepsis”, “febrile neutropenia” and “neutropenia and pneumonia” would all have been captured. The search is performed using ICD10 codes rather than plain text (meaning incidences where neutropenic sepsis was implied on the death certificate but not coded as such may not have been captured). The numbers of patients recorded as having died from neutropenic sepsis was also compared to the number of cancer diagnoses in the same year in England (Office of National Statistics) and Wales (Wales Health Statistics). A summary of the ICD10 codes used in this search is listed in Appendix 1 of the full needs assessment report.

Results

The total number of deaths from neutropenic sepsis has more than doubled over the period 2001 to 2010 (Figure 1.1).

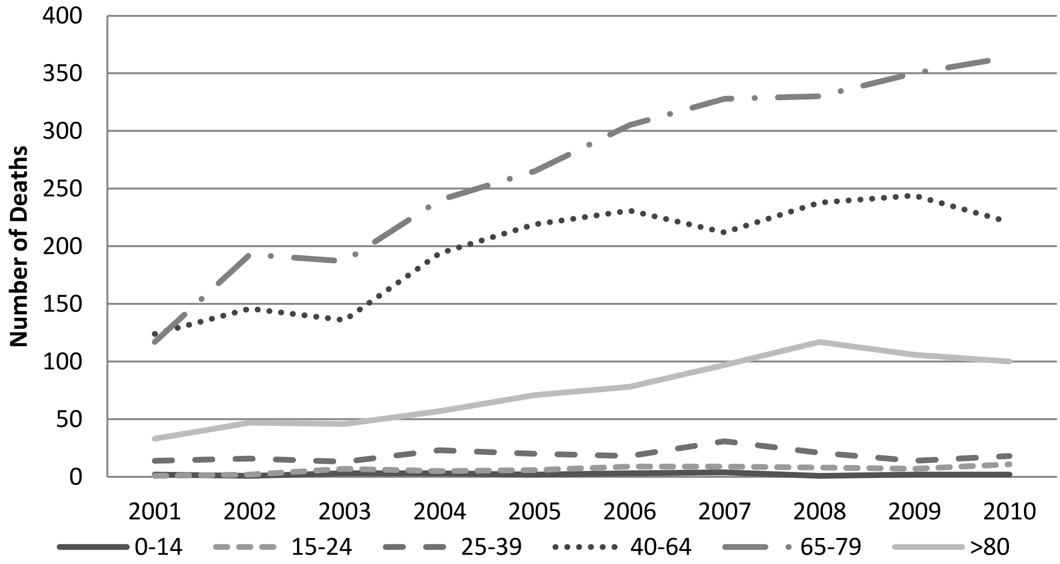
Figure 1.1 Total deaths from neutropenic sepsis (paediatric and adult) England and Wales 2001-2010.
Data source: ONS



There is a significant positive relationship between the year and total number of neutropenic sepsis deaths ($p<0.001$). Fitting fractional polynomials with the Multivariable Fractional Polynomials (MFP) package reported the best fit was achieved from a simple linear form.

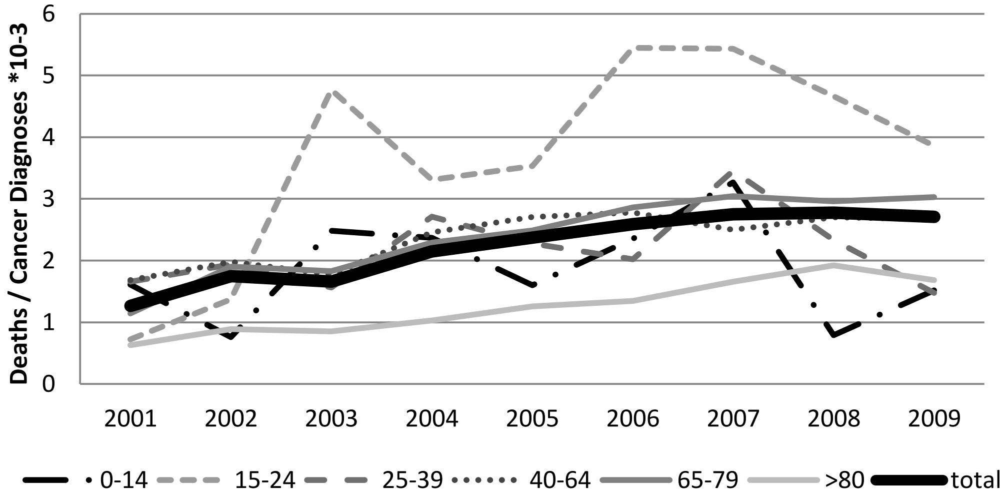
The age range 65 to 79 contains the majority of deaths. The death rate for younger patients appears to have remained fairly static over the years, although there has been an increase (Figure 1.2). The rate of this increase has been assessed and has been found to be the same over all the age ranges examined.

Figure 1.2 Deaths from neutropenic sepsis by age groups England and Wales 2001-2010.
Data source: ONS



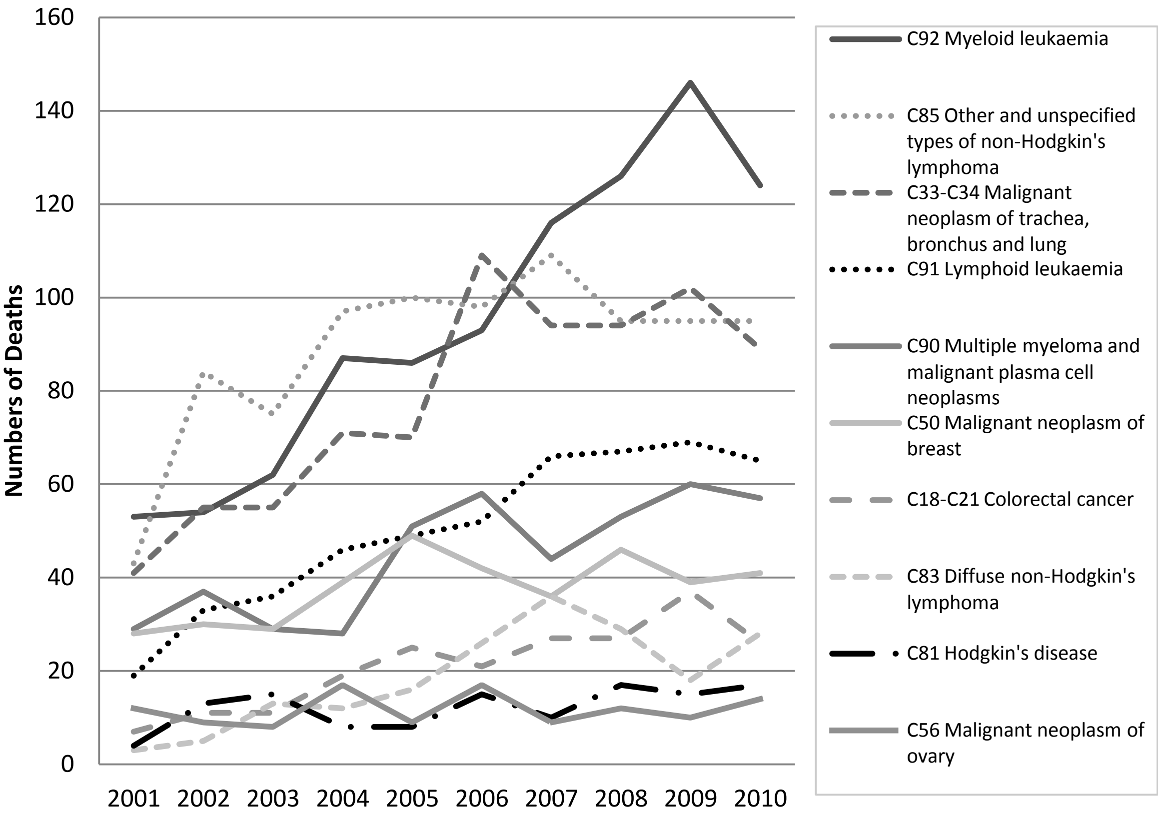
The number of deaths from neutropenic sepsis each year from 2000 to 2009 as a proportion of the annual total of cancer diagnoses (not including non-melanoma skin cancer) in each age group has been examined. Relative to the increased numbers of cancer diagnoses, the proportion of deaths due to neutropenic sepsis continues to rise for all groups. The rate of increase of neutropenic sepsis deaths is significantly higher for the 15-24 year old age group, and significantly lower for the >80 age group (Figure 1.3).

Figure 1.3 Ratio of numbers of neutropenic sepsis deaths to total cancer diagnoses by age group, England and Wales
Data source: ONS



The 10 most common cancers where death involved neutropenic sepsis are shown in Figure 1.4.

Figure 1.4 Absolute numbers of cancer deaths from neutropenic sepsis by diagnosis, (paediatric and adult) England and Wales 2001-2010.
Data source: ONS



Conclusions

The numbers of neutropenic sepsis deaths recorded by the ONS has more than doubled in 10 years, and there are now approximately two deaths each day in England and Wales from this complication of anticancer treatment.

There are several possible explanations for the increase in death rates. The numbers of cancers diagnosed each year is increasing, but as a proportion of those, the relative rate of neutropenic sepsis deaths also continues to rise. The NCAG report (NCAG 2009) stated that 60% more chemotherapy was given in 2006 than 2002. If this rise has continued, this alone is likely to be responsible for the increase in neutropenic sepsis deaths. Increasing intensity of chemotherapy regimens may be having an effect. It is also possible that more patients who previously might have been thought to have been too high risk for treatment are being given chemotherapy, and the NCEPOD report (NCEPOD, 2008) highlighted that selecting less fit patients for chemotherapy risks a higher rate of fatal complications, including neutropenic sepsis.

Patients aged 15 to 24 have a significantly higher risk of dying of neutropenic sepsis. It has been documented for many conditions that teenagers and young adults are less compliant with medical treatment and advice than older adults. This has certainly been seen for epilepsy (Asadi-Pooya, 2005) and diabetes (Cramer, 2004) amongst others, and is likely to impact on chemotherapy compliance with medical advice regarding neutropenic sepsis too

(Gesundheit, *et al.,* 2007). This, combined with the higher intensity of many of the chemotherapy regimens given to patients with cancer in this age group is likely to explain this finding.

Patients with a cancer diagnosis aged 80 or more have a significantly lower risk of dying of neutropenic sepsis. While there are still a large number of cancers being diagnosed in this group, considerably fewer patients are fit enough to receive chemotherapy, thus reducing the overall risk of neutropenic sepsis.

The most common underlying cancer diagnoses for patients dying of neutropenic sepsis are haematological malignancies, which have a relatively high rate of neutropenic sepsis, and the common solid tumours affecting adults.

It is well documented that the accuracy of death certificate completion has been poor (Swift and West 2002), and there have been recent drives to improve the quality and accuracy. Potentially, the increase in reported deaths may be due, at least in part, to increased accuracy of death certificate completion. There are currently pilot programs introducing a medical examiner role with the aim of introducing this system nationally by 2013. This may further improve the quality of the documentation.

It is unknown whether patients had a death certificate completed implying neutropenic sepsis which was not coded as such on the ONS database. Potentially, the increased death rate from neutropenic sepsis may in part be demonstrating an improvement in ONS coding accuracy, but there is no evidence either to support or refute this. Unfortunately, it was not possible to investigate this in more detail.

1.2.3 Influence of chemotherapy regimen on neutropenic sepsis

The risk of a patient developing neutropenic sepsis varies greatly according to the treatment regimen and, with certain regimens, whether prophylaxis has been given (Martin, *et al.,* 2006). Risk factors for neutropenic sepsis can include advanced age, poor performance status, poor nutritional status, underlying haematological malignancy and intensity of chemotherapy (Lyman, 2005).

In 2006, as part of an American Society of Clinical Oncology (ASCO) guideline document, a review was performed of the published likelihood of the occurrence of neutropenic sepsis with various cytotoxic chemotherapy regimens thought to be of intermediate or high risk. In 2010 the European Organisation for the Research and Treatment of Cancer (EORTC) published a similar document (Aapro, *et al.,* 2011) and also repeated the review. A selection of the more commonly used regimens to treat adult cancers in the UK is included in Table 1.2.

Table1.2 Risk of neutropenic sepsis from differing chemotherapy regimens

Tumour site	Regimen	Likelihood of neutropenic sepsis (%)	Trial
Breast	TAC[1]	28.8	Martin, *et al.,* 2005
	FEC100-T[2]	25	Head, *et al.,* 2008
	FAC[3]	4.4	Martin, *et al.,* 2005
Lung	Carboplatin / Etoposide	10-20	Crawford, *et al.,* 2011
	Gemcitabine / Cisplatin	7	Cardenal, 1999
Colorectal	FOLFIRI[4]	11	Douillard, *et al.,* 2000
	FOLFOX4[5]	6	Rotheberg, *et al.,* 2003
Gastric / Oesophageal	EOX[6]	10	Cunningham, *et al.,* 2010
NHL	CHOP[7]	35	Lyman, *et al.,* 2003
Hodgkin disease	ABVD[8]	2-12%	Vakkalanka, Link, 2011
Germ cell	BEP[9] (including CBOP-BEP)[10]	18	Teoh, *et al.,* 2006
Head and neck	TPF[11]	9	Vermorken, 2007

[1] Docetaxel 75mg/m^2, doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2 d1 of 21 day cycle
[2] Fluorouracil 500mg/m^2, epirubucin 100mg/m^2, cyclophosphamide 500mg/m^2, d1 of 21 day cycle for 3 cycles then docetaxel 100mg/m^2 d1 of 21 day cycle for 3 cycles
[3] Fluorouracil 500mg/m^2, doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2 d1 of 21 day cycle
[4] Either irinotecan 80mg/m^2, fluorouracil infusion (24h) 2300mg/m^2, calcium folinate 500mg/m^2 d1 weekly OR irinotecan 180mg/m^2, fluorouracil 400mg/m^2 bolus and 600mg/m^2 22 hour infusion and calcium folinate 500mg/m^2 d1 of 14 day cycle
[5] Oxaliplatin 85mg/m^2 d1, leucovarin 200mg/m^2, fluorouracil 400mg/m^2 bolus and 600mg/m^2 22 hour infusion d1 and 2 of 14
[6] Epirubicin 50mg/m^2, oxaliplatin 130mg/m^2 and d1 capecitabine 625mg/m^2 bd daily 21 day cycle
[7] Cyclophosphamide 750mg/m^2, doxorubicin 50mg/m^2, vincristine 1.4mg/m^2 d1 and prednisolone 100mg d1-5 of 21 day cycle
[8] Doxorubicin 25mg/m^2, bleomycin 10,000u, vinblastine 6mg/m^2 and dacarbazine 375mg/m^2 d1 and 15 of 28 day cycle
[9] Bleomycin, etoposide and cisplatin (exact doses not specified from this source)
[10] Bleomycin, etoposide, cisplatin, vincristine and carboplatin (exact dose and schedule not specified from this source)
[11] Docetaxel 75mg/m^2, Cisplatin 75 mg/m^2, fluorouracil 750mg/m^2, d1 of 21 day cycle

1.3 Current service provision for neutropenic sepsis in England and Wales

1.3.1 Methods

In order to determine the current practice concerning the prevention and treatment of neutropenic sepsis a questionnaire was distributed via the cancer networks to all acute trusts in England and Wales. A copy of the questionnaire can be found in the full needs assessment report. It was requested that this questionnaire be completed by a senior clinician (doctor or nurse) from any institution which may have to assess or treat a patient at risk of neutropenic sepsis. Several supporting documents were also requested, including any neutropenic sepsis, GCSF or relevant antibiotic policy documents, patient information, audits involving neutropenic sepsis and teaching materials. Where an institution had more than one neutropenic sepsis policy (it was recognised that policies for paediatrics, solid adult tumours and adult haemato-oncology could be different), it was requested that one questionnaire be completed for each policy, meaning some institutions were expected to return up to three questionnaires. The questionnaire covered all the main areas set out in the scope of the neutropenic sepsis guideline.

Where a questionnaire entry appeared to be incorrect or included a typographical error, any submitted documentation such as local neutropenic sepsis protocols was analysed and if necessary a correction was made. The range and scope of these questionnaire responses was described qualitatively or quantitatively as appropriate.

1.3.2 Results

Demographics

A total of 80 valid questionnaires were returned. 51 centres returned a single questionnaire, 11 returned two, 1 returned three and 1 returned four (as there was a separate policy covering lung cancer in this centre). The geographical distribution included representation from all areas of England and Wales. As the questionnaire was distributed via the cancer networks to the cancer leads for each hospital rather then directly to the trusts, it was not possible to determine a response rate.

These 80 questionnaires represented:

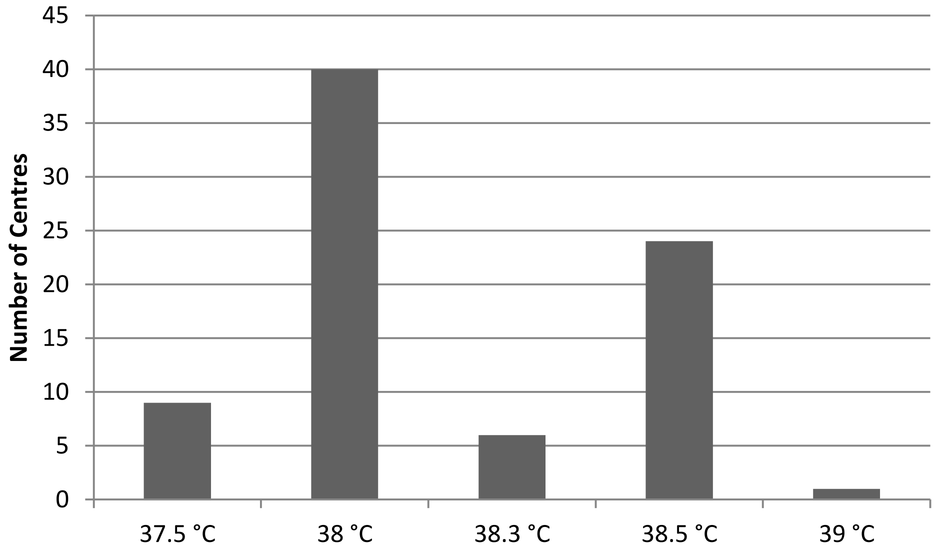
- 53 adult solid tumour policies
    - 1 stand-alone centre
    - 23 cancer centres within an acute trust
    - 29 cancer units
- 44 haematology policies (Matthey, *et al.,* 2009)
    - 15 level 1
    - 19 level 2
    - 10 level 3&4 (including two level 4 units)
- 30 paediatric oncology policies
    - 7 primary treatment centres
    - 9 level 1 shared care units
    - 4 level 2 shared care units
    - 5 level 3 shared care units
    - 5 paediatric departments without oncology

Definition of neutropenic sepsis

Temperature criteria

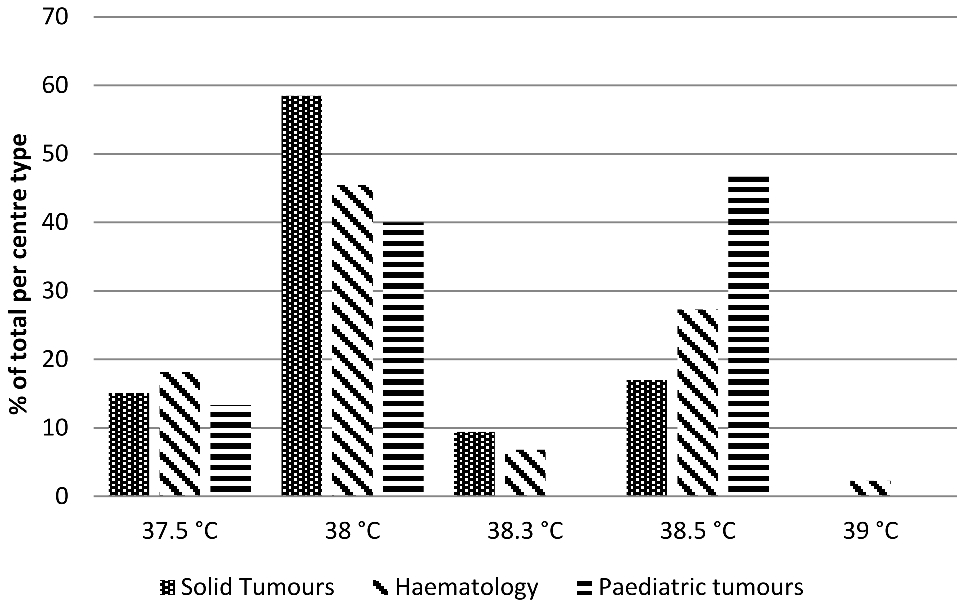
All centres had a single temperature above which the patient is considered to be at risk of neutropenic sepsis. The range of single readings varied from 37.5°C to 39°C (Figure 1.5).

Figure 1.5 Single temperature defining neutropenic sepsis



When split into paediatrics, adult solid tumours and adult haematology, the most common single temperature used for adults is 38°C and for children is 38.5°C (Figure 1.6).

Figure 1.6 Single temperature defining neutropenic sepsis by patient group

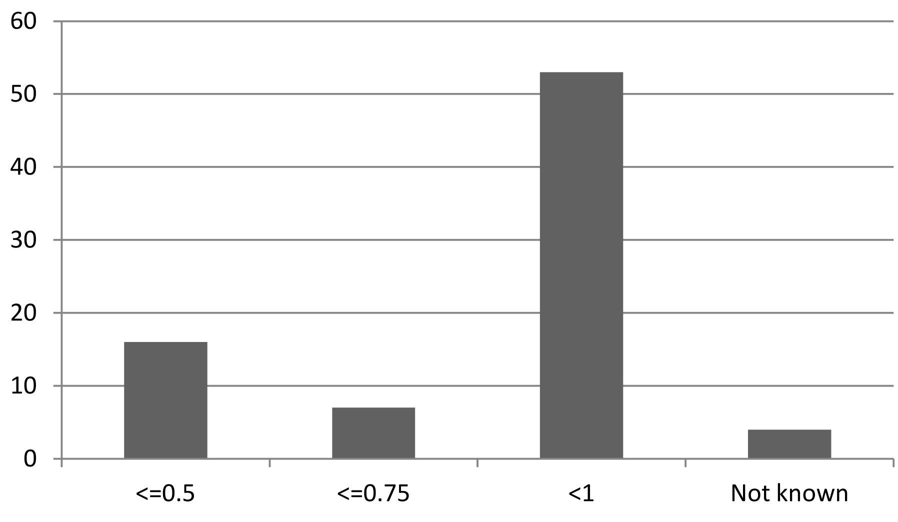


In 36 (45%) of protocols, two temperature readings recorded over a period of time of a slightly lower grade fever than the single reading described above would trigger a potential "neutropenic sepsis" diagnosis. Of these, 20 (56%) listed two readings of 38°C over one hour. There were nine different criteria listed in total ranging from two temperatures of 37.5°C in 2 hours (adult and paediatric) to two readings of 38° over 4 hours (all paediatric). 19 (24%) of protocols included a minimum temperature for defining potential neutropenic sepsis.

Neutrophil criteria

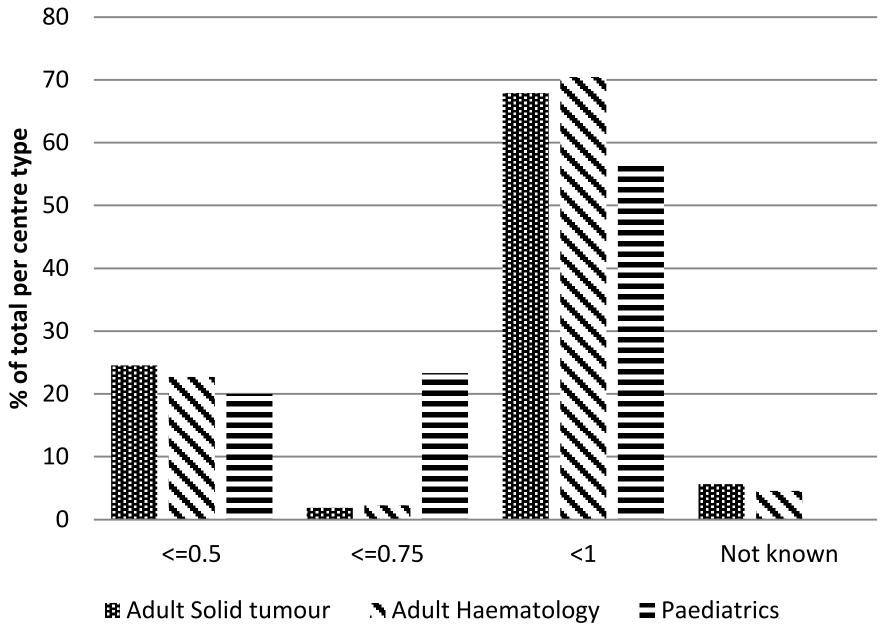
As with temperature criteria, the neutrophil count below which neutropenic sepsis was diagnosed varied between protocols (Figure 1.7).

Figure 1.7 Neutrophil count x10^9 diagnostic of neutropenia



There appeared to be little difference between paediatric, adult solid tumour and adult haematology criteria for neutropenia (Figure 1.8).

Figure 1.8 Neutrophil Count x10[9] diagnostic of neutropenia by patient group



Other criteria

The majority of protocols stated that if a patient was systemically unwell or shocked they would be treated as potentially having neutropenic sepsis regardless of the temperature. For the protocols where this was not explicitly stated, none suggested that a normal temperature excluded the diagnosis of neutropenic sepsis.

Prevention of neutropenic sepsis in adults and children

The two methods of prophylaxis against neutropenic sepsis covered by the guideline scope are antibiotics and GCSF.

Prophylactic antibiotics – primary prophylaxis

Primary antibiotic prophylaxis was reported as never used in 18 (23%) centres, was given for all regimens in 3 (4%) centres, and there were widely varying indications in the remaining 73%. The latter group were generally “high risk” regimens, including acute leukaemia, lung regimens, and high risk breast cancer regimens. Many of these centres gave antibiotic prophylaxis on cycle 1 alone.

There was no clear difference in the pattern of usage of prophylactic antibiotics between paediatric, adult solid tumour and adult haematology centres. The choice of prophylactic antibiotic was known for 35 policies. 77% used ciprofloxacin and 23% used levofloxacin.

Prophylactic antibiotics – secondary prophylaxis

Following an episode of neutropenic sepsis, secondary prophylactic antibiotic use was reported as never used in 31 (39%) policies, and used universally in 12 (15%). Where specified, ciprofloxacin was the commonest choice of antibiotic.

Prophylactic growth factors – primary prophylaxis

It was reported that growth factors (G-CSF) were never used in 4 (5%) protocols (including adult solid tumour, adult haematology and paediatrics) and were used in all regimes by 3 (4%). For the remainder, indications were very varied, and included “high risk” regimens in 39 (49%) protocols and only “high risk” regimens which were potentially curative in 8 (10%) protocols. Further criteria (for the remaining 32%) included a high risk of complications due to comorbidities, age, or regimen, or subjective criteria, for example “consultant decision”.

Where used for primary prophylaxis, G-CSF (as opposed to GM-CSF) was always prescribed. Around 80% of protocols for primary G-CSF prophylaxis used a once daily preparation and 20% used a long acting (pegylated) preparation for the majority of their regimens.

Prophylactic growth factors – secondary prophylaxis

Growth factors were used for secondary prophylaxis following an episode of neutropenic sepsis in 24 (30%) of centres for all further cycles, never used in 2 (3%) centres, and variably in the remainder. Most of the G-CSF used for this indication was given as a once daily rather than pegylated preparation.

Patient education

Written information

Of the 79 eligible centres (one was from an institute which did not deliver chemotherapy), 3 (4%) respondents stated their centres did not give written information which included information about neutropenic sepsis prior to chemotherapy. 57 (72%) gave written information at the initial visit, and the remainder gave the information at a subsequent clinic visit or just prior to chemotherapy. 51 (65%) routinely gave written information during more than one meeting.

Examples of written information given to patients ranged from a 76 page patient held record book covering all aspects of chemotherapy to single sided sheets reminding patients about neutropenic sepsis. The emphasis on neutropenic sepsis in the written information varied between it being the sole topic covered or it being discussed as part of a more general information resource, with no more emphasis on neutropenic sepsis than other chemotherapy toxicities. 29 (81%) information leaflets included advice concerning specific temperatures. 30 (83%) included a telephone number to call for advice.

Verbal information before chemotherapy

All centres where chemotherapy was administered reported that verbal information concerning neutropenic sepsis was routinely given prior to chemotherapy. 38 (48%) respondents reported their centres used a checklist for this.

Chemotherapy alert cards

62 (78%) respondents reported their centre provided a card or letter designed to be carried at all times while on chemotherapy. Examples contained either information for the patient, management advice to healthcare professionals or both. The information could include patient name and hospital number, the chemotherapy regimen, dates of delivery, symptoms of neutropenic sepsis, contact telephone numbers and specific advice to healthcare professionals on the treatment of neutropenic sepsis. While the majority were credit card sized, some were larger (still pocket sized) and there were a small number of examples of A4 sized letters.

Criteria for referral to secondary or tertiary care

Many protocols specified that advice should be sought if the patient was feeling generally unwell, experiencing rigors or had other concerns. Specific information about fever or hypothermia was given in most protocols. 54 (71%) protocols specified the same criteria as for diagnosing neutropenic sepsis in their centre, and 21 (27%) used a lower temperature to trigger a referral. 34 (44%) protocols also included instructions that the patient seek help if they developed a low temperature.

No policy mandated that patients had to have a certain temperature before seeking assistance.

Immediate management of neutropenic sepsis in adults and children

Initial antibiotic timing

76 (95%) respondents reported antibiotics were routinely given to patients presenting with suspected neutropenic sepsis before the full blood count was known. Of these, 57 (75%) would recommend antibiotics were started in all patients, and the remainder would perform a risk assessment (using a risk stratification tool such as the MASCC criteria (Kern, 2006) or clinical judgement.

75 (94%) respondents stated a “door to needle” time target was in place, and times were submitted for 73. (Table 1.3).

Table 1.3 Door to needle times

Door to needle time	Number of protocols
30 minutes	5 (7%)
1 hour	65 (89%)
2 hours	3 (4%)

Several audits were submitted where “door to needle” time was evaluated. These tended to show that the “door to needle” time targets were initially poorly met, but improved on re-audit.

Initial empiric intravenous antibiotic choice (where oral antibiotics are not being considered)

Initial empiric intravenous antibiotic choice in patients not allergic to penicillin varied (Table 1.4). 27 (36%) use a single antibiotic while 48 (64%) used two or more antibiotics as their standard treatment.

Table 1.4 Antibiotic protocols

Antibiotic regimen	Number of protocols
Piperacillin / tazobactam and gentamicin	43 (57%)
Piperacillin / tazobactam monotherapy	19 (25%)
Meropenem monotherapy	8 (11%)
Piperacillin / tazobactam and amikacin	3 (4%)
Ceftazadime and gentamicin	1 (1%)
Ceftriaxone and gentamicin	1 (1%)

The pattern of antibiotic use was generally the same in adult haematology, adult solid tumour and paediatric centres.

17 (21%) protocols used a risk assessment to identify those patients at higher risk of severe sepsis. 10 of these added gentamicin to the previous “standard” regimen and the 7 others changed to a completely different antibiotic regimen.

In patients with a central venous catheter, a different antibiotic regimen was recommended by 12 (15%) protocols; 9 added vancomycin and 3 added teicoplanin when a line infection was not suspected. Where infection was suspected 60 (75%) centres reported a specific policy; 33 added teicoplanin and 27 added vancomycin.

For a reported history of penicillin allergy but perceived low risk of anaphylaxis or angio-oedema, 64 (80%) protocols included a beta lactam-containing antibiotic such as ceftazadime or meropenem, while 12 (15%) policies contained no beta lactam antibiotics. For patients at high risk of penicillin related anaphylaxis, 28 (35%) respondents to the questionnaire quoted a regimen including a beta-lactam containing drug (mainly meropenem).

No centres in this study reported delivering first line intravenous antibiotics for neutropenic sepsis in an ambulatory care setting.

Empirical oral antibiotics

Empirical oral antibiotics were given to lower risk patients in 23 (29%) protocols. Most centres using such a policy discharged patients immediately, with the minority observing for up to 24 hours or more.

Where a specific risk scoring system was used, the MASCC score (Kern, 2006) was most frequently quoted. Some high risk tumour types such as acute leukaemia were specifically excluded from receiving oral antibiotics in most of these regimens. Some centres only used such an oral antibiotic policy for palliative chemotherapy regimens. Where the patient had been on prophylactic oral antibiotics or G-CSF they were generally excluded from receiving oral antibiotics to treat neutropenic sepsis.

Ciprofloxacin and co-amoxiclav were the most common antibiotic choices. Clindamycin was most commonly used if the patient was allergic to penicillin.

On-going management of neutropenic sepsis

Two situations were considered:

- Uncomplicated admission, where the patient's pyrexia settles
- Failure to respond to first line antibiotics

Uncomplicated admission

Approximately two-thirds of centres of all types routinely switched from intravenous to oral antibiotics before discharge. Criteria for switching varied, including: after a set number of days (from 1 to 5); when the patient was apyrexial and had a rising neutrophil count; when the patient had been apyrexial for a given length of time, regardless of neutrophil count.

The majority of centres observed the patient 24 hours after stopping intravenous antibiotics before discharge. This was the case both if they had been changed to oral antibiotics or when antibiotics had been stopped completely.

Failure to respond to first line antibiotics

54 (68%) centres routinely changed the antibiotic regimen after 48 hours without improvement. 16 (20%) centres changed after 24 hours, and 10 (12%) considered changing after 3 or 4 days.

Documentation concerning neutropenic sepsis

All but one centre had a written neutropenic sepsis policy, and all but two had a specific antibiotic policy for neutropenic sepsis.

Staff training

Staff training varied across trusts and disciplines. The majority of respondents reported some form of training for junior doctors and nurses, and provided this information through direct education and provision of internet and various written information sources.

1.4 Summary

Neutropenic sepsis is common, resulting in hundreds of hospital admissions every month and potentially causing the deaths of over 1 in 500 people diagnosed with cancer. There is evidence that the number of deaths from neutropenic sepsis is increasing at a faster rate than the number of cancers being diagnosed. The most likely explanation for this is the increase in the amount of chemotherapy administered in recent years (NCAG 2009). If each chemotherapy cycle prescribed carries a risk of neutropenic sepsis, it is highly likely that the incidence, and therefore the rare event of a death from neutropenic sepsis will have increased too. Despite the very small numbers, there is a significantly greater risk of death from neutropenic sepsis in patients aged 15-24 years old.

Unfortunately it has not been possible to determine the overall burden of neutropenic sepsis on the NHS in England and Wales, largely because the GDG did not feel the accuracy of coding for neutropenic sepsis in clinical coding databases could be relied on at present, although it is recognised that efforts are being made to improve this.

Despite the significance of neutropenic sepsis and the national recognition of the importance of the condition, there is surprisingly little agreement throughout England and Wales regarding its definition, prevention, diagnosis and treatment. This echoes the findings of recent studies covering haemato-oncology (Clarke, *et al.,* 2011) and paediatric oncology (Phillips, et.,2007).

- Definitions of neutropenia ranged from a neutrophil count of $0.5x10^9$/L to 1.0 $x10^9$/L. A temperature at which a patient would be treated empirically varied from 37.5 °C to 39°C, with the majority using 38°C.
- Policies concerning prophylaxis with G-CSF and/or antibiotics were very varied for both primary and secondary prophylaxis.
- Almost all centres had a “door to needle” time of one hour or less, when giving intravenous antibiotics to a patient suspected of having neutropenic sepsis, as mandated in the recent NCAG report (NCAG 2009). The antibiotics given varied considerably, but the majority of centres used either gentamicin and piperacillin / tazobactam or piperacillin/tazobactam alone.
- Approximately a third of centres had a policy where lower risk patients are given oral instead of intravenous antibiotics. Most patients were discharged immediately if started on this pathway.
- It was almost universal that patients received written and verbal information about neutropenic sepsis before chemotherapy was administered, or occasionally (in paediatric settings) before discharge following in-patient chemotherapy.
- Almost all centres had a written neutropenic sepsis policy, communicated to staff via training, posters, hospital intranets and handbooks.

A major methodological challenge in assessing the rate of neutropenic sepsis, infections and death in England and Wales was the variable quality and lack of consistency of death certification and clinical coding. This makes assessing the impact of neutropenic sepsis on patients, carers and the health service as a whole very difficult and probably impossible. While neutropenic sepsis is a complication of anticancer treatment rather than a diagnosis in itself, consideration should be given to assigning it a unique ICD10 code to better define the effect of this complication.

The dramatic variations seen here concerning the definitions, prevention and treatment of neutropenic sepsis highlight the need for an evidence based guideline to guide and unify UK practice.

Research Recommendation

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

Linking Evidence to Recommendations

The GDG noted that during the needs assessment work it had been difficult to assess the incidence and burden of treating neutropenic sepsis. They agreed that further research needs to be undertaken to assess the incidence of suspected and proven neutropenic sepsis.

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2 Diagnosis of neutropenic sepsis

Neutropenic sepsis is a life threatening complication of anticancer treatment, the term is used to describe a significant inflammatory response to a presumed bacterial infection in a person with or without fever.

The objective of this chapter is to define neutropenic sepsis to identify those patients for whom treatment for bacterial sepsis should be undertaken before any clear diagnosis of infection is established.

2.1 Definition of neutropenia and fever

The risk of a life threatening infection in patients receiving treatment for cancer is related to the degree of immunosuppression, commonly assessed by the absolute neutrophil count (ANC). The risks of mortality and other adverse clinical outcomes increase as the absolute neutrophil count falls. It has been considered necessary to set thresholds to initiate empiric antibiotic treatment to ensure that occult infection is treated promptly and that patients with very low risk of infection are not exposed to unnecessary antibiotics. The neutrophil count and the degree of fever at the time of hospital presentation influence the decision on whether inpatient admission is necessary.

Protocols for neutropenic sepsis usually define neutropenia as an absolute neutrophil count of less than 0.5×10^9 /litre, or less than 1.0×10^9 /litre and "falling", the interpretation of which requires some knowledge of chemotherapy regimens and expected patterns of myelosuppression. Fever is a common but not the only manifestation of infection (for example patients may present with hypothermia). A clinically significant fever has been defined variously as 37.5^0C, 38^0C or 38.5^0C over different time points.

An evaluation of how the risk of mortality and other adverse clinical outcomes relate to the absolute neutrophil count and the degree of fever should determine the appropriate threshold for initial empiric treatment. This could reduce unnecessary hospitalisation of those without risk of life threatening infection. Also, there would be consistent advice from health care professionals working in different healthcare settings

Clinical question: How do neutrophil count and temperature relate to the risk of complications of sepsis, in cancer patients with suspected neutropenic sepsis?

Clinical evidence (see also full evidence review)

Study quality and results

No evidence comparing definitions of neutropenia or fever in cancer patients with possible neutropenic sepsis was found.

Eleven observational studies were found about temperature and neutrophil count as prognostic factors in patients receiving treatment for fever and neutropenia. Seven studies included paediatric patients and ten included only patients with fever (definitions ranged from a single temperature measurement greater than 38.0°C to 38.0°C for at least four hours) and neutropenia (ANC $<0.5 \times 10^9$/litre or 1.0×10^9/litre and falling). These studies probably underestimate the usefulness of neutropenia and fever as prognostic factors in neutropenic sepsis because they are limited to a restricted range of ANC and temperature values, excluding patients with low risk of neutropenic sepsis. The evidence is therefore of low quality.

Literature searches identified no evidence about the relationship between mortality or length of stay and definitions of neutropenia and fever.

Evidence statements

A single study in 102 patients (Apostolopoulou, *et al.,* 2010) reported that ANC >0.5 x 10^9/litre has high negative predictive value for bacteraemia. All other evidence came from studies of patients with both neutropenia and fever and thus had limited value due to the restricted range of possible temperature and ANC values.

Low quality evidence suggests that defining fever as temperature >39.0°C (instead of >38.0°C) increases the positive predictive value (PPV) of neutropenia and fever for bacteraemia, severe infection and adverse events (Ammann, *et al.,* 2003, Ha, *et al.,* 2010, Hakim *et al.,* 2010, Klassen *et al.,* 2000 and Santolaya, *et al.,* 2001). Although the negative predictive value (NPV) of this definition was not estimable, using the >39.0°C definition would probably decrease NPV (relative to >38.0°C).

Low quality evidence suggests that defining neutropenia as ANC <0.1 x10^9/litre (instead of <0.5 X10^9/litre or 1.0 X10^9/litre and falling) increases the PPV of neutropenia and fever for bacteraemia, severe infection and adverse events (Apostolopoulou, *et al.,* 2010, Ha *et al.,* 2010, Hakim, *et al.,* 2010, Klassen, *et al.,* 2000, Santolaya *et al.,* 2001 and Tezcan, *et al.,* 2006). Again the effect of this change on NPV was not estimable but would probably decrease NPV.

There was low quality evidence from one paediatric study (West, *et al.,* 2004), that each additional degree in temperature above 38.0°C was associated with a relative increase of 1.74 (95% C.I. 1.25 to 2.43) in the odds of receiving critical care within 24 hours of presentation.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Further health economic analysis was not undertaken as the topic was about the definition of neutropenic sepsis and therefore did not lend itself to economic evaluation as there was no comparative analysis of cost and outcomes.

Recommendation

- Diagnose neutropenic sepsis in patients having anticancer treatment whose neutrophil count is 0.5 x 10^9 per litre or lower and who have either:
  - a temperature higher than 38°C **or**
  - other signs or symptoms consistent with clinically significant sepsis.

Linking Evidence to Recommendations

The aim of this topic was to see how the neutrophil count and temperature relate to the risk of complications of sepsis in patients with cancer and suspected neutropenic sepsis.

The GDG considered that outcomes of serious infection, mortality, critical care, clinically documented infection and complications to be the most clinically relevant to the question. Avoiding death or the complications of severe infections, which include the need for admission to a critical care facility, are the main reason for treatment of people with reduced immune function and potential infection. Length of stay was also considered an important outcome but no evidence was found about the relationship between length of stay and the definition of neutropenia or fever.

The GDG noted that there was no evidence available comparing the definitions of neutropenia or fever in cancer patients with possible neutropenic sepsis. They also noted that the evidence probably underestimated the usefulness of neutrophil count and temperature as predictive factors for neutropenic sepsis because the studies are limited to a restricted range of absolute neutrophil count and temperature values. The overall quality of the evidence was low.

The GDG acknowledged that having a very narrow definition of neutropenic sepsis could result in some patients with sepsis being missed and going on to develop life-threatening infection (a poor negative predictive value, NPV). Conversely a broad definition could result in over treatment or unnecessary investigation of patients without such infections (a poor positive predictive value PPV). The GDG recognised that neutropenic sepsis may also present in patients who are unwell together with other constellations of symptoms in the absence of fever (see also section 4.1). In recommending a definition of neutropenic sepsis, the GDG sought an appropriate balance between under and over diagnosis and treatment.

It was the opinion of the GDG that although some patients receiving anticancer treatment who present unwell and are subsequently found to have a neutrophil count above 0.5 x 10^9/litre will not be categorised as having neutropenic sepsis but will require management of their sepsis.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG was that this recommendation would results in a change in practice and that the potential costs of dealing with a patient whose neutropenic sepsis had been missed would be higher than those of a patient without neutropenic sepsis who was over-treated. The GDG agreed that it was higher priority to prevent patients with neutropenic sepsis from developing life-threatening infection and therefore chose to recommend a relatively broad definition, accepting that this could result in some patients without neutropenic sepsis receiving over treatment.

The GDG concluded that neutropenic sepsis should be diagnosed in patients receiving anticancer treatment with a neutrophil count is 0.5 x 109 per litre or lower and a temperature higher than 38^{o}C or with other symptoms and signs consistent with significant sepsis

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3 Information, support and training

Patients who are receiving anti-cancer treatment and their carers can be given confusing and inconsistent information in different ways by different people. The training of healthcare professionals in this area is variable.

The objectives of this chapter are to identify:
- What information should be given to patients and carers?
- How this information should be given?
- What is the best way of training healthcare professionals?

3.1 Information and support for patients and carers

3.1.1 Content of information and support

The complications of anticancer treatment are unknown to many patients and carers. At this stressful time of initiating treatment and at all subsequent stages there is a lot of information to take in.

Patients and carers are informed about the nature of anticancer treatment, the potential complications (including neutropenic sepsis), the actions to be taken and the support offered should any problems arise.

A failure to recognise relevant symptoms could lead to a delayed diagnosis of infection and an increased risk of adverse clinical outcomes.

These issues have been widely acknowledged in the National Cancer Action Team, Manual of Cancer Services (NCAT 2011) and National Chemotherapy Advisory Group report (NCAG 2009).

Clinical question: What information and support for patients receiving anticancer treatment, and their carers, reduces the adverse effects of neutropenic sepsis?

Clinical evidence (see also full evidence review)

The literature searches identified no published evidence for this question.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Further health economic analysis was not undertaken as the topic did not lend itself to economic evaluation as there was no comparative analysis of cost and outcomes.

Recommendation
- Provide patients having anticancer treatment and their carers with written and oral information, both before starting and throughout their anticancer treatment, on:
  - neutropenic sepsis
  - how and when to contact 24-hour specialist oncology advice
  - how and when to seek emergency care.

Linking Evidence to Recommendations

The aim of this topic was to see what information and support reduce the adverse effects of neutropenic sepsis for patients receiving anticancer treatment and their carers.

The GDG considered the outcomes of mortality, ICU admissions, door to needle time, length of stay and patient knowledge to be the most clinically relevant to the topic. No evidence was identified that was relevant to this question and therefore none of these outcomes were reported.

The GDG noted that there was a lack of evidence on what information and support patients needed to reduce the adverse effects of neutropenic sepsis. The GDG agreed that despite this lack of evidence it was essential to recommend that information on neutropenic sepsis was provided to patients receiving anticancer treatment. The GDG noted a recommendation should represent best practice, and also be in line with existing Department of Health (NCAT 2011) and national guidelines (NCAG 2009). However the GDG decided that due to the lack of evidence it would not be possible to make definitive recommendations on exactly what information should be provided.

The GDG noted that the NCEPOD report (2008) had highlighted the lack of immediate 24 hour access to specialist oncology advice and appropriate emergency care. They believed it was important to recommend such access for patients with potential neutropenic sepsis to improve patient care and outcomes.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG was that there were potential cost implications for providing immediate 24hour access to specialist oncology advice and appropriate emergency care. However they were uncertain what these implications would be since some centres may already have resources in place to provide this service. The GDG also agreed based on their clinical expertise that providing this service could potentially result in cost savings at some centres by preventing unnecessary admissions and patients presenting earlier preventing later complications.

Therefore the GDG recommended that patients and carers be provided with information on how and when to contact 24-hour specialist oncology advice and access emergency care, together with written and verbal information on neutropenic sepsis before starting and throughout anticancer treatment.

3.1.2 Delivery of information and support for patients and carers

Patients with cancer and their carers receive many pieces of information regarding their treatment, the intended benefits, the potential harms, and support to meet the challenges of being treated for cancer. Information and support on neutropenic sepsis is provided as part of this process.

A range of different methods and formats are used to deliver information about neutropenic sepsis. These include pre-printed leaflets, personalised written information, verbal communication, video and other multi-media presentations. The methods may be delivered by various healthcare professionals. There is no clear consensus on which of these formats, methods or type of healthcare professional supplying the information and support is most beneficial.

Clinical question: What types of information and support have patients with neutropenic sepsis (and their carers) found useful or requested?

Clinical evidence (see also full evidence review)

Study quality and results

The literature search identified one qualitative study (Higgins, 2008) designed to evaluate an alert card containing information for patients and healthcare professionals.

The overall quality of evidence was low, because it only included a single study of one intervention. This study was not designed to explore which types of information and support patients with neutropenic sepsis (and their carers) find useful.

Evidence statements

Higgins, *et al.,* (2008) reported recurring themes from patient responses to their alert card intervention. These included 'Made me feel safe', 'Gave me assurance that if I needed help there was someone to give it to me at the earliest possible moment', 'Symptoms clearly explained', 'Great to have contact numbers'. The authors state that "Overall, the results showed a high level of patient satisfaction."

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Further health economic analysis was not undertaken as the topic did not lend itself to economic evaluation as there was no comparative analysis of cost and outcomes.

Research recommendation

- A descriptive study involving patients who have had neutropenic sepsis and their carers should 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.

Linking Evidence to Recommendations

The aim of this topic was to see what type of information and support patients with neutropenic sepsis and their carers required or found helpful.

The evidence reported one qualitative study of patient satisfaction of an alert card containing information for patients and healthcare professionals. However the GDG felt that there was potential bias as this study only covered a small limited group of patients experience satisfaction. The GDG noted that the evidence was of 'low' quality.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.

The GDG felt that due to the limited evidence available they were unable to make a recommendation for clinical practice. They agreed that further research needs to be undertaken to identify what type of support and information have been offered to patients and their carers, and what were felt to be helpful or unhelpful, and what other types of support and information is felt to be needed.

3.2 Training for healthcare professionals

Patients with suspected neutropenic sepsis may present to a variety of healthcare settings including primary care, emergency departments and hospital wards.

Healthcare professionals within these settings are often unfamiliar with the management and potentially life threatening complications of neutropenic sepsis and have varying levels of expertise within this field.

Some healthcare professionals may receive training in this topic as part of their continued professional development. The methods used vary widely and include lectures, workshops and bedside teaching as well as the use of teaching aids such as DVDs or simulators which allow healthcare professionals to role-play the practical treatment of patients. There is no clear consensus on whether training by these methods is effective, which of the methods is most efficient and whether training delivery should differ by healthcare profession.

Clinical question: Does training healthcare professionals on the identification and management of neutropenic sepsis improve outcomes for patients receiving anticancer treatment?

Clinical evidence (see also full evidence review)

Evidence statements

Door to needle time

There was very low quality evidence from two observational studies about the effect of training on door to needle time (Table 3.1). Lim, *et al.,* (2010) reported a shorter time from triage to first antibiotic in hospitals which used an electronic clinical practice guideline for febrile neutropenia. Sastry, *et al.,* (2009) evaluated staff re-education about febrile neutropenia and found that the proportion of patients receiving antibiotics within 30 minutes of their first assessment did not differ significantly before and after re-education.

Mortality, ICU admissions, length of stay, patient satisfaction and healthcare professionals' knowledge of neutropenic sepsis management

Literature searches identified no evidence about the impact of training healthcare professionals on the identification and management of neutropenic sepsis on these outcomes.

Table 3.1 GRADE profile: Does training healthcare professionals on the identification and management of neutropenic sepsis improve outcomes for patients receiving anticancer treatment?

Quality assessment							Summary of findings				
							Summary of findings		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Enhanced training of healthcare professionals on the identification and management of neutropenic sepsis**	**standard training of healthcare professionals on the identification and management of neutropenic sepsis**	**Relative (95% CI)**	**Absolute**	
Door-to-needle time (Better indicated by lower values)											
2	observational studies	very serious[1]	serious[2]	serious[3]	serious[4]	none	163	104	Not pooled		VERY LOW

[1] One study is a retrospective study with a high risk of bias and the other study, which is an audit, is only reported in abstract form and can therefore not be comprehensively evaluated
[2] The studies report different results, both statistically and numerically.
[3] The interventions are under-specified in the studies.
[4] The sample sizes were small in both studies.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. The potential health benefits from this intervention were likely to be small and difficult to attribute to the training of healthcare professionals, therefore further health economic analysis was not considered appropriate.

Recommendation
• Healthcare professionals and staff who come into contact with patients having anticancer treatment should be provided with training on neutropenic sepsis. The training should be tailored according to the type of contact.

Linking Evidence to Recommendations

The aim of this topic was to see if training of healthcare professionals on the identification and management of neutropenic sepsis could improve outcomes for patients receiving anticancer treatment.

The GDG considered the outcomes of mortality, ICU admissions, door to needle time, length of stay, patient satisfaction, and healthcare professionals knowledge of neutropenic sepsis management, were the most relevant to the question. Evidence was only available for door to needle time. The overall quality of the evidence classified by GRADE was 'very low'.

Despite this limited evidence, the GDG agreed it was essential to recommend training was provided on the identification and management of neutropenic sepsis because this represents best practice, and is in line with existing Department of Health guidance (NCAT, 2011; NCAG, 2009). In addition, it was the opinion of the GDG that providing this training would improve the patient experience. However, the GDG did not feel able to make definitive recommendations on what specific training should be provided due to the lack of evidence. They noted that patients might benefit from receiving better care because healthcare professionals would be trained in the early identification of patients with neutropenic sepsis leading to earlier treatment, more appropriate ongoing management, and reducing complications.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG agreed based on their clinical experience that there may be additional costs or cost savings of recommending training, though it was not possible to quantify these.

Therefore the GDG agreed to recommend that training on the identification and management of neutropenic sepsis for healthcare professionals who come into contact with patients at risk of neutropenic sepsis should be provided.

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4 Identification and assessment

Whilst neutropenic sepsis is a potentially life threatening complication of anticancer treatment, there are many patients who have fever and neutropenia who do not have a serious or life threatening infection. Some patients with life threatening sepsis may not have the classical features of infection.

The objectives of this chapter are:

- To identify patients who require assessment in secondary or tertiary care.
- To identify best practice in the initial emergency assessment of a patient.
- To evaluate risk stratification systems.

4.1 Signs and symptoms that necessitate referral to secondary/tertiary care

Most people receive anticancer treatments as outpatients. The symptoms and/or signs that might predict the development of neutropenic sepsis often occur in patients in the community.

There is considerable variation in the symptoms and/or signs that may indicate neutropenic sepsis and their interpretation. This leads to patients being given varied information on the criteria for urgent admission to hospital.

Over-diagnosis can result in inappropriate admission to hospital and may delay anticancer treatments. Under-diagnosis or delay in diagnosis can put patients at risk of serious or fatal complications. A clearer understanding of how effective specific signs and/or symptoms are in predicting neutropenic sepsis may improve the experience of patients by reducing unnecessary visits to hospitals but improve the early treatment of serious infections.

Clinical question: Which symptoms and/or signs experienced by patients in the community predict neutropenic sepsis?

Clinical evidence (see also full evidence review)

Study quality and results

There was no direct evidence about signs and symptoms of cancer patients in the community that might predict neutropenic sepsis. The available evidence came from retrospective studies of patients who had presented at hospital with treatment induced neutropenia and fever. This evidence is summarised in Table 4.1. By including only patients with confirmed neutropenia and fever these studies are not a representative spectrum of patients in the community (according to the QUADAS checklist in the NICE Technical Manual 2009). The sensitivity and specificity of symptoms or signs for neutropenic sepsis in the community might differ from that in secondary care. Studies typically reported composite outcomes encompassing severe bacterial infection, death and critical care. For these reasons the evidence is of very low quality.

Table 4.1 Signs and symptoms as predictors of adverse outcome in patients with fever and neutropenia.

Sign or symptom	Number of studies (patients)	Prevalence of adverse outcome* (range)	Sensitivity for adverse outcome (range)	Specificity for adverse outcome (range)	LR+ (range)	LR- (range)	References
Mucositis	5 (1605)	12% to 56%	3% to 39%	60% to 100%	0.64 to 2.82	0.71 to 1.24	Ammann, *et al.,* (2003, 2004, 2010), Chayakulkeeree, et al (2003) and West, et al (2004)
General appearance unwell	4 (855)	17% to 33%	31% to 75%	31% to 78%	1.08 to 1.82	0.75 to 0.90	Ammann, *et al.,* (2003, 2004), Hakim, *et al.,* (2010) and Klaassen, *et al.,* (2010)
Temperature >39°C	8 (2602)	15% to 38%	12% to 58%	53% to 95%	1.17 to 2.91	0.71 to 0.92	Ammann, *et al.,* (2003, 2004, 2010), Chayakulkeeree, *et al.,* (2003), Hakim, *et al.,* (2010), Klaassen, *et al.,* (2000) and Klastersky, *et al.,* (2000)
Clinical signs of infection	2 (677)	23% to 37%	21% to 23%	65% to 75%	0.59 to 0.90	1.03 to 1.23	Ammann, *et al.,* (2003, 2004, 2010),
Chills	2 (586)	12% to 36%	10% to 11%	96% to 97%	2.47 to 2.91	0.93	Ammann, *et al.,* (2003, 2004) and West, *et al.,* (2004)
Altered mental state	2 (1023)	15% to 60%	16% to 17%	95% to 97%	3.67 to 6.09	0.86 to 0.87	Chayakulkeeree, *et al.,* (2003) and Klastersky, *et al.,* (2000)
No evidence found for the following symptoms or signs: flu-like symptoms, rigor, parental or carer concern, diarrhoea and vomiting							

*Adverse outcome was a composite outcome including death, critical care, unresolved fever and bacteraemia.
Abbreviations, LR+, likelihood ratio for a positive test result; LR-, likelihood ratio for a negative test result.

Evidence statements

There was uncertainty about which signs and symptoms predict neutropenic sepsis and its complications in cancer patients in the community due to a lack of published evidence.

Chills and altered mental status were associated with adverse outcome in two secondary care studies, but most patients with neutropenic sepsis did not experience either of these symptoms.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Further health economic analysis was not undertaken as the topic did not lend itself to economic evaluation as there was no comparative analysis of cost and outcomes.

Recommendation

- Suspect neutropenic sepsis in patients having anticancer treatment who become unwell.
- Refer patients with suspected neutropenic sepsis immediately for assessment in secondary or tertiary care.

Linking Evidence to Recommendations

The aim of this topic was to identify what symptoms and/or signs experienced by patients in the community predict neutropenic sepsis, to ensure patients avoid a delay in their diagnosis, therefore avoiding an adverse experience or outcome.

The GDG identified neutropenic sepsis, severe sepsis and mortality as the target conditions to be used to assess the sensitivity/specificity of the different symptoms/signs, as these were considered the most relevant end points.

The GDG noted that no evidence was available for the signs and symptoms in the community that might predict severe sepsis, neutropenic sepsis or mortality. The GDG recognised this as an important shortcoming as the sensitivity and specificity of symptoms or signs in the community might differ greatly from their sensitivity and specificity in secondary care. However they agreed that data from secondary care should be used because it was the only data available.

The evidence from secondary care reported largely retrospective data on patients who had presented at hospital with treatment induced neutropenia and fever. The GDG noted that the quality of the evidence was of “very low” quality. The GDG also noted that the patient population in the majority of included studies were children, even though such patients comprise only a small proportion of the total cancer population. Therefore this data may not be representative of the entire clinical population.

The GDG did not consider there was sufficient evidence to recommend which symptoms and signs experienced by patients in the community predict neutropenic sepsis. They therefore decided to make a research recommendation for a prospective study to investigate this. However they felt that because patients in the community receiving anticancer treatment are at risk of developing neutropenic sepsis, recommendations were needed on what to do for this group of patients.

The GDG noted the evidence had shown that although in secondary care some symptoms (confused mental state, chills, feeling or looking unwell) correlated with a poor outcome, the absence of these same symptoms did not predict a good outcome. The GDG felt that patients who become unwell at home should be urgently assessed in hospital to allow a rapid diagnosis to be made. This would ensure appropriate treatment to be given and avoiding the complications of neutropenic sepsis and associated mortality. They noted that urgent assessment of a patient who did not turn out to have neutropenic sepsis could cause unnecessary hospital attendance/care, unnecessary use of antibiotics and patient anxiety. However the GDG considered that the benefits conferred by urgent assessment outweighed the potential harms.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG considered based on their clinical experience that there would be costs associated with urgent assessment of patients who are unwell. However in their opinion early assessment would probably result in greater cost savings via reduction in hospital stay, reduction in complications for example, ICU admission) and prevention of severe sepsis.

They therefore decided to recommend that patients who are unwell in the community should be urgently assessed in hospital for neutropenic sepsis.

Research recommendation

- 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.

4.2 Emergency assessment in secondary/tertiary care

Patients with suspected neutropenic sepsis often present to secondary/tertiary care (local/district general or specialist hospital) by self referral or from primary care.

As part of clinical assessment in hospital, such patients will have a variable series of tests performed according to local practice. These tests may include a physical examination, full blood count, biochemical profile and other blood, urine or imaging investigations. They are performed to predict the risk of complications and identify the underlying cause of the symptoms and signs and thus guide management.

Some of the tests are invasive to the patient, costly to the health service and may not inform clinical management.

4.2.1 Investigations appropriate for clinical management and risk stratification

The majority of protocols for the management of suspected neutropenic sepsis recommend certain laboratory investigations. The function of these is to guide patient management by assessing organ function and determining the risk of adverse clinical complications. These predictive tests include C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and other inflammatory markers. Lactate is routinely used in the management of patients with septic shock, but is not frequently measured at the outset of neutropenic sepsis.

Although the absolute neutrophil count is generally used in clinical management to assess neutropenic sepsis, other white cell counts, such as monocyte count or lymphocyte count may also be measured in order to assess the risk of adverse clinical outcomes.

Tests which enable early identification of patients at higher risk of an adverse outcome may prompt more aggressive management and intensive monitoring with a potential reduction in mortality rates. Tests which accurately predict patients at low, or no, risk of adverse clinical outcome may allow reduced intensity treatment.

Clinical question: Which tests predict outcome and response to treatment in patients with suspected neutropenic sepsis?

Clinical evidence (see also full evidence review)

Study quality and results

There were relatively few studies of tests to predict mortality in patients admitted for fever and neutropenia. There was very limited evidence about CRP, lactate, full blood count, liver function tests or kidney function tests for the prediction of length of hospital stay. Our searches identified no studies of tests to predict the requirement for critical care; however there was some evidence about tests to predict severe sepsis and documented infection. This evidence is summarised in Table 4.2.

Tests were typically done on admission for fever and neutropenia, before the initiation of antimicrobial therapy. Some studies repeated tests over the first few days of fever, to compare how serum levels of biomarkers changed over time in patients with and without severe infection.

25 of the 42 studies were prospective. It was unclear in 16/42 studies how patients were selected for inclusion (for example whether it was a consecutive or random sample of

eligible patients) this is a potential source of bias. Blinding was explicitly used in 6/42 studies.

Table 4.2 Diagnostic Accuracy for Investigations appropriate for risk stratification and management

Test	Cut-off	No. of studies (episodes)	Proportion with outcome (range)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	LR+ (range)	LR- (range)	Analysis method for Sn and Sp	References
Mortality									
Lactate	3 mmol/L	1 (110)	6%	0.43 [0.10, 0.82]	0.93	6.31	0.61	Not pooled	Ramzi, *et al.,* 2007
AMC	0.1 X 10^9/L	2 (931)	4%	Range 0.37 to 1.00 ,	Range 0.51 to 0.58	0.88 to 2.04	0 to 1.08	Not pooled	Santolaya, *et al.,* 2007; Tezcan, *et al.,* 2006
ANC	0.1 X 10^9/L	3 (1388)	4% to 8%	0.67 [0.10, 0.97]	0.71 [0.49, 0. 86]	0.66 to 3.18	0 to 1.17	Univariate random effects model	Santolaya, *et al.,* 2007; Tezcan, *et al.,* 2006; Wilbur, *et al.,* 2000
CRP	90 mg/L	1 (373)	4%	0.79 [0.49, 0.95]	0.62	2.07	0.34	Not pooled	Santolaya,*et al.,* 2007;
Creatinine	17 mg/L	1 (393)	8%	0.53 [0.35, 0.71]	0.89	4.92	0.53	Not pooled	Wilbur, *et al.,* 2000
BUN	180 to 260 mg/L	2 (764)	4% to 8%	Range 0.43 to 0.69	Range 0.86 to 0.94 [	5.04 to 7.33	0.36 to 0.61	Not pooled	Santolaya, *et al.,* 2007; Wilbur, *et al.,* 2000
Albumin	25 g/L	1 (268)	10%	0.29 [0.13, 0.49]	0.88 [	2.36	0.81	Not pooled	Wilbur, *et al.,* 2000
Platelets	25,000 /mm^3	1 (394)	8%	0.44 [0.26, 0.62]	0.76	1.82	0.74	Not pooled	Wilbur, *et al.,* 2000
Severe sepsis									
Lactate	2 to 3 mmol/L	2 (340)	13% to 20%	Range 0.26 to 0.57	Range 0.97 to 0.98	8.00 to 27.43	0.44 to 0.76	Not pooled	Mato, *et al.,* 2010; Ramzi, *et al.,* 2007
CRP	60 mg/L to 100 mg/L	4 (829)	20% to 58%	0.75 [0.52, 0.89]	0.64 [0.60, 0.67]	1.47 to 2.31	0 to 0.72	Univariate random effects model	Erten *et al.,* 2000; Karan *et al.,* 2002; Moon *et al.,* 2009; Santolaya *et al.,* 2008
Creatinine	2 to 20 mg/L	3(1215)	15% to 60%	0.07 [0.03, 0.14]	0.97 [0.80, 0.99]	0.68 to 7.34	0.88 to 1.02	Univariate random effects model	Chayakulkeeree *et al.,* 2003; Moon *et al.,* 2009; Klastersky *et al.,* 2000
BUN	200 mg/L	2(459)	26% to 60%	Range 0.27 to 0.44	Range 0.88 to 0.93	2.25 to 6.25	0.96 to 1.02	Not pooled	Chayakulkeeree, *et al.,* 2003; Moon, *et al.,* 2009
Albumin	25 to 30 mg/L	3 (1215)	20% to 60%	0.11 [0.05, 0.23]	0.95 [0.89, 0.98]	1.91 to 2.83	0.89 to 0.97	Univariate random effects model	Chayakulkeeree, *et al.,* 2003; Klastersky *et al.,* 2000; Moon *et al.,* 2009
ANC	0.1 X 10^9/L	2 (948)	15% to 20%	Range 0.63 to 0.79	Range 0.33 to 0.41	1.07 to 1.18	0.63 to 0.90	Not pooled	Klastersky *et al.,* 2000; Moon *et al.,* 2009
AMC	0.1 X 10^9/L	1 (192)	20%	0.68 [0.51, 0.82]	0.57	1.60	0.55	Not pooled	Moon *et al.,* 2009
Platelets	50,000 /mm3	2 (948)	15% to 20%	Range 0.11 to 0.53	Range 0.83 to 0.92	1.45 to	0.57 to	Not pooled	Klastersky *et al.,* 2000;

Test	Cut-off	No. of studies (episodes)	Proportion with outcome (range)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	LR+ (range)	LR- (range)	Analysis method for Sn and Sp	References
						3.12	0.96		Moon *et al.,* 2009
Bilirubin	20 mg/L	2 (1023)	24% to 60%	Range 0.04 to 0.18	Range 0.96 to 0.96	1.05 to 4.92	0.85 to 1.00	Not pooled	Chayakulkeeree *et al.,* 2003; Klastersky *et al.,* 2000;
Haemoglo-bin	80 g/L	2 (1023)	15% to 60%	Range 0.18 to 0.50	Range 0.61 to 0.86	1.28	0.82 to 0.95	Not pooled	Chayakulkeeree *et al.,* 2003; Klastersky *et al.,* 2000;
WBC	0.5 X 10^9/L	1 (192)	20%	0.61 [0.43, 0.76]	0.61	1.55	0.65	Not pooled	Moon *et al.,* 2009
Documented infection									
CRP	5 to 20 mg/L	6 (692)	29% to 75%	0.84 [0.5, 0.96]	0.35 [0.08, 0.78]	0.85 to 3.45	0.25 to 1.39	Bivariate model	Ammann *et al.,* 2003; Avabratha *et al.,* 2009; Diepold *et al.,* 2008; Hitoglu-Hatzi *et al.,* 2005; Katz *et al.,* 1992; Riikonen *et al.,* 1993
CRP	>30 to 40 mg/L	4 (373)	26% to 66%	0.95 [0, 1]	0.26 [0, 1]	0.89 to 4.05	0 to 3.00	Bivariate model	Yonemori *et al.,* 2001; Massaro *et al.,* 2007; Santolaya *et al.,* 1994; Manian *et al.,* 1995
CRP	50 mg/L	6 (683)	29% to 64%	0.58 [0.13, 0.93]	0.69 [0.57, 0.79]	0.53 to 3.83	0.13 to 1.20	Bivariate model	Ammann *et al.,* 2003; Hatzistilianou *et al.,* 2007; Hitoglu-Hatzi *et al.,* 2005; Katz *et al.,* 1992; Riikonen *et al.,* 1993; Secmeer *et al.,* 2007
CRP	90 to 100 mg/L	6 (850)	33% to 69%	0.67 [0.27, 0.92]	0.81 [0.44, 0.96]	1.49 to 4.98	0.31 to 0.82	Bivariate model	El-Maghraby *et al.,* 2007; Hitoglu-Hatzi *et al.,* 2005; Santolaya *et al.,* 2001; Martinez-Albarran *et al.,* 2009; Katz *et al.,* 1992; Manian *et al.,* 1995
ANC	0.05 to 0.1 X 10^9/L	6 (2898)	16% to 56%	0.58 [0.35, 0.78]	0.52 [0.26, 0.78]	0.91 to 2.03	0.51 to 1.75	Univariate random effects model	Ha *et al.,* 2010; Hakim *et al.,* 2010; Klaassen *et al.,* 2000; Rondinelli *et al.,* 2006; Santolaya *et al.,* 2001;

Test	Cut-off	No. of studies (episodes)	Proportion with outcome (range)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	LR+ (range)	LR- (range)	Analysis method for Sn and Sp	References
									Tezcan *et al.,* 2006
AMC	0.1 X 10^9/L	5 (1709)	19% to 56%	0.73 [0.29, 0.95]	0.45 [0.10, 0.86]	1.02 to 1.73	0.40 to 0/83	Bivariate model	Ammann *et al.,* 2003; Rondinelli *et al.,* 2006; Santolaya *et al.,* 2001; Tezcan *et al.,* 2006; Klaassen *et al.,* 2000
Haemoglo-bin	70g/L	2 (750)	33% to 40%	Range 0.24 to 0.30	Range 0.79 to 0.82	1.16 to 1.68	0.85 to 0.96	Not pooled	Rondinelli *et al.,* 2006; Santolaya *et al.,* 2001
Platelets	20,000 to 75,000 /mm3	4 (1053)	14% to 40%	0.59 [0.25, 0.999]	0.63 [0.00, 0.90]	1.20 to 1.75	0.49 to 0.83	Bivariate model	Hakim *et al.,* 2010; Rondinelli *et al.,* 2006; Santolaya *et al.,* 2001; Klaassen *et al.,* 2000
Creatinine	75 mg/L	1 (237)	38%	Range 0.02 to 0.11	Range 0.91 to 0.99	1.19	0.98	Not pooled	Ammann *et al.,* 2003;

Abbreviations: ANC, absolute neutrophil count; AMC, absolute monocyte count; CRP, C-reactive protein; BUN, blood urea nitrogen, Sn, sensitivity; Sp, specificity. WBC, white blood cell count; LR+, likelihood ratio for a positive test result; LR-, likelihood ratio for a negative test result.

Evidence statements

Mortality

Lactate, albumin and creatinine levels had reasonable specificity (93%, 88% and 89% respectively) but low sensitivity (53% or less) to predict short term mortality in patients with fever and neutropenia, with only data from a single study for each of these tests. Santolaya, *et al.,* (2007) and Wilbur, *et al.,* (2000) reported blood urea nitrogen (at thresholds of 180 and 260 mg/L respectively) had good specificity (86% to 94%) but moderate to low sensitivity (43% to 69%) to predict short term mortality.

Santolaya, *et al.,* (2007) only reported the sensitivity and specificity of laboratory tests whose results differed significantly between patients who died and survived. In their study ANC, AMC, CRP and BUN differed significantly between the two groups, whereas there was no significant difference between the groups in terms of platelets, creatinine, glycemia or lactate dehydrogenase (LDH).

Length of hospital stay

Pastura, *et al.,* (2004) carried out a prospective study to derive a predictive model for length of hospital stay in children with haematological malignancy, neutropenia and presumed infection. Granulocyte count < 0.1 X 10^9/L was considered as a predictive factor in this study, but was excluded from the final multivariate model due to lack of statistical significance. Pastura, *et al.,* final predictive model included ill appearance, age ≥6 years, presence of CVC and disease status as relapse.

Critical care and severe sepsis

Ammann, *et al.,* (2010) reported a prospective study of predictive factors for serious medical complications in children with fever and chemotherapy induced neutropenia. Serious medical complications were defined as death, complication requiring intensive care treatment or complication judged as potentially life threatening by the treating doctor. Ammann, *et al.,* (2010) constructed a multivariate risk score for serious complications, by selecting factors (from a list of 31 candidates) significantly associated with serious complications on univariate analysis. Their final model included four predictive factors: chemotherapy more intensive than that used as maintenance therapy for Acute Lymphoblastic Leukaemia, haemoglobin level ≥90 g/L at presentation, leukocyte count <0.3 g/L at presentation and platelet count <50 g/L at presentation.

Five studies (Ahn, *et al.,* 2010; Erten, *et al.,* 2004; Hamalainen, *et al.,* 2008, 2010 and Santolaya, 2008) compared the mean levels of serum CRP at admission in patients who did and did not develop severe sepsis. Although mean serum CRP level was higher in patients who went on to develop severe sepsis (mean difference 45 mg/L higher, 95% C.I. 32 to 58 mg/L higher) there was considerable overlap between the two groups. Hamalainen, *et al.,* (2008, 2010) recorded CRP levels in the days following admission for fever and neutropenia. They observed a widening difference between the serum CRP levels of patients with severe sepsis and others over the first days of fever – from 53 mg/L on admission to 135 mg/L after four days.

Documented infection

Meta-analysis according to cut-off threshold was done for CRP (Table 4.2). In theory sensitivity should decrease and specificity should increase as the CRP threshold is raised, but this was not the case perhaps due to heterogeneity. AMC and ANC were poor predictors of documented infection.

Some studies (Arber, *et al.,* 2000, El-Maghraby, *et al.,* 2007, Engel, *et al.,* 1998 Hitoglou-Hatzi 2005, Katz, *et al.,* 1993, Massaro, *et al.,* 2007, Martinez-Albarran, *et al.,* 2009, Santolaya, *et al.,* 1994, Tezcan, *et al.,* 2006 and Yonemori, *et al.,* 2001) compared the mean levels of serum CRP at admission for fever and neutropenia in those patients who went on to have a documented infection and patients with fever of unknown or viral origin. Mean CRP level was invariably higher in the patients who went on to have a documented infection: mean difference 35 mg/L higher (95% C.I. 26 to 44 mg/L higher). The greatest differences were seen in studies involving children, however there was significant heterogeneity in the results from paediatric studies.

There was a large range of serum CRP levels recorded in those with documented infections and in those with fever of unknown origin with considerable overlap in the distribution of CRP levels in the two groups. Thus it is unlikely that a single CRP threshold could achieve acceptable sensitivity and specificity for the prediction of documented infection.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. The topic focused on the identification of patients at high risk of an adverse outcome. However management of these patients was beyond the scope of the guideline, as they would be managed by intensive/critical care units. Therefore further health economic analysis was not undertaken

Recommendation

- 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 (see also recommendations in section 4.2.2).

Linking Evidence to Recommendations

The aim of this topic was to identify which tests can predict the risk of adverse clinical complications in patients with suspected neutropenic sepsis, thereby guiding clinical management

The GDG considered the outcomes of mortality, documented infection and length of stay to be the most important outcomes to the question. However the evidence on both mortality and length of stay was limited. No evidence was found for the outcome of critical care; however studies reported on the ability of tests to predict severe sepsis (a composite outcome including septic shock (and its related complications), prolonged fever or death). The GDG agreed to use severe sepsis as a proxy for critical care.

The overall quality of the evidence was low and the number of studies reporting the effectiveness of each test was small. The GDG agreed, based on clinical experience that examining the patient and performing a full blood count, kidney and liver function tests and blood culture provided useful information in identifying patients at high risk of complications. The GDG also noted that the evidence indicated that raised levels of lactate, and to a lesser extent CRP, were suggestive of a patient being at increased risk of severe sepsis.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. However it was the opinion of the GDG that recommending patient examination, full blood count, liver and kidney function tests, CRP, and blood culture was unlikely to represent an additional cost because these tests were already in common use in this group of patients. The GDG also agreed that whilst lactate testing was not in common use, the benefit provided in terms of early identification of patients at high risk of complications outweighed the minimal costs associated with undertaking this test.

The GDG therefore decided to recommend examining the patient and performing a full blood count, liver and kidney function tests, CRP, lactate and blood culture to assess patients with suspected neutropenic sepsis. The GDG agreed to specifically recommend albumin as part of the liver function tests because albumin is not reported by some laboratories in the ‘liver function test’ panel and the evidence had shown it was effective.

4.2.2 Further assessment

Certain additional investigations may be undertaken to determine the underlying cause of the sepsis to guide management of specific infections. These tests include peripheral blood culture, chest x-ray and urinalysis.

There is considerable variation in which investigations are performed both between hospital and clinicians. These investigations can be invasive for the patient and expensive to the hospital. Therefore it is useful to identify which investigations are most effective in determining the underlying cause of the sepsis.

Clinical question: Should additional peripheral blood culture (in patients with a central line), CRP (c-reactive protein), urinalysis, chest x-ray, lactate and blood gases be used in the emergency empiric assessment of a person with suspected neutropenic sepsis?

Clinical evidence (see also full evidence review)

Study quality and results

The overall quality of the 38 included observational studies was low, because most did not include a representative spectrum of patients. 32/38 of the studies included only patients with confirmed neutropenia and fever, a subset of the relevant population of patients presenting with fever where neutropenia is suspected but not yet confirmed. The accuracy of tests in the emergency department setting could be different from that reported in the included studies.

Only 2/38 studies were carried out in emergency departments: Ha, *et al.,* 2010 (but including only low risk patients – MASCC ≥21) and Moon, *et al.,* (2009).

Evidence statements

The evidence is summarised in Table 4.3.

Chest X-ray

Diagnosis of sepsis

Chest X-ray had a high sensitivity for bacterial pneumonia in two studies (Oude Nihuis, *et al.,* 2003 and Renoult, *et al.,* 2004), all cases of bacterial pneumonia were evident on the chest X-ray. A systematic review of the clinical features of radiographic pneumonia in children with fever and neutropenia (Phillips, et al,, 2011), identified 4 studies with 278 patients. The prevalence of pneumonia was 5% and Philips, *et al.,* (2011) estimated that symptoms of respiratory distress had a negative predictive value of 98% (95% C.I. 96% to 99%). The probability of pneumonia in a child without respiratory symptoms was 1.9%.

In five studies, chest X-ray had widely varying sensitivity and specificity for severe sepsis or its complications (Badiei, *et al.,* 2011, Chayakulkeeree, *et al.,* 2003, Klastersky, *et al.,* 2000, Moon, *et al.,* 2009, and Wilbur, *et al.,* 2000). Moon, *et al.,* (2009) considered the use of chest X-ray in the emergency department to predict complicated fever in patients presenting with fever and neutropenia. In this study chest X-ray had a high positive likelihood ratio of 20.26 for complicated fever – a positive chest X-ray increased the odds of complicated fever by a factor of 20.

Clinical value of test

Two studies considered the influence of chest X-ray on clinical management (Oude Nihuis, *et al.,* 2003 and Renoult, *et al.,* 2004). Both concluded that the results of chest X-ray did not influence the choice of antibiotic treatment.

Time to diagnosis or initiation of treatment

None of the included studies reported this outcome.

Peripheral blood culture (in patients with a central line)

Diagnosis of sepsis

Scheienmann, *et al.,* (2010) found that peripheral blood cultures were positive in some cases where central cultures were not. In their series of 228 episodes of bacteraemia the peripheral blood culture was the only positive culture in 28 cases. Thus doing both peripheral blood cultures and central cultures could improve sensitivity for the detection of bacteraemia.

Blot, *et al.,* (1998) reported that in patients where both central venous and peripheral blood cultures were positive the differential time to positivity (DPT) could help indicate catheter related sepsis. Earlier positivity of the central venous culture of two or more hours, when compared to the peripheral culture, increased the odds of catheter-related sepsis by three times.

Clinical value of test

There was no direct evidence about the influence of peripheral blood cultures on clinical management decisions. However, Scheienmann, *et al.,* (2010) surveyed Canadian healthcare professionals about their attitudes to obtaining peripheral blood cultures. The main reason given by the healthcare professionals for not obtaining peripheral blood cultures was that they do not provide any additional information and that phlebotomy is associated with a risk of complications

Time to diagnosis or initiation of treatment

None of the included studies reported this outcome.

CRP, lactate and blood gases

Evidence for these tests was reviewed in section 4.2.1.

Urinalysis

Diagnostic accuracy

Moon, *et al.,* (2009) reported a positive test for urine nitrates had sensitivity of 5% and specificity of 90% for complications of neutropenic sepsis. Thus a positive test was unlikely both in those with and without complications. Other studies mentioned using urinalysis in their initial assessment of patients with suspected neutropenic sepsis (for example Katz, *et al.,* 1992) but did not report its results.

Clinical value of test, time to diagnosis or initiation of treatment

The influence of urinalysis on treatment decisions, time to diagnosis or initiation of treatment was not reported.

Table 4.3 Chest X-ray and additional peripheral blood cultures in the emergency assessment of patients with suspected neutropenic sepsis

Test	N studies (episodes)	Prevalence (range)	Sensitivity (range)	Specificity (range)	LR + (range)	LR – (range)	References
Bacterial pneumonia							
Chest X-ray	2 (349)	2% to 5%	100%	68% to 92%	3.15 to 12.42	Not calculable	Oude Nihuis 2003, Renoult 2004
Severe sepsis or its complications							
Chest X-ray	5 (1684)	15% to 60%	23% to 72%	17% to 98%	0.87 to 20.26	0.62 to 1.66	Badiei 2011, Chayakulkeeree 2003, Klastersky 2000, Moon 2009, Wilbur 2000
DPT between central & peripheral blood cultures	1 (58)	44%	95%	69%	3.12	0.07	Blot 1998

Abbreviations: DPT, differential time to positivity ; LR+, likelihood ratio for a positive test result; LR-, likelihood ratio for a negative test result.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. This was considered an important topic because doing an initial assessment could avoid over-treatment and guide the subsequent treatment strategy; but it may also cause a delay in treatment and thus increase the risk to the patient. However due to the lack of a clear definition of 'treatment' it was not possible to measure the cost of treatment, nor was it possible to define a standard treatment for all patients as this would depend on each patients individual health status. Therefore, further health economic analysis was not undertaken.

Recommendations

- After completing the initial clinical assessment (see recommendations in section 4.2.1), try to identify the underlying cause of the sepsis by carrying out:
    - additional peripheral blood culture in patients with a central venous access device if clinically feasible
    - urinalysis in all children aged under 5 years.
- Do not perform a chest X-ray unless clinically indicated.

Linking Evidence to Recommendations

The aim of this topic was to identify the value of additional investigations in identifying the underlying cause of the sepsis

The GDG considered that the outcomes of time to diagnosis or initiation of treatment together with the diagnostic accuracy and clinical value of each test to be the most relevant to the question. No evidence was reported for time to diagnosis or initiation of treatment. Evidence was reported for the diagnostic accuracy and clinical value of each test.

The GDG acknowledged that the available data was indirect because the population in the evidence was mostly patients with proven neutropenic sepsis, rather than suspected neutropenic sepsis. Therefore the values of the tests were likely to be exaggerated compared to their value in the larger population of patients with suspected neutropenic sepsis. In order to extrapolate this data to the population of interest the GDG decided to assume that the clinical utility of different tests would be less than reported in the evidence.

The overall quality of the evidence addressing CRP and peripheral blood culture was of low quality, and of low quality or non-existent in relation to the other tests.

The GDG recognised that a chest x-ray may be relevant in certain clinical situations but concluded that the evidence did not show that routine use in the initial assessment resulted in a change to the immediate management of a patient and therefore recommended that it is not performed unless clinically indicated.

The GDG unanimously agreed that despite the low quality of the evidence a blood culture should be performed due to the potential effect the results may have on a patient's subsequent management. The GDG recognised that undertaking venepuncture for peripheral blood cultures may be an unpleasant experience, particularly in children, and may delay commencing antimicrobial treatment. They also noted that the quality of evidence for the additional value of peripheral blood cultures was low. Consequently the GDG decided to recommend that in patients with central venous access devices an additional peripheral venous culture should be taken if clinically feasible.

The GDG noted that in their clinical experience, children under the age of 5 are not always able to verbalise their symptoms and agreed that performing urinalysis would pick up any urinary tract infections, which would require specific treatment.

The GDG noted that the tests of lactate and CRP are already recommended as part of the initial clinical assessment of a patient (Section 4.2.1).

The GDG acknowledged that as a result of recommending a reduced number of tests as part of the initial assessment, there is a potential risk of missing the underlying cause of the infection. However the GDG felt that this risk was minimal and that reducing the number of tests would reduce the investigative burden on patients and simplify the investigative pathway.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG considered based in their clinical experience that there may be potential cost savings as a result of the reduced investigations.

Therefore the GDG decided to recommend that the additional investigations of peripheral blood culture and urinalysis in children should be performed, as part of the initial assessment of a patient with suspected neutropenic sepsis. They have also recommended not performing a chest x-ray unless clinically indicated.

4.3 Assessing the patient's risk of septic complications

Many patients treated for neutropenic sepsis are found not to have either clinical or microbiologically proven infection. These patients are at low risk of serious adverse outcomes and may be suitable for either outpatient management from the outset or for early discharge after a period of inpatient observation and investigation (a "step-down" approach).

The ideal stratification system would accurately identify a group of low risk patients with no risk of mortality from sepsis, would be simple to use by healthcare professionals without specific oncology or haematology experience, and use clinical features and laboratory tests which are widely available and inexpensive. There are a number of stratification or "early warning" scoring systems used in both general paediatric and adult practice which may be useful in supporting a step-down approach.

There is no single system in widespread use in either adult or paediatric practice and there are considerable variations in whether a system is used and which one. A simple, reliable and safe system has the potential to significantly reduce hospitalisation without increasing adverse clinical outcomes

Clinical question: Which is the best validated risk stratification score or algorithm for influencing management and predicting outcome in patients with neutropenic sepsis?

Clinical evidence (see also full evidence review)

Study quality and results

Eight prospective or retrospective observational studies were identified that validated the Multinational Association of Supportive Care in Cancer (MASCC) risk index (Baskaran, *et al.,* 2008; De Souza Viana, *et al.,* 2008; Innes, *et al.,* 2008; Ahn, *et al.,* 2010; Uys, *et al.,* 2007; Klastersky, *et al.,* 2006; Hui, *et al.,* 2010 and Cherif, *et al.,* 2006). These papers provided data on the sensitivity and specificity of this risk score in determining which adult patients presenting with neutropenia and fever, were at low risk of developing ‘serious medical complications’. There was no specific evidence on ‘early warning signs’ in neutropenic sepsis.

Phillips, *et al.,* (2010) presented a systematic review of the discriminatory performance of risk prediction rules in febrile neutropenic episodes in children and young people. Only six of the twenty included studies were prospective, but the studies were at low risk of verification procedure bias and unclear risk of interpretation bias (according to the QUADAS criteria). Three other papers about paediatric clinical decision rules were identified (Dommett, *et al.,* 2009; Ammann, *et al.,* 2010 and Macher, *et al.,* 2010).

The evidence for risk scores evaluated in at least three studies is summarised in Table 4.4. For both paediatric and adult studies there was inconsistency in results, with unexplained heterogeneity so the overall quality of evidence was low.

Table 4.4 Studies of clinical decision rules to identify patients at low risk of adverse outcome in patients with fever and neutropenia.

Studies (febrile neutropenic episodes)	Prevalence of adverse outcome (range)	Sensitivity for adverse outcome (range)	Specificity for adverse outcome (range)	LR + (range)	LR - (range)	References
MASCC score (<21) in adults for the prediction of adverse outcome						
8 (1951)	5% to 62%	40% to 88%	59% to 95%	2.11 to 11.21	0.14 to 0.66	Ahn (2010),Baskaran (2010), Carmona-Bayonas (2011), Cherif (2006), De Souza Viana (2008), Hui (2010), Innes (2008) and Klastersky (2006)
Klaassen rule						
6 (3218)	4% to 29%	37% to 100%	23% to 58%	0.88 to 1.69	0 to 1.08	Phillips, *et al.,* (2010), Amman, *et al.,* (2010) and Macher, *et al.,* (2009)
Ammann rule						
3 (1038)	17% to 37%	95% to 100%	9% to 22%	1.05 to 1.29	0 to 0.52	Phillips, *et al.,* (2010), Amman, *et al.,* (2010) and Macher, et al .,(2009)
PINDA rule						
4 (1342)	16% to 53%	67% to 93%	20% to 76%	1.15 to 3.91	0.10 to 0.69	Phillips, *et al.,* (2010), Amman, *et al.,* (2010) and Macher, *et al.,* (2009)
Alexander rule						
3 (1278)	14% to 29%	59% to 94%	9% to 65%	1.03 to 2.39	0.24 to 0.71	Phillips, *et al.,* (2010), Amman, *et al.,* (2010) and Dommett, *et al.,* (2009)

Abbreviations: MASCC, Multinational Association of Supportive Care in Cancer; LR+, likelihood ratio for a positive test result; LR-, likelihood ratio for a negative test result.

Evidence statements

Six studies evaluated the Klaassen rule which uses a single feature: an absolute monocyte count of greater than 100/mm^3 to predict paediatric patients with significant infection. Sensitivity ranged from 37% to 100% and specificity from 23% to 58%.

Evidence from three studies suggests the Amman rule (Ammann, *et al.,* 2003) to predict paediatric patients at low risk of significant bacterial infection has high sensitivity (95% to 100%) but low specificity (9% to 22%). This means that most patients at low risk of adverse outcome would be labelled as high risk.

The Alexander rule to predict adverse clinical consequences in paediatric patients with fever and neutropenia was evaluated by three studies (Alexander, *et al.,* 2002; Ammann, *et al.,* 2010 and Dommet, *et al.,* 2009). Results were heterogeneous with sensitivity ranging from 59% to 94% and specificity 9% to 65%.

Four studies evaluated the PINDA rule for identification of paediatric patients at low risk of significant bacterial infection. Two South American studies from the rule's authors (Santoloya, *et al.,* 2002 and 2003) showed high sensitivity and specificity, however these findings were not replicated by two European validation studies (Ammann, *et al.,* 2010 and Macher, *et al.,* 2009).

Other paediatric clinical decision rules have been proposed (Phillips, *et al.,* 2010) but are validated by less than three studies.

Eight studies reported the sensitivity and specificity of the MASCC risk score to identify adult patients with neutropenia and fever at low risk of serious medical complications. There was considerable heterogeneity in study results which precluded statistical meta-analysis, but no obvious explanatory factor was identified. The sensitivity of MASCC score < 21 (for the prediction of serious medical complications) ranged between 40% and 80% whilst the specificity ranged between 59% and 95%.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. It was noted that a comparative analysis of the impact of choosing one risk stratification algorithm on actual patient outcomes would be of questionable relevance as well as feasibility for de novo modelling. Therefore further health economic analysis was not undertaken.

Recommendation

- A healthcare professional with competence in managing complications of anticancer treatment should assess the patient's risk of septic complications within 24 hours of presentation to secondary or tertiary care, basing the risk assessment on presentation features and using a validated risk scoring system[9].

Linking Evidence to Recommendations

The aim of this topic was to identify the best validated risk stratification score or algorithm for influencing management and predicting outcome in patients with neutropenic sepsis.

The GDG considered the outcomes of mortality, critical care and length of stay to be the most important to the question. However the evidence for critical care and length of stay was limited. The GDG therefore considered an alternative outcome reported by the evidence of early discharge for outpatient antimicrobial therapy.

The overall quality of the evidence was low. There was also unexplained heterogeneity which precluded pooling the data for adult risk stratification scoring systems, however, the overall effect in individual studies was positive.

The GDG noted that the evidence had shown use of a risk stratification scoring system resulted in reduced hospitalisation and medical intervention, however there was not enough evidence to support recommending one system over another. The GDG noted the evidence was drawn from the use of such systems by specialists, and agreed that this was an

[9] Examples of risk scoring systems include 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

important limitation. The GDG also agreed, based on their clinical experience, that it was important to promote early assessment of patients to improve clinical management and patient experience by appropriate stratification of risk of septic complications. The GDG considered that 24 hours was a practical timescale to achieve this.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. However it was the opinion of the GDG that any additional costs associated with performing risk stratification were likely to be offset by a reduction in cost of inpatient treatment for those patients stratified as low-risk and sent home. The GDG also noted based on their clinical experience that as a result of risk stratification patients may be identified as high-risk earlier and admitted to hospital, preventing complications and the costs associated with this.

The GDG therefore decided to recommend that a validated risk stratification be performed by an oncology team member within 24 hours of presentation. The usefulness in assessing patients for early discharge outweighed the potential disadvantages of patients having unpredicted complications at home.

It was recommended that the risk stratification be based on presentation features because all of the validated systems in the evidence had used presenting information to make the assessment. MASCC was given as an example of a risk stratification scoring system for adults because it has good sensitivity. No specific risk stratification rule could be recommended by the GDG to be more effective than any other for children. In the UK, there is considerable experience with a modified version of the Alexander rule and this was considered a suitable example for healthcare professionals to consider using.

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5 Reducing the risk of septic complications of anticancer treatment

Increasing depth and duration of neutropenia increases the risk of infection. One approach to reducing the risk of life-threatening neutropenic sepsis is to prevent or reduce the likelihood of infection, another is to prevent or moderate the degree of neutropenia.

The objective of this chapter is to evaluate the role of growth factors and/or antibiotics to prevent neutropenic sepsis.

5.1 Preventing the septic complications of anticancer treatment

The likelihood of infection may be reduced by the prophylactic use of antibiotics, chosen to cover the most likely pathogens, and the time period of greatest risk for infection. The most serious bacterial infections are likely to arise from gram-negative organisms, but as the duration and degree of immunocompromise increases, significant infections can arise from other organisms too. Typical antibiotics used for prophylaxis include the quinolones, and historically cotrimoxazole. These are given orally, but may cause diarrhoea, vomiting or allergic reaction. There are concerns that the use of prophylactic antibiotics may lead to antibiotic resistance in the local community.

Granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) raise neutrophil counts, and shorten the duration of neutropenia, by stimulating the bone marrow to produce neutrophils. However, side effects include bone pain, headache and nausea. G-CSF and GM-CSF must be given daily by injection, and this may lead to uncomfortable local reactions. Long acting formulations which are given infrequently are available but are more expensive.

Either of these strategies may be used in patients regardless of whether they have experienced neutropenic sepsis or not. This is described as primary prophylaxis. An alternative approach is to use either of these strategies only in patients who have experienced neutropenic sepsis. This is described as secondary prophylaxis.

Clinical question: Does prophylactic treatment with growth factors, granulocyte infusion and/or antibiotics improve outcomes in patients at risk of neutropenic sepsis?

Clinical evidence (see also full evidence review)

Evidence statements for primary prophylaxis with G(M)-CSF versus no primary prophylaxis with G(M)-CSF

The evidence for primary prophylaxis with colony stimulating factors comes from systematic reviews of randomised trials by Sung, *et al.,* (2007), Bohlius, *et al.,* (2008) and Cooper, *et al.,* (2011). This evidence is summarised in Table 5.1.

Mortality

There was high quality evidence that primary prophylaxis using G(M)-CSF did not reduce short-term all cause mortality when compared to no primary prophylaxis. No reduction in short-term mortality with G(M)-CSF was seen in subgroup analyses according to age group (paediatric, adult or elderly), type of cancer treatment (leukaemia, lymphoma/solid tumour or stem cell transplant) use of prophylactic antibiotics, colony stimulating factor type (G-CSF or GM-CSF)., *Febrile neutropenia*

There was moderate quality evidence that prophylaxis using G(M)-CSF reduced the rate of febrile neutropenia when compared to no prophylaxis. The pooled estimate suggested an episode of febrile neutropenia would be prevented for every nine chemotherapy cycles that used G(M)-CSF prophylaxis.

Moderate quality evidence from subgroup analyses suggested that the effectiveness of prophylaxis with colony stimulating factors may vary according to the type of cancer treatment. In the subgroup of leukaemia studies, G(M)-CSF would need to be used for 13 cycles to prevent an additional episode of febrile neutropenia. In solid tumour/lymphoma studies the corresponding number of cycles was nine. In stem cell transplant studies there was serious uncertainty about whether G(M)-CSF helps prevent febrile neutropenia.

Antibiotic resistance

Antibiotic resistance was not reported in the included systematic reviews (Sung, *et al.,* 2007; Bohlius, *et al.,* 2008 and Cooper, *et al.,* 2011).

Length of hospital stay

There was moderate quality evidence that the use of prophylactic G(M)-CSF was associated with a shorter hospital stay: the mean hospital stay was 2.41 days shorter with G(M)-CSF prophylaxis than without.

Quality of life

Quality of life was not reported in the included systematic reviews (Sung, *et al.,* 2007; Bohlius, *et al.,* 2008 and Cooper, *et al.,* 2011).

Table 5.1 GRADE profile: Is primary prophylaxis with G(M)-CSF (with or without antibiotics) more effective than no primary prophylaxis with G(M)-CSF (with or without antibiotics) at improving outcomes in patients at risk of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**G(M)-CSF**	**No G(M)-CSF**	**Relative (95% CI)**	**Absolute**	
Mortality											
80	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	465/6146 (7.6%)	472/5913 (8%)	RR 0.95 (0.84 to 1.08)	4 fewer per 1000 (from 13 fewer to 6 more)	HIGH
Mortality (paediatric patients)											
7	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	None	6/301 (2%)	4/303 (1.3%)	RR 1.46 (0.42 to 5.11)	6 more per 1000 (from 8 fewer to 54 more)	VERY LOW
Mortality (adult patients)											
34	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	None	105/1986 (5.3%)	117/1780 (6.6%)	RR 0.85 (0.66 to 1.11)	10 fewer per 1000 (from 22 fewer to 7 more)	LOW
Mortality (elderly patients)											
8	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	None	311/3778 (8.2%)	317/3586 (8.8%)	RR 1.04 (0.87 to 1.24)	4 more per 1000 (from 11 fewer to 21 more)	HIGH
Mortality (prophylactic antibiotics used)											
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	None	51/1045 (4.9%)	59/1056 (5.6%)	RR 0.92 (0.64 to 1.32)	4 fewer per 1000 (from 20 fewer to 18 more)	MODERATE
Mortality (prophylactic antibiotics not mandated)											
66	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	414/5101 (8.1%)	413/4857 (8.5%)	RR 0.96 (0.84 to 1.09)	3 fewer per 1000 (from 14 fewer to 8 more)	HIGH

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G(M)-CSF	No G(M)-CSF	Relative (95% CI)	Absolute	
Mortality (leukaemia studies)											
30	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision[5]	None	263/2725 (9.7%)	277/2597 (10.7%)	RR 0.95 (0.81 to 1.12)	5 fewer per 1000 (from 20 fewer to 13 more)	HIGH
Mortality (lymphoma or solid tumour studies)											
27	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	None	109/2204 (4.9%)	113/2155 (5.2%)	RR 0.91 (0.64 to 1.28)	5 fewer per 1000 (from 19 fewer to 15 more)	MODERATE
Mortality (stem cell transplant studies)											
21	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	None	93/1098 (8.5%)	79/1044 (7.6%)	RR 1.02 (0.77 to 1.34)	2 more per 1000 (from 17 fewer to 26 more)	MODERATE
Mortality (G-CSF studies)											
46	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	267/3726 (7.2%)	265/3531 (7.5%)	RR 0.98 (0.83 to 1.15)	2 fewer per 1000 (from 13 fewer to 11 more)	HIGH
Mortality (GM-CSF studies)											
34	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	None	193/1957 (9.9%)	193/1917 (10.1%)	RR 0.95 (0.84 to 1.08)	5 fewer per 1000 (from 16 fewer to 8 more)	HIGH
Infection related mortality											
67	randomised trials	no serious risk of bias[1,6]	no serious inconsistency	no serious indirectness	serious[5,7]	none	150/4901 (3.1%)	179/4673 (3.8%)	RR 0.82 (0.66 to 1.02)	7 fewer per 1000 (from 13 fewer to 1 more)	MODERATE
Infection related mortality (prophylactic antibiotics used)											

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**G(M)-CSF**	**No G(M)-CSF**	**Relative (95% CI)**	**Absolute**	
14	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	Serious[5]	None	18/1177 (1.5%)	42/1181 (3.6%)	RR 0.47 (0.28 to 0.8)	19 fewer per 1000 (from 7 fewer to 26 fewer)	LOW
Infection related mortality (prophylactic antibiotics not mandated)											
53	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	None	132/3724 (3.5%)	137/3492 (3.9%)	RR 0.91 (0.72 to 1.16)	4 fewer per 1000 (from 11 fewer to 6 more)	MODERATE
Febrile neutropenia											
49	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	None	1293/4529 (28.5%)	1649/4470 (36.9%)	RR 0.71 (0.63 to 0.8)	107 fewer per 1000 (from 74 fewer to 136 fewer)	MODERATE
Febrile neutropenia (leukaemia studies)											
10	randomised trials	serious	no serious inconsistency	no serious indirectness	no serious imprecision	None	389/867 (44.9%)	339/808 (42%)	RR 0.81 (0.66 to 0.99)	80 fewer per 1000 (from 4 fewer to 143 fewer)	MODERATE
Febrile neutropenia (lymphoma or solid tumour studies)											
32	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	None	730/3381 (21.6%)	1070/3412 (31.4%)	RR 0.64 (0.53 to 0.76)	113 fewer per 1000 (from 75 fewer to 147 fewer)	MODERATE
Febrile neutropenia (stem cell transplant studies)											
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	135/193 (69.9%)	127/172 (73.8%)	RR 0.94 (0.74 to 1.2)	44 fewer per 1000 (from 192 fewer to 148 more)	MODERATE
Documented infection											
60	randomised	serious[9]	no serious	no serious	no serious	None	1874/5921	2043/5704	Rate ratio 0.85	54 fewer per 1000 (from 29	

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G(M)-CSF	No G(M)-CSF	Relative (95% CI)	Absolute	
	trials		inconsistency	indirectness	imprecision		(31.7%)	(35.8%)	(0.79 to 0.92)	fewer to 75 fewer)	MODERATE
Resistance to the antibiotic used for prophylaxis - not reported											
0	-	-	-	-	-	None	-	-	-	-	
Length of hospital stay (Better indicated by lower values)											
43	randomised trials	no serious risk of bias[11]	no serious inconsistency	serious indirectness[12]	no serious imprecision	None	0	-	-	Mean difference 2.41 days less with G(M)-CSF (3.13 to 1.7 lower)	MODERATE
Quality of life - not reported											
0	-	-	-	-	-	None	-	-	-	-	

[1] This review included 80 trials: 26/80 trials had adequate allocation concealment and 35/80 had double blinding. Sensitivity analyses according to allocation concealment and double blinding, did not show a significant effect of CSF treatment on mortality, infectious mortality or febrile neutropenia.
[2] None of the 7 paediatric mortality studies had adequate allocation concealment, 2/7 had double blinding
[3] Low number of events
[4] 11/34 adult mortality studies had adequate allocation concealment, 15/34 had double blinding.
[5] Low number of events
[6] 67 trials reported infection related mortality: 19/67 had adequate allocation concealment and 29/67 had double blinding.
[7] The confidence interval for the pooled estimate spans both no effect and significant benefit.
[8] 2/14 trials had adequate allocation concealment, 4/14 double blinding.
[9] Most of the trials did not have adequate allocation concealment or double blinding
[10] Of the studies reporting febrile neutropenia 9/49 had adequate allocation concealment and 15/49 had double blinding.
[11] The quality of studies of duration of hospital stay was not reported.
[12] Hospital discharge criteria in these studies were likely to incorporate neutrophil count and thus influenced by the use of colony stimulating factors.

Evidence statements for primary prophylaxis with G(M)-CSF plus antibiotic (quinolone or cotrimoxazole) versus primary prophylaxis with antibiotic

The trials were identified from the systematic review by Sung, *et al.,* (2007) and from the list of excluded studies in a Cochrane review of prophylactic antibiotics versus G-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy (Herbst, *et al.,* 2009). Most (18/27) of the trials used cotrimoxazole only (specifically for *Pneumocystis pneumonia* prophylaxis) – these were analysed separately from the nine trials that used quinolones. Three trials that used both quinolones and cotrimoxazole were included in the quinolone group for analysis. The trials were not designed to test the interaction of G(M)-CSF with antibiotics – rather prophylactic antibiotics were part of standard care (many of the these trials also used antiviral and antifungal prophylaxis). This evidence is summarised in Table 5.2.

Mortality and febrile neutropenia

The evidence was of low quality for febrile neutropenia and moderate quality for short term mortality from any cause. There was uncertainty as to whether primary prophylaxis with G(M)-CSF plus quinolone or quinolone alone was better in terms of these outcomes due to the wide confidence intervals of the pooled estimates.

Infectious mortality

Moderate quality evidence suggested that infectious mortality was lower when G(M)-CSF plus quinolone was used for prophylaxis than with quinolone.

Antibiotic resistance, length of hospital stay, quality of life

These outcomes were not reported for this subgroup of studies in Sung, *et al.,* (2007).

Table 5.2 GRADE profile: Is primary prophylaxis with G(M)-CSF plus antibiotics more effective than primary prophylaxis with antibiotics at improving outcomes for patients at risk of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**G(M)-CSF+ABX**	**Antibiotics alone**	**Relative (95% CI)**	**Absolute**	
Febrile neutropenia (quinolone studies) – one trial in patients with solid tumours and one in non-Hodgkin lymphoma											
2	randomised trials	serious[1]	serious[6]	no serious indirectness	serious[2]	none	53/432 (12.3%)	71/410 (17.3%)	RR 0.703 (0.414 to 1.193)	51 fewer per 1000 (from 101 fewer to 33 more)	VERY LOW
Mortality from any cause (quinolone studies) – one trial each in patients with solid tumours , non-Hodgkin lymphoma, leukaemia and stem cell transplant											
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25/408 (6.1%)	33/401 (8.2%)	RR 0.817 (0.491 to 1.36)	15 fewer per 1000 (from 42 fewer to 30 more)	MODERATE
Infectious mortality (quinolone studies) – one trial each in patients with non-Hodgkin lymphoma, leukaemia and stem cell transplant; two in patients with solid tumours											
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	13/498 (2.6%)	29/486 (6%)	RR 0.478 (0.254 to 0.898)	31 fewer per 1000 (from 6 fewer to 45 fewer)	MODERATE
Febrile neutropenia (cotrimoxazole studies) – five leukaemia, two non-Hodgkin and two stem cell transplant trials											
9	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	349/504 (69.2%)	372/483 (77%)	RR 0.928 (0.86 to 1.002)	55 fewer per 1000 (from 108 fewer to 2 more)	MODERATE
Mortality from any cause (cotrimoxazole studies) – five leukaemia, two non-Hodgkin and four stem cell transplant trials											
11	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	32/706 (4.5%)	29/705 (4.1%)	RR 1.102 (0.685 to 1.773)	4 more per 1000 (from 13 fewer to 32 more)	LOW
Infectious mortality (cotrimoxazole studies) – four leukaemia, three non-Hodgkin and two stem cell transplant trials											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	G(M)-CSF+ABX	Antibiotics alone	Relative (95% CI)	Absolute	
9	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	7/731 (0.96%)	14/728 (1.9%)	RR 0.6 (0.264 to 1.367)	8 fewer per 1000 (from 14 fewer to 7 more)	LOW
Length of Hospital stay - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] 1/2 double blind, 0/2 adequate allocation concealment
[2] Low number of events
[3] 1/9 had adequate allocation concealment, 2/9 double blinding
[4] 1/11 had adequate allocation concealment, 2/11 double blinding
[5] 0/9 had adequate allocation concealment, 1/9 was double blind
[6] Significant heterogeneity (I^2=67%)

Evidence statements for primary prophylaxis with antibiotic (ciprofloxacin, levofloxacin, ofloxacin or cotrimoxazole) versus no primary prophylaxis

The evidence came from a Cochrane review of antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following anticancer treatment by Gafter-Gvili, *et al.,* (2005). Data from trials of ciprofloxacin, levofloxacin, ofloxacin or cotrimoxazole were extracted from this review and analysed. Evidence about colonisation with resistant bacteria came from a second systematic review by the same authors (Gafter-Gvili, *et al.,* 2007). An additional trial (Rahman and Khan, 2009) of levofloxacin prophylaxis was identified in our literature search. The evidence is summarised in Table 5.3.

Mortality

There was moderate quality evidence that prophylactic quinolones (ciprofloxacin or levofloxacin) reduced short-term all cause mortality when compared with no prophylaxis. From the pooled estimate, 59 patients would need prophylactic quinolones to prevent one additional death.

No ofloxacin studies reported the rates of all cause mortality.

Febrile neutropenia

The review analysed the rates of febrile neutropenia by patient (rather than by cycle). When patient rates were not reported, febrile episodes were used for the numerator. There was moderate quality evidence that antibiotic prophylaxis reduced the rate of febrile neutropenia, however there was inconsistency between individual study's estimates of effectiveness.

Subgroup analysis according to antibiotic suggested that levofloxacin, ofloxacin and cotrimoxazole might be more effective than ciprofloxacin in preventing febrile neutropenia.

However, even after grouping studies according to antibiotic used, there was still heterogeneity within the ofloxacin and cotrimoxazole groups.

The highest quality evidence came from the three levofloxacin trials. The pooled estimate from these trials suggested that 11 patients would need antibiotic prophylaxis to prevent one additional episode of febrile neutropenia.

Antibiotic resistance

There was moderate quality evidence that infection with bacteria resistant to the antibiotic used for prophylaxis was more likely in patients receiving antibiotic prophylaxis. The pooled estimate suggested an additional resistant infection for every 77 patients who received antibiotic prophylaxis.

Low quality evidence from four quinolone studies suggests uncertainty about the effect of quinolone prophylaxis on the rate of infection with bacteria resistant to quinolones.

Two quinolone trials reported only 8 cases of colonisation with resistant bacteria, in 93 patients. Low quality evidence suggests that colonisation with bacteria resistant to quinolones is more likely in patients who had received quinolone prophylaxis. It is impossible to get an accurate estimate of the impact of antibiotic prophylaxis on resistant colonisation with such a low number of events.

None of the trials reported the rates of colonisation with resistant bacteria before antibiotic prophylaxis or how these related to rates following prophylaxis.

Length of hospital stay

Although the Gafter-Gvili, *et al.,* (2005) review considered this outcome, data on the length of hospital stay were too sparse to allow analysis

Quality of life

Quality of life was not considered as an outcome in the systematic review.

Table 5.3 GRADE profile: Is primary prophylaxis with antibiotics more effective than no primary prophylaxis at improving outcomes in patients at risk of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	No primary prophylaxis	Relative (95% CI)	Absolute	
Mortality (quinolone studies)											
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	32/1295 (2.5%)	57/1286 (4.4%)	RR 0.615 (0.4 to 0.946)	17 fewer per 1000 (from 2 fewer to 27 fewer)	MODERATE
Infection related mortality (quinolone studies)											
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,3]	none	19/1295 (1.5%)	36/1286 (2.8%)	RR 0.58 (0.336 to 1.001)	12 fewer per 1000 (from 19 fewer to 0 more)	LOW
Febrile neutropenia (quinolone studies)											
10	randomised trials	serious[1,4]	serious[5]	no serious indirectness	no serious imprecision	none	419/1339 (31.3%)	594/1341 (44.3%)	RR 0.727 (0.62 to 0.852)	121 fewer per 1000 (from 66 fewer to 168 fewer)	LOW
Febrile neutropenia (ciprofloxacin studies)											
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2,6]	none	19/56 (33.9%)	26/56 (46.4%)	RR 0.95 (0.66 to 1.35)	23 fewer per 1000 (from 158 fewer to 163 more)	LOW
Febrile neutropenia (levofloxacin studies)											
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	347/1160 (29.9%)	460/1160 (39.7%)	RR 0.76 (0.7 to 0.82)	95 fewer per 1000 (from 71 fewer to 119 fewer)	HIGH
Febrile neutropenia (ofloxacin studies)											
4	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	serious[2,6]	none	34/111 (30.6%)	70/106 (66%)	RR 0.35 (0.1 to 1.23)	429 fewer per 1000 (from 594 fewer to 152 more)	LOW

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	No primary prophylaxis	Relative (95% CI)	Absolute	
Febrile neutropenia (TMP-SMZ studies)											
16	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	no serious imprecision	none	367/713 (51.5%)	473/711 (66.5%)	RR 0.80 (0.69 to 0.92)	133 fewer per 1000 (from 53 fewer to 206 fewer)	MODERATE
Infection with bacteria resistant to the antibiotic used for prophylaxis											
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	74/1680 (4.4%)	50/1654 (3%)	RR 1.43 (1 to 2.03)	13 more per 1000 (from 0 more to 31 more)	MODERATE
Infection with bacteria resistant to quinolones (quinolone studies)											
4	randomised trials	no serious risk of bias	serious inconsistency[5]	no serious indirectness	serious[2]	none	44/1185 (3.7%)	39/1180 (3.3%)	RR 0.87 (0.18 to 4.15)	4 fewer per 1000 (from 27 fewer to 104 more)	LOW
Colonisation with bacteria resistant to quinolones (quinolone studies)											
2	randomised trials	serious risk of bias[7]	no serious inconsistency	no serious indirectness	serious[2]	none	6/47 (12.8%)	2/46 (4.3%)	RR 3.30 (1.03 to 12.56	113 more per 1000 (from 1 more to 503 more)	LOW
Length of hospital stay - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Most studies did not have clear allocation concealment or double blinding.
[2] Low number of events.
[3] Confidence interval of the pooled estimate crosses both no effect and significant benefit.
[4] 9/25 had adequate allocation concealment and 13/25 double blinding
[5] Statistically significant heterogeneity
[6] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm.
[7] Both trials had unclear allocation concealment

Evidence statements for primary prophylaxis with quinolone (ciprofloxacin, levofloxacin or ofloxacin) versus primary prophylaxis with cotrimoxazole

Evidence came from a Cochrane review of antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following anticancer treatment by Gafter-Gvili, *et al.,* (2005). Evidence about colonisation with resistant bacteria came from a second systematic review by the same authors (Gafter-Gvili, *et al.,* 2007). Data from trials comparing ciprofloxacin, Levofloxacin and ofloxacin to cotrimoxazole was extracted and analysed. The evidence is summarised in Table 5.4.

Mortality

There was uncertainty as to whether prophylaxis with quinolones or cotrimoxazole was better in terms of short-term mortality. The 95% confidence intervals of the pooled estimate was wide enough to include the possibility that either antibiotic was significantly better than the other.

Febrile neutropenia

There was low quality evidence to suggest that prophylaxis of febrile neutropenia was more effective with ofloxacin than with cotrimoxazole. There was uncertainty about whether ciprofloxacin was more effective than cotrimoxazole, and there were no studies comparing levofloxacin with cotrimoxazole.

Antibiotic resistance

Low quality evidence suggested both infection and colonisation with bacteria resistant to the antibiotic used for prophylaxis was more likely with cotrimoxazole than with a quinolone.

Length of hospital stay and quality of life

Data on length of stay were sparse and not analysed. Quality of life was not reported

Table 5.4 GRADE profile: Is primary prophylaxis with quinolone more effective than primary prophylaxis with cotrimoxazole at improving outcomes in patients at risk of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ciprofloxacin, levofloxacin or ofloxacin	Co-trimoxazole	Relative (95% CI)	Absolute	
Mortality											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	26/372 (7%)	17/317 (5.4%)	RR 1.24 (0.57 to 2.67)	13 more per 1000 (from 23 fewer to 90 more)	LOW
Febrile neutropenia (ciprofloxacin vs TMP-SMZ studies)											
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2,3]	none	161/219 (73.5%)	143/212 (67.5%)	RR 1.34 (0.88 to 2.04)	229 more per 1000 (from 81 fewer to 702 more)	LOW
Febrile neutropenia (levofloxacin vs TMP-SMZ studies) - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Febrile neutropenia (ofloxacin vs TMP-SMZ studies)											
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	none	65/142 (45.8%)	84/131 (64.1%)	RR 0.39 (0.23 to 0.67)	391 fewer per 1000 (from 212 fewer to 494 fewer)	LOW
Colonisation with bacteria resistant to the antibiotic used for prophylaxis											
2	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[2]	none	39/98 (39.8%)	58/86 (67.4%)	RR 0.58 (0.44 to 76)	283 fewer per 1000 (from 378 fewer to 1000 more)	LOW
Infection with bacteria resistant to the antibiotic used for prophylaxis											
3	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	3/100 (3%)	6/100 (6%)	RR 0.24 (0.08 to 0.77)	46 fewer per 1000 (from 14 fewer to 55 fewer)	VERY LOW

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ciprofloxacin, levofloxacin or ofloxacin**	**Co-trimoxazole**	**Relative (95% CI)**	**Absolute**	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Length of hospital stay - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] 1/6 trials had adequate allocation concealment, 1/6 had double blinding
[2] Low number of events
[3] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm.
[4] 1/3 had adequate allocation concealment, 1/3 had double blinding
[5] No allocation concealment or blinding
[6] 1 trial had adequate allocation concealment, none had double blinding
[7] Very low number of events

Evidence statements for primary prophylaxis with G(M)-CSF versus antibiotics

Evidence came from a Cochrane review of prophylactic antibiotics or G-CSF for the prevention of infections and improvement of survival in cancer patients undergoing chemotherapy (Herbst, *et al.,* 2009). This review included two randomised trials directly comparing G(M)-CSF with antibiotics, remarkably few given the large number of trials comparing primary prophylaxis with G(M)-CSF or antibiotics to no primary prophylaxis. Schroeder. *et al.,* (1999) compared G-CSF to ciprofloxacin plus amphotericin-B, Sculier, *et al.,* (2001) compared GM-CSF to cotrimoxazole. The evidence is summarised in Table 5.5.

Mortality

One trial reported short term mortality. Due to the very low number of events there was serious uncertainty and it is not possible to conclude that the treatments are equivalent or that one is superior to the other.

Febrile neutropenia

One trial reported febrile neutropenia. Due to the very low number of events there was serious uncertainty and it is not possible to conclude that the treatments are equivalent or that one is superior to the other.

Antibiotic resistance

This outcome was not considered in the systematic review.

Length of hospital stay

One trial reported the median length of hospital stay was 6 days with G-CSF compared with 7 days with antibiotic prophylaxis. This difference was not statistically significant.

Quality of life

Neither of the trials reported this outcome.

Table 5.5 GRADE profile: Is primary prophylaxis with G(M)-CSF more effective than primary prophylaxis with antibiotics at improving outcomes for patients at risk of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**G-CSF**	**Antibiotics**	**Relative (95% CI)**	**Absolute**	
Mortality											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	7/78 (9%)	5/77 (6.5%)	RR 1.42 (0.43 to 4.68)	27 more per 1000 (from 37 fewer to 239 more)	VERY LOW
Febrile neutropenia											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	none	7/18 (38.9%)	7/22 (31.8%)	RR 1.22 (0.53 to 2.84)	70 more per 1000 (from 150 fewer to 585 more)	VERY LOW
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Antibiotic resistance - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Length of hospital stay (Better indicated by lower values)											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Median 6 days (range 5 to 9)	Median 7 days (range 5 to 10)	-	median 1 day less with G-CSF	LOW

[1] No blinding or unclear allocation concealment
[2] Very low number of events
[3] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm

Evidence statements for primary prophylaxis with pegfilgrastim versus filgrastim

Evidence came from a systematic review and meta-analysis of prophylactic G-CSFs which included a comparison of pegfilgrastim versus filgrastim for the prevention of neutropenia in adult cancer patients with solid tumours or lymphoma undergoing chemotherapy (Cooper, *et al.,* 2011). This review included five randomised trials. The literature search identified an additional phase II randomised trial comparing pegfilgrastim to filgrastim for prophylaxis in children with sarcoma receiving chemotherapy (Spunt, *et al.,* 2010). The evidence is summarised in Table 5.6.

Short term mortality

Short term mortality was not considered in Cooper, *et al.,* (2011). One trial included in the systematic review reported mortality, but there was only one death (in the filgrastim group). Spunt, *et al.,* (2010) did not report mortality.

Febrile neutropenia

Low quality evidence from five randomised trials (Cooper, *et al.,* 2011) suggested pegfilgrastim was more effective than filgrastim in the prevention of febrile neutropenia, RR = 0.66 (95% C.I. 0.44 to 0.98).

Antibiotic resistance, length of hospital stay and quality of life

These outcomes were not considered in the systematic review.

Table 5.6 GRADE profile: Is primary prophylaxis with pegfilgrastim more effective than primary prophylaxis with filgrastim at improving outcomes for patients at risk of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pegfilgrastim**	**Filgrastim**	**Relative (95% CI)**	**Absolute**	
Mortality - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Febrile neutropenia											
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	35/315 (11.1%)	51/291 (17.5%)	RR 0.66 (0.44 to 0.98)	60 fewer per 1000 (from 4 fewer to 98 fewer)	LOW
Antibiotic resistance - not reported											
0	-	-	-	-	-	none	-	-	-	-	
length of hospital stay - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] 2/5 trials had double blinding, 2/5 were open label. 3/5 trials were phase II studies
[2] Low number of events
[3] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm.

Evidence statements for primary prophylaxis with granulocyte infusion versus no prophylaxis with granulocyte infusion

Evidence came from a Cochrane review of granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction (Massey, *et al.,* 2009). This review included ten trials, all but one of which were carried out before 1988. The evidence is summarised in Table 5.7.

Mortality

Due to the relatively low number of events, there was uncertainty as to whether prophylactic granulocyte infusions reduce short-term all cause mortality in this population.

Febrile neutropenia

Due to the relatively low number of events, there was uncertainty as to whether prophylactic granulocyte infusions reduce the rate of febrile neutropenia in this population.

Antibiotic resistance

This outcome was not considered in the systematic review.

Length of hospital stay

Massey, *et al.,* (2009) found little consistency in the reporting of duration of treatment and length of hospital stay, and chose not analyse this outcome further.

Quality of life

No trials reported this outcome.

Table 5.7 GRADE profile: Is primary prophylaxis with granulocyte infusion more effective than no such prophylaxis at improving outcomes in patients at risk of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylaxis with granulocyte infusion	No prophylaxis with granulocyte infusion	Relative (95% CI)	Absolute	
Mortality											
10	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	62/347 (17.9%)	64/358 (17.9%)	RR 0.94 (0.71 to 1.25)	11 fewer per 1000 (from 52 fewer to 45 more)	LOW
Febrile neutropenia											
2	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[2]	none	46/66 (69.7%)	92/109 (84.4%)	RR 0.85 (0.69 to 1.05)	127 fewer per 1000 (from 262 fewer to 42 more)	VERY LOW
Antibiotic resistance - not reported											
0	-	-	-	-	-	-	-	-	-	-	
Length of hospital stay - not reported											
0	-	-	-	-	-	-	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	-	-	-	-	-	

[1] One trial had adequate allocation concealment, blinding was unclear in all trials
[2] Low number of events
[3] 95% confidence interval around the pooled estimate of effect includes both no effect and appreciable benefit or appreciable harm.
[4] Unclear allocation concealment and blinding
[5] Unexplained statistically significant heterogeneity

Evidence statements for secondary prophylaxis with G(M)-CSF versus placebo or nothing (with or without antibiotics)

The literature search identified one randomised trial (Leonard, *et al.,* 2009) published in abstract form only. This trial compared secondary prophylaxis using G-CSF with standard management (dose delay or reduction) in patients with early stage breast cancer receiving anthracyline or anthracycline-taxane sequential regimes. The evidence is summarised in Table 5.8.

Incidence of neutropenic sepsis

The rate of neutropenic sepsis was not reported. The trial reported the rate of neutropenic events, indirectly related to neutropenic sepsis and for this reason the evidence was considered low quality. The evidence suggested approximately two patients would need secondary prophylaxis with G-CSF to prevent one additional neutropenic event.

Overtreatment, death, critical care, length of stay, duration of fever, quality of life

These outcomes were not reported.

Table 5.8 GRADE profile: Is secondary prophylaxis with G(M)-CSF more effective than no secondary prophylaxis at improving outcomes in patients with a prior episode of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Secondary prophylaxis with G(M)-CSF	No secondary prophylaxis	Relative (95% CI)	Absolute	
Neutropenic events											
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	36/204 (17.6%)	132/203 (65%)	RR 0.27 (0.2 to 0.37)	475 fewer per 1000 (from 410 fewer to 520 fewer)	LOW
Overtreatment, death, critical care, length of stay, duration of fever, quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Neutropenic events were defined as ANC <1.0 X10^9/l or neutropenic fever: thus were indirectly related to neutropenic sepsis.
[2] Low number of events

Evidence statements for secondary prophylaxis with antibiotics versus no secondary prophylaxis (with or without G(M)-CSF)

No trials of antibiotics for secondary prophylaxis were identified. One low quality randomised trial compared G-CSF plus ciprofloxacin or ofloxacin to G-CSF alone for secondary prophylaxis (Maiche and Muhonen, 1993). The evidence is summarised in Table 5.9.

Incidence of neutropenic sepsis

The rate of neutropenic sepsis was not reported, but Maiche and Muhonen (1993) reported the rate of documented infections. There was uncertainty as to whether prophylaxis with antibiotics plus G-CSF was more effective than G-CSF alone in preventing documented infection, due to the low number of documented infections and small size of the study.

Overtreatment, death, critical care, length of stay, duration of fever, quality of life

These outcomes were not reported.

Table 5.9 GRADE profile: Is secondary prophylaxis with quinolone plus G-CSF more effective than secondary prophylaxis with G-CSF alone at improving outcomes in patients with a prior episode of neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics plus G-CSF	G-CSF alone	Relative (95% CI)	Absolute	
Documented infection											
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	none	6/44 (13.6%)	15/48 (31.3%)	RR 0.44 (0.19 to 1.02)	175 fewer per 1000 (from 253 fewer to 6 more)	LOW
Overtreatment, death, critical care, length of stay, duration of fever, quality of life (Copy) - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Unclear allocation concealment, no blinding mentioned.
[2] Low number of events
[3] 95% C.I. includes both no-effect and appreciable benefit

Evidence statements for secondary prophylaxis with G-CSF versus antibiotics for secondary prophylaxis

No trials were identified.

Cost-effectiveness evidence for primary and secondary prophylaxis (see also full evidence review)

Ten studies were included for this topic. The results of all included studies are summarised in Table 5.10.

Study quality and results

All included papers were deemed partially applicable to this guideline. The most common reason for partial applicability was that the analyses did not include all options considered relevant for the topic. For example, most economic studies about G(M)-CSF omit quinolones. Other reasons for partial applicability included: analysis conducted in countries other than the UK, health effects not expressed in QALYs.

Seven papers were deemed to have very serious limitations. The most common reason for serious limitation was that the analyses considered the combined effectiveness of chemotherapy and G(M)-CSF, but did not count the cost of chemotherapy (Borget, *et al.,* (2009); Danova, *et al.,* (2008); Liu, *et al.,* (2009); Lyman, (2009 a); Lyman, (2009 b); Ramsey, (2009). except Whyte, *et al.,* (2011) is the only study that counted the cost of chemotherapy. However this study was also deemed to have very serious limitations as it did not use data from the best available source (ideally data should come from a recently conducted systematic review); and the estimates of clinical data used in Whyte, *et al.,* (2011) differ substantively from the data reported by best available evidence (Note 28, Table 5.10)

The other three papers were deemed to have potentially serious limitations (Lathia, *et al*., 2009; Timmer-Bonte, *et al*., 2008; Timmer-Bonte, *et al*., 2006). The most common reason for potentially serious limitation was that the analyses did not use data from the best available source (ideally data should come from a recently conducted systematic review), but are similar in magnitude to the best available estimates.

Evidence statements

Eight studies were identified for patients with a solid tumour and two studies for patients with non-Hodgkin lymphoma. No economic evidence has been identified for patients with other types of cancer.

Solid tumour (adult)

Six out of the ten included studies looked at female patients with stage II breast cancer with at least 20% risk of febrile neutropenia. All six studies had conflicts of interest. Four of these papers (Borget, *et al.,* 2009; Danova, *et al.,* 2008; Liu, *et al.,* 2009; Lyman, 2009 (b)) compared primary PEG-G-CSF G(M)-CSF with primary PEG-G-CSF; and all four papers reported PEG-G-CSF to be more cost-effective than G(M)-CSF. One paper (Ramsey, 2009) compared primary PEG-G-CSF with secondary PEG-G-CSF and reported that the latter strategy was more cost-effective. Only one study (Whyte, *et al.,* 2011) compared different types of G(M)-CSF with nothing/placebo; this paper reported that at NICE willingness-to-pay threshold of £20,000 per QALY:

- for patients with a febrile neutropenia risk level of 11% -37%, secondary PEG-G-CSF is the most cost-effective strategy.
- for patients with a febrile neutropenia risk greater than 38%, primary PEG-G-CSF is the most cost-effective strategy.

Two of the ten papers identified looked at patients with small-cell lung cancer with at least 20% risk of febrile neutropenia. Both papers compared G(M)-CSF with quinolones against quinolones alone; one paper (Timmer-Bonte, *et al.,* 2006) looked at primary prophylaxis while another (Timmer-Bonte, *et al.,* 2008) looked at secondary prophylaxis. Both papers showed that G(M)-CSF with quinolones was more clinically effective than quinolones alone, but was associated with a very high ICER (£0.29[10] million per febrile neutropenia free cycle (Timmer-Bonte, *et al.,* 2008) and £329.28[11] per percent decrease of the probability of febrile neutropenia (Timmer-Bonte, *et al.,* 2006). No conflicts of interest have been declared for these two papers.

Non-Hodgkin lymphoma (adult)

Two out of ten included studies looked at elderly patients with non-Hodgkin lymphoma with at least 20% risk of febrile neutropenia. The base-case analysis for both studies considered a cohort of 64-year-old men and women. Lyman, (2009)(a) compared primary G(M)-CSF with PEG-G-CSF, and reported that PEG-G-CSF was more cost-effective. Lathia, (2009) compared three prophylaxis strategies: primary (M)-CSF, primary PEG-G-CSF and nothing/placebo, and reported that the ICER associated with G(M)-CSF and PEG-G-CSF is £0.99[12] million/QALY and £2.52[12] million/QALY separately, compared to nothing/placebo.

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[10] Converted from 2005 Netherlandish Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 109% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

[11] Converted from 2002 Netherlandish Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 115% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

[12] Converted from 2009 Canadian dollars using a PPP exchange rate of 0.55 then uprated by inflation factor of 106% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Table 5.10 Modified GRADE profile: Cost effectivness of primary and secondary prophylaxis.

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2010 £)**	**Incremental effects**	**ICER**	**Uncertainty**
Borget, *et al.,* 2009	Very serious limitations[1]	Partially applicable[2]	A theoretical cohort of women with breast cancer. The base case is a 45-year-old woman with stage II breast cancer receiving four cycles of chemotherapy with a ≥20% risk of febrile neutropenia (FN).	Primary filgrastim (11-day)	Primary PEG-G-CSF	£1282.78[3]	<0 QALYs	Dominated	Results were also robust to changes in model inputs.
				Primary filgrastim (6-day)	Primary PEG-G-CSF	- £506.69[3]	-0.106 QALYs	£4770.00 per QALY gained[3]	
Danova, *et al.,* 2008	Very serious limitations[4]	Partially applicable[5]	A hypothetical cohort of 45-year-old women with stage II breast cancer receiving 4 cycles of chemotherapy associated with a ≥20% risk of FN.	Primary PEG-G-CSF	Primary filgrastim (6-day)	£36.70[6]	0.10 QALYs	£349.86 per QALY gained[6]	One-way and two-way sensitivity analysis was conducted but range of ICER was not reported. The paper only reported when the highest PEG-G-CSF and the lowest filgrastim price were used, ICER is still below per £43,522[6] QALY.
Lathia, *et al.,* 2009	Potentially serious limitations[7]	Partially applicable[8]	Patients with diffuse large B-cell lymphoma (the most common subtype of non-Hodgkin Lymphoma) receiving induction chemotherapy. Base-case analysis considered a cohort of 64-year-old men and women	Primary filgrastim (did not report if it is 6 or 11 days)	Nothing	£1992.48[9]	0.002 QALYs	£0.99 million per QALY gained[9]	All one-way sensitivity analysis yielded ICERs of greater than £0.58 million[9] per QALY gained.
				Primary PEG-G-CSF	Nothing	£5765.08[9]	0.004 QALYs	£2.52million per QALY gained	
Liu, *et al.,* 2009	Very serious limitations[10]	Partially applicable[11]	Women aged 30-80 years with early stage (I-III) breast cancer	Primary PEG-G-CSF	Primary filgrastim (6-day)	£505.54[12]	0.052 QALYs depends on scenarios	£ 9773.87 per QALY gained[12]	When the relative risk of FN was ≤1.3 for 6-day filgrastim versus pegfilgastim, the ICER exceeded

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2010 £)**	**Incremental effects**	**ICER**	**Uncertainty**
				Primary filgrastim (11-day)	Primary PEG-G-CSF	£ 1046.63[12]	-0.028 QALYs depends on scenarios	Dominated	
Lyman, 2009 (a)	Very serious limitations [13]	Partially applicable [14]	A hypothetical cohort of patients with intermediate- or high-grade non-Hodgkin lymphoma receiving myelosuppressive chemotherapy (e.g, CHOP-21) with an FN risk of approximately ≥20%. A 65-year-old was chosen as base line.	Primary PEG-G-CSF	Primary filgrastim (6-day)	£192.96[15]	Range: 0.042-0.155 QALYs (depends on scenarios)	Range: £1244.61-4594.00 15 per QALY gained (depends on scenarios)	The probability for PEG-G-CSF to become more cost-effective over filgrastim was 50% with the threshold of £11132.47[15] per QALY gained, 80% for £22,264.94[15] per QALY gained, and 91% for £37,108.23[15] per QALY gained.
Lyman, 2009 (b)	Very serious limitations [16]	Partially applicable [17]	Women 30-80 years with early stage (I to III) breast cancers who were receiving adjuvant myelosuppressive chemotherapy and had an FN risk of ≥20%.	Primary filgrastim (6-day)	Primary PEG-G-CSF	-£ 1005.63[18]	Range: -(0.043-0.094) QALYs depends on scenarios	Range: -£(10698.30-23386.35) 18 per QALY gained	Probabilistic sensitivity analysis show that the probability that strategy A is cost-effective compared with B was 50% for a threshold value of £14,843.29[18] per QALY gained, 80% for a threshold value of £22,264.94[18] per QALY gained, and 90% for a threshold value of £29,686.58[18] per QALY gained.
				Primary filgrastim (11-day)	Primary PEG-G-CSF	-£ 4899.77[18]	-(0.022-0.050) QALYs depends on scenarios	Dominated	
Ramsey, 2009	Very serious limitations[19]	Partially applicable[20]	Women aged 30 to 80 years with early stage (I to III) breast cancer receiving myelosuppressive chemotherapy with an FN risk of approximately 20%. The reference patient was 49 years old with stage II breast cancer receiving six cycles of chemotherapy.	Primary PEG-G-CSF	Secondary PEG-G-CSF	£6459.06[21]	0.076 QALYs	£86091.09[21] per QALY gained	One-way: when FN case fatality was less than 2%, the ICER exceeded £148,432.9[21] per QALY gained. The probability that pegfilgastim primary prophylaxis would be considered cost-effective at the threshold value compared with secondary prophylaxis was 12% for a WTP of £37,108.23[21] per QALY gained, 40% of a WTP of £74,216.46 [21] per QALY gained,

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2010 £)**	**Incremental effects**	**ICER**	**Uncertainty**
									and 75% for a WTP of £148,432.92[21] per QALY gained.
Timmer-Bonte, *et al.,* 2008	Potentially serious limitations[22]	Partially applicable[23]	Patients with small cell lung cancer at risk of FN defined as 60 years of age or older, extensive disease, a Karnofsky performance stats of 40% to 70%, and/or having received prior chemotherapy. Patients have received primary prophylaxis with antibiotics or with antibiotics plus G(M)-CSF.	Secondary antibiotics + G(M)-CSF	Secondary antibiotics	£4970.03[24]	0.02 FN-free cycle	£0.29 million [24] per FN free cycle	Result is robust to probability of FN and treatment cost of FN (although when using higher FN-related costs, the strategies are less distinct in their monetary effects, but still favour antibiotics).
				Secondary sequential approach (Antibiotics after the first episode of FN and antibiotics plus G(M)-CSF after another episode of FN.)	Secondary antibiotics	£1839.87[24]	-0.11 FN-free cycle	Dominated	
Timmer-Bonte, *et al.,* 2006	Potentially serious limitations [25]	Partially applicable [26]	Small-cell lung cancer patients receiving standard dose chemotherapy.	Primary antibiotics + G(M)-CSF	Primary antibiotics	First cycle: £611.78[27]	First cycle: 14% decrease of the probability of FN Entire treatment	First cycle: £44.98[27] per percent decrease of the probability of FN Entire treatment: £329.28[27]per	Sensitivity analysis has only been conducted for cycle 1. G(M)-CSF is cost saving if the probability of FN is more than 84%, the price of prophylactic G(M)-CSF is less than £421.95[27] per patient, or the cost of an episode of FN amount to greater than £10,366.07[27]. The acceptability for the

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2010 £)**	**Incremental effects**	**ICER**	**Uncertainty**
						Entire treatment period: £4609.04[27]	period: 23% decrease of the probability of FN	percent decrease of the probability of FN	willingness to pay was approximately 50%.
Whyte, *et al.*, 2011	Very serious limitations[28]	Partially applicable[29]	The base case consisted of a cohort of 52-year-old female	Secondary lenograstim (11 days)	Nothing	£968	0.023 QALYs	Dominated	Results are highly sensitive to baseline FN risk. When willingness to pay is £20,000 per QALY, for a

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2010 £)**	**Incremental effects**	**ICER**	**Uncertainty**
				Secondary lenograstim (6 days)	Nothing	£462	0.023 QALYs	Dominated	
				Secondary filgrastim (11 days)	Nothing	£852	0.024 QALYs	Dominated	
				Secondary filgrastim (6 days)	Nothing	£397	0.024 QALYs	Dominated	
				Secondary PEG-G-CSF	Nothing	If baseline risk =24%: £274 If baseline risk =31%:£253	If baseline risk =24%: 0.042 QALYs If baseline risk =31%: 0.069 QALYs	If baseline risk =24%: £6,500 per QALY gained If baseline risk =31%: £3,651 per QALY gained	
				Primary lenograstim (11 days)	Nothing	£8326	0.075 QALYs	Dominated	
				Primary lenograstim (6 days)	Nothing	£4355	0.075 QALYs	Dominated	
				Primary filgrastim (11 days)	Nothing	£7434	0.077 QALYs	Dominated	
				Primary filgrastim (6 days)	Nothing	£3865	0.077 QALYs	Dominated	
				Primary PEG-G-CSF	Nothing	If baseline risk =24%: £3559	If baseline risk =24%: 0.128	If baseline risk =24%:	

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2010 £)**	**Incremental effects**	**ICER**	**Uncertainty**
						If baseline risk =31%:£3252	QALYs If baseline risk =31%:0.181 QALYs	£38,482 per QALY gained If baseline risk =31%: £26,824 per QALY gained	

1 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Not all estimates of input data come from the best available source (systematic review). Have conflicts of interest.
2 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study doesn't look at all interventions of interest. Health effects are not discounted at an annual rate of 3.5%.
3 Uprated from 2006 British Pounds using inflation factor of 115% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
4 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Have conflicts of interest.
5 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study is conducted in Italy, not in the UK. Doesn't look at all interventions of interest.
6 Converted from 2008 Italian Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 105% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
7 Only the abstract of this study has been published at the moment, so it is unclear whether all input data of this study come from the best available source.
8 This study is conducted in Canada, not in the UK. Doesn't look at all interventions of interest.
9 Converted from 2009 Canadian dollars using a PPP exchange rate of 0.55 then uprated by inflation factor of 106% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
10 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. No costs were modelled beyond 1 year; while on the other hand, the effectiveness was modelled for lifetime. Have conflicts of interest.
11 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study doesn't look at all interventions of interest.
12 Uprated from 2006 British Pounds using inflation factor of 115% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
13 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Not all estimates of input data come from the best available source (systematic review). Have conflicts of interest.
14 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study is conducted in the U.S.A, not in the UK. Doesn't look at all interventions of interest.
15 Converted from 2006 U.S.A dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
16 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Not all estimates of input data come from the best available source (systematic review). Have conflicts of interest.
17 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study is conducted in the U.S.A, not in the UK. Doesn't look at all interventions of interest.
18 Converted from 2006 U.S.A dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
19 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF; however it only counts the cost of G(M)-CSF without counting cost of chemotherapy. Not all estimates of input data come from the best available source (systematic review). Have conflicts of interest.
20 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. This study is conducted in the U.S.A, not in the UK. Doesn't look at all interventions of interest.
21 Converted from 2006 U.S.A dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 108% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
22 Not all estimates of input data come from the best available source (systematic review).
23 This study is conducted in the Netherlands, not in the UK. Doesn't look at all interventions of interest. The value of health effects is not expressed in terms of quality-adjusted life years (QALYs).
24 Converted from 2005 Netherlandish Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 109% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

25 Not all estimates of input data come from the best available source (systematic review).
26 This study is conducted in the Netherlands, not in the UK. Doesn't look at all interventions of interest. The value of health effects is not expressed in terms of quality-adjusted life years (QALYs).
27 Converted from 2002 Netherlandish Euros using a PPP exchange rate of 0.78 then uprated by inflation factor of 115% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
28 Whyte *et al* 2011 modelled three functions of G-CSF: 1). Reducing incidence of febrile neutropenia. 2). Reducing short-term mortality (by preventing febrile neutropenia). 3). Reducing long-term mortality (by maintaining chemotherapy dose). Only the efficacy data for the first function of G-CSF (reducing incidence of febrile neutropenia) was obtained from a systematic review. Efficacy data for the other two functions of G-CSF were estimated based on assumptions, and are in contrast with more direct evidence: Sung et al (2007), Papaldo et al (2005), Pettengell (2008), and Shitara, et al., 2011)
29 This study is looking at a combined effectiveness of chemotherapy and G(M)-CSF, not just G(M)-CSF. Doesn't look at all interventions of interest.

Health economic evaluation (see also Appendix A)

Because of the large patient group covered by this topic and the potentially significant difference in cost of different treatment options this topic is identified as a high priority for economic analysis. A systematic review of the economic evidence was conducted, a summary of which is presented in the previous section. All included studies were deemed to be partially applicable to this topic, and deemed to have very serious or potentially serious limitations. No studies were found which directly addressed our question. As a result, *de novo* models have been built to inform recommendations.

Aim

The aim of this economic analysis was to examine which of the following prophylactic strategies is the most cost-effective for cancer patients who are receiving chemotherapy

- Nothing/placebo
- Primary prophylaxis with quinolones
- Primary prophylaxis with G-CSF
- Primary prophylaxis with G-CSF and quinolones
- Primary prophylaxis with PEG-G-CSF
- Secondary prophylaxis with quinolones
- Secondary prophylaxis with G-CSF
- Secondary prophylaxis with G-CSF and quinolones
- Secondary prophylaxis with PEG-G-CSF

Evidence was reported for both quinolones and cotrimoxazole as antibiotic prophylaxis. However the GDG chose to focus on the evidence related to quinolones because of concerns that changing anti-microbial resistance patterns meant the cotrimoxazole trials may no longer be applicable (Gafter-Gvili, et al., 2005).

A subgroup analysis was conducted for the following three patient groups:

- Patients with a Solid tumour (aged over 18 years)
- Patients with Non-Hodgkin lymphoma (aged over 18 years)
- Patients with Hodgkin lymphoma (aged over 18 years)

The economic analysis does not cover:

- Cancer patients whose chemotherapy regimen includes G-CSF.
- Cancer patients with planned inpatient treatment of greater than 10-days post-chemotherapy. It is acknowledged that the costs of prophylaxis and treatment of neutropenic sepsis for inpatient-only management are lower than outpatient management.
- Paediatric cancer patients (aged less than 18 years). Due to considerable clinical heterogeneity in the treatment regimens for this patient group, and a paucity of direct evidence, a representative model for economic analysis could not be built
- The impact of different prophylactic strategies on subsequent courses of chemotherapy. The consequence of this bias is discussed in detail in section A9.2.3.
- Antibiotic resistance. The best available evidences identified to address the issue of antibiotic resistance caused by use of quinolones was derived from two systematic reviews: one was a review conducted for this guideline (see Page 79-83); and the other was a Cochrane review undertaken by Gafter-Gvili, et al., (2005). The conclusions of these two reviews were very similar. After use of quinolones, although there is an increase in colonisation with bacteria resistant to quinolones, there was no statistically significant increase in the number of infections caused by pathogens resistant to quinolones. The GDG were aware of the potential limitations of these two reviews but could not find any better evidence to answer the clinical question.

Therefore the GDG decided to qualitatively consider the potential increase in antibiotic resistance and its impact on cancer patients when agreeing their recommendations, instead of quantitatively model it in the economic analysis.

Model structure

Decision trees are used to reflect key events in the clinical pathway in order to compare costs and health effects for the interventions of interest. In this economic analysis, two decision trees were constructed to cover two different populations:

- model A for adult patients with Hodgkin lymphoma, and
- model B for adult patients with a solid tumour or non-Hodgkin lymphoma.

The details of both models can be found below. A Markov process was embedded in both decision trees to model the recurrence of neutropenic sepsis within one course of chemotherapy.

- Model A: 'Continue to receive full dose chemotherapy'

This model assumes patients will continue to receive full-dose chemotherapy regardless of previous episodes of neutropenic sepsis.

- Model B: 'Dose-reduction chemotherapy'

This model assumes that if patients develop one episode of neutropenic sepsis, they will then receive dose-reduction chemotherapy. If they develop two episodes of neutropenic sepsis chemotherapy will be discontinued.

The time horizon of both models was one course of chemotherapy as the GDG were only interested in short-term outcomes.

The volume of clinical data to inform the relative risk of overall mortality (each prophylactic strategy versus nothing/placebo) was very sparse for the three patient subgroups included in the model. What's more, of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. The GDG decided to assume that the overall mortality would be the same for each prophylactic strategy, and only looked at the efficacy of each strategy in terms of preventing neutropenic sepsis. Since the baseline short-term overall mortality rate for our target population group is normally very low; unless there were any prophylactic strategies that could significantly reduce short-term overall mortality, this bias is unlikely to change our conclusion.

Model inputs

Cost-effectiveness analysis requires clinical evidence, health-related preferences (utilities), healthcare resource use and costs. High quality evidence on all relevant parameters was essential; however these data were not always available. Where published evidence was sparse, the expert opinion of the GDG was used to estimate relevant parameters. To test the robustness of the results of the cost-effectiveness analysis, a series of sensitivity analysis were undertaken.

The effectiveness of each prophylactic strategy in terms of incidence of neutropenic sepsis, and short-term overall mortality, were obtained from the systematic reviews of the clinical evidence conducted for this topic (See Appendix 4 of the full evidence review).

Utility weights were required to estimate quality adjusted life years (QALYs). Estimates of health state utility for cancer patients with and without neutropenic sepsis were obtained from published studies (Brown, 2001).

The costs considered in this analysis were those relevant to the UK NHS, and included the cost of each prophylactic strategy, the costs of diagnostic investigation, and the costs of inpatient/outpatient treatment. Unit costs were based on British National Formulary (BNF 62), NHS reference cost (2009-10) and the Unit Costs of Health and Social Care (Curtis, 2010). The cost of chemotherapy was not included; as the economic model was only looking at the prevention and treatment of neutropenic sepsis.

Due to the short time horizon of the base-case model (less than 1 year), costs and health outcomes were not discounted.

Sensitivity Analysis

Three different kinds of sensitivity analysis were conducted to test the robustness of the results for each economic model. These were structural sensitivity analysis (for patients with a solid tumour and non-Hodgkin lymphoma only), probabilistic sensitivity analysis and one-way sensitivity analysis.

For each model, over sixteen scenarios were considered and are detailed below:

- Number of cycles of chemotherapy (varies for each patient subgroup)
- Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards[13] (5 - 100%)
- Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards (1-10)
- Relative risk of a neutropenic sepsis episode: previous neutropenic sepsis versus no previous neutropenic sepsis (1-10)
- Relative risk of a neutropenic sepsis episode: each prophylactic strategy versus nothing/placebo (0.1 – 0.95)
- Probability of self administrating PEG-G-CSF or G(M)-CSF (0-100%)
- Probability of using an ambulance for patients with neutropenic sepsis (0-100%)
- Probability of patients with neutropenic sepsis who are at high risk of serious adverse events (varies for each patient subgroup)
- Days of using G(M)-CSF for each cycle of chemotherapy (5-11 days)
- Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events (1-6 days)
- Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events (6-14 days)
- Cost per hospital bed day (£100 - £1000)
- Daily cost of G(M)-CSF per person (£60.69[14] – £98.57[15])
- Drug discounts of PEG-G-CSF and G(M)-CSF (0% - 90%)
- Utility decrement due to inpatient treatment of neutropenic sepsis (0.14-0.38)
- Utility decrement due to outpatient treatment of neutropenic sepsis (0-0.15).

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[13] In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.

[14] Average cost of filgrastim and lenograstim assuming that the daily dose of G(M)-CSF for all adult patients is one vial (one single 30 million-unit syringe of filgrastim or one single 33.6 million-unit syringe of lenograstim) regardless of patient weight.

[15] Average cost of filgrastim and lenograstim, based on BNF recommended dose (500,000 units/kg daily) and patient weight distribution reported by: Green 2003, Romieu 2007, and Gigg 2003. The detailed calculation process is reported in Appendix A10

Results

Adult/elderly patients with a solid tumour who can take fluoroquinolone

For adult patients with a solid tumour and who can take quinolone clinical evidence was available for all nine strategies of interest (Section A3.1.2). Compared to quinolone alone, G(M)-CSF and G(M)-CSF + quinolone are more expensive and less effective in terms of preventing neutropenic sepsis. Therefore all primary and secondary prophylactic strategies involving G(M)-CSF and G(M)-CSF + quinolone were excluded from the analysis. As a result cost-effectiveness was only formally examined for the following five strategies:

- Nothing/placebo
- Primary prophylaxis with quinolone
- Secondary prophylaxis with quinolone
- Primary prophylaxis with PEG-G-CSF
- Secondary prophylaxis with PEG-G-CSF

The incremental costs and incremental QALYs in the base case analysis for each of the five strategies are summarised in Table 5.11. Taking primary prophylaxis with quinolone as the reference (least expensive) strategy, all other strategies were shown to be less effective and also more costly except primary prophylaxis with PEG-G-CSF. Compared to the reference strategy, use of primary PEG-G-CSF produces 3.3×10^{-4} more QALYs and incurs £1,899.8 in additional costs. This yields an incremental cost-effectiveness ratio (ICER) of £5.7 million/QALY, which exceeds the NICE willingness to pay (WTP) threshold of £20,000/QALY. Therefore primary prophylaxis with PEG-G-CSF was considered not to be cost effective. At a willingness to pay (WTP) threshold of £20,000/QALY, primary prophylaxis with a quinolone is the most cost-effective strategy. This conclusion was robust to structural sensitivity analysis and all one-way sensitivity analysis tested (Section A4.2) except for relative risk of neutropenic sepsis (quinolones versus nothing/placebo).

When the relative risk of neutropenic sepsis (quinolones versus nothing/placebo) was above 0.787, nothing/placebo became the most cost-effective strategy, at a WTP threshold of £20,000/QALY. Primary or secondary prophylaxis with PEG-G-CSF is never the most cost-effective strategy, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount of PEG-G-CSF, extended length of hospital stay for neutropenic sepsis patients (6-day for low-risk patients and 14-day for high-risk patients) etc.

The result of the probabilistic sensitivity analysis shows that the probability of primary prophylaxis with quinolone becoming cost-effective is always 100%, at a willingness to pay between £10,000 to £40,000 per QALY.

Table 5.11 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can take quinolone (baseline risk of neutropenic sepsis of one course of chemotherapy: 34.41%)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Primary prophylaxis with quinolone	£270.4	-8.9×10^{-4}	—	—	Comparator	Comparator
Secondary prophylaxis with quinolone	£423.7	-1.9×10^{-3}	£153.3	-1.0×10^{-3}	Dominated	Dominated
Nothing/Placebo	£473.9	-2.3×10^{-3}	£203.5	-1.4×10^{-3}	Dominated	Dominated
Secondary prophylaxis with PEG-G-CSF	£773.6	-1.8×10^{-3}	£503.2	-8.9×10^{-4}	Dominated	Dominated

Primary prophylaxis with PEG-G-CSF	£2170.2	$-5.6*10^{-4}$	£1,899.8	$3.3*10^{-4}$	£5.7 million	£5.7 million

Adult/elderly patients with a solid tumour who cannot take fluoroquinolone

For adult patients with a solid tumour who cannot take quinolone, cost-effectiveness was only formally examined for the following strategies (all strategies containing quinolone were excluded):

- Nothing/placebo
- Primary prophylaxis with G(M)-CSF
- Secondary prophylaxis with G(M)-CSF
- Primary prophylaxis with PEG-G-CSF
- Secondary prophylaxis with PEG-G-CSF.

The incremental costs and incremental QALYs in the base case analysis for each of the five strategies are summarised in Table 5.12. Taking nothing/placebo as the reference (least expensive) strategy, the other four strategies were shown to be more effective but were each associated with a very high ICER (all > £0.6 million/QALY) and were not considered to be cost-effective. Therefore at a willingness to pay (WTP) threshold of £20,000/QALY, nothing/placebo is the most cost-effective strategy. This conclusion was robust to structural sensitivity analysis and all one-way sensitivity analysis tested (Section A4.2),except for discounting the cost of PEG-G-CSF. At a WTP threshold of £20,000/QALY:

- When the discount to the cost of PEG-G-CSF was over 73.85% (corresponding price: £179.5 per single subcutaneous injection (6mg), secondary prophylaxis with PEG-G-CSF became the most cost-effective strategy.
- When the discount to the cost of PEG-G-CSF was over 84.13% (corresponding price: £108.9 per single subcutaneous injection (6mg), primary prophylaxis with PEG-G-CSF became the most cost-effective strategy.

Primary or secondary prophylaxis with G(M)-CSF is never the most cost-effective strategy for any of the three patient groups of interest, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount, reduced days of using G(M)-CSF (5-day per cycle of chemotherapy), reduced daily dose (one vial of G(M)-CSF for all adult patients regardless of weight) etc.

The result of the probabilistic sensitivity analysis shows that the probability of nothing/placebo becoming cost-effective is always 100%, at a willingness to pay between £10,000 to £40,000 per QALY.

Table 5.12 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can not take quinolone (baseline risk of neutropenic sepsis of one course of chemotherapy: 34.41%)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nothing/Placebo	£473.9	$-2.3*10^{-3}$	—	—	Comparator	Comparator
Secondary prophylaxis with PEG-G-CSF	£773.6	$-1.8*10^{-3}$	£299.7	$4.7*10^{-4}$	£0.6 million	£0.6 million
Secondary prophylaxis with G(M)-CSF	£898.3	$-2.0*10^{-3}$	£424.3	$2.4*10^{-4}$	£1.8 million	Dominated
Primary prophylaxis with PEG-G-CSF	£2170.2	$-5.6*10^{-4}$-	£1,696.3	$1.7*10^{-3}$	£1.0 million	£1.0 million
Primary prophylaxis with G(M)-CSF	£2826.9	$-1.3*10^{-3}$	£2352.9	$9.2*10^{-4}$	£2.6 million	Dominated

Adult/elderly patients with non-Hodgkin lymphoma

For adult patients with non-Hodgkin lymphoma, no clinical evidence was identified for the use of quinolone alone for either primary or secondary prophylaxis therefore neither strategy was included in this analysis.

Compared to G(M)-CSF alone, G(M)-CSF + quinolone is more expensive and less effective in terms of preventing neutropenic sepsis so both primary and secondary prophylactic G(M)-CSF + quinolone strategies were excluded. As a result cost-effectiveness was only formally examined for the following five strategies:

- Nothing/placebo
- Primary prophylaxis with G(M)-CSF
- Secondary prophylaxis with G(M)-CSF
- Primary prophylaxis with PEG-G-CSF
- Secondary prophylaxis with PEG-G-CSF

The incremental costs and incremental QALYs in the base case analysis for each of the five strategies are summarised in Table 5.13. Taking nothing/placebo as the reference (least expensive) strategy, the other four strategies were shown to be more effective, but were each associated with a very high ICER (all > £1.2 million/QALY) and were not considered to be cost effective. Therefore at a WTP threshold of £20,000/QALY, nothing/placebo is the most cost-effective strategy. This conclusion was robust to structural sensitivity analysis and all one-way sensitivity analysis tested (Section A4.2), except for discounting the cost of PEG-G-CSF. At a WTP threshold of £20,000/QALY:

- When the discount to the cost of PEG-G-CSF was over 83.49% (corresponding price: £113.3 per single subcutaneous injection (6mg), secondary prophylaxis with PEG-G-CSF became the most cost-effective strategy.

- When the discount to the cost of PEG-G-CSF was over 89.12% (corresponding price: £74.7 per single subcutaneous injection (6mg), primary prophylaxis with PEG-G-CSF became the most cost-effective strategy.

Primary or secondary prophylaxis with G(M)-CSF is never the most cost-effective strategy, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount of G(M)-CSF, reduced days of using G(M)-CSF (5-day per cycle of chemotherapy), reduced daily dose (one vial of G(M)-CSF for all adult patients regardless of weight) etc.

The result of probabilistic sensitivity analysis shows that the probability for nothing/placebo becoming cost-effective is always 100%, at a willingness to pay between £10,000 to £40,000 per QALY.

Table 5.13 Incremental costs and effectiveness by treatment strategy for non-Hodgkin lymphoma patients (baseline risk of neutropenic sepsis of one course of chemotherapy: 44.22%)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nothing/Placebo	£729.2	$-3.3*10^{-3}$	—	—	Comparator	Comparator
Secondary prophylaxis with PEG-G-CSF	£1,510.7	$-2.9*10^{-3}$	£781.4	$6.7*10^{-4}$	£1.2 million	£1.2 million
Secondary prophylaxis with G(M)-CSF	£1,629.0	$-2.6*10^{-3}$	£899.7	$3.2*10^{-4}$	£2.8 million	Dominated
Primary prophylaxis with PEG-G-CSF	£4,238.1	$-2.1*10^{-3}$	£3,508.9	$2.2*10^{-3}$	£1.6 million	£1.8 million
Primary prophylaxis with G(M)-CSF	£5,242.0	$-1.1*10^{-3}$	£4,512.8	$1.1*10^{-3}$	£4.1 million	Dominated

Adult/elderly patients with Hodgkin lymphoma

For adult/elderly patients with Hodgkin lymphoma, clinical evidence was only available for the use of G(M)-CSF for either primary or secondary prophylaxis. Therefore cost-effectiveness was only formally examined for the following three strategies:

- Nothing/placebo
- Primary prophylaxis with G(M)-CSF
- Secondary prophylaxis with G(M)-CSF

The incremental costs and incremental QALYs in the base case analysis for each of the three strategies are summarised in Table 5.14. Taking nothing/placebo as the reference (least expensive) strategy, the other two strategies were shown to be more effective, but were each associated with a very high ICER (both > £18.2 million/QALY) and were therefore not considered to be cost effective. Therefore at a WTP threshold of £20,000/QALY, nothing/placebo is the most cost-effective strategy. This conclusion was robust to all one-way sensitivity analysis tested (Section A4.2).

Primary or secondary prophylaxis with G(M)-CSF is never the most cost-effective strategy, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount of G(M)-CSF, reduced days of using G(M)-CSF (5-day per cycle of chemotherapy), reduced daily dose (one vial of G(M)-CSF for all adult patients regardless of weight) etc.

The result of the probabilistic sensitivity analysis shows that the probability of nothing/placebo becoming cost-effective is always 100%, at a willingness to pay between £10,000 to £40,000 per QALY.

Table 5.14 Incremental costs and effectiveness by treatment strategy for Hodgkin lymphoma patients (baseline risk of neutropenic sepsis of one course of chemotherapy: 20.27%)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nothing/Placebo	£235.8	$-1.2*10^{-3}$	—	—	Comparator	Comparator
Secondary prophylaxis with G(M)-CSF	£1,608.8	$-1.1*10^{-3}$	£1,372.0	$7.5*10^{-5}$	£18.2 million	£18.2 million
Primary prophylaxis with G(M)-CSF	£11,921.8	$-9.3*10^{-4}$	£11,686.0	$2.5*10^{-4}$	£47.2 million	£59.9 million

Recommendations

- For adult patients (aged 18 years and older) with acute leukaemias, stem cell transplants or solid tumours in whom significant neutropenia (neutrophil count 0.5 x 10^9 per litre or lower) is an anticipated consequence of chemotherapy, offer prophylaxis with a fluoroquinolone during the expected period of neutropenia only
- Rates of antibiotic resistance and infection patterns should be monitored in treatment facilities where patients are having fluoroquinolones for the prophylaxis of neutropenic sepsis[16].
- Do not routinely offer granulocyte-colony stimulating factor (G-CSF) for the prevention of neutropenic sepsis in adults receiving chemotherapy unless they are receiving G-CSF as an integral part of the chemotherapy regimen or in order to maintain dose intensity.

Linking Evidence to Recommendations

The aim of this topic was to identify if prophylactic treatment with antibiotics, growth factors and/or granulocyte infusion could improve short term outcomes in patients receiving anticancer treatment. This topic did not investigate the effect of G-CSF as an integral part of a chemotherapy regimen (for example, CHOP-14) or on dose intensity of chemotherapy.

The GDG assessed the clinical effectiveness of antibiotics, growth factors and granulocyte infusions in all patient groups. No evidence was found of a clinical benefit for granulocyte infusions and so cost-effectiveness analysis was undertaken only for growth factors and antibiotics. Because of the heterogeneity and complexity of anticancer treatment, formal cost-effectiveness analysis focused on the group of adult patients receiving outpatient treatment for solid tumours, Hodgkin lymphoma and non-Hodgkin lymphoma.

Studies of patients with stem cell transplants or leukaemia were excluded from the formal cost-effectiveness analysis because the GDG recognised that the costs of prophylaxis for inpatient-only management are very different from outpatient management. Paediatric patients were also excluded from the formal cost-effectiveness analysis because of considerable clinical heterogeneity in the treatment regimens, and a paucity of direct evidence which precluded building a meaningful model for analysis.

The GDG considered that the outcomes of death (short-term mortality), incidence of neutropenic sepsis, bacterial resistance, secondary infection, critical care, length of hospital stay and quality of life were the most clinically relevant. No evidence was reported for secondary infection, critical care or quality of life. Evidence was available for short-term mortality, bacterial resistance, and incidence of neutropenic sepsis. Overall the evidence for all outcomes was of 'low' quality with potential bias as assessed by GRADE.

The GDG noted that evidence directly comparing growth factors and antibiotics (ciprofloxacin and cotrimoxazole) was very sparse and of low quality. The GDG were surprised to find that the vast majority of evidence compared growth factors, predominately G-CSF, against no prophylaxis. The GDG also noted that there were very limited data available on the combination of growth factors with fluoroquinolones.

The GDG noted that the clinical evidence comparing antibiotics with placebo was of low quality and showed that antibiotics were effective at reducing overall short term mortality and incidence of neutropenic sepsis. The clinical evidence comparing growth factors against placebo was of low quality and showed no difference in effect on overall short term mortality.

[16] For more information see the Department of Health's Updated guidance on the diagnosis and reporting of *Clostridium difficile* and guidance from the Health Protection Agency and the Department of Health on *Clostridium difficile* infection: how to deal with the problem.

However this evidence did show that growth factors reduce the incidence of neutropenic sepsis and they were also reported to shorten the length of hospital stay. The GDG considered that reduced overall short term mortality was the most important outcome.

Sparse evidence also reported antibiotic resistance with the use of prophylactic antibiotics. This demonstrated that whilst isolation of bacteria resistant to the prophylactic antibiotic may have increased there was still a reduction in overall mortality. The GDG recognised that prophylactic antibiotics contribute to antibiotic resistance but concluded that in patients receiving anticancer treatment the evidence suggests the benefits outweigh the risk.

Evidence was reported for both fluoroquinolones and cotrimoxazole as antibiotic prophylaxis. However the GDG chose to focus on the evidence related to fluoroquinolones because of concerns that changing anti-microbial resistance patterns meant the cotrimoxazole trials may no longer be applicable (Gafter-Gvili, et al., 2005). Consequently the GDG acknowledged that any recommendations made would only be able to focus on fluoroquinolones, because these studies were more recent include a large study undertaken in the UK population and would therefore more accurately reflect the current microbiological environment. The GDG were aware that this approach would exclude all evidence related to antibiotic prophylaxis with cotrimoxazole and that the smaller number of studies would decrease the precision in the estimates of effect, with the potential to increase uncertainty around any recommendation.

The GDG noted that international guidelines such as American Society of Clinical Oncology (Smith et al, 2006), The National Comprehensive Cancer Network (NCCN, 2011) and European Organisation for Research and Treatment of Cancer (Aapro, *et al.,* 2010) recommend the use of G-CSF in selected patients who have a neutropenic sepsis risk of greater than 20%. The GDG also noted that these guidelines were based on the comparison of G-CSF with no prophylaxis, rather than with antibiotics, and did not assess the cost-effectiveness of their recommendations. In addition these guidelines had been developed in non UK healthcare settings.

The GDG considered the issue of paediatric patients carefully, balancing the potential benefits of extrapolating evidence from adult patients against the risks of adverse effects from the medications. Potential similarities between children undergoing stem cell transplantation and treatment for acute leukaemia in adults were considered, as were the documented differences between children and adults in the range of infecting organisms, underlying malignant diagnoses and treatment regimens. The GDG noted a large RCT was in progress by the Children’s Oncology Group in North America addressing this question. They also noted the very different treatments used in treating the majority of children and young people with solid tumours compared to the majority of adult solid tumours. The GDG therefore concluded that there was too little evidence to recommend the use of either antibiotics or GCSF in this group, but identified this as an area for research.

The results of the cost-effectiveness analysis showed that for adult patients with solid tumours, primary prophylaxis with fluoroquinolones was more cost-effective than other strategies. This conclusion was robust to sensitivity analysis. For adult patients with solid tumours who cannot receive fluoroquinolones, no prophylaxis was shown to be the most cost-effective strategy. However, this result was shown to be sensitive to adjustments in several of the inputs to the model. As a result of this uncertainty the GDG did not feel able to make a recommendation for adult patients with solid tumours who cannot receive fluoroquinolones.

Little clinical evidence was found comparing fluoroquinolones with no prophylaxis for patients with lymphoma (Hodgkin or non-Hodgkin). Therefore the cost-effectiveness analysis only compared G-CSF or G-CSF + fluoroquinolone with no prophylaxis in these patients. The results showed that although G-CSF or G-CSF + fluoroquinolone could reduce the incidence of neutropenic sepsis; the ICER of both strategies was far above NICE's £20,000 per QALY threshold and consequently the strategy of no prophylaxis was the most cost effective. However given that data were not available to compare all the strategies of interest the GDG was uncertain whether prophylaxis with antibiotics and/or G-CSF was clinically and cost-effective for lymphoma patients. They therefore decided not to make any recommendations on this issue.

Based on their clinical experience the GDG considered that for patients undergoing stem-cell transplantation and during intensive treatment for acute leukaemia the additional costs of antibiotic prophylaxis would be small and vastly outweighed by the improvement in short term mortality.

A systematic review of published economic evidence for this topic identified 10 papers that were relevant. However all papers had either very serious or potentially serious limitations. Therefore the GDG decided to use the results of the cost-effectiveness analysis conducted as part of this guideline to inform their recommendations.

The GDG considered that the benefits of recommending the use of fluoroquinolones in primary prophylaxis for this subset of patients would be fewer deaths and hospital admissions and potentially improved quality of life. The GDG noted that there are risks associated with recommending primary prophylaxis with fluoroquinolones, such as resistant bacterial infections and super-infection with *Clostridium difficile* and that monitoring for antimicrobial resistance should be carefully undertaken. However, the GDG noted, based on their clinical experience, that the death rate from such infections in this population is likely to be less than the death rate from neutropenic sepsis. The GDG also noted that the use of fluoroquinolones can have side effects, but agreed that the benefit of saving lives outweighed any potential harms.

The GDG noted the high ICER for G(M)-CSF in the prevention of neutropenic sepsis. Whilst the GDG acknowledged that clinicians in some settings are able to source G(M)-CSF products at substantially reduced prices, it was noted that these arrangements are fluid and regional, and therefore no national recommendations can be based on these costs. Not withstanding this, the GDG noted that the nursing costs of administering G(M)-CSF for preventing neutropenic sepsis result in this intervention not being cost effective, even at reduced prices.

One-way sensitivity analysis has shown that the economic model was sensitive to discounting the cost of PEG-G-CSF. PEG-G_CSF becomes cost-effective for secondary prophylaxis in patients with solid tumours who cannot take fluoroquinolones at less than £179.83 per single subcutaneous injection (6mg). However the GDG considered that is was unlikely that PEG-G-CSF would be available at these levels of discount. It was not possible to calculate similar thresholds for other patient groups because of a lack of clinical evidence (see Appendix A). These elements of uncertainty along with the high ICER described by the economic model led the GDG not to recommend the routine use of G(M)-CSF for the prevention of infectious complications and death from neutropenic sepsis. The GDG were aware that G(M)-CSF is an integral part of some chemotherapy regimens, or is used for maintaining dose intensity. Although this was outside the scope of this guideline and the evidence on this has not been reviewed, the GDG agreed that the use of G(M)-CSF for these indications should be acknowledged in the recommendation.

Based on the clinical evidence and the results of the cost-effectiveness analysis the GDG decided to recommend primary prophylaxis with fluoroquinolones for patients with acute leukaemias, stem cell transplants and adult patients with solid tumours during the period of expected neutropenia. They also recommended further research be undertaken in examining the cost-effectiveness of antibiotics and G-CSF in preventing neutropenic sepsis in children and young people. The GDG noted that in making a recommendation for primary prophylactic treatment a recommendation for secondary prophylactic treatment was no longer relevant. Because of the limited data available on the combination of growth factors with antibiotics, the GDG did not feel able to make any recommendations on this.

Research recommendation

- Randomised studies should investigate primary prophylaxis of neutropenic sepsis in 2 populations: children and young people (aged under 18) having treatment for solid tumours or haematological malignancies, or stem cell transplantation; and adults (aged 18 and older) diagnosed with lymphoma. The studies should compare the effectiveness of fluoroquinolone antibiotics given alone, fluoroquinolone antibiotics given together with granulocyte-colony stimulating factor (G-CSF) preparations, and G-CSF preparations given alone. Outcome measures should include overall mortality, infectious episodes and adverse events. In addition, quality of life should be determined using quantitative and qualitative methods. The resulting data should be used to develop a cost-effectiveness analysis comparing these 3 forms of prophylaxis in children and young people having anticancer treatment, and in adults diagnosed with lymphoma.

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6 Initial treatment

Neutropenic sepsis is an acute medical emergency. The most important decision in such patients is the choice and delivery of initial empiric treatment to help prevent septic shock, multi organ failure and death.

The objectives of this chapter are:

- To determine the effect of timing of initial antibiotic treatment upon clinical outcome.
- To identify the best initial empiric antibiotic strategy.
- To assess the role of additional interventions in patients with central venous access devices.
- To determine whether treatment can safely be given in an outpatient setting.

6.1 Timing of initial antibiotic treatment

Early studies of the active management of neutropenic sepsis showed that delaying treatment, for instance while waiting for blood culture results, was dangerous and carried a significant risk of death. This led to the concept of empiric broad-spectrum antibiotic therapy administered before the results of microbiological tests are available. A further extension of this concept implies that if time to treatment is critical, empiric treatment should be given to potentially neutropenic patients with clinical signs of sepsis even before the neutrophil count is known.

Many factors influence the time from onset of symptoms of neutropenic sepsis to the delivery of antibiotics and it would therefore be useful to establish if there is a safe or optimum interval. Although it would appear obvious that shortening this interval is beneficial, it is possible that over-hasty treatment of patients with suspected neutropenic sepsis may have disadvantages. For instance, patients who are not neutropenic and have an extremely low risk of serious infection may be given unnecessary antibiotics with potential adverse side effects.

Clinical question: Does the length of time before empiric antibiotics are given influence patient outcomes?

Clinical evidence (see also full evidence review)

Evidence statements

Short term mortality (febrile neutropenia studies)

A multivariate analysis by Larche, *et al.,* (2003) found that 30 day mortality was higher when time to antibiotic therapy was more than two hours (odds ratio (OR) = 7.05 (95% CI, 1.17 to 42.21 (P = 0.03)). (Table 6.1).

A multivariate analysis by Lin, *et al.,* found that mortality was higher in patients with an absolute neutrophil count (ANC) of <0.1 X 10^9/L when time to antibiotic therapy was > 24 hours in a non-ICU setting (OR = 18.0; 95% CI, 2.84 - 114.5; P < 0.01); and in an ICU setting (OR, 5.56; 95% CI, 0.85 - 36.3; P = 0.07). However, for patients who were non-neutropenic (ANC, >0.5 X 10^9/L) or had ANCs of 0.1 - 0.5 X 10^9/L, delay was not associated with increased mortality in ICU (OR (ANC 0.1 - 0.5 X 10^9/L) = 0.59; 95% CI, 0.06 - 6.22; P = 0.66; OR (ANC > 0.5 X 10^{-9}/L) = 0.55; 95% CI 0.29 - 1.02) or non-ICU (OR (ANC 0.1 to 0.5 X 10^{-9}/L) = 1.92; 95% CI, 0.17 to 21.3; P = 0.60; OR (ANC > 500) = 1.78; 95% CI 0.89 to 3.44).

This evidence is of very low quality and is indirect on the basis that patients had bacteraemia or septic shock.

Overtreatment, severe sepsis, length of stay, duration of fever and quality of life

These outcomes were not reported by the identified studies. The outcome of severe sepsis was not relevant to the included studies, which included only participants who had bacteraemia or severe sepsis at study entry.

Table 6.1 GRADE profile: Does the length of time before empiric antibiotics are given influence patient outcome.

Quality assessment							No of patients		Effect		Quality
No of study	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Non-delayed antibiotic therapy	Delayed antibiotic therapy	Relative (95% CI)	Absolute	
Short term mortality: in cancer patients with septic shock [1]											
1	observational study	serious[2]	no serious inconsistency	serious[3]	very serious[6]	none	18/20 (90%)	39/68 (57.4%)	OR 6.5 (1.39 to 30.49)	324 more per 1000 (from 78 more to 403 more)	VERY LOW
Short-term mortality: in patients with bacteraemia (67/1523 (4.4%) had ANC < 500)											
1	observational study	serious[2]	no serious inconsistency	serious[4]	very serious[6]	strong association	79/983 (8%)	50/540 (9.3%)	OR 0.85 (0.59 to 1.24)-	93 fewer per 1000 (from 93 fewer to 93 fewer)	VERY LOW
Short-term mortality: in non-ICU patients with bacteremia and ANC < 100											
1	observational study	serious[2]	no serious inconsistency	serious[5]	very serious[6]	strong association	Not reported	Not reported	OR 18 (2.84 to 113.5)	Not calculable	VERY LOW
Short-term mortality: in non-ICU patients with bacteremia and ANC 100-500											
1	observational study	serious[2]	no serious inconsistency	very serious[5,7]	very serious[6]	none	Not reported	Not reported	OR 1.92 (0.17 to 21.6)	Not calculable	VERY LOW
Short-term mortality: in non-ICU patients with bacteraemia and ANC > 500											
1	observational study	serious[2]	no serious inconsistency	very serious[5,8]	very serious[6]	none	Not reported	Not reported	OR 1.78 (0.91 to 3.45)	Not calculable	VERY LOW

Short-term mortality: in ICU patients with bacteremia and ANC < 100											
1	observational study	serious[2]	no serious inconsistency	serious[5]	very serious[6]	none	Not reported	Not reported	OR 5.56 (0.85 to 36.3)	Not calculable	VERY LOW
Short-term mortality: in ICU patients with bacteremia and ANC 100-500											
1	observational study	serious[2]	no serious inconsistency	very serious[5,7]	very serious[6]	none	Not reported	Not reported	OR 0.59 (0.06 to 6.22)	Not calculable	VERY LOW
Short-term mortality: in ICU patients with bacteremia and ANC > 500											
1	observational study	serious[2]	no serious inconsistency	very serious[5,8]	very serious[6]	none	Not reported	Not reported	OR 0.55 (0.29 to 1.02)	Not calculable	VERY LOW

[1] Mortality was not reported by group. These figures were calculated from the overall mortality rate and the odds ratio
[2] Observational study
[3] Cancer patients with septic shock. Very high mortality rate.
[4] Patients with bacteremia (not all neutropenic)
[5] Patients with bacteremia
[6] Very small number of events
[7] Patients with ANC 100-500
[8] Patients with ANC >500

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. This topic focused on the optimal timing of a change in management strategy. The difference between strategies were considered unlikely to lead to large differences in cost, but rather be guided by differences in patient outcomes and other considerations such as service configuration that. It was agreed that these considerations would probably be difficult to accurately capture using economic modelling and therefore further health economic analysis was not undertaken

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

Linking Evidence to Recommendations

The aim of this topic was to see if the length of time before empiric antibiotics are given influences a patient's outcome. For this topic the GDG considered the outcomes of overtreatment, mortality, severe sepsis, length of stay, duration of fever and quality of life to be the most relevant to this patient population as these are the adverse consequences of unnecessarily being given antibiotics and staying in hospital. No evidence was reported for any of these outcomes.

The search was therefore widened to include patients with general suspected bacterial infections. Evidence was found for short term mortality but this was not directly relevant to the patient population and the study reported patients who had bacteraemia or septic shock. The GDG noted that the evidence was classified by GRADE as being of 'very low' quality and no studies defined the optimal time for administering antibiotics. The GDG agreed that data for short term mortality could be used as it was the only data available.

The GDG also acknowledged the one hour to antibiotic pathway from the National Cancer Peer Review Programme, Manual for Cancer Services. The GDG felt that there was insufficient evidence to support recommending a specific time period for administering antibiotics. However the GDG recognised that benefits such as increased patient survival and a reduction in complications could be gained from administering antibiotics as soon as possible.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG was that there may be potential cost implications of unnecessary treatment. However they felt that improvements in patients' survival outweigh any potential costs. The GDG also noted that adverse events for the patient, and the costs associated with dealing with these would be avoided as a result of urgent antibiotic intervention.

Therefore the GDG decided to recommend that patients with suspected neutropenic sepsis should be treated as an acute medical emergency and receive empiric antibiotic therapy without delay.

6.2 Empiric intravenous antibiotic monotherapy or intravenous antibiotic dual therapy

Early studies focussed on empiric antibiotic treatment combinations using two, or more different drugs. These early trials were small and produced inconsistent and clinically poor outcomes by today's standards. In 1973 the European Organisation for Research on

Treatment of Cancer (EORTC) formed a cooperative group to research the problem. In parallel over the next three decades, a stream of new drugs based on the beta-lactam structure entered the market. Some of these and the older drugs have now become obsolete.

Combination therapy including a beta lactam antibiotic (penicillin or cephalosporin) combined with an aminoglycoside formed the backbone of the early studies due to theoretical and *in vitro* synergism and also because of known gaps in microbiological sensitivities for the a earlier beta lactam antibiotics. From the early 1980s onwards trials were undertaken of monotherapy based on newer beta-lactam antibiotics with a very broad spectrum of activity, including effectiveness against dangerous organisms such as *Pseudomonas,* versus combination therapy with the older beta-lactam antibiotics plus aminoglycoside.

Potential advantages of monotherapy could include savings in cost, resources and the need for monitoring aminoglycoside drug levels. It could also reduce potential side effects, such as kidney toxicity, which is usually immediately apparent and can interfere with ongoing cancer treatment, and inner ear toxicity (deafness and balance problems) which can often be insidious and of late onset.

Despite this, combination regimens are still widely used. The reasons why aminoglycosides are still used include concerns about secondary infection with *Clostridium difficile* and that monotherapy may promote antibiotic resistance. In addition, particular subgroups of patients are thought to fare better with combination therapy. Local knowledge of microbiological flora also affects treatment choices because of demonstrated resistance to beta lactam monotherapy.

Clinical question: Is there a difference in the effectiveness of empiric intravenous antibiotic monotherapy and empiric intravenous dual therapy in the treatment of patients with neutropenic sepsis?

Clinical evidence (see also full evidence review)

Evidence statements

Evidence from trials directly comparing single agent with combined treatment

There was moderate quality evidence from 44 studies extracted from a systematic review by Paul et al (2007) with over seven thousand episodes of neutropenia and fever which did not show a significant difference in the risk of all cause mortality between monotherapy and combined therapy. This evidence is summarised in Table 6.2.

Moderate quality evidence from 55 studies showed that treatment failure was less likely with monotherapy than combined therapy, when combined therapy used a narrower spectrum antibiotic than was used for monotherapy (52 studies from Paul et al, 2007; Pereira *et al.,* 2009; Yildirim *et al.,* 2008 and Zengin *et al.,* 2011). Fifteen studies where the same beta-lactam was used for both monotherapy and combined therapy, however, found treatment failure more likely with monotherapy.

Moderate quality evidence showed that monotherapy was associated with fewer adverse events, including nephrotoxicity (Paul et al, 2007).

Moderate quality evidence showed that monotherapy and combined therapy had similar rates of bacterial secondary infection.

Low quality evidence showed fungal secondary infection was more likely with combined therapy.

Very low quality evidence from two studies with 152 patients suggested that colonisation of resistant Gram-negative bacteria was more likely with monotherapy, but such bacteria were only detected in six patients overall.

There was no evidence about quality of life and no useful evidence about the duration of hospital stay.

Table 6.2 GRADE profile: Is empiric IV antibiotic monotherapy more effective than empiric IV antibiotic combined therapy in the treatment of patients with neutropenic sepsis

Quality assessment							Summary of findings				
							No of patients (or episodes)		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	empiric intravenous antibiotic monotherapy	empiric intravenous antibiotic combined therapy	Relative (95% CI)	Absolute	
Death from any cause											
44	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	267/3666 (7.3%)	292/3505 (8.3%)	RR 0.88 (0.75 to 1.03)	10 fewer per 1000 (from 21 fewer to 2 more)	MODERATE
Treatment failure (same beta-lactam)											
15	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	603/1355 (44.5%)	561/1406 (39.9%)	RR 1.11 (1.02 to 1.21)	44 more per 1000 (from 8 more to 84 more)	MODERATE
Treatment failure (different beta-lactam)											
55	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1573/3919 (40.1%)	1603/3749 (42.8%)	RR 0.92 (0.87 to 0.96)	34 fewer per 1000 (from 17 fewer to 56 fewer)	MODERATE
Any adverse event											
48	randomised trials	serious[1]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	872/3675 (23.7%)	988/3665 (27%)	RR 0.86 (0.8 to 0.93)	38 fewer per 1000 (from 19 fewer to 54 fewer)	MODERATE
Any nephrotoxicity											
37	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	78/3187 (2.4%)	187/3224 (5.8%)	RR 0.47 (0.36 to 0.61)	31 fewer per 1000 (from 23 fewer to 37 fewer)	LOW

Severe nephrotoxicity											
18	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	1/1998 (0.1%)	19/2004 (0.9%)	RR 0.16 (0.05 to 0.49)	8 fewer per 1000 (from 5 fewer to 9 fewer)	LOW
Bacterial superinfection											
29	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	258/2421 (10.7%)	252/2415 (10.4%)	RR 1.00 (0.86 to 1.18)	0 fewer per 1000 (from 15 fewer to 19 more)	MODERATE
Fungal superinfection											
20	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	46/1716 (2.7%)	68/1721 (4%)	RR 0.70 (0.49 to 1)	12 fewer per 1000 (from 20 fewer to 0 more)	LOW
Colonization of resistant Gram negative bacteria											
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	Very serious[4]	none	5/152 (3.3%)	1/152 (0.7%)	not pooled	not pooled	VERY LOW
Length of stay											
4	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0	0	-	not pooled	
Quality of life											
0	no evidence available					none	0	0	-	not pooled	

[1] Less than half of studies had adequate allocation concealment or reported blinding.
[2] 4/15 trials had adequate allocation concealment, 2/15 used blinding, details about randomisation method were given in 8/15 and 4/15 reported intention to treat analysis.
[3] There was significant heterogeneity but this appears to be due to the type of beta-lactam used for monotherapy.
[4] Low or very low number of events
[5] No blinding, information on allocation concealment, one of the studies reported the method of randomisation.

[6] No blinding, allocation concealment was acceptable in 2 of the 4 trials.

Evidence from mixed treatment comparison

A mixed treatment comparison was done for this guideline using 108 trials identified in two Cochrane reviews by Paul, *et al.,* (2007 and 2010). These trials were either comparing single agent beta-lactams with each other (Paul, *et al.,* 2010) or comparing single agent beta-lactams with combined beta-lactam/aminoglycoside treatment (Paul, *et al.,* 2007).

The summary estimates from the mixed treatment comparisons showed good model fit (residual deviance ~ 126, compared with 148 data points). The Deviance Information Criterion was minimised when covariates indicating year of publication, age of patients, and proportion of haematological malignancy were not entered into the model. Additionally, none of these covariates were significant (i.e. their 95% credible intervals all crossed log-zero; no effect).

The treatment most likely to be best at reducing overall mortality was the use of a single agent ureidopenicillin. This was reflected in direct and indirect estimates (Tables 6.3 to 6.5). Carbapenems alone compared with ureidopenicillin had higher overall mortality, equivalent infectious mortality and marginally less risk of 'treatment failure'.

Table 6.3 Results of mixed treatment comparison of empiric antibiotic monotherapies and empiric combined therapies

n Trials	Comparators	Mortality		Infectious Deaths		Clinical failure	
		Indirect OR	95% CrI	Indirect OR	95% CrI	Indirect OR	95% CrI
3	ureidopenicillin vs carbapenem	0.57	0.38 to 0.88	0.94	0.55 to 1.57	1.13	0.9 to 1.43
9	3rdGenCephalosporin vs carbapenem	0.84	0.62 to 1.19	1.03	0.68 to 1.65	1.03	0.86 to 1.22
5	4thGenCephalosporin vs carbapenem	1.18	0.81 to 1.66	1.16	0.64 to 2.22	0.97	0.78 to 1.23
4	ureidopenicillin +aminoglycoside vs carbapenem	1.03	0.77 to 1.4	1.87	1.04 to 3.82	1.1	0.87 to 1.39
10	3rdGenCephalosporin+aminoglycoside vs carbapenem	1.07	0.75 to 1.54	1.31	0.8 to 2.06	1.19	0.99 to 1.44
	4thGenCephalosporin+aminoglycoside vs carbapenem	1.27	0.54 to 2.59	1.71	0.15 to 6.08	0.9	0.55 to 1.47
1	3rdGenCephalosporin vs ureidopenicillin	1.5	0.91 to 2.26	1.11	0.72 to 1.73	0.91	0.72 to 1.14
3	4thGenCephalosporin vs ureidopenicillin	2.06	1.28 to 3.11	1.25	0.68 to 2.15	0.86	0.68 to 1.11
2	ureidopenicillin +aminoglycoside vs ureidopenicillin	1.83	1.2 to 2.7	1.98	1.1 to 3.84	0.97	0.74 to 1.27
3	3rdGenCephalosporin+aminoglycoside vs ureidopenicillin	1.87	1.13 to 2.97	1.4	0.74 to 2.54	1.06	0.83 to 1.37
	4thGenCephalosporin+aminoglycoside vs ureidopenicillin	2.21	0.81 to 4.93	1.8	0.2 to 6.97	0.8	0.49 to 1.32
7	4thGenCephalosporin vs 3rdGenCephalosporin	1.4	0.93 to 1.96	1.12	0.64 to 2.05	0.95	0.77 to 1.19
5	ureidopenicillin +aminoglycoside vs 3rdGenCephalosporin	1.22	0.9 to 1.69	1.8	1.03 to 3.6	1.06	0.86 to 1.34
7	3rdGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin	1.25	0.89 to 1.86	1.26	0.76 to 2.11	1.16	0.96 to 1.42
	4thGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin	1.48	0.62 to 3.16	1.62	0.17 to 6.23	0.87	0.54 to 1.44
	ureidopenicillin +aminoglycoside vs 4thGenCephalosporin	0.88	0.59 to 1.34	1.61	0.72 to 3.61	1.12	0.86 to 1.49
2	3rdGenCephalosporin+aminoglycoside vs 4thGenCephalosporin	0.89	0.61 to 1.46	1.09	0.58 to 2.29	1.23	0.95 to 1.58
2	4thGenCephalosporin+aminoglycoside vs 4thGenCephalosporin	1.08	0.48 to 2.13	1.47	0.17 to 5.34	0.92	0.58 to 1.48
	3rdGenCephalosporin+aminoglycoside vs ureidopenicillin +aminoglycoside	1.02	0.7 to 1.53	0.69	0.28 to 1.43	1.09	0.83 to 1.44
	4thGenCephalosporin+aminoglycoside vs ureidopenicillin +aminoglycoside	1.2	0.49 to 2.54	0.9	0.11 to 3.55	0.82	0.49 to 1.36
	4thGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin+aminoglycoside	1.18	0.47 to 2.51	1.39	0.16 to 5.19	0.75	0.45 to 1.26

Table 6.4 Comparison of results from pairwise and mixed treatment comparisons of empiric antibiotic monotherapies and empiric combined therapies for mortality

n Trials	Comparators	Direct OR	95% CI	Indirect OR	95% CrI
3	ureidopenicillin vs carbapenem	0.4	0.115 to 1.388	0.57	0.38 to 0.88
9	3rdGenCephalosporin vs carbapenem	0.997	0.597 to 1.664	0.84	0.62 to 1.19
5	4thGenCephalosporin vs carbapenem	1.368	0.714 to 2.624	1.18	0.81 to 1.66
4	ureidopenicillin +aminoglycoside vs carbapenem	1.004	0.565 to 1.786	1.03	0.77 to 1.4
10	3rdGenCephalosporin+aminoglycoside vs carbapenem	1.065	0.691 to 1.641	1.07	0.75 to 1.54
	4thGenCephalosporin+aminoglycoside vs carbapenem	NA	NA	1.27	0.54 to 2.59
1	3rdGenCephalosporin vs ureidopenicillin	1.178	0.072 to 19.167	1.5	0.91 to 2.26
3	4thGenCephalosporin vs ureidopenicillin	1.56	0.73 to 3.33	2.06	1.28 to 3.11
2	ureidopenicillin +aminoglycoside vs uridipenicillin	1.488	0.859 to 2.576	1.83	1.2 to 2.7
3	3rdGenCephalosporin+aminoglycoside vs ureidopenicillin	2.155	0.871 to 5.333	1.87	1.13 to 2.97
	4thGenCephalosporin+aminoglycoside vs ureidopenicillin	NA	NA	2.21	0.81 to 4.93
7	4thGenCephalosporin vs 3rdGenCephalosporin	1.558	0.937 to 2.589	1.4	0.93 to 1.96
5	ureidopenicillin +aminoglycoside vs 3rdGenCephalosporin	1.247	0.903 to 1.722	1.22	0.9 to 1.69
7	3rdGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin	1.204	0.685 to 2.118	1.25	0.89 to 1.86
	4thGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin	NA	NA	1.48	0.62 to 3.16
	ureidopenicillin +aminoglycoside vs 4thGenCephalosporin	NA	NA	0.88	0.59 to 1.34
2	3rdGenCephalosporin+aminoglycoside vs 4thGenCephalosporin	0.593	0.07 to 4.996	0.89	0.61 to 1.46
2	4thGenCephalosporin+aminoglycoside vs 4thGenCephalosporin	1.696	0.154 to 18.673	1.08	0.48 to 2.13
	3rdGenCephalosporin+aminoglycoside vs ureidopenicillin +aminoglycoside	NA	NA	1.02	0.7 to 1.53
	4thGenCephalosporin+aminoglycoside vs ureidopenicillin +aminoglycoside	NA	NA	1.2	0.49 to 2.54
	4thGenCephalosporin+aminoglycoside vs 3rdGenCephalosporin+aminoglycoside	NA	NA	1.18	0.47 to 2.51

Cost-effectiveness evidence

A literature review of published cost effectiveness analyses identified two relevant papers, Corapcioglu and Sarper (2005) and Paladino, (2000). The results of both studies are summarised in Table 6.5. No further health economic analysis was undertaken as the cost difference between monotherapy and dual therapy was relatively low.

Study quality and results

Both papers were deemed partially applicable to the topic. The most common reasons for partial applicability were that the analyses were conducted in countries other than the UK or did not conform to one or more aspects of the NICE reference case. Both papers were deemed to have very serious limitations.

Evidence statements

The population of both studies were cancer patients with febrile neutropenia; but Corapcioglu and Sarper (2005) looked at children aged <18 years while Paladino (2000) looked at adults aged ≥16 years.

Effectiveness data in Corapcioglu and Sarper (2005) was obtained from a prospective randomised trial; whilst the effectiveness data in Paladino, (2000) was obtained from the pooled result of two prospective randomised trials. Neither of the two papers quantified health effects in terms of QALYs.

Corapcioglu and Sarper (2005) compared cefepime with ceftazidime + amikacin, and reported that monotherapy was more cost-effective than dual therapy. This conclusion was not tested by sensitivity analysis. Paladino, (2000) compared cefepime with gentamicin + ureidopenicillin or mezlocillin, and reported that there were no statistically significant differences in cost-effectiveness between monotherapy and dual therapy. However, this conclusion was sensitive to success rates of both interventions. For the majority of the tested range of success rate, monotherapy was more cost effectiveness than dual therapy.

Table 6.5 GRADE profile: Cost effectiveness of antibiotic monotherapy compared with antibiotic dual therapy

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
Corapcioglu and Sarper, 2005	Serious limitations[1]	Partially applicable[2]	Cancer patients under 18 years with fever and neutropenia	Dual therapy with ceftazidime (150 mg/kg/day (maximum daily dose 6 g) in 3 divided doses) and amikacin (15 mg/kg/day in a single dose)	Monotherapy with cefepime (150 mg/kg/day in 3 divided doses (maximum daily dose 6g))	£4240[3] per episode of febrile neutropenia	Monotherapy: Duration of fever < 10 days: 13 (52%) ≥ 10 days: 12 (48%) Response without modification: 13 (52%) Infection-related mortality: 0 Dual therapy: Duration of fever < 10 days: 9 (36%) ≥ 10 days: 16 (64%) Response without modification: 10 (40%) Infection-related mortality: 0	Can't be calculated	Sensitivity analysis was not conducted.
Paladino, 2000	Serious limitations[4]	Partially applicable[5]	Adult cancer patients ≥16 years with febrile neutropenia.	Dual therapy with gentamicin (1.5mg/kg intravenously every 8 hours) and ureidopenicillin (either piperacillin 3g intravenously every 4 hours in 1 trail or mezlocillin 3g intravenously every 4 hours in a second trial)	Monotherapy with cefepime (2g intravenously every 8 hours)	£1127[6]	Monotherapy: Treatment outcome no. (%) Cure: 27 (37%) failure: 23 (31%) indeterminate: 24 (32%) Patients experiencing adverse effects (no. (%)): 15 (20%) Total adverse effects (no. (%)): 22 (30%) Antibacterial-related length of stay (days (range)): 16 (7-49) Dual therapy: Treatment outcome no. (%) Cure: 27 (36%) failure: 31 (41%) indeterminate: 17 (23%) Patients experiencing: 17 (23%)	Can't be calculated	Sensitivity analysis was not conducted.

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
							adverse effects (no. (%))		
							Total adverse effects (no. (%)) 20 (27%)		
							Antibacterial-related length of stay (days (range)) 17 (7-46)		

[1] Effectiveness data is based on one single randomised trial conducted in one centre; impact on quality of life was not considered in the analysis; no sensitivity analysis was conducted. Therefore the relevance of these results for informing the current guideline is limited (in the absence of an appropriate willingness to pay threshold).
[2] The analysis does not meet one or more aspects of the NICE reference case.
[3] Converted from 2004 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 116% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[4] Impact on quality of life was not considered in the analysis; potential conflict of interest: this study was funded in part by an unrestricted grant from Bristol-Myers Squibb Company. Therefore the relevance of these results for informing the current guideline is limited (in the absence of an appropriate willingness to pay threshold).
[5] The analysis does not meet one or more aspects of the NICE reference case.
[6] Converted from 1997 U.S dollars using a PPP exchange rate of 0.69 then uprated by inflation factor of 132% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Recommendations

- Offer beta lactam monotherapy with piperacillin with tazobactam[17]. as initial empiric antibiotic therapy to patients with suspected neutropenic sepsis who need intravenous treatment unless there are patient-specific or local microbiological contraindications
- Do not offer an aminoglycoside, either as monotherapy or in dual therapy, for the initial empiric treatment of suspected neutropenic sepsis unless there are patient-specific or local microbiological indications.

Linking Evidence to Recommendations

The aim of this topic was to consider what was the most effective empiric intravenous antibiotic treatment of patients with neutropenic sepsis.

The GDG considered the outcomes of overall mortality, adverse effects and allocated treatment failure to be the most clinically relevant to the question. The adverse effects that the GDG considered included nephrotoxicity, the development of antibiotic resistance and development of *Clostridium difficile* infection. The GDG decided that overall mortality was more important than allocated treatment failure, based on available evidence from studies and current clinical practice. The overall quality of the evidence as classified by GRADE was 'moderate' in addressing mortality and treatment failure, and low or very low in relation to adverse effects.

To aid the GDG in making a recommendation they undertook a meta-analysis derived from data from published systematic reviews and using a mixed treatment comparison analysis. This demonstrated reduced mortality with empiric ureidopenicillin monotherapy, compared to carbapenem therapy or treatment with the addition of aminoglycosides, with reduced nephrotoxicity in this group. This was despite an increased chance of needing to alter therapy during the episode. Subgroups relating to age, cancer type and methodology of the studies included did not show significant differences in outcomes, and so were considered to support a universal recommendation. Additionally, concerns about the use of cephalosporins and their effect in promoting *Clostridium difficile* infection limited the recommended monotherapy to piperacillin with tazobactam. Local microbiological resistance patterns were also felt to be very important, as high rates of resistance to the chosen empiric agent could lead to treatment failure and avoidable mortality.

The GDG noted that patients with penicillin allergy would not be able to receive piperacillin with tazobactam. However the evidence appraised did not support recommending a specific alternative for this group of patients. The opinion of the GDG was that in this situation, clinicians would need to be able to use their clinical judgement – taking into account whether the allergy was severe (anaphylaxis, angio-oedema and bullous skin eruptions) in which case no beta-lactams should be given, or the more common adverse events of skin rash or nausea where an alternative beta-lactam may be considered. The GDG therefore did not make a specific recommendation on what empiric antibiotic therapy to give patients with a penicillin allergy.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. Both of these papers

[17] At the time of publication (September 2012) piperacillin with tazobactam did not have a UK marketing authorisation for use in children aged under 2 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The child's parent or carer should provide informed consent, which should be documented. See the GMC's Good practice in prescribing medicines – guidance for doctors and the prescribing advice provided by the Joint Standing Committee on Medicines (a joint committee of the Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group) for further information.

were partially applicable to the question, but both had serious limitations. The conclusion derived from these papers was that monotherapy can be cost effective compared to dual therapy.

The GDG considered the possible clinical scenarios for resource usage, potential costs of delivering excess drug, with intensive monitoring of aminoglycoside levels and subsequent costs of toxicity, against the potential reduced likelihood of resistance to both chosen empiric agents being present.

Therefore the GDG decided to recommend that patients with suspected neutropenic sepsis should be offered beta lactam antibiotic monotherapy with piperacillin with tazobactam as initial empiric treatment, unless there are local microbiological contraindications. They also agreed that aminoglycoside, either in mono or dual antibiotic therapy should not be used for the initial empiric treatment of patients with suspected neutropenic sepsis unless there are local microbiological indications.

6.3 Empiric glycopeptide antibiotics in patients with central venous access devices

Some patients with cancer have central venous access devices inserted to support long-term therapy and improve quality of life by reducing venepuncture and the risks of extravasation injury from vesicant and irritant cytotoxic infusions. They also facilitate the infusion of multiple therapies for example concurrent chemotherapy, parenteral nutrition and antibiotics.

Most protocols for neutropenic sepsis include specific guidance on the management of patients who have a central venous access device, to minimise the potential risk of life threatening bacteraemia originating from the device. There is usually an assessment of the likelihood of infection in or around the device and the addition of a more targeted antibiotic therapy if an infection of the device is suspected. Targeted antibiotic glycopeptide therapy is usually aimed at aerobic and anaerobic Gram-positive bacteria, including multi-resistant *Staphylococci*.

It has been suggested that, if there are no clear signs of device infection, the use of empiric glycopeptide antibiotics may be justified as external signs of device infection may be absent in immunocompromised patients

Patients who have no apparent sign of device infection at presentation can go on to have proven bacteraemia which requires glycopeptide therapy. The addition of a glycopeptide carries with it the possibility of further antibiotic related side effects.

Clinical question: In patients with a central venous access device with no external signs of line infection but with suspected neutropenia or neutropenic sepsis, what are the benefits and risks of adding vancomycin, teicoplanin or linezolid to first-line antibiotics?

Clinical evidence (see also full evidence review)

Evidence statements

The evidence for all outcomes is summarised in Table 6.6.

Short term mortality

Five studies reported short term mortality (de Pauw, *et al.,* 1990; EORTC, 1991; Ramphal, *et al.,* 1992; Molina, *et al.,* 1993; Novakova, *et al.,* 1991). There was very low quality evidence of uncertainty about the difference between antibiotics administered alone, and the same empiric antibiotics administered with the addition of glycopeptides, RR = 0.97 (95% CI 0.63 – 1.50) in four studies with1083 participants.

Critical care, length of stay and line preservation

These outcomes were not reported by any of the included studies.

Antibiotic resistance

Only one study reported antibiotic resistance (Novakova, *et al.,* 1991). Rates of resistance were very low in both groups (2/51 (4%) in the group who received empiric antibiotics alone and 0/52 (0%) in the group who received empiric antibiotics plus glycopeptides).

Proven Bacteraemia

Two studies with 150 participants reported proven bacteremia as an outcome (Del Favero, *et al.,* 1987; Novakova, *et al.,* 1991). There was very low quality evidence of uncertainty about whether antibiotics administered alone or empiric antibiotics administered with glycopeptides was more effective in terms of proven bacteraemia, RR = 0.80 (95% CI 0.42 – 1.53).

Nephrotoxicity

In five studies with 1160 participants, there was very low quality evidence of a significant difference between antibiotics administered alone, and the same empiric antibiotics administered with glycopeptides, with a greater number of individuals receiving the latter regimen experiencing nephrotoxicity, RR = 0.57 (95% CI 0.33 – 0.99).

Hepatic toxicity

Two studies with 856 participants reported hepatic toxicity as an outcome. There was very low quality evidence of a significant difference between empiric antibiotics administered alone, and antibiotics administered with the addition of glycopeptides. A greater number of individuals in the latter group experienced hepatic toxicity, RR = 0.53 (95% CI 0.33 – 0.99).

Table 6.6 GRADE profile: What is the role of empiric glycopeptide antibiotics (antibiotics chosen in the absence of an identified bacterium) in patients with central lines and suspected neutropenia or neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Empiric antibiotics only	Empiric antibiotics plus glycopeptides	Relative (95% CI)	Absolute	
All cause (short term) mortality											
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	Serious[3]	none	37/534 (6.9%)	39/549 (7.1%)	RR 0.97 (0.61 to 1.55)	2 fewer per 1000 (from 27 fewer to 38 more)	VERY LOW
Critical care											
0	no evidence available					none	-	-	-	-	
Line preservation/catheter remains in situ											
0	no evidence available					none	-	-	-	-	
Nephrotoxicity											
5	randomised trials	serious[1]	no serious inconsistency	serious[2]	Serious[3]	none	19/571 (3.3%)	34/589 (5.8%)	RR 0.57 (0.33 to 0.99)	14 fewer per 1000 (from 0 fewer to 22 fewer)	VERY LOW
Hepatotoxicity											
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	51/421 (12.1%)	90/435 (20.7%)	RR 0.53 (0.36 to 0.76)	57 fewer per 1000 (from 29 fewer to 78 fewer)	VERY LOW
Length of stay											
0	no evidence available					none	-	-	-	-	
Proven bacteremia											
2	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	29/77 (37.7%)	32/73 (43.8%)	RR 0.80 (0.42 to 1.53)	75 fewer per 1000 (from 218 fewer to 200 more)	VERY LOW
Antibiotic resistance											
0	no evidence available					none	-	-	-	-	

[1] Few studies were blinded. Sequence generation/allocation concealment were unclear in several studies.
[2] Only a proportion of the participants had a central venous access device. Unclear exactly how many.
[3] Low event rate.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Although this topic was identified as important for further health economic analysis, due to the large patient subgroup and potentially significant differences in costs of the interventions; the lack of directly relevant clinical and economic evidence meant that it was not possible to undertake further health economic analysis.

Recommendation

- Do not offer empiric glycopeptide antibiotics to patients with suspected neutropenic sepsis who have central venous access devices unless there are patient-specific or local microbiological indications

Linking Evidence to Recommendations

The aim of this topic was to identify the benefits and risks of adding vancomycin, teicoplanin or linezolid to first line antibiotics in patients with a central venous access device with no external signs of line infection but with suspected neutropenia or neutropenic sepsis.

The GDG considered the outcomes of death, critical care, length of stay, line preservation (device remains *in situ*), antibiotic resistance, proven bacteraemia and toxicity to be the most clinically relevant to the question. No evidence was reported for critical care, length of stay or line preservation. Evidence was available for proven bacteraemia, toxicity, antibiotic resistance and death which was reported as short term mortality. They also considered an additional outcome reported by the evidence of the presence of a super-infection, as this was also relevant to the question.

The GDG noted that there was very little evidence available for this topic. The evidence that was available was assessed by GRADE as being of 'low' quality for all outcomes due to imprecision (low number of events) and indirectness (only one study reported on patients with a central line, and the standard empiric drugs used in the available studies are no longer recommended in clinical practice).

The GDG noted that the evidence had shown no significant difference in the incidence of death or proven bacteraemia between antibiotics administered alone or antibiotics administered with the addition of a glycopeptide. In addition, the GDG were aware that the evidence had shown increased harms such as kidney and liver toxicity from the empiric use of glycopeptide antibiotics. They also noted that there is no available evidence to show that not using glycopeptide antibiotics has any detrimental effect on line preservation.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The GDG based on their clinical experience considered that there may be potential cost savings from stopping the use of empiric glycopeptide antibiotics in this setting along with a reduction in therapeutic drug monitoring costs.

Given the lack of evidence of clinical benefit and the evidence of increased harms, the GDG recommended that empiric glycopeptide antibiotics should not be used in patients with a central venous access device.

6.4 Indications for removing central venous access devices

Tunnel, intra-luminal or pocket infections associated with a central venous access device are potentially life threatening complications, with a heightened risk in immunocompromised patients. Such infections require prompt intervention to prevent morbidity and mortality which may include the need to remove the device. Should the device need to be replaced there is a risk and inconvenience to the patient and also cost implications.

Clinical question: Which patients with central venous access devices and neutropenic sepsis will benefit from removal of their central line?

Clinical evidence (see also full evidence review)

Study quality and results

The evidence was of very low quality because there was a lack of studies comparing criteria for central line removal. Instead studies reported outcomes according to the site of the infection or infecting micro-organism. All 14 included studies were observational of which five were prospective. Six studies included only children or teenagers, nine studies included a majority of patients with haematological cancers and five studies reported results only for patients with presumed central venous catheter related infections.

Evidence statements

Mortality

No studies considered prognostic factors for overall survival, but some reported infectious mortality.

Two studies (Al Bahar, *et al.,* 2000; Elishoov, *et al.,* 1998) reported infectious mortality according to the site of infection. All 16 cases of infectious mortality were associated with bacteraemia or fungaemia and there were no cases of infectious mortality attributed to tunnel or exit site infections.

Elishoov, *et al.,* (1998) reported ten occurrences of infectious mortality according to the infecting microorganisms. Microorganisms associated with infectious mortality were coagulase negative *Staphylococcus aureus* (1 infectious mortality in 29 infections), *Streptococcus viridans* (1/3), *Pseudomonas aeruginosa* (4/13), Candida species (2/10). There were 2 polymicrobial infectious deaths involving *Escherichia coli, Enterococcus faecalis*, *Klebsiella pneumoniae* and *Proteus vulgaris* in one case and *Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae* in another.

Park, *et al.,* (2010) reported 2 infectious deaths in a series of 48 cases of catheter-related *Staphylococcus aureus* bacteraemia.

Length of hospital stay, duration of fever and duration of antibiotics

None of the included studies reported length of hospital stay.

Millar, *et al.,* (2011) considered prognostic factors for length of the febrile episode in a prospective multicentre study of children with central venous catheters and fever. The febrile neutropenia episode was longer in patients with fever, rigors and chills (FRC): HR 0.49 (95% CI 0.27 - 0.88), than in those without FRC. Children infected with pathogens (organisms which would normally prompt central venous catheter removal such as *Staphylococcus aureus* or *Pseudomonas aeruginosa*) had longer febrile episodes than children without microbiologically documented infections: HR 0.48 (95% CI 0.19 - 1.17).

Similarly children infected with organisms typically treated with antibiotic lock or skin bacteria had longer febrile episodes than children without microbiologically documented infections: HR 0.57 (95% CI 0.38 - 0.84).

The total duration of IV treatment was 3.61 times longer in patients with FRC (95% CI 0.55 - 6.68) than without, 4.39 times longer in patients with pathogenic organisms (95% CI -0.39 - 9.18) than those without microbiologically documented infections and 2.99 times longer in patients with other organisms or skin bacteria than in those without microbiologically documented infections (95% CI 0.91 - 5.08).

Line preservation

Several studies (Viscoli, *et al.,* 1988, Junqueria, *et al.,* 2010, Holloway, *et al.,* 1995, Al Bahar., *et al.,* 2000, Hartman, *et al.,* 1987, Elishoov, *et al.,* 1998 and Hanna, *et al.*, 2004) reported whether or not the central venous catheter was removed according to the site of infection. Central venous catheters were often preserved in those with exit site infection or bacteraemia, but were removed in all but one case of tunnel infection.

In Millar *et al.,* (2011) the presence of fever, rigors, chills and/or hypotension was associated with a greatly increased likelihood of central venous catheter removal, HR=16.39 (95% CI. 4.73 - 56.79).

Park, *et al.,* (2010) reported the outcome of attempted Hickman catheter salvage in 33 patients with presumed catheter-related *Staphylococcus aureus* bacteraemia. Several factors were associated with an increased chance of salvage failure: external signs of infection (tunnel or exit-site infection), positive follow up blood cultures (at 48 to 96 hours) and methicillin resistance (at a statistical significance level of $P<0.05$). Catheter salvage failed in both patients with septic shock in this study.

Joo, *et al.,* (2011) reported the outcome of attempted catheter salvage in 38 patients with a central venous catheter related infection. There was a greater proportion of Gram-negative bacteria in the salvage failure group (8/18) than in the successful salvage group (2/20), ($P=0.027$). The majority of the successful central venous catheter salvage attempts (13/20) were in patients with coagulase negative *Staphylococcus* infections.

Millar, *et al.,* (2011) found in children infected with pathogens traditionally leading to central venous catheter removal, the time to central venous catheter removal was much shorter than when there was no microbiologically documented infection (HR 25.71; 95% CI 4.27 - 154.7). If the child was infected with a microorganism usually treated with antibiotic lock or a skin bacteria, the time to central venous catheter removal was also shorter than if there was no microbiologically documented infection (HR 8.40; 95% CI 2.01 - 35.14).

Infection-control complications

This outcome was not reported in the included studies.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. Further health economic analysis was not undertaken as the topic did not lend itself to economic evaluation as there was no comparative analysis of cost and outcomes

Recommendation

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

Linking Evidence to Recommendations

The aim of this topic was to identify if patients with central venous access devices and neutropenic sepsis would benefit from the immediate removal of their central line.

The GDG considered the outcomes of mortality, severe sepsis, length of stay, duration of fever, line preservation and complications to be the most clinically relevant to the question. No evidence was reported for overall mortality, severe sepsis, length of stay or complications. Evidence was available for duration of fever, line preservation and duration of antibiotics. The GDG considered the additional outcome of infectious mortality as a surrogate marker for overall mortality. The reported evidence for duration of fever and duration of antibiotics was not considered useful by the GDG as it did not relate to empiric management.

The evidence for all outcomes was 'low' quality. The GDG acknowledged that the available evidence was indirect as it focused on targeted rather than empiric management and would therefore need to be extrapolated backwards. The GDG also noted that the number of events reported in the data was low, and the studies investigated disparate practice, making it difficult to compare and draw meaningful conclusions.

From the available evidence, the GDG were unable to identify a group of patients that would benefit from the removal of their central lines during the empiric phase of treatment. They considered that not removing a line would have the benefit of maintaining venous access during a period of acute illness, together with a reduction in possible traumatic or invasive interventions.

The GDG noted that not removing a line might be associated with an increased risk of complications from a central line infection such as severe sepsis. The GDG recognised that there will be some patients with uncontrolled infection where there is a strong clinical suspicion of a central line infection, who may require central line removal. The management of specific infections is outside the scope of the guideline. The GDG emphasised that this would only relate to a small proportion of episodes, and have used the phrased "initial" empiric management to indicate that line removal should not be the first response in every patient with a central line. The opinion of the GDG was that the benefits from not removing the line outweigh any risks associated with removing the central line empirically.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG was that there may be potential additional costs associated with extending treatment in those patients who have a proven line infection. However the GDG also noted that there may be potential cost savings by avoiding the replacement of central lines. The GDG were unable to determine whether the costs and savings would balance but believed that the clinical benefits far outweigh any potential increase in costs.

Therefore the GDG recommend that central venous access devices should not be removed as part of the initial empiric treatment of patients with neutropenic sepsis.

6.5 Inpatient versus outpatient management strategies

Not all patients with neutropenic sepsis are at the same risk of developing severe sepsis and treatment and location of treatment may be tailored according to risk factors and other circumstances. (Section 4.3)

Ambulatory care strategies as an alternative to inpatient treatment have been proposed for those patients at low risk of complication. Such strategies include intravenous as well as oral antibiotic regimens. The advantages of ambulatory care are obvious. Most patients prefer to be treated at home, the risks of hospital acquired infections are reduced and there are potential cost and resource savings. On the other hand, some ambulatory care strategies may be resource intensive and some patients prefer the reassurance of inpatient care. Additionally, where the ambulatory care strategy uses a different antibiotic there may be an increased risk of treatment failure compared with inpatient treatment.

Clinical question: Is there any difference between the outcome of patients with neutropenic sepsis managed in hospital and those managed as outpatients?

Clinical evidence (see also full evidence review)

The evidence for all outcomes is summarised in Table 6.7 and Table 6.9.

Evidence statements

Short term mortality

Low quality evidence from seven randomised trials (reviewed in Teuffel, *et al.,* 2011), showed no statistically significant difference in the 30 day mortality of inpatients and outpatients, RR 1.11 (95% C.I. 0.41 to 3.05). Low quality evidence from eight randomised trials found no statistically significant difference in 30 day mortality according to route of drug administration in the outpatient setting (intravenous versus oral), but no patients died in these studies

Critical care

Critical care was not considered as an outcome by the Teuffel, *et al.,* (2011), systematic review. However critical care events were probably included in the composite outcome of treatment failure. Which was defined as one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms; any addition to, or modification of the assigned intervention, including readmission.

Low quality evidence from six randomised trials showed no significant difference between the rate of treatment failure of inpatients and outpatients RR = 0.81; (95% CI 0.55 - 1.19).
Low quality evidence from eight randomised trials showed no association between route of drug administration in the outpatient setting (intravenous versus oral) and treatment failure, RR 0.93 (95% CI 0.65 –1.32)).

Three of the six studies comparing inpatient to outpatient treatment reported critical care admission. No patients were admitted to ICU in these studies (350 episodes). Four of the eight studies of outpatient IV versus outpatient oral antibiotics reported critical care admission. No patients were admitted to ICU in these studies (520 episodes).

Length of stay

Only three studies comparing inpatient to outpatient management reported length of stay in the inpatient group. Means were reported as 4.41 days, range 2 – 8 (Innes, *et al.,* 2003), 10.4 days, range 7-19 (Ahmed et al 2007) and 5.3 days, range 3-9 (Santolaya, *et al.,* 2004). Length of stay was not a relevant outcome in studies considering only outpatients.

Hospital readmission (outpatients)

Low quality evidence from four studies (Rubenstein *et al.,* 1993; Gupta *et al.,* 2009 and Paganini *et al.,* 2000,2003) suggested that hospital readmission was less likely in patients treated with outpatient intravenous therapy than in those who received outpatient oral therapy, RR 0.46 (95% CI 0.22 - 0.97).

Quality of life

Quality of life was not considered as an outcome by the Teuffel, *et al.,* (2011), a systematic review, and none of the included studies reported quality of life. A later study (Talcott, *et al.,* 2011) reported results from subscales of the EORTC QLQ C-30. Moderate quality evidence suggested that role function (ability to carry out typical daily activities) increased more for hospitalised patients than home care patients (mean change 0.78 versus 0.58 respectively, $P = 0.05$). Moderate quality evidence showed emotional function scores declined for hospitalised patients but increased for home care patients (mean change -6.94 versus 3.27; $P = 0.04$). No other QLQ-C30 subscale differences were evident but the data for these subscales were not reported.

Table 6.7 GRADE profile: Is inpatient management more effective than outpatient management for patients with neutropenic sepsis

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Inpatient treatment**	**Outpatient treatment**	**Relative (95% CI)**	**Absolute**	
30 day mortality											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/365 (1.9%)	6/377 (1.6%)	RR 1.11 (0.41 to 3.05)	2 more per 1000 (from 9 fewer to 33 more)	LOW
Treatment failure (death; persistence, recurrence or worsening of clinical signs or symptoms; any addition to, or modification of the assigned intervention, including readmission)											
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/363 (10.7%)	50/375 (13.3%)	RR 0.81 (0.55 to 1.19)	25 fewer per 1000 (from 60 fewer to 25 more)	LOW
Critical care											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/174 (0%)	0/176 (0%)	Not estimable	-	LOW
Hospital readmission - not reported											
0[3]	-	-	-	-	-	none	-	-	-	-	
Length of stay - not reported											
0[3]	-	-	-	-	-	none	-	-	-	-	
Quality of life (measured with: EORTC QLQ C-30 Role Function subscale; Better indicated by higher values)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	50	-	MD 0.20 higher (C.I. not reported)	MODERATE
Quality of life (measured with: EORTC QLQ C-30, Emotional Function subscale; Better indicated by higher values)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	50	-	MD 10.21 lower (C.I. not reported)	MODERATE

[1] Few studies used adequate sequence generation and concealment; none of the studies were blinded; few reported ITT analysis
[2] Low event rate
[3] Not a relevant comparison in studies of inpatient vs. outpatient management
[4] Trial stopped early due to poor accrual

Table 6.8 GRADE profile: Is outpatient oral antibiotic treatment more effective than outpatient intravenous antibiotic treatment

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient IV antibiotic treatment	Outpatient oral antibiotic treatment	Relative (95% CI)	Absolute	
30 day mortality											
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/426 (0%)	0/431 (0%)	Not estimable	-	LOW
Treatment failure											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/426 (16.7%)	80/431 (18.6%)	RR 0.93 (0.65 to 1.32)	13 fewer per 1000 (from 65 fewer to 59 more)	LOW
Critical care											
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/256 (0%)	0/264 (0%)	Not estimable	-	LOW
Hospital readmission											
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/299 (3.3%)	22/308 (7.1%)	RR 0.46 (0.22 to 0.97)	39 fewer per 1000 (from 2 fewer to 56 fewer)	LOW
Length of stay											
0	no evidence available					none	-	-	-	-	
Quality of life											
0	no evidence available					none	-	-	-	-	

[1] Few studies used adequate sequence generation and concealment; none of the studies were blinded; few reported ITT analysis
[2] Low event rate

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses identifed two Canadian studies (Teuffel, *et al.,* 2010; Teuffel, *et al.,* 2011b) comparing the cost-effectiveness of inpatient care with ambulatory management strategies. The results of both studies are summarised in Table 6.10.

As there was no definition of what constitutes a specific inpatient management strategy for this question, costing and evaluating health outcomes using economic modelling was not feasible. The GDG anticipated that the different management strategies were unlikely to result in large differences in patient outcomes and those strategies that minimise or reduce the duration of inpatient care would generally be less costly. Given that there was little uncertainty surrounding the economics of this question, further health economic analysis was not undertaken.

Study quality and results

Both papers were deemed partially applicable to the guideline because they were conducted in Canada, not the UK. The quality of life data reported by Teuffel, *et al.,* (2010) was derived from cancer patients who did not have direct experience of neutropenic sepsis.

Both papers were deemed to have minor limitations because of two reasons:

- The estimates of resource use were not derived from a recent well-conducted systematic review (but were similar in magnitude to the best available estimates)
- Structural sensitivity analysis was not conducted.

Evidence statements

Teuffel, *et al.,* (2010) looked at adult cancer patients with a first episode of low-risk febrile neutropenia; while Teuffel, *et al.,* (2011b) looked at paediatric cancer patients with a low-risk of febrile neutropenia who were receiving standard-dose chemotherapy. Both studies investigated four inventions:

- Home IV (entire outpatient management with intravenous antibiotics)
- Hospital IV(entire treatment in hospital with intravenous antibiotics)
- Early DC (early discharge strategy consisting of 48 hours inpatient observation with intravenous antibiotics, subsequently followed by oral outpatient treatment)
- Home PO (entire outpatient management with oral antibiotics).

Effectiveness data came from formal systematic review and meta-analysis. Outcomes were reported in terms of ICER or QAFNE (quality-adjusted febrile neutropenia episode). Teuffel, *et al.,* (2010) found that Home IV was more effective and less expensive than all other strategies. Teuffel, *et al.,* (2011b) found that Home IV was more effective and less expensive than Home PO and Hospital IV; however it was less effective than Early DC. The ICER of Early DC was £76,968.01 per quality-adjusted febrile neutropenia episode, compared to Home IV.

Table 6.9 Modified GRADE profile: Inpatient versus Ambulatory care (all different forms)

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
Teuffel, *et al.*,2010	Minor limitations [1]	Partially applicable[2]	An adult cancer patient with a first episode of low-risk febrile neutropenia.	HospIV(entire treatment in hospital with intravenous antibiotics)	Home IV (Entire outpatient management with intravenous antibiotics)	£6249.85[3]	-0.011333333 QALYs	Dominated	Results were sensitive to several event probabilities, utilities and costs. Beyond certain thresholds, the best strategy changed from HomeIV to the Home PO strategy. However, Hosp IV or Early DC management were never the preferred strategy in sensitivity analysis.
				EarlyDC (Early discharge strategy consisting of 48 hours inpatient observation with intravenous antibiotics, subsequently followed by oral outpatient treatment)	Home IV (Entire outpatient management with intravenous antibiotics)	£1930.72[3]	-0.011083333 QALYs	Dominated	
				HomePO (entire outpatient management with oral antibiotics)	Home IV (Entire outpatient management with intravenous antibiotics)	£98.79[3]	-0.002833333 QALYs	Dominated	
Teuffel., *et al.,* 2011 (b)	Minor limitations[4]	Partially applicable[5]	Paediatric cancer patient (hypothetical cohort) with low-risk of febrile neutropenia who were receiving stand-dose chemotherapy.	HomePO (entire outpatient management with oral antibiotics)	Home IV (Entire outpatient management with intravenous antibiotics)	£1558.60[6]	-0.1098 QAFNE (QAFNE= quality-adjusted febrile neutropenia episode)	Dominated	Results were sensitive to costs for a home care nurse per visit, duration of outpatient treatment, utility for HomeIV, and utility for HomePO. Beyond certain thresholds, superiority changed from the HomeIV to the HomePO strategy. On the contrary, there was no variable identified that changed the dominance from

Quality assessment			Summary of findings						
Study	**Limitations**	**Applicability**	**Population**	**Intervention**	**Comparator**	**Incremental cost (2011 £)**	**Incremental effects**	**ICER**	**Uncertainty**
				EarlyDC (Early discharge strategy consisting of 48 hours inpatient observation with intravenous antibiotics, subsequently followed by oral outpatient treatment)	Home IV (Entire outpatient management with intravenous antibiotics)	£3153.95[6]	0.0209 QAFNE	£76968.01[6] per QAFNE	
				HospIV (entire treatment in hospital with intravenous antibiotics)	Home IV (Entire outpatient management with intravenous antibiotics)	£8193.27 [6]	-0.0345 QAFNE	Dominated	

[1] The estimates of resource use were not derived from a recent well-conducted systematic review, but is similar in magnitude to the best available estimates. Structural sensitivity analysis was not conducted.
[2] This study was not conducted in the UK. Utility data was derived from cancer patients who might don't have direct experience of neutropenic sepsis.
[3] Converted from 2009 Canadian dollars using a PPP exchange rate of 0.55 then uprated by inflation factor of 106% (http://eppi.ioe.ac.uk/costconversion/default.aspx).
[4] The estimates of resource use were not derived from a recent well-conducted systematic review, but is similar in magnitude to the best available estimates. Structural sensitivity analysis was not conducted. The value of health effects expressed in terms of quality-adjusted life years (QALYs).
[5] This study was not conducted in the UK. Utility data was derived from parents of children who might don't have direct experience of neutropenic sepsis. 1-(1-VAS) was used instead of EQ-5D.
[6] Converted from 2009 Canadian dollars using a PPP exchange rate of 0.55 then uprated by inflation factor of 106% (http://eppi.ioe.ac.uk/costconversion/default.aspx).

Recommendation

- Consider outpatient antibiotic therapy for 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.

Linking Evidence to Recommendations

The aim of this topic was to see if there is any difference between the outcomes of patients with neutropenic sepsis who are given antibiotics in hospital compared to those given antibiotics at home.

The GDG considered the outcomes of death within 30 days, critical care, clinically documented infection, length of stay, hospital re-admission and quality of life to be the most clinically relevant outcomes that would benefit patient care. No evidence was found for critical care, clinically documented infection or quality of life. Evidence was reported for mortality (30 days), hospital re-admission and length of stay. The GDG also considered an additional outcome reported by the evidence of treatment failure (a composite outcome of readmission and modification of antibiotics), which showed no significant association between outpatient management, drug administration and treatment failure. The GDG noted that the evidence was classified by GRADE as being of 'low' to 'moderate' quality.

The GDG acknowledged that the available data was limited due to the low event rate, very few patients experiencing adverse outcomes, and also the study design, (few studies used adequate sequence generation and concealment and none of the studies were blinded, few reported intention to treat analysis). The GDG also noted that the risk of treatment failure for this patient population was low, and providing they have been properly risk assessed the risk of death was minimal.

The GDG noted that there was a potential risk of treatment failure and death in the low risk population but this was minimal in the evidence. However it was the clinical opinion of the GDG that the benefits of offering outpatient antibiotic therapy would improve a patient's quality of life. Choice of antibiotics will be influenced by prior prophylaxis. One clinical indication not to offer oral antibiotics may be the use of prophylactic quinolones. For those patients without prior prophylaxis oral antibiotic regimes with a quinolone and/or co-amoxiclav have been most frequently used.

The GDG noted that no additional economic analysis had been undertaken in this area. A literature review of published cost-effectiveness analyses identified two relevant papers, both of which were partially applicable to the question. These studies had minor limitations and concluded that IV antibiotics administered at home was the most cost-effective regimen. However the GDG noted that these studies were based on once daily administration of an antibiotic that is not available in the UK.

The GDG recognised that some patients would not be suitable for out patient therapy due to their clinical and social circumstances, for example those patients who are not thought to recognise there illness or are able to return to hospital. Therefore the GDG decided to recommend that patients at low risk of severe sepsis can be considered for outpatient antibiotic therapy but did not specify a route of administration.

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7 Subsequent treatment

The challenge in the subsequent treatment of the patient with neutropenic sepsis is to decide if and when to discontinue or change the empiric clinical care.

The objectives of this chapter are:

- To determine the benefit of altering empiric treatment in unresponsive fever.
- To determine the optimal time to switch from intravenous to oral antibiotics
- To determine the optimal duration of inpatient care.
- To determine the optimal duration of empiric antibiotic treatment.

7.1 Changing the initial empiric treatment in unresponsive fever

Some patients admitted to hospital with neutropenic sepsis continue to have fever, despite being treated with initial empiric antibiotics.

There are concerns that patients with unresponsive fever have an unidentified but resistant bacterial infection; this has led to a strategy of changing the empiric antibiotic after a period of time, varying between 24 and 96 hours.

The advantage to this approach is that unresponsive infection may be treated earlier. The disadvantages are that this may be unnecessary, may promote antibiotic resistance and could expose patients to the side effects of extra antibiotics and increase hospital resource usage.

Clinical question: What is the optimal time to change the initial empiric treatment in unresponsive fever?

Clinical evidence (see also full evidence review)

Evidence statements

Mortality

There was very low quality evidence from four studies (Cometta *et al.,* 2003; EORTC, 1989; Erjavec *et al.,* 2000 and Pizzo *et al.,* 1982) about when to change empiric antibiotics in patients with unresponsive fever (Table 7.1). No study compared changing empiric therapy at two different time points. Patients (N=461) with persistent fever were randomised to either remain on the empiric antibiotic or to primary treatment with the addition of another agent. No study detected a significant difference between the short term mortality of those who changed treatment and those who remained on the initial empiric treatment.

Critical care, quality of life and length of stay

The included studies did not report these outcomes.

Duration of fever

There was very low quality evidence about this outcome and none of the studies reported the influence of time of treatment change. Pizzo, *et al.,* (1982) and Cometta, *et al.,* (2003) reported shorter median time to defervesence in patients whose empiric therapy was changed (8 versus 6 days and 4.3 versus 3.5 days respectively), but there was no statistically significant difference. Erjavec, *et al.,* (2000) reported similar rates of defervesence within 72 hours in patients who did or did not change empiric treatment.

Table 7.1 GRADE profile: What is the optimal time to change the primary empiric treatment in unresponsive fever

Quality assessment						Summary of findings					
						No of patients			Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	No empiric antibiotic	Empiric antibiotic ± placebo	Antibiotic & additional drug	Relative RR (95%CI) P value	Absolute effect	
Mortality Pizzo, *et al.,* (1982)											
1	randomised trial	v. serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	5	5	2	-	-	VERY LOW
Median time to defervescence (range). Pizzo, *et al.,* (1982)											
1	randomised trial	v. serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	11 days (3-22 days)	8 days (3-23 days)	6 days (2-20 days)	-	-	VERY LOW
Mortality (within 30 days). EORTC International anti-microbial therapy co-operative group (1989)											
1	randomised trial	serious limitations[3]	N/A	no serious indirectness	serious imprecision[4]	-	14	11	P=0.04	-	VERY LOW
Median time to defervescence (95%CI). Cometta, *et al.,* (2003)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	serious imprecision[5]	-	4.3 days (3.5-5.1 days)	3.5 days (2.4-4.4 days)	P=0.75	-	LOW
Mortality between days 14 and 31. Cometta, *et al.,* (2003)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	serious imprecision[5]	-	8/79	4/86	RR=0.46 (0.15-1.38) P=0.29	-	LOW
Defervescence within 72 hours. Erjavec, *et al.,* (2000)											
1	randomised trial	serious limitations[6]	N/A	no serious indirectness	serious imprecision[4]	-	27/58	25/56	RR=0.96 (0.64-1.43) P=0.98	-	VERY LOW
Mortality whilst aplastic. Erjavec, *et al.,* (2000)											
1	randomised trial	serious limitations[6]	N/A	no serious indirectness	serious imprecision[4]	-	4/58	6/56	RR=1.55 (0.49-4.98) P=0.70	-	VERY LOW

[1] No mention of allocation concealment; randomisation method not discussed; blinding not apparent.
[2] Low patient numbers and/or event rates.
[3] No mention of allocation concealment; randomisation method not discussed; blinding of assessment may have occurred but not of treatment.
[4] Low patient numbers and/or event rates.
[5] Low patient numbers and /or event rates. Trial terminated early.
[6] No mention of allocation concealment, scant details of randomisation of treatment.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. This topic focused on the optimal timing of a change in management strategy. The difference between strategies were considered unlikely to lead to large differences in cost, but rather be guided by differences in patient outcomes and other considerations such as service configuration that. It was agreed that these considerations would probably be difficult to accurately capture using economic modelling and therefore further health economic analysis was not undertaken.

Recommendations

- For patients with confirmed neutropenic sepsis and a high risk of developing septic complications, a healthcare professional with competence in managing complications of anticancer treatment should daily:
  - review the patient's clinical status
  - reassess the patient's risk of septic complications using a validated risk scoring system[18]
- Do not switch initial empiric antibiotics in patients with unresponsive fever unless there is clinical deterioration or a microbiological indication.

Linking Evidence to Recommendations

The aim of this topic was to identify the optimal time to change the initial empiric treatment in unresponsive fever.

The GDG considered that the outcomes of over-treatment, death/critical care, length of stay, duration of fever and quality of life were clinically relevant to the question. No studies reported length of stay, the incidence of over-treatment or patients' quality of life. Limited evidence was available on mortality. Duration of fever was reported as an outcome but it was inconsistent and imprecise, and the GDG did not think this outcome was useful in agreeing recommendations.

The GDG noted that the evidence was classified by GRADE as being of 'low' or 'very low' quality. None of the studies dealt adequately with the methods of randomisation, allocation or blinding and, although some authors stated that appropriate statistics had been used for data analysis, the details were sometimes scant or absent and very few outcomes had more than a probability value reported.

The GDG were aware that there is a perception that empiric antibiotics should be changed after 48 hours in patients with unresponsive fever. However they noted that the evidence had not demonstrated a significant difference between patients kept on initial empiric antibiotics and those given an additional or different drug or drugs. The GDG also considered that it was important to prevent unnecessary extra treatment in this group of patients, which would reduce the risk of side effects associated with receiving additional drugs.

The GDG noted that consideration would have to be given to other causes of infection or fever but making recommendations on this was outside the scope of the guideline.

[18] Examples of risk scoring systems include 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG was that there would probably be cost savings associated with reducing over-treatment and the corresponding reduction of adverse effects, in addition to cost savings from the early interventions in patients developing septic complications.

Therefore the GDG decided to recommend that empiric antibiotics should not be changed unless there was a clinical deterioration or a microbiological indication. However the GDG were concerned that this recommendation could result in patients not receiving proper clinical and laboratory surveillance. They therefore made an additional recommendation based on their clinical experience that the clinical status of the patient should be reviewed daily to prevent this from happening. The GDG noted from the evidence on paediatric risk assessment tools (section 4.3 & 7.3) that reassessment using a validated tool was an effective way of identifying those at low risk of septic complications. The GDG felt it was appropriate to extrapolate the data to the adult setting.

7.2 Switching from intravenous to oral antibiotic treatment

Empiric antibiotic treatment for patients with neutropenic sepsis is, by definition, given without a microbiological diagnosis. If an organism is subsequently identified, the treatment regimen and duration can be adjusted appropriately. However, for a substantial proportion of patients, ongoing treatment remains empiric. These individuals may have an undetected bacterial infection or could be unwell for other reasons. Policies for neutropenic sepsis typically recommend treatment to continue with empiric antibiotics for a predetermined length of time after resolution of the fever or symptoms or neutrophil recovery.

Almost all currently used empiric antibiotic regimens comprise of intravenous drugs with a broad microbiological spectrum given in multiple daily doses. Treatment is heavily dependant on resources such as nursing time and likely to have to be administered in hospital. Strategies have been devised to allow step-down from empiric intravenous to empiric oral antibiotics. The decision as to who should receive such treatment is based on specific clinical criteria, pre-treatment risk scores and response to current treatment. The advantages of a step-down approach are reduced need for nursing time, the possibility of treatment at home and reduced drug costs. On the other hand there are risks of failure if treatment is stepped down too soon and potential complications with oral antibiotics, such as diarrhoea and infection with *Clostridium difficile*.

Clinical question: When is the optimal time to switch (step down) from intravenous to oral antibiotic therapy?

Clinical evidence (see also full evidence review)

Evidence statements

Death or critical care

Very low quality evidence from a Cochrane review (Vidal, *et al.,* 2004, Table 7.2) suggested uncertainty about the relative effectiveness of the two treatment strategies for IV-to-oral versus IV-only the relative risk of short term mortality was 1.14 (95% CI 0.48 - 2.73). Critical care was not included as an outcome in any of the included studies, although one study (Paganini *et al.*, 2003) did report that none of their patients required admission to the intensive care unit.

Overtreatment, length of stay and quality of life

These outcomes were not reported in any of the included studies.

Duration of fever / treatment failure

Duration of fever was not reported in the systematic review (Vidal, *et al.,* 2004). Three of the included trials reported this outcome but none of these reported a statistically significant difference in the duration of fever between treatment groups.

Vidal, *et al.,* (2004) reported treatment failure as a composite outcome comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention. Low quality evidence suggested no significant difference in the rate of treatment failure in the IV-to-oral group compared to the IV only group, RR 1.07 (95% C.I. 0.9 to 1.27).

Table 7.2 GRADE profile: When is the optimal time to switch from intravenous to oral antibiotic therapy for patients with neutropenic sepsis.

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV-to-oral antibiotics at any time	IV antibiotics	Relative (95% CI)	Absolute	
Death (in trials where IV to oral switch was at any time)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/442 (2.5%)	8/422 (1.9%)	RR 1.14 (0.48 to 2.73)	3 more per 1000 (from 10 fewer to 33 more)	VERY LOW
Treatment failure (composite measure[3]; in trials where IV to oral switch was at any time)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	158/482 (32.8%)	137/464 (29.5%)	RR 1.07 (0.9 to 1.27)	21 more per 1000 (from 30 fewer to 80 more)	LOW
Death (in trials where IV to oral switch was after 72 hours of IV antibiotics following response to antibiotics)											
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/173 (6.4%)	8/152 (5.3%)	RR 1.14 (0.48 to 2.73)	7 more per 1000 (from 27 fewer to 91 more)	VERY LOW
Treatment failure (in trials where IV to oral switch was after 72 hours of IV antibiotics following response to antibiotics)											
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	98/180 (54.4%)	87/162 (53.7%)	RR 1.01 (0.83 to 1.23)	5 more per 1000 (from 91 fewer to 124 more)	LOW
Death (in trials where IV to oral switch was after 48-72 hours of IV antibiotics)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	0/174 (0%)	0/180 (0%)	Not estimable	-	VERY LOW

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	IV-to-oral antibiotics at any time	IV antibiotics	Relative (95% CI)	Absolute	
Treatment failure (in trials where IV to oral switch was after 48-72 hours of IV antibiotics)											
2	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	29/174 (16.7%)	29/180 (16.1%)	RR 1 (0.64 to 1.56)	0 fewer per 1000 (from 58 fewer to 90 more)	VERY LOW

[1] The designs of the included trials were both compromised either by providing no information about the method of randomisation and about whether allocation concealment or blinding was used or by not using intention to treat analysis
[2] Low number of events
[3] Treatment failure defined as a composite end-point comprising one or more of the following: death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention.
[4] There were no events in either trial.

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. This topic focused on the optimal timing of a change in management strategy. The difference between strategies were considered unlikely to lead to large differences in cost, but rather be guided by differences in patient outcomes and other considerations such as service configuration. It was agreed that these considerations would probably be difficult to accurately capture using economic modelling and therefore further health economic analysis was not undertaken.

Recommendation

- Switch from intravenous to oral antibiotic therapy after 48 hours of treatment in patients whose risk of developing septic complications has been reassessed as low by a healthcare professional with competence in managing complications of anticancer treatment using a validated risk scoring system[19].

Linking Evidence to Recommendations

The aim of this topic was to identify when is the optimal time to switch (step down) from intravenous to oral antibiotic therapy.

The GDG considered the outcomes of over treatment, critical care, length of stay and quality of life to be clinically relevant to the question. No evidence was available for any of the outcomes required. Limited evidence was found relating to duration of fever. The available evidence largely reported an outcome of treatment failure, which was a composite outcome comprising one or more of death; persistence, recurrence or worsening of clinical signs or symptoms of presenting infection; any addition to or modification of the assigned intervention. The GDG agreed that this was an important and relevant outcome and used this as the basis for their recommendation.

The overall quality of the evidence classified by GRADE was ‘low’ for addressing mortality and treatment failure, and ‘very low’ in relation to adverse outcomes.

The GDG noted that mortality for patients switching to oral antibiotics was low and equivalent to that of patients receiving intravenous antibiotics. In addition, the clinical experience of the GDG was that switching to oral antibiotics would probably be beneficial to patients because they would spend less time in hospital and have reduced exposure to broad spectrum IV antibiotics – with a corresponding reduction in side effects and risk of developing antimicrobial resistance.
The GDG also noted that the evidence only included patients who had been classified as low risk at the time of the decision to switch to oral antibiotics. The clinical experience of the GDG was that switching to oral antibiotics was not appropriate for patients at high risk of complications. The GDG recognised that in studies which undertook an early switch patients were more likely to have treatment failure than those with a later time of switch. Based on their clinical experience the GDG agreed that most adverse events would be clinically apparent within the first 48 hours of admission, so there would be less risk associated with switching after this time.

The recommendations allow for stepping down to oral antibiotics with or without discharge of patients. This is because while most patients who could be discharged early are able to tolerate oral antibiotics, some may have a specific contraindication which requires IV

[19] Examples of risk scoring systems include 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

antibiotics. The social circumstances of some patients may mean they are not able to be discharged but are still able to step down to less resource intensive regimens for example oral antibiotics.

The GDG noted that a literature review of published cost effectiveness analyses identified one relevant paper, however this paper was excluded due to serious selection bias. No additional economic analysis had been undertaken. The GDG agreed based on their opinion that a continued intravenous strategy would probably be more costly than switching to oral antibiotics.

Therefore the GDG decided to recommend that patients who have reassessed as being low risk of severe sepsis using a validated risk scoring system should switch to oral antibiotics after 48 hours. Since the studies appraised did not show striking differences in outcomes according to age, the GDG decided not to make a separate recommendation for children. The GDG were aware that local microbiological resistance patterns vary and choice of antibiotics may be influenced by prior quinolone prophylaxis. Consequently they were unable to recommend a specific antibiotic strategy but for those patients without prior prophylaxis oral antibiotic regimes with a quinolone and/or co-amoxiclav have been most frequently used.

The GDG noted that there was potential to achieve very large gains in improved patient experience by switching to oral antibiotics after an even shorter time period than recommended (for example after 8-16 hours). However there is currently no strong evidence in this area. The GDG therefore decided to recommend further research.

Research recommendation

- 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.

7.3 Duration of inpatient care

Patients with neutropenic sepsis are usually admitted to hospital and commenced on empiric intravenous antibiotic treatment.

There is great variation in the duration of inpatient care; many paediatric centres discharge low risk patients after 2 days and adult units may routinely keep patients in hospital until they are afebrile for at least 48 hours. Shortened length of stay may have considerable benefits for patients and reduce hospital resource use.

Clinical question: What is the optimal duration of inpatient care for patients receiving empiric treatment for neutropenic sepsis?

Clinical evidence (see also full evidence review)

Evidence statements

Two randomised trials compared early discharge with continued inpatient care in adults (Innes, *et al.,* 2003) or children (Santolaya, *et al.,* 2004) treated for neutropenic sepsis. There was very sparse evidence about the relative effectiveness of early discharge and continued inpatient care in terms of short term mortality and hospital readmission. This evidence is summarised in Table 7.3.

Early discharge rates

In four observational studies the percentage of adult patients meeting the criteria for early hospital discharge ranged from 38% to 90% (Cherif. *et al.,* 2006; Girmenia, *et al.,* 2007; Klastersky, *et al.,* 2006 and Tomiak, *et al.,* 1994). In order to be discharged early, low risk patients were required to meet additional criteria including ability to tolerate oral antibiotics, no history of poor compliance and ability to read a thermometer. The percentage of patients who were actually discharged early ranged from 13% to 69% (Cherif, *et al.,* 2006; Girmenia, *et al.,* 2007; Klastersky. *et al.,* 2006 and Tomiak. *et al.,* 1994).

In eleven observational studies the percentage of paediatric patients meeting the criteria for early hospital discharge ranged from 27% to 63% (Lau, *et al.,* 1994; Dommett, *et al.,* 2009; Lehrnbecher, *et al.,* 2002; Bash, *et al.,* 1994; Tordecilla, *et al.,* 1994; Aquino, *et al.,* 1997; Mullen, *et al.,* 1990; Griffin, *et al.,* 1992; Wakcker, *et al.,* 1997; Hodgson-Veiden, et al., 2005 and Santos-Muchado, *et al.,* 1999). Most of these studies were retrospective and patients were not prospectively assigned to high/low risk groups. These studies reported the outcomes of those who were actually discharged early, which ranged from 19% to 68%.

Hospital readmission

In the Innes, *et al.,* (2003) randomised trial, 5% of patients discharged early required hospital readmission.

In four observational studies (Cherif. *et al.,* 2006; Girmenia, *et al.,* 2007; Klastersky, *et al.,* 2006 and Tomiak, *et al.,* 1994) the rate of hospital re-admission for adult patients discharged early ranged from 0% - 13%. Re-admission rates ranged from 0% - 9% in eleven observational studies of paediatric patients (Lau, *et al.,* 1994; Dommett, *et al.,* 2009; Lehrnbecher, *et al.,* 2002; Bash, *et al.,* 1994; Tordecilla, *et al.,* 1994; Aquino, *et al.,* 1997; Mullen, *et al.,* 1990; Griffin, *et al.,* 1992; Wakcker, *et al.,* 1997; Hodgson-Veiden, *et al*., 2005 and Santos-Muchado, *et al.,* 1999).

Short term mortality

Patients selected for early discharge were at low risk of adverse events thus mortality data were sparse: in the Innes, *et al.,* (2003) trial there were no deaths during follow-up. The reported short term (within 30 days of follow up) mortality rate was 0% for patients discharged early from hospital in all but one study of adult patients (Tomiak, *et al.,* 1994). This study reported one death (a mortality rate of 3%). This was the only study of adult patients that did not use the MASCC criteria to stratify patients according to risk.

The reported short term mortality rate was 0% for patients discharged early from hospital in all studies of paediatric patients.

Quality of life and overtreatment

These outcomes were not reported by any of the identified studies of adult or paediatric patients.

Table 7.3 GRADE profile: Is early discharge more effective than continued inpatient care in patients receiving empiric treatment for neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Early discharge**	**Continued inpatient care**	**Relative (95% CI)**	**Absolute**	
Short term mortality in paediatric observational studies											
11	observational studies[1]	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	0/934 (0%)	-	-	-	VERY LOW
Hospital readmission in paediatric observational studies											
9	observational studies[1]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	42/889 (4.7%)	-	-	-	VERY LOW
Short term mortality in adult case series using MASCC ≥ 21 as criteria for early discharge											
3	observational studies	no serious limitations	no serious inconsistency	no serious indirectness	very serious[3]	none	0/215 (0%)	-	-	-	VERY LOW
Hospital readmission in adult case series using MASCC ≥ 21 as criteria for early discharge											
3	observational studies[1]	no serious limitations	no serious inconsistency	no serious indirectness	serious[3]	none	8/215 (3.7%)	-	-	-	VERY LOW
Short term mortality in paediatric RCT (Santolaya, *et al.*, 2004)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	0/78 (0%)	1/71 (1.4%)	-	-	LOW
Short term mortality in adult RCT (Innes, *et al.*, 2003)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	0/66	0/60	-	-	LOW
Overtreatment - not reported											

Quality assessment							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Early discharge	Continued inpatient care	Relative (95% CI)	Absolute	
0	-	-	-	-	-	none	-	-	-	-	
Quality of life - not reported											
0	-	-	-	-	-	none	-	-	-	-	
Adverse events - not reported											
0	-	-	-	-	-	none	-	-	-	-	

[1] Case series
[2] Case series
[3] Low number of events
[4] Method of randomisation was unclear. No blinding (but this was unlikely to affect outcome)

Cost-effectiveness evidence

A literature review of published cost-effectiveness analyses did not identify any relevant papers. As there was no definition of what constitutes a specific inpatient management strategy for this question, costing and evaluating health outcomes using economic modelling was not feasible. The GDG anticipated that the different management strategies were unlikely to result in large differences in patient outcomes and those strategies that minimise or reduce the duration of inpatient care would generally be less costly. Given that there was little uncertainty surrounding the economics of this question, further health economic analysis was not undertaken.

Recommendation
• Offer discharge to patients having empiric antibiotic therapy for neutropenic sepsis only after: - the patient's risk of developing septic complications has been reassessed as low by a healthcare professional with competence in managing complications of anticancer treatment using a validated risk scoring system[20] **and** - 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

Linking Evidence to Recommendations

The aim of this topic was to define the optimal duration of inpatient care for adults and children with neutropenic sepsis to avoid any adverse experiences or outcome. For this topic the GDG considered the outcomes of overtreatment, death/critical care, quality of life, re-admission rate and adverse events (hospital acquired infection) to be the most relevant.

No evidence was found for overtreatment, quality of life or adverse events. Evidence was reported on the re-admission rate and death/critical care for those patients that were discharged early. The overall quality of the evidence as classified by GRADE across all outcomes was "low" to "very low".

The evidence identified two RCTs that addressed the question of inpatient duration in the management of suspected bacterial infection in children and adults with low-risk febrile neutropenia. However the majority of the evidence for this topic was derived from large retrospective case series. The GDG acknowledged that much of the evidence base for this question came from specialist centres and were cautious as to how the findings should be extrapolated across all settings.

From the available evidence the GDG were unable to define an optimum duration of inpatient care for patients receiving empiric treatment for neutropenic sepsis. Instead the GDG focused their discussion on when these patients could be safely discharged from hospital.

The recommendations allow for discharge of patients and/or stepping down to oral antibiotics. This is because while most patients who could be discharged early are able to tolerate oral antibiotics, some may have a specific contraindication which requires IV antibiotics. However, these patients can be discharged if facilities exist to deliver outpatient IV antibiotics.

[20] Examples of risk scoring systems include 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 2000; 18: 3038–51) and the modified Alexander rule for children (aged under 18) (European Journal of Cancer 2009; 45: 2843–9).

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area. The opinion of the GDG was that there may be potential cost implications for carrying out appropriate risk assessment in secondary care. However they also expected that discharging patients early could bring cost savings particularly via a reduction in hospital stay.

Therefore the GDG recommended that patients receiving empiric treatment for neutropenic sepsis and who have been reassessed as being low risk of complications using a validated risk assessment tool (Section 4.3) and taking into account their social and clinical circumstances can be discharged from inpatient care.

7.4 Duration of empiric antibiotic treatment

Patients admitted with neutropenic sepsis receive empiric antibiotic treatment for variable periods of time. This can range from 48 hours to 14 days with different criteria being applied to determine when the empiric antibiotic treatment should be discontinued. These criteria are usually based on resolution of fever and/or recovery of neutrophil count.

The risks of early discontinuation of treatment include relapsed/recurrent infection which needs to be distinguished from a new infective episode and long-term complications including empyema, endocarditis, osteomyelitis or abscesses.

The disadvantages of prolonged antibiotic treatment include adverse drug events, organ toxicity, super-infection with fungi and multi-resistant organism and antibiotic-associated diarrhoea.

Clinical question: What is the optimal duration of empiric antibiotic therapy in patients with neutropenic sepsis?.

Clinical evidence (see also full evidence review)

The evidence is summarised in Table 7.4.

Evidence statements

Death (short term mortality)

Very low quality evidence from four randomised trials suggested an increased odds of short term mortality in patients whose empirical antibiotics were stopped early compared with those who continued treatment, OR = 5.18 (95% CI 0.95 - 28.16). In two studies (Klaassen, *et al.,* 2000; Santolaya, *et al.,* 1997) there were no deaths while in the other two studies seven deaths occurred within 30 days (Bjornsson, *et al.,* 1977 Pizzo,*et al.,* 1979). The two studies in which deaths occurred were both from the 1970s and used first generation empiric antibiotic treatment.

Overtreatment, critical care and quality of life

These outcomes were not reported by any of the included trials.

Length of stay

One paediatric study (Santolaya, *et al.,* 997) reported this outcome. There was low quality evidence that stopping antibiotics before resolution of neutropenia and fever had uncertain benefit in terms of length of stay. The mean length of stay was 0.7 days less in those who stopped empirical antibiotics early (95% CI 5.54 less to 4.41 more).

Duration of fever

One paediatric study (Santolaya,*et al.,* 1997) reported this outcome. There was low quality evidence that stopping antibiotics before resolution of neutropenia and fever had uncertain benefit in terms of duration of fever. The mean duration of fever was 0.8 days less in those who stopped empirical antibiotics early (95% CI 2.08 days less to 0.48 more).

Table 7.4 GRADE profile: What is the optimal duration of empiric antibiotic therapy in patients with neutropenic sepsis.

Quality assessment							No of patients		Effect		Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Shorter duration empiric antibiotics**	**Longer duration empiric antibiotics**	**Relative (95% CI)**	**Absolute**	
Death (within 30 days)											
4	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	5/95 (5.3%)	2/103 (1.9%)	OR 5.18 (0.95 to 28.16)	74 more per 1000 (from 1 fewer to 339 more)	VERY LOW
Length of stay (Better indicated by lower values)											
1	randomised trials	serious	no serious inconsistency	no serious indirectness	serious[3]	none	36	39	-	mean 0.7 days lower (5.54 lower to 4.41 higher)	LOW
Duration of fever (Better indicated by lower values)											
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	36	39	-	mean 0.8 days lower (2.08 lower to 0.48 higher)	LOW

[1] 3 of the 4 studies were not placebo-controlled and reported no detail about the method of randomisation employed, whether there was allocation concealment and no power analysis.
[2] 2 of the 4 studies were from the 1970s and used first generation antibiotic agents and all the deaths occurred in these two older trials.
[3] Very low event rate.
[4] Unclear allocation concealment, insufficient details about randomisation and not placebo controlled
[5] Uncertainty in the estimate of effect, the confidence interval spans both appreciable benefit and harm.

Cost-effectiveness evidence

A literature review of published cost effectiveness analyses did not identify any relevant papers. This topic focused on the optimal timing of a change in management strategy. The difference between strategies were considered unlikely to lead to large differences in cost, but rather be guided by differences in patient outcomes and other considerations such as service configuration. It was agreed that these considerations would probably be difficult to accurately capture using economic modelling and therefore further health economic analysis was not undertaken.

Recommendations

- Continue inpatient empiric antibiotic therapy in all patients who have unresponsive fever unless an alternative cause of fever is likely.
- Discontinue empiric antibiotic therapy in patients whose neutropenic sepsis has responded to treatment, irrespective of neutrophil count.

Linking Evidence to Recommendations

The aim of this topic was to identify the optimal duration of empiric antibiotic therapy in patients with neutropenic sepsis.

The GDG considered the outcomes of over-treatment, death/critical care, length of stay, duration of fever and quality of life to be important to the question. Over-treatment and quality of life were not reported in the evidence. There was limited data on mean length of stay and duration of fever. The main outcome reported by the evidence was death. However, due to very low event rates and methodologically compromised trials, the evidence on this outcome was classified by GRADE as being of 'very low' quality.

The GDG noted that the evidence was insufficient to determine whether stopping empiric antibiotics early was more or less effective than continuing empiric antibiotics until the patient was afebrile with a recovered neutrophil count. Nor did the evidence indicate whether or not these two strategies were equivalent. The GDG noted that consideration would have to be given to other causes of infection or fever but making recommendations on this was outside the scope of the guideline.

Based on their clinical experience, the GDG agreed that prolonged antibiotic treatment was associated with organ toxicity, increased side effects and increased risk of super-infection with fungi and/or multi-resistant organisms. Conversely, early discontinuation of treatment risked patients having relapsed/recurrent infection or significant complications such as endocarditis, osteomyelitis and abscesses. The GDG noted that relapsed infection needs to be distinguished from a new infective episode, and the studies reviewed were inadequate to assess this.

The clinical experience of the GDG was that stopping antibiotics earlier would probably be beneficial to patients because they would have reduced exposure to antibiotics, a corresponding reduction in side effects and reduced risk of developing antibiotic resistance. The patient experience of the GDG was that spending less time in hospital was preferable.

The GDG noted that no relevant, published economic evaluations had been identified and no additional economic analysis had been undertaken in this area.. The GDG considered based on their clinical experience that stopping antibiotics earlier would also probably reduce costs because patients would spend less time in hospital and there would be a reduction in spend on antibiotics and treating their associated side effects. The GDG felt that this reduction in cost would probably be greater than any additional costs associated with patients discontinuing treatment too early.

Therefore the GDG decided to recommend that empiric antibiotics should be continued in persistently febrile, but clinically stable patients, unless an alternative source of fever is established. The GDG also agreed to recommend that antibiotics could be discontinued in patients who have clinically responded, irrespective of neutrophil count.

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Appendix A

A cost-utility analysis of primary and secondary prophylaxis with G(M)-CSF and/or quinolones for the prevention of neutropenic sepsis

A1 Introduction

Neutropenic sepsis causes significant morbidity and mortality in patients receiving chemotherapy and can lead to reduced chemotherapy dose intensity and increased overall treatment costs (Cullen 2009). There are two approaches to preventing neutropenic sepsis: destroying potentially dangerous bacteria or enhancing immunity. Because there is great uncertainty over the cost-effectiveness of the different prophylactic medicines and whether primary or secondary prophylaxis is more cost effective, the guideline Development Group (GDG) prioritised this topic for health economic analysis (See Economic Plan in the full Evidence Review).

A1.1 Prophylactic medicines

There are two commonly used prophylactic medicines for preventing neutropenic sepsis, namely antibiotics and G-CSF. Evidence was reported for two types of antibitioics: quinolones and cotrimoxazole. However the GDG chose to focus on the evidence related to quinolones because of concerns that changing anti-microbial resistance patterns meant the cotrimoxazole trials may no longer be applicable (Gafter-Gvili, et al., 2005). The quinolones are a family of synthetic broad-spectrum antibiotics which can be used to kill or slow down the growth of bacteria. The most commonly used subset of quinolones is fluoroquinolone. Pre-emptive use of oral quinolones can reduce the likelihood of neutropenic sepsis (Gafter-Gvili, 2005), but may incur patient-related risks of gut disturbance, allergy, etc and more general risks related to the development of antibiotic resistance within the population.

Recently, the use of Granulocyte colony-stimulating factor (G-CSF) to prevent neutropenic sepsis has increased substantially (Aapro, *et al.,* 2006). G-CSF is a colony-stimulating factor hormone which can be used to raise neutrophil counts, and shorten the duration of neutropenia, by stimulating the bone marrow to produce neutrophils. However, adverse effects include bone pain, headache and nausea, and rarely more serious complications such as anaphylaxis, respiratory failure and splenic rupture. G-CSF must be given by injection, and this may lead to local reactions at the site of administration, and repeated injections may not be desired by patients. Pegylated G-CSF only needs to be given once with each cycle of chemotherapy, but the cost-effectiveness is unknown, comparing to quinolones.

A1.2 Eligibility criteria for prophylaxis

Patients who have had a prior episode of neutropenic sepsis are more likely to become neutropenic with repeated doses of chemotherapy than patients who have never experienced this complication, thus putting them at greater risk of neutropenic sepsis (Cullen 2007). There is uncertainty over the eligibility criteria for prophylaxis. Should it be provided to all cancer patients receiving chemotherapy which is likely to cause neutropenia (primary prophylaxis) or should it only be provided to patients with a previous episode of neutropenic sepsis (secondary prophylaxis)? Compared to primary prophylaxis, secondary prophylaxis prevents less episodes of neutropenic sepsis, and thus is associated with a higher cost. However, secondary prophylaxis may reduce the overall use of prophylactic medicine and thus avoid potential side effects such as antibiotic resistance.

Because of the large patient group covered by this topic and the potentially significant difference in cost of different treatment options, this topic was identified as a high economic priority by the GDG.

A systematic review of the economic evidence for this topic was carried out (Chapter 5). No cost-effectiveness analysis was found which directly addressed the clinical question. As a result, *de novo* models have been built to inform recommendations.

A2 De novo economic model (overview)

A2.1 Aim

The aim of this economic analysis was to examine which of the following prophylactic strategies is the most cost-effective for cancer patients who are receiving outpatient chemotherapy (defined as patients with planned inpatient treatment of less than 10-days post- chemotherapy):

- Nothing/placebo
- Primary prophylaxis with quinolones
- Primary prophylaxis with G-CSF
- Primary prophylaxis with G-CSF and quinolones
- Primary prophylaxis with PEG-G-CSF
- Secondary prophylaxis with quinolones
- Secondary prophylaxis with G-CSF
- Secondary prophylaxis with G-CSF and quinolones
- Secondary prophylaxis with PEG-G-CSF

A subgroup analysis was conducted for the following three patient groups:

- Patients with a solid tumour (aged 18 years and older)
- Patients with non-Hodgkin lymphoma (aged 18 years and older)
- Patients with Hodgkin lymphoma (aged 18 years and older)

This economic analysis does not cover:

- Cancer patients whose chemotherapy regimen includes G-CSF for dose intensity reasons.
- Cancer patients with planned inpatient treatment of greater than 10-days post-chemotherapy. It is acknowledged that the costs of prophylaxis and treatment of neutropenic sepsis for inpatient-only management are lower than outpatient management.
- Paediatric cancer patients (aged less than 18 years). Due to considerable clinical heterogeneity in the treatment regimens for this patient group, and a paucity of direct evidence, a representative model for economic analysis could not be built.
- The impact of different prophylactic strategies on subsequent courses of chemotherapy. The consequence of this bias is discussed in detail in section A9.2.3.
- Antibiotic resistance. The best available evidence identified to address the issue of antibiotic resistance caused by use of quinolones was derived from two systematic reviews: one was a review conducted for this guideline (see Section 5.1) and the other was a Cochrane review undertaken by Gafter-Gvili, et al., (2005). The conclusions of these two reviews were very similar. After use of quinolones, although there is an increase in colonisation with bacteria resistant to quinolones, there was no statistically significant increase in the number of infections caused by pathogens resistant to quinolones. The GDG were aware of the potential limitations of these two reviews but could not find any better evidence to answer the clinical question. Therefore the GDG decided to qualitatively consider the potential increase in antibiotic resistance and its impact on cancer patients when agreeing their recommendations, instead of quantitatively model it in the economic analysis.

A2.2 Key model assumptions

- None of the prophylaxis strategies included in the model could improve patient's short-term mortality.
- The sensitivity and specificity of diagnosing neutropenic sepsis is 100%.
- Patients could only develop one episode of neutropenic sepsis during one cycle of chemotherapy.
- If a patient stops receiving chemotherapy, he or she would not be at risk of developing neutropenic sepsis.
- The effectiveness of each prophylactic strategy (relative reduction of neutropenic sepsis) would be the same for patients at different levels of risk of developing neutropenic sepsis.
- The effectiveness of each prophylactic strategy **(**relative reduction of neutropenic sepsis) would be the same for patients who are receiving primary or secondary prophylaxis.

A2.3 Model structure

Decision trees are used to reflect key events in the clinical pathway in order to compare costs and health effects for the interventions of interest. In this economic analysis, two decision trees were constructed to cover two different populations:

- model A for adult patients with Hodgkin lymphoma, and
- model B for adult patients with a solid tumour or non-Hodgkin lymphoma.

The details of both models can be found below. A Markov process was embedded in both decision trees to model the recurrence of neutropenic sepsis within one course of chemotherapy.

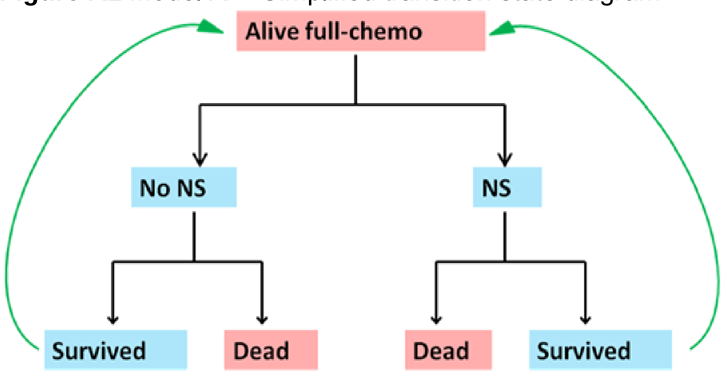
- *Model A: 'Continue to receive full dose-chemotherapy*

  This model assumes patients will continue to receive full-dose chemotherapy regardless of previous episodes of neutropenic sepsis. Figure A1 illustrates the key health states in the model and possible transitions between them.

- *Model B: 'Dose-reduction chemotherapy'*

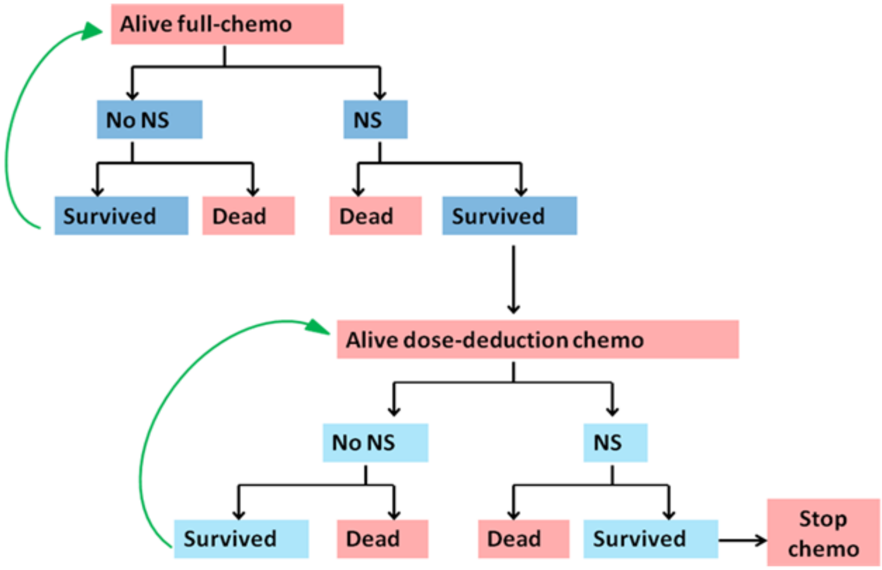
  This model assumes that if patients develop one episode of neutropenic sepsis, they will then receive dose-reduction chemotherapy. If they develop two episodes of neutropenic sepsis chemotherapy will be discontinued. Figure A2 illustrates the key health states in the model and possible transitions between them.

Figure A1 Model A – Simplified transition state diagram



Alive full-chemo = Alive caner patients who are receiving full-dose chemotherapy
NS = neutropenic sepsis.

Figure A2 Model B – Simplified transition state diagram



Alive full-chemo = Alive cancer patients who are receiving full-dose chemotherapy
Alive dose-reduction chemo = Alive cancer patients who are receiving dose-reduction chemotherapy
NS = neutropenic sepsis.

The volume of clinical data to inform the relative risk of overall mortality (each prophylactic strategy versus nothing/placebo) was very sparse for the three patient subgroups included in the model. What's more, of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. Therefore the GDG decided to assume that the overall mortality would be the same for each prophylactic strategy, and only looked at the efficacy of each strategy in terms of preventing neutropenic sepsis. Since the baseline short-term overall mortality rate for our target population group is normally very low; unless there were any prophylactic strategies that could significantly reduce short-term overall mortality, this bias is unlikely to change our conclusion.

A2.4 Time horizon

The time horizon of both models (A and B) was one course of chemotherapy, as the GDG were only interested in short-term outcomes. The number of cycles within one course of chemotherapy, and length of each cycle were estimated for each patient subgroup by the GDG (Table A1).

Table A1 Number and length of chemotherapy cycle for each patient subgroup

	No. of cycles within one course		**Length of one chemotherapy cycle**	
	Value	*Range*	*Value*	*Range*
Solid tumour	3	1-6	21 d	7-21 d
Non-Hodgkin lymphoma	6	3-6	21 d	14-28 d
Hodgkin lymphoma	14	12-16	14 d	14-14 d

A2.5 Software

The cost-effectiveness analyses were conducted using TreeAge pro 2010.

A3 Cost-effectiveness model - inputs

The cost-effectiveness analysis required clinical evidence, health-related preferences (utilities), healthcare resource use and costs. High quality evidence on all relevant parameters was essential; however, these data were not always available. Where published evidence was sparse, the expert opinion of the GDG was used to estimate relevant parameters.

A3.1 Clinical data

A3.1.1 Risk of neutropenic sepsis

Risk of neutropenic sepsis – baseline risk

The baseline risk of neutropenic sepsis for each patient subgroup was obtained from the clinical evidence review of this topic (Appendix 4 of full evidence review) and is presented in Table A2. A range of different risk levels (5-100% per cycle of chemotherapy) were tested in a one-way sensitivity analysis.

Table A2 Baseline risk of neutropenic sepsis (one course of chemotherapy)

	Probability distribution	Parameters	
		Mean	*SD*
Solid tumour	Beta	0.3441	0.0531
Non-Hodgkin lymphoma	Beta	0.4422	0.0848
Hodgkin lymphoma	Beta	0.2027	0.0605

The relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards was calculated as 3.69 (Cullen, 2007) (Table A3). The relative risk of further febrile neutropenia episodes in a patient who had experienced previous episodes was calculated as 5.96 (Cullen, 2007) (Table A3). This means that once patients have experienced one episode of neutropenic sepsis, their baseline risk of neutropenic sepsis will be increased with any subsequent chemotherapy.

Table A3 Relative risk of neutropenic sepsis (different cycles, with or without previous neutropenic sepsis)

Relative risk of neutropenic sepsis	Value	Probability distribution	Parameters		Source
			Mean of logs	*SD of logs*	
Cycle 1 versus Cycle 2 onwards	3.69	Log-normal	1.31	0.07	Cullen 2007
Previous neutropenic sepsis versus no previous neutropenic sepsis	5.96	Log-normal	1.79	0.07	Cullen 2007

Model B (‘*Dose-reduction chemotherapy*’) assumes that once a patient develops one episode of neutropenic sepsis they will start to receive dose-reduction chemotherapy. It is generally considered that a reduction in chemotherapy dose is likely to reduce the patient’s risk of neutropenic sepsis, and thus decrease short-term mortality. However, very little clinical evidence comparing chemotherapy dose and the risk of neutropenic sepsis was identified. Therefore in our economic model, it is assumed that chemotherapy dose has no impact on the risk of neutropenic sepsis or short-term mortality. This bias favours all prophylactic strategies except nothing/placebo.

Risk of neutropenic sepsis - relative effects

The relative risk of neutropenic sepsis for each prophylactic strategy was obtained from the clinical evidence review of this topic (Appendix 4 of full evidence review) and is presented in Table A4.

Table A4 Relative risk of neutropenic sepsis (each prophylaxis strategy versus nothing/placebo)

	Mean value	Probability distribution	Parameters	
			Mean of logs	*SD of logs*
Solid tumour				
Quinolones	0.437	Log-normal	-0.83	0.22
G(M)-CSF	0.666	Log-normal	-0.41	0.04
G(M)-CSF + quinolones	0.517	Log-normal	-0.66	0.12
PEG-G-CSF	0.284	Log-normal	-1.26	0.33
Non-Hodgkin lymphoma				
Quinolones	*No data*			
G(M)-CSF	0.772	Log-normal	-0.26	0.04
G(M)-CSF + quinolones	0.891	Log-normal	-0.12	0.11
PEG-G-CSF	0.407	Log-normal	-0.90	0.32
Hodgkin lymphoma				
Quinolones	*No data*			
G(M)-CSF	0.667	Log-normal	-0.40	0.73
G(M)-CSF +quinolones	*No data*			
PEG-G-CSF	*No data*			

Only a very small volume of clinical evidence for secondary prophylaxis was identified. Therefore it was assumed that the effectiveness of each prophylactic strategy (relative reduction of neutropenic sepsis, and relative reduction of short-term overall mortality) would be the same for patients who are receiving primary or secondary prophylaxis.

A3.1.2 Overall mortality

Overall mortality - baseline risk

The baseline overall mortality for a patient with neutropenic sepsis was obtained from the systematic reviews of the clinical evidence conducted for this topic (Appendix 4 of full evidence review) and is presented in Table A5.

Table A5 Overall mortality for patients with neutropenic sepsis who received no prophylaxis (baseline risk within our course of chemotherapy)

	Probability distribution	Parameters	
		Mean	*SD*
Solid tumour	Beta	0.0460	0.0098
Non-Hodgkin lymphoma	Beta	0.0536	0.0346
Hodgkin lymphoma	Beta	0.0863	0.0907

Overall mortality - relative effects

The volume of clinical data to inform the relative risk of overall mortality (each prophylactic strategy versus nothing/placebo) was very sparse for the three patient subgroups included in the model. What's more, of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. The GDG decided to assume that the overall mortality would be the same for each prophylactic strategy, and only looked at the efficacy of each strategy in terms of preventing neutropenic sepsis. Since the baseline short-term overall mortality rate for our target population group is very low; unless there were any prophylactic strategies that could significantly reduce short-term overall mortality, this bias is unlikely to change our conclusion.

For those patients who died during chemotherapy, the probability of dying from infection (infection-related mortality divided by all cause mortality) was obtained from the clinical evidence reviews conducted for this topic (Appendix 4 of full evidence review) and is presented in Table A6.

Table A6 Probability of dying from infection (infection-related mortality/all cause mortality)

	Probability distribution	Parameters	
		Mean	*Se*
Solid tumour	Beta	0.5117	0.0841
Non-Hodgkin lymphoma	Beta	0.8020	0.2562
Hodgkin lymphoma	Beta	0.2907	0.1323

A3.2 Utility scores

Utility weights were required to estimate quality adjusted life years (QALYs).

In this analysis the utility decrement due to incidence and treatment of neutropenic sepsis (base-case model) and death were all considered. Utility decrement due to neutropenia was not considered in the economic model for two reasons. Firstly, neutropenia often coincides with other side-effects of chemotherapy, so it is difficult to judge whether the utility decrement is caused by neutropenia alone or other side-effects of chemotherapy. Secondly little evidence was identified which reported utility decrement of neutropenia using EQ-5D, which is the tool recommended by NICE.

A3.2.1 Utility decrement due to neutropenic sepsis and its treatment

Wherever possible, utility data was taken from studies conducted in the UK and using EQ-5D.

Many studies reported utility decrement due to neutropenic sepsis. However, none of those studies were considered to be entirely applicable to the UK settings except Brown, (2001). The most common reasons for inapplicability were:

- Studies were conducted in countries other than the U.K.
- Studies didn't specify the treatment settings for neutropenic sepsis patients: entire inpatient, entire outpatient or inpatient followed by outpatient.

It is generally considered that patients receiving outpatient treatment have better quality of life, comparing with patients receiving inpatient treatment.

Only one paper reported separate utility data for neutropenic sepsis patients receiving treatment in both inpatient and outpatient settings (Brown, 2001). The utility data reported by Brown, (2001) is presented in Table A7.

Table A7 Utility decrement of neutropenic sepsis in different settings

	Value	Range	Distribution	Parameters	Source
Inpatient	0.38	0.14-0.38	Beta	Assumed se = 0.1	Brown 2001
Outpatient	0.14	0-0.15	Beta	Assumed se = 0.1	Brown 2001

A3.2.2 Utility decrement due to death

Wherever possible, the utility data was taken from studies using EQ-5D. The utility decrements due to death for each patient subgroup are provided in Table A8.

Table A8 Utility data for each patient subgroup

	Value	Range	Distribution	Parameter	Source
Solid tumour	0.68*	0.21-0.84	Beta	Assumed se = 0.1	Bertaccini 2003, Best 2010 etc
Non-Hodgkin lymphoma	0.61	0.53-0.805	Beta	Assumed se = 0.1	Briggs 2006; Doorduijn 2005; Pettengell 2008
Hodgkin lymphoma	0.78	0.71-0.84	Beta	Assumed se = 0.1	Norum 1996; Slovacek 2005

*Calculated from patients with breast, lung, colorectal (bowel) and prostate cancer, weighted by their percentage of the total.

A3.3 Resource use and cost

The costs considered in this economic analysis were those relevant to the UK NHS, and included the cost of each prophylactic strategy, the costs of each diagnostic investigation and the costs of inpatient and outpatient treatment. Unit costs were based on the British National Formulary (BNF 62), NHS reference costs (2009-10) or the Unit Costs of Health and Social Care (Curtis, 2010).

The cost of chemotherapy was not included as the economic model was only looking at the prevention and treatment of neutropenic sepsis.

Due to the short time horizon of this economic analysis(less than one year), costs and health outcomes were not discounted.

A3.3.1 Prophylactic medicine cost

The costs of each prophylactic medicine included in the model are provided in Table A9.

TableA9 Prophylactic medicine cost per person per cycle

	Dose/ schedule	Cost per vial/ unit[1]	Daily cost (£)	Administration fee (£)	Total cost per cycle (£)
Quinolone	Assume 500 mg once daily; used for 7 days[2]	500 mg (scored), 10-tab pack = £12.49	£ 1.25	0	£ 8.75
PEG-G-CSF	6 mg for each chemotherapy cycle	0.6-mL (6-mg) prefilled syringe = £686.38	N/A	£10.5/injection[3]	£ 703.18
G(M)-CSF	500,000 units/kg daily; assume used for 8 days [4] (range: 5-11 d)	Filgrastim: • One single 30 million-unit syringe=£58.84; • One single 48 million-unit syringe=£93.93. Lenograstim: • One single 13.4 million-unit syringe=£31.39; • One single 33.6 million-unit syringe=£62.54.	£ 98.57 [5]	£10.5/injection[3]	£ 872.56 (Range: £ 545.35-1199.77)
G(M)-CSF + quinolone	G-CSF: See Row 3 above.	G-CSF: See Row 3 above.	G-CSF: £ 98.57 Quinolone:	G-CSF: £10.5/injection[3] Quinolone: £ 0	£ 881.31 (Range: £ 554.1-1208.52)
	Quinolone: See Row 1 above.	Quinolone: See Row 1 above.	£ 1.25		

[1] All unit costs used in calculation were obtained from BNF 62.
[2]: The daily dose and dose schedule of quinolone was obtained from Cullen 2007.
[3]: The cost of administrating a PEG-G-CSF or G(M)-CSF injection by nurse is assumed to be £21.0 per injection. However it is assumed that 50% of patients will administer PEG-G-CSF or G(M)-CSF by themselves. So the weighted administration fee of PEG-G-CSF or G(M)-CSF is £ 10.5 per person (£21 * 50% = £ 10.5). Different probability of self-administrating PEG-G-CSF or G(M)-CSF (0-100%) was tested in one-way sensitivity analysis.

[4]: Most included clinical trials used G(M)-CSF for six or eleven days; so the average length of using G-CSF is assumed to be 8-day.
[5]: Average cost of filgrastim and lenograstim, calculated based on patient weight distribution reported by three studies: Green 2003, Romieu 2007 and Gigg 2003. Detailed calculation process can be found in appendix A10. The GDG acknowledged that many British hospitals will use one vial of G(M)-CSF (one single 30 million-unit syringe of filgrastim or one single 33.6 million-unit syringe of lenograstim) for all adult patients regardless of their weight. One-way sensitivity analysis has been conducted to test the impact of different daily cost of G(M)-CSF.

A3.3.2 Single ambulance journey

Patients with suspected neutropenic sepsis need to see a healthcare professional as soon as possible. However, there is a scarcity of evidence for the use of an ambulance for the target population. It is reported that the use of an ambulance is positively associated with age (Health and Social Care Information Centre, 2009-10). Therefore the use of an ambulance for each patient subgroup was estimated based on their age distribution. The age distribution of each patient subgroup was obtained from the Cancer Research UK website (http://info.cancerresearchuk.org/cancerstats/).

Table A10 shows the estimated ambulance use and associated cost for each patient subgroup. The detailed calculation process can be found in section A11: Cost of ambulance.

Table A10 Estimated ambulance use and cost for each patient subgroup

	Ambulance use Point estimate (range)	**Unit cost of a single journey ambulance (£)**	**Average cost per neutropenic sepsis case (£)** Value (range)
Solid tumour	43.75% (0-1)	£ 246	£ 107.63 (0-246)
Non-Hodgkin lymphoma	41.73% (0-1)	£ 246	£ 102.65 (0-246)
Hodgkin lymphoma	28.22% (0-1)	£ 246	£ 69.42 (0-246)

A3.3.3 Cost of treating neutropenic sepsis

There is a HRG code for ‘Febrile neutropenia associated with malignancy’: £5,373 (Department of Health, 2011). However, this HRG cost was considered to be inappropriate to our model for two reasons:

- Different target population. This economic analysis only looks at adult patients who are receiving outpatient chemotherapy (defined as patients with inpatient treatment of less than 10-day post-chemotherapy). In contrast to patients who are receiving inpatient chemotherapy (defined as patients with inpatient treatment of greater than 10-day post-chemotherapy), our target population rarely use Intensive Care/Therapy Unit (ICU/ITU) or antifungal drugs; both of which are very expensive. This means the treatment cost for our target population (outpatient group) will be much lower than it for the inpatient group. The HRG code, however, didn’t report separate results for patients who are receiving chemotherapy in different settings.
- The recommendations of this guideline (Chapter 6: ‘Initial treatment’ and Chapter 7: ‘Subsequent treatment’), once implemented, are likely to significantly reduce the cost of treating neutropenic sepsis.

Therefore, the cost of treating neutropenic sepsis was estimated based on the clinical pathway desgined by this guideline (Algorithm: Summary of recommendations).

Unit cost of hospital bed day

According to the NHS reference cost (2009-10), the average cost of an excess bed day is £255, which includes the cost of staff, medication, routine examination and treatment. Therefore the cost of any diagnostic tests and intravenous antibiotic were not double counted. The average cost of an excess bed day is provided in Table A11.

TableA11 Cost of an excess hospital bed day

	Value	Range	Source
Cost of an excess hospital bed day (£)	£255	Assumed £100-1000	NHS references cost 2009-10

Length of hospital stay

Several recent large-scale studies (Schilling, 2011, Lingaratnam, 2011, Lathia, 2009) reported the average length of hospital stay for patients with febrile neutropenia. However, none of these studies were considered to be applicable to our model for three reasons:

- None of the studies were conducted in the UK
- It is generally considered that the length of hospital stay is different for patients who are at different risk of serious adverse outcomes: low-risk patients can receive outpatient management from the outset or for early discharge after a period of inpatient observation and investigation (Section 4.4); while high-risk patients need to stay in hospital until they are afebrile. However, none of the studies reported separate outcomes (length of stay) for patients who are receiving outpatient chemotherapy (defined as patients with inpatient treatment of less than 10-day post-chemotherapy) at different risk of serious adverse outcomes.
- The recommendations for other topics in this guideline, once implemented, (Chapter 6: 'Initial treatment' and Chapter 7: 'Subsequent treatment') are likely to reduce the length of hospital stay for patients with neutropenic sepsis in the future.

Therefore, an estimate of the baseline hospital stay for the economic model was made by the GDG (Table A12), based upon the recommendation in this guideline. The GDG also estimated the percentage of high-risk patients for all three patient subgroups (Table A13).

Table A12 Baseline length of hospital stay for neutropenic sepsis patients who did not receive any prophylaxis

	High-risk of complications		**Low-risk of complications**	
	Days of inpatient treatment	*Days of outpatient treatment*	*Days of inpatient treatment*	*Days of outpatient treatment*
Solid tumour	7	0	2	3
Non-Hodgkin lymphoma	7	0	2	3
Hodgkin lymphoma	7	0	2	3

Table A13 Percentage of neutropenic sepsis patients at high risk of serious adverse outcome

	High-risk of serious adverse outcome	
	Value	*Range*
Solid tumour	10%	5-20%
Non-Hodgkin lymphoma	25%	10-35%
Hodgkin lymphoma	10%	5-15%

A recent systematic review by Sung, *et al.,* (2007) reported that the use of prophylactic CSF is associated with a reduction of hospital stay of 2.41 days (95% CI: 1.70-3.13 days) (see Table A14). However this paper did not report baseline hospital days used in the included studies; therefore, an estimate of baseline hospital day was made by the GDG. If it is assumed the average length of hospital stay is 8-day, then the relative reduction of hospital days due to use of G-CSF would be 2.41/8=30.13%. In this model, the average hospitalisation duration for high-risk patients was assumed to be 7 days. So the reduction in hospital days due to use of G-CSF was calculated as 2.11 days (=7*30.13%). It is assumed that the use of prophylactic CSF won't reduce the length of hospital stay for neutropenic sepsis patients at low risk of serious adverse outcomes.

As the Sung, *et al.,* review (2007) did not report separate data for patients with different types of cancer it was assumed that the reduction of hospital days would be the same for all three patient subgroups.

It was noted that whilst the Sung, *et al.,* review (2007) included 148 papers comparing G-CSF with placebo/nothing, only 43 reported the reduction of hospital days due to prophylactic G-CSF. So the pooled data might be affected by publication bias. This bias favours G-CSF.

Table A14 Reduced hospital bed days due to use of prophylactic G-CSF (for neutropenic sepsis patients at high risk of serious adverse outcomes only)

	Value	Probability distribution	Parameters		Source
			Mean of logs	*SD of logs*	
Reduced hospital bed days	2.11	Log-normal	0.75	0.16	Sung 2007, adjusted for baseline hospital day

Outpatient treatment and daily telephone contact after discharge (for neutropenic sepsis patients at low risk of serious adverse outcomes only)

In the economic model, it is assumed that neutropenic sepsis patients at a low-risk of serious adverse outcomes can step down to outpatient treatment with oral antibiotics, after the first 48-hour inpatient observation and investigation. For this group of patients, it is assumed that telephone follow-up will last for two days after the patient is discharged from hospital.

Oral antibiotics

Patients who are allergic to penicillin will receive different oral antibiotics to patients who are not allergic. It is estimated that about 10% of neutropenic sepsis patients are allergic to penicillin. The weighted cost of oral antibiotics is presented in Table A15.

Table A15 Weighted cost of oral antibiotic for patients with neutropenic sepsis who are at low risk of serious adverse outcomes

	Percentage	Cost
Standard risk	90%	£ 3.10/day
Penicillin allergy	10%	£ 7.07/day
Estimated (weighted) cost for all patients		**£ 3.50/day**

Daily telephone contact

For patients with neutropenic sepsis and a low-risk of serious adverse outcomes, it is assumed that telephone follow-up will last for two days after the patient is discharged from hospital. It is assumed that each phone call will take a nurse about 10 minutes to complete. The estimated cost of this telephone follow-up is presented in Table A16.

Table A16 Cost of daily telephone contact

	Unit cost	Duration of telephone call	Daily cost	Distribution	Source
Cost of telephone follow-up	£ 26/hour	10 mins	£ 4.34/ NS case	Assumed fixed	Curtis 2010

A4 Sensitivity analysis

Three different kinds of sensitivity analysis were conducted to test the robustness of the results of each economic model.

A4.1 Structural sensitivity analysis

A structural sensitivity analysis was conducted to test the robustness of results in each model structure. In model B patients could only develop a maximum of two episodes of neutropenic sepsis and then their chemotherapy would be discontinued, so these patients would no longer be at risk of neutropenic sepsis. However, in Model A, patients who have developed two episodes of neutropenic sepsis will keep on receiving full-dose chemotherapy, and will continue to be at high risk of neutropenic sepsis. Therefore model A (*'carry on regardless'*) is a high-risk model when compared to model B (*'dose-reduction model'*), even when their baseline risks are the same. This is because the baseline risk can be increased after the patient has developed one episode of neutropenic sepsis.

This means if one prophylactic strategy is not cost-effective in model B, it could potentially become cost-effective in model A (as the risk of neutropenic sepsis has been increased). However if one prophylactic strategy is not cost-effective in model A, then using model B will only make this intervention even less cost-effective. Therefore structural sensitivity analysis has only been conducted for model B (i.e. patients with solid tumour and non-hodgkin lymphoma).

A4.2 One-way sensitivity analysis

For each model, over sixteen scenarios (including the data ranges) were considered and are detailed below:

- Number of cycles of chemotherapy (varies for each patient subgroup)
- Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards[21]: (5 - 100%)
- Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards (1-10)
- Relative risk of a neutropenic sepsis episode: previous neutropenic sepsis versus no previous neutropenic sepsis (1-10)
- Relative risk of a neutropenic sepsis episode: each prophylactic strategy versus nothing/placebo (0.1 – 0.95)
- Probability of self administrating PEG-G-CSF or G(M)-CSF (0-100%)
- Probability of using an ambulance for patients with neutropenic sepsis (0-100%)
- Probability of patients with neutropenic sepsis who are at high risk of serious adverse events (varies for each patient subgroup)

[21] In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.

- Days of using G(M)-CSF for each cycle of chemotherapy (5-11 days)
- Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events (1-6 days)
- Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events (6-14 days)
- Cost per hospital bed day (£100 - £1000)
- Daily cost of G(M)-CSF per person (£60.69[22] – £98.57[23])
- Drug discounts of PEG-G-CSF and G(M)-CSF (0% - 90%)
- Utility decrement due to inpatient treatment of neutropenic sepsis (0.14-0.38)
- Utility decrement due to outpatient treatment of neutropenic sepsis (0-0.15).

A4.3 Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis was performed to assess the robustness of the model results against plausible variations in the model parameters. For each patient subgroup, the main results were re-calculated 5000 times.

A summary of all parameters used in the probabilistic sensitivity analysis for each patient subgroup is provided in Table A17 to A19.

[22] Average cost of filgrastim and lenograstim assuming that the daily dose of G(M)-CSF for all adult patients is one vial (one single 30 million-unit syringe of filgrastim or one single 33.6 million-unit syringe of lenograstim) regardless of patient weight.

[23] Average cost of filgrastim and lenograstim, based on BNF recommended dose (500,000 units/kg daily) and patient weight distribution reported by: Green 2003, Romieu 2007, and Gigg 2003. The detailed calculation process is reported in Appendix A10.

Table A17 Summary of parameters used in probabilistic sensitivity analysis (Solid tumour adult)

Description of parameters	Mean value	Probability distribution	Parameters	Source
Resource use				
Reduced hospital days due to prophylactic G-CSF	2.11	LogNormal	Mean of logs: 0.75 SD of logs: 0.16	Sung, (2007), adjusted for baseline hospital day
Utility				
Cancer patients	0.68	Beta	Assumed se = 0.1	Bertaccini, (2003), Best, (2010) et al
Utility decrement due to neutropenic sepsis (inpatient)	0.38	Beta	Assumed se = 0.1	Brown, (2001)
Utility decrement due to neutropenic sepsis (outpatient)	0.14	Beta	Assumed se = 0.1	Brown, (2001)
Risk of neutropenic sepsis				
Relative risk of a neutropenic sepsis event (Cycle 1 versus Cycle 2 onwards)	3.69	LogNormal	Mean of logs: 1.31 SD of logs: 0.07	Clinical evidence reviews (Appendix 4 of full evidence review)
Relative risk of a neutropenic sepsis event if patient has already had a neutropenic sepsis event	5.96	LogNormal	Mean of logs: 1.79 SD of logs: 0.07	Same as above
Baseline risk of neutropenic sepsis for patient who received no prophylaxis	0.344	Beta	Se: 0.0531	Same as above
Relative risk of a neutropenic sepsis event (quinolone versus nothing)	0.437	LogNormal	Mean of logs: -0.83 SD of logs: 0.22	Same as above
Relative risk of a neutropenic sepsis event (PEG-G-CSF versus nothing)	0.284	LogNormal	Mean of logs: -1.26 SD of logs: 0.33	Same as above
Relative risk of a neutropenic sepsis event (G(M)-CSF versus nothing)	0.666	LogNormal	Mean of logs: -0.41 SD of logs: 0.04	Same as above
Relative risk of a neutropenic sepsis event (quinolone + G(M)-CSF versus nothing)	0.517	LogNormal	Mean of logs: -0.66 SD of logs: 0.12	Same as above
Overall mortality				
Baseline overall mortality for patients who received no prophylaxis	0.046	Beta	Se: 0.0098	Clinical evidence reviews (Appendix 4 of full evidence review)
Probability of dying from infection (infection-related mortality/all cause mortality)	0.5117	Beta	Se: 0.0841	Same as above

Table A18 Summary of parameters used in probabilistic sensitivity analysis (non-Hodgkin lymphoma adult)

Description of parameters	Mean value	Probability distribution	Parameters	Source
Resource use				
Reduced hospital days due to prophylactic G-CSF	2.11	LogNormal	Mean of logs: 0.75 SD of logs: 0.16	Sung, (2007), adjusted for baseline hospital day
Utility				
Cancer patients	0.61	Beta	Assumed se = 0.1	Briggs, (2006); Doorduijn, (2005); Pettengell, (2008)
Utility decrement due to neutropenic sepsis (inpatient)	0.38	Beta	Assumed se = 0.1	Brown, (2001)
Utility decrement due to neutropenic sepsis (outpatient)	0.14	Beta	Assumed se = 0.1	Brown, (2001)
Risk of neutropenic sepsis				
Relative risk of a neutropenic sepsis event (Cycle 1 versus Cycle 2 onwards)	3.69	LogNormal	Mean of logs: 1.31 SD of logs: 0.07	Clinical evidence reviews (Appendix 4 of full evidence review)
Relative risk of a neutropenic sepsis event if patient has already had a neutropenic sepsis event	5.96	LogNormal	Mean of logs: 1.79 SD of logs: 0.07	Same as above
Baseline risk of neutropenic sepsis for patient who received no prophylaxis	0.4422	Beta	Se: 0.0848	Same as above
Relative risk of a neutropenic sepsis event (quinolone versus nothing)	No data			
Relative risk of a neutropenic sepsis event (PEG-G-CSF versus nothing)	0.407	LogNormal	Mean of logs: -0.90 SD of logs: 0.15	Clinical evidence reviews (Appendix 4 of full evidence review)
Relative risk of a neutropenic sepsis event (G(M)-CSF versus nothing)	0.772	LogNormal	Mean of logs: -0.26 SD of logs: 0.04	Same as above
Relative risk of a neutropenic sepsis event (quinolone + G(M)-CSF versus nothing)	0.891	LogNormal	Mean of logs:-0.12 SD of logs: 0.11	Same as above
Overall mortality				
Baseline overall mortality for patients who received no prophylaxis	0.0536	Beta	Se: 0.0346	Clinical evidence reviews (Appendix 4 of full evidence review)
Probability of dying from infection (infection-related mortality/all cause mortality)	0.8020	Beta	Se: 0.2562	Clinical evidence reviews (Appendix 4 of full evidence review)

Table A19 Summary of parameters used in probabilistic sensitivity analysis (Hodgkin lymphoma adult)

Description of parameters	Mean value	Probability distribution	Parameters	Source
Resource use				
Reduced hospital days due to prophylactic G-CSF	2.11	LogNormal	Mean of logs: 0.75 SD of logs: 0.16	Sung, (2007), adjusted for baseline hospital day
Utility				
Cancer patients	0.78	Beta	Assumed se = 0.1	Norum, (1996); Slovacek, (2005)
Utility decrement due to neutropenic sepsis (inpatient)	0.38	Beta	Assumed se = 0.1	Brown, (2001)
Utility decrement due to neutropenic sepsis (outpatient)	0.14	Beta	Assumed se = 0.1	Brown, (2001)
Risk of neutropenic sepsis				
Relative risk of a neutropenic sepsis event (Cycle 1 versus Cycle 2 onwards)	3.69	LogNormal	Mean of logs: 1.31 SD of logs: 0.07	Clinical evidence reviews (Appendix 4 of full evidence review)
Relative risk of a neutropenic sepsis event if patient has already had a neutropenic sepsis event	5.96	LogNormal	Mean of logs: 1.79 SD of logs: 0.07	Same as above
Baseline risk of neutropenic sepsis for patient who received no prophylaxis	0.2027	Beta	Se: 0.0605	Same as above
Relative risk of a neutropenic sepsis event (quinolone versus nothing)	No data			
Relative risk of a neutropenic sepsis event (PEG-G-CSF versus nothing)	No data			
Relative risk of a neutropenic sepsis event (G(M)-CSF versus nothing)	0.667	LogNormal	Mean of logs: -0.40 SD of logs: 0.73	Clinical evidence reviews (Appendix 4 of full evidence review)
Relative risk of a neutropenic sepsis event (quinolone + G(M)-CSF versus nothing)	No data			
Overall mortality				
Baseline overall mortality for patients who received no prophylaxis	0.0863	Beta	Se: 0.0907	Clinical evidence reviews (Appendix 4 of full evidence review)
Probability of dying from infection (infection-related mortality/all cause mortality)	0.2907	Beta	Se: 0.1323	Clinical evidence reviews (Appendix 4 of full evidence review)

A5 Interpreting results

The results of cost-effectiveness analyses are usually presented as incremental cost-effectiveness ratios (ICERs). This is calculated by dividing the difference in cost associated with two alternatives by the difference in QALYS (formula below).

$$\text{ICER} = \frac{\textbf{Costs (B) — Costs (A)}}{\textbf{QALYs (B) – QALYs (A)}}$$

By calculating the difference in benefits, a cost per QALY can be calculated for each comparison.

NICE's report 'Social value judgments: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.

In general, an intervention is considered to be cost effective by NICE if either of the following criteria applied:

- The intervention is less costly and more clinically effective compared with all the other relevant alternative strategies. In this case, an ICER is not calculated, or
- Compared with the next best strategy, the intervention has an ICER of less than £20,000 per quality adjusted life-year (QALY).

A6 Results ─ Solid tumour sub group

The results for adult patients with a solid tumour are presented below in the following order:

- base case analysis (Section A6.1)
- structural sensitivity analysis (Section A6.2)
- one-way sensitivity analysis (Section A6.3)
- probabilistic sensitivity analysis (Section A6.4)

For all sections, separate results are presented for patients who can or cannot take quinolones.

A6.1 Base case analysis

A6.1.1 For patients who can take quinolone

For adult patients with a solid tumour and who can take quinolone, clinical evidence was available for all nine strategies of interest (Section A2.1). Compared to quinolone alone, G(M)-CSF and G(M)-CSF + quinolone are more expensive and less effective in terms of preventing neutropenic sepsis (Table A4 and A11). Therefore all primary and secondary prophylactic strategies involving, G(M)-CSF and G(M)-CSF + quinolone were excluded from the analysis. As a result cost-effectiveness was only formally examined for the following five strategies:

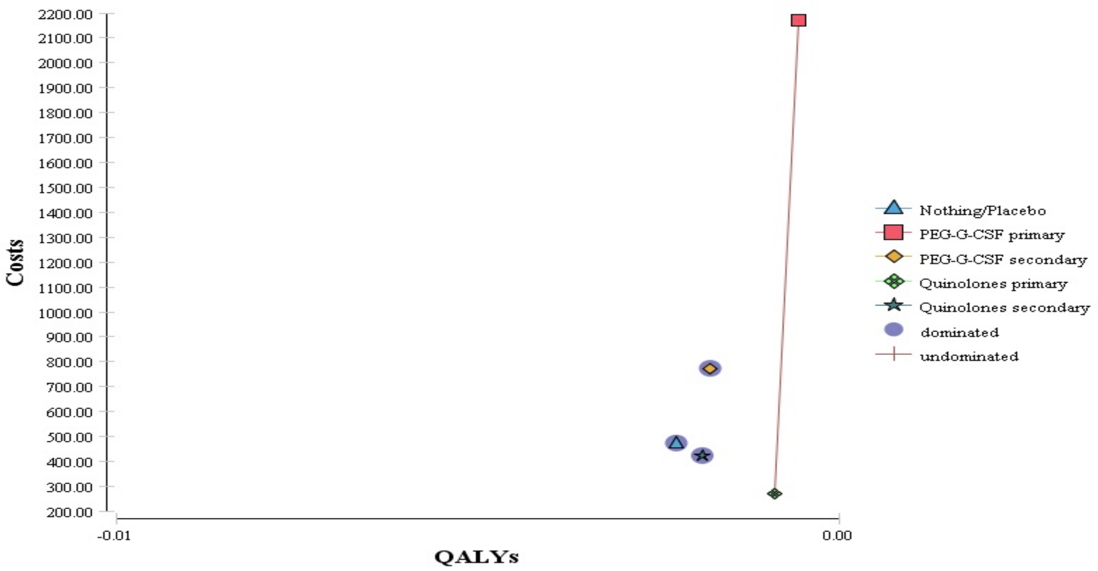
- Nothing/placebo
- Primary prophylaxis with quinolone
- Secondary prophylaxis with quinolone
- Primary prophylaxis with PEG-G-CSF
- Secondary prophylaxis with PEG-G-CSF

The incremental costs and incremental QALYs in the base case analysis for each of the five strategies are summarised in Table A20, and shown graphically in Figure A3. Taking primary prophylaxis with quinolone as the reference (least expensive) strategy, all other strategies were shown to be less effective and also more costly except primary prophylaxis with PEG-G-CSF. Compared to the reference strategy, use of primary PEG-G-CSF produces 3.3×10^{-4} more QALYs and incurs £1,899.8 in additional costs. This yields an incremental cost-effectiveness ratio (ICER) of £5.7 million/QALY, which exceeds the NICE willingness to pay (WTP) threshold of £20,000/QALY. Therefore primary prophylaxis with PEG-G-CSF was considered not to be cost effective. At a willingness to pay (WTP) threshold of £20,000/QALY, primary prophylaxis with quinolone is the most cost-effective strategy.

Table A20 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can take quinolone (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 34.41%).

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Primary prophylaxis with quinolone	£270.4	$-8.9*10^{-4}$	—	—	Comparator	Comparator
Secondary prophylaxis with quinolone	£423.7	$-1.9*10^{-3}$	£153.3	$-1.0*10^{-3}$	Dominated	Dominated
Nothing/Placebo	£473.9	$-2.3*10^{-3}$	£203.5	$-1.4*10^{-3}$	Dominated	Dominated
Secondary prophylaxis with PEG-G-CSF	£773.6	$-1.8*10^{-3}$	£503.2	$-8.9*10^{-4}$	Dominated	Dominated
Primary prophylaxis with PEG-G-CSF	£2170.2	$-5.6*10^{-4}$	£1,899.8	$3.3*10^{-4}$	£5.7 million	£5.7 million

Figure A3 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can take quinolone (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 34.41%).



A6.1.2 For patients who cannot take quinolone

For adult patients with a solid tumour who cannot take quinolone, cost-effectiveness was only formally examined for the following strategies (all strategies containing quinolone were excluded):

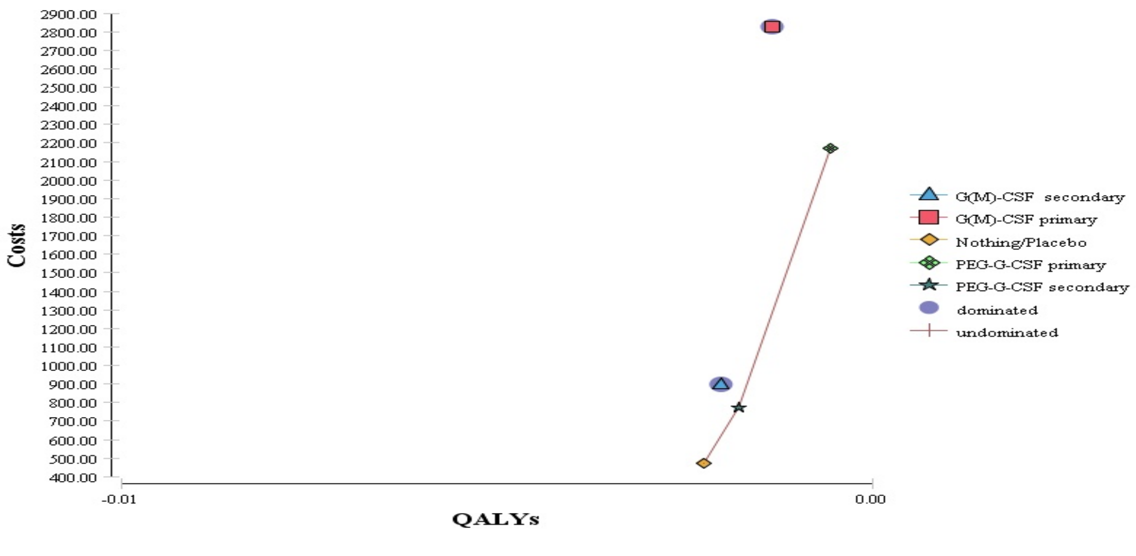
- Nothing/placebo
- Primary prophylaxis with G(M)-CSF
- Secondary prophylaxis with G(M)-CSF
- Primary prophylaxis with PEG-G-CSF
- Secondary prophylaxis with PEG-G-CSF.

The incremental costs and incremental QALYs in the base case analysis for each of the five strategies are summarised in Table A21, and shown graphically in Figure A4. Taking nothing/placebo as the reference (least expensive) strategy, the other four strategies were shown to be more effective but were each associated with a very high ICER (all > £0.6 million/QALY) and were not considered to be cost effective. Therefore at a willingness to pay (WTP) threshold of £20,000/QALY, nothing/placebo is the most cost-effective strategy.

Table A21 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can not take quinolone (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 34.41%).

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nothing/Placebo	£473.9	$-2.3*10^{-3}$	—	—	Comparator	Comparator
Secondary prophylaxis with PEG-G-CSF	£773.6	$-1.8*10^{-3}$	£299.7	$4.7*10^{-4}$	£0.6 million	£0.6 million
Secondary prophylaxis with G(M)-CSF	£898.3	$-2.0*10^{-3}$	£424.3	$2.4*10^{-4}$	£1.8 million	Dominated
Primary prophylaxis with PEG-G-CSF	£2170.2	$-5.6*10^{-4}$-	£1,696.3	$1.7*10^{-3}$	£1.0 million	£1.0 million
Primary prophylaxis with G(M)-CSF	£2826.9	$-1.3*10^{-3}$	£2352.9	$9.2*10^{-4}$	£2.6 million	Dominated

Figure A4 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can not take quinolone (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 34.41%)



A6.2 Structural sensitivity analysis

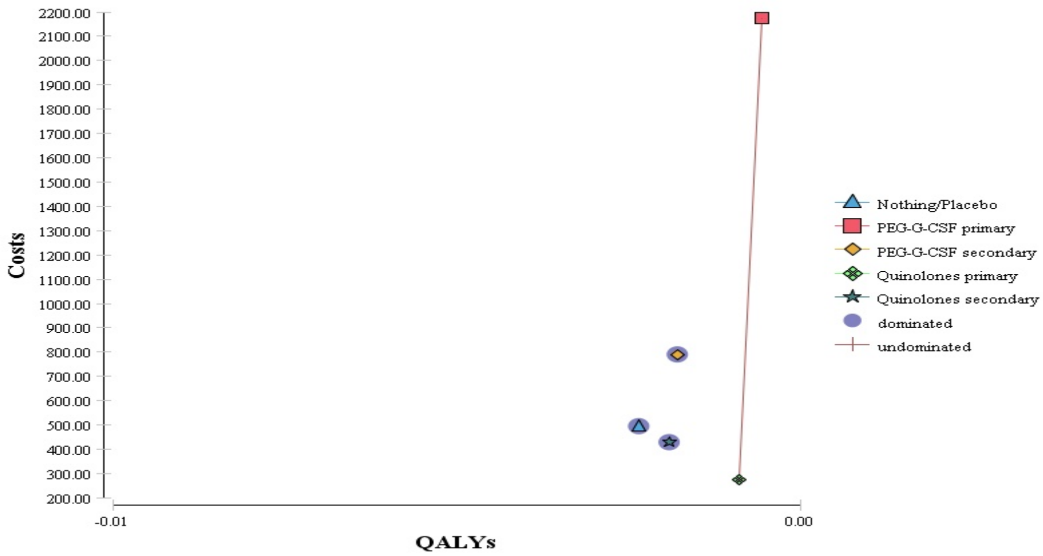
A6.2.1 For patients who can take quinolone

For patients with a solid tumour who can take quinolone, the results of the structural sensitivity analysis are summarised in Table A22, and shown graphically in Figure A5. When using the high-risk model (Model A, 'carry on regardless'), primary prophylaxis with quinolone remains the most cost-effective strategy at a WTP threshold of £20,000/QALY.

Table A22 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can take quinolone (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 34.41%)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Primary prophylaxis with quinolone	£272.8	$-9.0*10^{-4}$	—	—	Comparator	Comparator
Secondary prophylaxis with quinolone	£429.2	$-1.9*10^{-3}$	£156.4	$-1.0*10^{-3}$	Dominated	Dominated
Nothing/Placebo	£495.1	$-2.4*10^{-3}$	£222.3	$-1.5*10^{-3}$	Dominated	Dominated
Secondary prophylaxis with PEG-G-CSF	£790.4	$-1.8*10^{-3}$	£517.7	$-8.9*10^{-4}$	Dominated	Dominated
Primary prophylaxis with PEG-G-CSF	£2,174.8	$-5.6*10^{-4}$	£1,902.1	$3.4*10^{-4}$	£5.6 million	£5.6 million

Figure A5 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can take quinolone (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 34.41%)



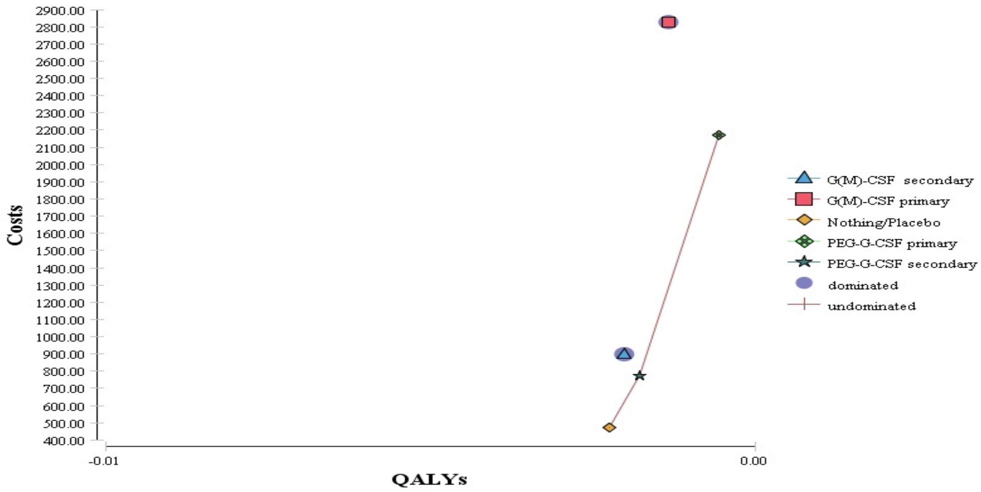
A6.2.2 For patients who can not take quinolone

For adult patients with a solid tumour who cannot take quinolone, the results of the structural sensitivity analysis are summarised in Table A23, and shown graphically in Figure A6. When using the high-risk model (Model A, 'carry on regardless'), nothing/placebo remains the most cost-effective strategy at a WTP threshold of £20,000/QALY.

Table A23 Incremental costs and effectiveness by treatment strategy for solid tumour patients who cannot take quinolone (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 34.41%).

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nothing/Placebo	£473.9	$-2.3*10^{-3}$	—	—	Comparator	Comparator
Secondary prophylaxis with PEG-G-CSF	£773.6	$-1.8*10^{-3}$	£299.7	$4.7*10^{-4}$	£0.6 million	£0.6 million
Secondary prophylaxis with G(M)-CSF	£898.3	$-2.0*10^{-3}$	£424.3	$2.3*10^{-4}$	£1.8 million	Dominated
Primary prophylaxis with PEG-G-CSF	£2,170.2	$-5.6*10^{-4}$	£1,696.3	$1.7*10^{-3}$	£1.0 million	£1.0 million
Primary prophylaxis with G(M)-CSF	£2,826.9	$-1.3*10^{-3}$	£2,352.9	$9.2*10^{-4}$	£2.6 million	Dominated

Figure A6 Incremental costs and effectiveness by treatment strategy for solid tumour patients who can not take quinolone (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 34.41%).



A6.3 One-way sensitivity analysis

A6.3.1 For patients who can take quinolone

Over sixteen scenarios were considered and tested using one-way sensitivity analysis (Section A4.2). The results of one-way sensitivity analyses for adult patients with a solid tumour who can take quinolones are presented below in the following order:

- Primary prophylaxis with quinolone v.s Secondary prophylaxis with quinolone (Table A24)
- Primary prophylaxis with quinolone v.s Nothing/Placebo (Table A25)
- Primary prophylaxis with quinolone v.s Secondary prophylaxis with PEG-G-CSF (Table A26)
- Primary prophylaxis with quinolone v.s Primary prophylaxis with PEG-G-CSF (Table A27)

For adult patients with a solid tumour who can take quinolones, the conclusion of the base case analysis (primary prophylaxis with quinolone being the most cost-effective prophylactic strategy) was robust to all scenarios tested, except for relative risk of a neutropenic sepsis episode (quinolones versus nothing/placebo). When the relative risk of a neutropenic sepsis episode (quinolones versus nothing/placebo) was above 0.787, nothing/placebo became the most cost-effective strategy, at a WTP threshold of £20,000 per QALY.

Table A26 and A27 show that primary or secondary prophylaxis with PEG-G-CSF is never the most cost-effective strategy, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount of PEG-G-CSF, extended length of hospital stay for neutropenic sepsis patients (6-day for low-risk patients and 14-day for high-risk patients) etc.

Table A24 One-way sensitivity analyses results for solid tumour patients who can take quinolone: Primary prophylaxis with quinolones v.s Secondary prophylaxis with quinolone

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	1	£105.1	$-7.1*10^{-4}$	Dominated	Primary quinolone [2]	100%
	6	£131.5	$-9.5*10^{-4}$	Dominated	Primary quinolone	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [3]	5%	£122.9	$-8.4*10^{-4}$	Dominated	Primary quinolone	100%
	100%	£217.0	$-1.7*10^{-3}$	Dominated	Primary quinolone	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£116.2	$-7.7*10^{-4}$	Dominated	Primary quinolone	100%
	10	£154.0	$-1.1*10^{-3}$	Dominated	Primary quinolone	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£113.2	$-8.5*10^{-4}$	Dominated	Primary quinolone	100%
	10	£182.2	$-1.1*10^{-3}$	Dominated	Primary quinolone	100%
SA5: Relative risk of a neutropenic sepsis episode: quinolones versus nothing/placebo	0.1	£278.8	$-1.5*10^{-3}$	Dominated	Primary quinolone	100%
	0.80	-£8.7	$-4.1*10^{-4}$	£20,959	Secondary quinolone [4]	56.9%
	0.95	-£84.5	$-1.4*10^{-4}$	£0.6 million	Secondary quinolone	100%
SA6: Probability of using an ambulance for patients with neutropenic sepsis	0	£124.1	$-1.0*10^{-3}$	Dominated	Primary quinolone	100%
	100%	£190.8	$-1.0*10^{-3}$	Dominated	Primary quinolone	100%
SA7: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£134.5	$-9.5*10^{-4}$	Dominated	Primary quinolone	100%
	20%	£190.9	$-1.1*10^{-3}$	Dominated	Primary quinolone	100%
SA8: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£91.1	$-7.5*10^{-4}$	Dominated	Primary quinolone	100%
	6	£401.9	$-2.0*10^{-3}$	Dominated	Primary quinolone	100%
SA9: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£146.4	$-9.7*10^{-4}$	Dominated	Primary quinolone	100%
	14	£201.6	$-1.2*10^{-3}$	Dominated	Primary quinolone	100%
SA10: Cost per hospital bed day	£100	£70.7	$-1.0*10^{-3}$	Dominated	Primary quinolone	100%
	£1000	£550.1	$-1.0*10^{-3}$	Dominated	Primary quinolone	100%
SA11: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£153.3	$-6.5*10^{-4}$	Dominated	Primary quinolone	100%
	0.38	£153.3	$-1.0*10^{-3}$	Dominated	Primary quinolone	100%
SA12: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£153.3	$-5.5*10^{-4}$	Dominated	Primary quinolone	100%
	0.15	£153.3	$-1.0*10^{-3}$	Dominated	Primary quinolone	100%

1: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
2: Primary quinolone = Primary prophylaxis with quinolone
3: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
4: Secondary quinolone = Secondary prophylaxis with quinolone

Table A25 One-way sensitivity analyses results for solid tumour patients who can take quinolone: Primary prophylaxis with quinolones v.s Nothing/Placebo

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	1	£105.1	$-7.1*10^{-4}$	Dominated	Primary quinolone [2]	100%
	6	£170.4	$-1.3*10^{-3}$	Dominated	Primary quinolone	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [3]	5%	£159.0	$-1.1*10^{-3}$	Dominated	Primary quinolone	100%
	100%	£291.7	$-2.8*10^{-3}$	Dominated	Primary quinolone	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£154.7	$-1.1*10^{-3}$	Dominated	Primary quinolone	100%
	10	£185.8	$-1.3*10^{-3}$	Dominated	Primary quinolone	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£119.4	$-9.3*10^{-4}$	Dominated	Primary quinolone	100%
	10	£251.5	$-1.6*10^{-3}$	Dominated	Primary quinolone	100%
SA5: Relative risk of a neutropenic sepsis episode: quinolones versus nothing/placebo	0.1	£396.5	$-2.1*10^{-3}$	Dominated	Primary quinolone	100%
	0.787	-£11.7	$-5.8*10^{-4}$	£20,155.2	Primary quinolone	39.3%
	0.95	-£120.3	$-1.8*10^{-4}$	£0.7 million	Nothing/ placebo	100%
SA6: Probability of using an ambulance for patients with neutropenic sepsis	0	£164.0	$-1.4*10^{-3}$	Dominated	Primary quinolone	100%
	100%	£254.4	$-1.4*10^{-3}$	Dominated	Primary quinolone	100%
SA7: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£177.6	$-1.3*10^{-3}$	Dominated	Primary quinolone	100%
	20%	£255.3	$-1.5*10^{-3}$	Dominated	Primary quinolone	100%
SA8: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£119.2	$-1.0*10^{-3}$	Dominated	Primary quinolone	100%
	6	£540.9	$-2.7*10^{-3}$	Dominated	Primary quinolone	100%
SA9: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£194.2	$-1.3*10^{-3}$	Dominated	Primary quinolone	100%
	14	£269.1	$-1.6*10^{-3}$	Dominated	Primary quinolone	100%
SA10: Cost per hospital bed day	£100	£96.2	$-1.4*10^{-3}$	Dominated	Primary quinolone	100%
	£1000	£719.6	$-1.4*10^{-3}$	Dominated	Primary quinolone	100%
SA11: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£203.5	$-9.1*10^{-4}$	Dominated	Primary quinolone	100%
	0.38	£203.5	$-1.4*10^{-3}$	Dominated	Primary quinolone	100%
SA12: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£203.5	$-1.4*10^{-3}$	Dominated	Primary quinolone	100%
	0.15	£203.5	$-7.2*10^{-4}$	Dominated	Primary quinolone	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: Primary quinolone = Primary prophylaxis with quinolone
[3]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.

Table A26 One-way sensitivity analyses results for solid tumour patients who can take quinolone: Primary prophylaxis with quinolones v.s Secondary prophylaxis with PEG-G-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	1	£105.1	$-7.1*10^{-4}$	Dominated	Primary quinolone [2]	100%
	6	£895.4	$-8.2*10^{-4}$	Dominated	Primary quinolone	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [3]	5%	£423.5	$-7.6*10^{-4}$	Dominated	Primary quinolone	100%
	100%	£1,054.9	$-9.8*10^{-4}$	Dominated	Primary quinolone	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£271.8	$-6.7*10^{-4}$	Dominated	Primary quinolone	100%
	10	£634.3	$-9.9*10^{-4}$	Dominated	Primary quinolone	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£512.8	$-8.4*10^{-4}$	Dominated	Primary quinolone	100%
	10	£496.2	$-9.4*10^{-4}$	Dominated	Primary quinolone	100%
SA5: Relative risk of a neutropenic sepsis episode: quinolones versus nothing/placebo	0.1	£696.2	$-1.6*10^{-3}$	Dominated	Primary quinolone	100%
	0.95	£179.4	$2.9*10^{-4}$	£0.6 million	Primary quinolone	100%
SA6: Relative risk of a neutropenic sepsis episode: PEG-G-CSF versus nothing/placebo	0.1	£485.1	$-7.5*10^{-4}$	Dominated	Primary quinolone	100%
	0.95	£551.3	$-1.3*10^{-3}$	Dominated	Primary quinolone	100%
SA7: Probability of self administrating PEG-G-CSF	0	£509.3	$-8.9*10^{-4}$	Dominated	Primary quinolone	100%
	100%	£497.2	$-8.9*10^{-4}$	Dominated	Primary quinolone	100%
SA8: Probability of using an ambulance for patients with neutropenic sepsis	0	£477.2	$-8.9*10^{-4}$	Dominated	Primary quinolone	100%
	100%	£536.8	$-8.9*10^{-4}$	Dominated	Primary quinolone	100%
SA9: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£486.9	$-8.5*10^{-4}$	Dominated	Primary quinolone	100%
	20%	£536.0	$-9.7*10^{-4}$	Dominated	Primary quinolone	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£447.7	$-6.7*10^{-4}$	Dominated	Primary quinolone	100%
	6	£725.6	$-1.8*10^{-3}$	Dominated	Primary quinolone	100%
SA11: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£497.1	$-8.7*10^{-4}$	Dominated	Primary quinolone	100%
	14	£546.5	$-1.1*10^{-3}$	Dominated	Primary quinolone	100%
SA12: Cost per hospital bed day	£100	£138.1	$-8.9*10^{-4}$	Dominated	Primary quinolone	100%
	£1000	£776.1	$-8.9*10^{-4}$	Dominated	Primary quinolone	100%
SA13: Drug discounts of PEG-G-CSF	0% [4]	£503.2	$-8.9*10^{-4}$	Dominated	Primary quinolone	100%
	90% [5]	£149.5	$-8.9*10^{-4}$	Dominated	Primary quinolone	98.1%
SA14: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£503.2	$-6.5*10^{-4}$	Dominated	Primary quinolone	100%
	0.38	£503.2	$-8.9*10^{-4}$	Dominated	Primary quinolone	100%
SA15: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£503.2	$-3.8*10^{-4}$	Dominated	Primary quinolone	100%
	0.15	£503.2	$-9.3*10^{-4}$	Dominated	Primary quinolone	100%

1: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
2: Primary quinolone = Primary prophylaxis with quinolone
3: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
4: Corresponding price of PEG-G-CSF (when 0% discount is used): £686.38 per single subcutaneous injection (6mg).

[5]: Corresponding price of PEG-G-CSF (when 90% discount is used): £68.6 per single subcutaneous injection (6mg).

Table A27 One-way sensitivity analyses results for solid tumour patients who can take quinolone: Primary prophylaxis with quinolones v.s Primary prophylaxis with PEG-G-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	1	£611.7	$1.9*10^{-4}$	£3.2 million	Primary quinolone [2]	100%
	6	£3987.8	$3.3*10^{-4}$	£11.9 million	Primary quinolone	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [3]	5%	£1925.3	$2.7*10^{-4}$	£7.1 million	Primary quinolone	100%
	100%	£1389.2	$1.4*10^{-3}$	£1.0 million	Primary quinolone	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£2136.1	$2.5*10^{-4}$	£7.8 million	Primary quinolone	100%
	10	£1893.1	$3.5*10^{-4}$	£5.4 million	Primary quinolone	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£1925.4	$2.7*10^{-4}$	£7.2 million	Primary quinolone	100%
	10	£1881.2	$3.8*10^{-4}$	£4.9 million	Primary quinolone	100%
SA5: Relative risk of a neutropenic sepsis episode: quinolones versus nothing/placebo	0.1	£2092.7	$-3.7*10^{-4}$	Dominated	Primary quinolone	100%
	0.95	£1576.0	$1.5*10^{-3}$	£1.0 million	Primary quinolone	100%
SA6: Relative risk of a neutropenic sepsis episode: PEG-G-CSF versus nothing/placebo	0.1	£1825.8	$7.1*10^{-4}$	£2.6 million	Primary quinolone	100%
	0.95	£2155.9	$-1.1*10^{-3}$	Dominated	Primary quinolone	100%
SA7: Probability of self administrating PEG-G-CSF	0	£1930.8	$3.3*10^{-4}$	£5.8 million	Primary quinolone	100%
	100%	£1868.8	$3.3*10^{-4}$	£5.6 million	Primary quinolone	100%
SA8: Probability of using an ambulance for patients with neutropenic sepsis	0	£1909.3	$3.3*10^{-4}$	£5.7 million	Primary quinolone	100%
	100%	£1887.5	$3.3*10^{-4}$	£5.7 million	Primary quinolone	100%
SA9: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£1906.9	$3.0*10^{-4}$	£6.4 million	Primary quinolone	100%
	20%	£1885.6	$4.1*10^{-4}$	£4.6 million	Primary quinolone	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£1920.1	$2.5*10^{-4}$	£7.7 million	Primary quinolone	100%
	6	£1818.5	$6.7*10^{-4}$	£2.7 million	Primary quinolone	100%
SA11: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£1902.1	$3.2*10^{-4}$	£5.9 million	Primary quinolone	100%
	14	£1884.0	$4.0*10^{-4}$	£4.7 million	Primary quinolone	100%
SA12: Cost per hospital bed day	£100	£1974.6	$3.3*10^{-4}$	£5.9 million	Primary quinolone	100%
	£1000	£1540.5	$3.3*10^{-4}$	£4.6 million	Primary quinolone	100%
SA13: Drug discounts of PEG-G-CSF	0% [4]	£1899.8	$3.3*10^{-4}$	£5.7 million	Primary quinolone	100%
	90% [5]	£78.5	$3.3*10^{-4}$	£0.2 million	Primary quinolone	81.0%
SA14: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£1899.8	$2.0*10^{-5}$	£113.5 million	Primary quinolone	100%
	0.38	£1899.8	$3.3*10^{-4}$	£5.7 million	Primary quinolone	100%
SA15: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£1899.8	$5*10^{-4}$	£3.8 million	Primary quinolone	100%
	0.15	£1899.8	$3.2*10^{-4}$	£5.9 million	Primary quinolone	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: Primary quinolone = Primary prophylaxis with quinolone
[3]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.

[4]: Corresponding price of PEG-G-CSF (when 0% discount is used): £686.38 per single subcutaneous injection (6mg).
[5]: Corresponding price of PEG-G-CSF (when 90% discount is used): £68.6 per single subcutaneous injection (6mg).

A6.3.2 For patients who can not take quinolone

Over sixteen scenarios were considered and tested using one-way sensitivity analysis (Section A4.2). The results of one-way sensitivity analyses for adult patients with a solid tumour who can take quinolones are presented below in the following order:

- Nothing/Placebo v.s Secondary prophylaxis with PEG-G-CSF (Table A28)
- Nothing/Placebo v.s Secondary prophylaxis with G(M)-CSF (Table A29)
- Nothing/Placebo v.s Primary prophylaxis with PEG-G-CSF (Table A30)
- Nothing/Placebo with quinolone v.s Primary prophylaxis with G(M)-CSF (Table A31)

For adult patients with a solid tumour who cannot take quinolones, the conclusion of the base case analysis (nothing/placebo being the most cost-effective prophylaxis strategy) was robust to all scenarios tested (Section A4.2), except for discounting the cost of PEG-G-CSF. At a WTP threshold of £20,000/QALY:

- When the discount to the cost of PEG-G-CSF was over 73.85% (corresponding price: £179.5 per single subcutaneous injection (6mg)), secondary prophylaxis with PEG-G-CSF became the most cost-effective strategy.
- When the discount to the cost of PEG-G-CSF was over 84.13% (corresponding price: £108.9 per single subcutaneous injection (6mg)), primary prophylaxis with PEG-G-CSF became the most cost-effective strategy.

Table A29 and A31 show that primary or secondary prophylaxis with G(M)-CSF is never the most cost-effective strategy, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount of G(M)-CSF, reduced days of using G(M)-CSF (5-day per cycle of chemotherapy), reduced daily dose (one vial of G(M)-CSF for all adult patients regardless of patient weight) etc.

Table A28. One-way sensitivity analyses results for solid tumour patients who cannot take quinolone: Nothing/placebo v.s Secondary prophylaxis with PEG-G-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	2 [2]	£117.9	$3.0*10^{-4}$	£0.4 million	Nothing/ placebo	100%
	6	£725.0	$4.9*10^{-4}$	£1.5 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [3]	5%	£264.5	$3.4*10^{-4}$	£0.8 million	Nothing/ placebo	100%
	100%	£763.2	$1.9*10^{-3}$	£0.4 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£117.1	$3.8*10^{-4}$	£0.3 million	Nothing/ placebo	100%
	10	£448.6	$3.1*10^{-4}$	£1.4 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£393.3	$9.0*10^{-5}$	£4.3 million	Nothing/ placebo	100%
	10	£244.7	$6.8*10^{-4}$	£0.4 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: PEG-G-CSF versus nothing/placebo	0.1	£281.6	$6.1*10^{-4}$	£0.5 million	Nothing/ placebo	100%
	0.95	£347.7	$7.0*10^{-5}$	£5.0 million	Nothing/ placebo	100%
SA6: Probability of self administrating PEG-G-CSF	0	£305.7	$4.7*10^{-4}$	£0.7 million	Nothing/ placebo	100%
	100%	£293.7	$4.7*10^{-4}$	£0.6 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£313.2	$4.7*10^{-4}$	£0.7 million	Nothing/ placebo	100%
	100%	£282.4	$4.7*10^{-4}$	£0.6 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high	5%	£309.2	$4.4*10^{-4}$	£0.7 million	Nothing/ placebo	100%

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
risk of serious adverse events	20%	£280.6	$5.3*10^{-4}$	£0.5 million	Nothing/ placebo	100%
SA9: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£328.4	$3.5*10^{-4}$	£0.9 million	Nothing/ placebo	100%
	6	£1226.5	$9.4*10^{-4}$	£0.2 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£302.9	$4.6*10^{-4}$	£0.7 million	Nothing/ placebo	100%
	14	£277.3	$5.6*10^{-4}$	£0.5 million	Nothing/ placebo	100%
SA11: Cost per hospital bed day	£100	£350.3	$4.7*10^{-4}$	£0.7 million	Nothing/ placebo	100%
	£1000	£56.5	$4.7*10^{-4}$	£0.1 million	Nothing/ placebo	77.1%
SA12: Drug discounts of PEG-G-CSF	0% [4]	£299.7	$4.7*10^{-4}$	£0.6 million	Nothing/ placebo	100%
	73.85% [5]	£9.5	$4.7*10^{-4}$	£20,127	Nothing/ placebo	52.2%
	90% [6]	-£54.0	$4.7*10^{-4}$	Dominate	Secondary PEG-G-CSF [7]	100%
SA13: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£299.7	$2.5*10^{-4}$	£1.2 million	Nothing/ placebo	100%
	0.38	£299.7	$4.7*10^{-4}$	£0.6 million	Nothing/ placebo	100%
SA14: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£299.7	$3.4*10^{-4}$	£0.9 million	Nothing/ placebo	100%
	0.15	£299.7	$4.8*10^{-4}$	£0.6 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In cycle 1, there is no clinical or cost difference between the two arms:

- 'Nothing/placebo'
- 'Secondary prophylaxis with G(M)-CSF'

as patients in the second arm will not receive G(M)-CSF until they have had one episode of neutropenic sepsis in previous cycles. Therefore in one-way sensitivity analysis, we only tested a range of 2-6 cycles.
[3]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[4]: Corresponding price of PEG-G-CSF (when 0% discount is used): £686.38 per single subcutaneous injection (6mg).
[5]: Corresponding price of PEG-G-CSF (when 73.85% discount is used): £179.5 per single subcutaneous injection (6mg).
[6]: Corresponding price of PEG-G-CSF (when 90% discount is used): £68.6 per single subcutaneous injection (6mg).
[7]: Secondary PEG-G-CSF = Secondary prophylaxis with PEG-G-CSF.

Table A29 One-way sensitivity analyses results for solid tumour patients who can not take quinolone: Nothing/placebo v.s Secondary prophylaxis with G(M)-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	2 [2]	£192.9	$1.6*10^{-4}$	£1.2 million	Nothing/ placebo	100%
	6	£851.2	$2.3*10^{-4}$	£3.8 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [3]	5%	£367.0	$1.7*10^{-4}$	£2.2 million	Nothing/ placebo	100%
	100%	£1,007.0	$5.9*10^{-4}$	£1.7 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£185.9	$1.8*10^{-4}$	£1.0 million	Nothing/ placebo	100%
	10	£594.5	$1.6*10^{-4}$	£3.7 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£502.3	$5.0*10^{-5}$	£10.6 million	Nothing/ placebo	100%
	10	£374.8	$3.2*10^{-4}$	£1.2 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: G(M)-CSF versus nothing/placebo	0.1	£384.9	$6.1*10^{-4}$	£0.6 million	Nothing/ placebo	100%
	0.95	£439.4	$7.0*10^{-5}$	£6.4 million	Nothing/ placebo	100%
SA6: Probability of self administrating G(M)-CSF	0%	£470.0	$2.4*10^{-4}$	£2.0 million	Nothing/ placebo	100%

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
	100%	£378.6	$2.4*10^{-4}$	£1.6 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£430.4	$2.4*10^{-4}$	£1.83 million	Nothing/ placebo	100%
	100%	£416.5	$2.4*10^{-4}$	£1.77 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£431.4	$2.1*10^{-4}$	£2.1 million	Nothing/ placebo	100%
	20%	£410.1	$2.9*10^{-4}$	£1.4 million	Nothing/ placebo	100%
SA9: Days of using G(M)-CSF for each cycle of chemotherapy	5 d	£246.3	$2.4*10^{-4}$	£1.0 million	Nothing/ placebo	100%
	11 d	£602.4	$2.4*10^{-4}$	£2.6 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£437.3	$1.8*10^{-4}$	£2.4 million	Nothing/ placebo	100%
	6	£372.4	$4.5*10^{-4}$	£0.8 million	Nothing/ placebo	100%
SA11: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£425.8	$2.3*10^{-4}$	£1.9 million	Nothing/ placebo	100%
	14	£414.2	$2.8*10^{-4}$	£1.5 million	Nothing/ placebo	100%
SA12: Cost per hospital bed day	£100	£450.6	$2.4*10^{-4}$	£1.9 million	Nothing/ placebo	100%
	£1000	£298.1	$2.4*10^{-4}$	£1.3 million	Nothing/ placebo	100%
SA13: Daily cost of G(M)-CSF per person	£60.69 [4]	£259.4	$2.4*10^{-4}$	£1.1 million	Nothing/ placebo	100%
	£98.57 [5]	£424.3	$2.4*10^{-4}$	£1.8 million	Nothing/ placebo	100%
SA14: Drug discounts of G(M)-CSF	0%[6]	£424.3	$2.4*10^{-4}$	£1.8 million	Nothing/ placebo	100%
	90% [7]	£38.1	$2.4*10^{-4}$	£0.2 million	Nothing/ placebo	100%
SA15: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£424.3	$1.2*10^{-4}$	£3.4 million	Nothing/ placebo	100%
	0.38	£424.3	$2.4*10^{-4}$	£1.8 million	Nothing/ placebo	100%
SA16: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£424.3	$1.8*10^{-4}$	£2.4 million	Nothing/ placebo	100%
	0.15	£424.3	$2.4*10^{-4}$	£1.8 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In cycle 1, there is no clinical or cost difference between the two arms:

- 'Nothing/placebo'
- 'Secondary prophylaxis with G(M)-CSF'

as patients in the second arm will not receive G(M)-CSF until they have had one episode of neutropenic sepsis in previous cycles. Therefore in one-way sensitivity analysis, we only tested a range of 2-6 cycles.

[3]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.

[4]: Average cost of filgrastim and lenograstim assuming the daily dose of G(M)-CSF is 30 million-units for all adult patients regardless of weight.

[5]: Calculated from filgrastim and lenograstim based on patient weight distribution reported by: Green 2003, Romieu 2007 and Gigg 2003 (see Appendix A10).

[6]: Corresponding price of G(M)-CSF (when 0% discount is used):

- Filgrastim (30 million-unit syringe): £58.84.
- Filgrastim (48 million-unit syringe): £93.93.
- Lenograstim (13.4 million-unit syringe): £31.39.
- Lenograstim (33.6 million-unit syringe): £62.54.

[7]: Corresponding price of G(M)-CSF (when 90% discount is used):

- Filgrastim (30 million-unit syringe): £5.9.
- Filgrastim (48 million-unit syringe): £9.4.
- Lenograstim (13.4 million-unit syringe): £3.1.
- Lenograstim (33.6 million-unit syringe): £6.3.

Table A30 One-way sensitivity analyses results for solid tumour patients who cannot take quinolone: Nothing/placebo v.s Primary prophylaxis with PEG-G-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	1	£506.5	$9.0*10^{-4}$	£0.6 million	Nothing/ placebo	100%
	6	£3,727.4	$1.6*10^{-3}$	£2.3 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [2]	5%	£1,766.3	$1.4*10^{-3}$	£1.3 million	Nothing/ placebo	100%
	100%	£1,097.4	$4.3*10^{-3}$	£0.3 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£1,780.3	$1.3*10^{-3}$	£1.4 million	Nothing/ placebo	100%
	10	£1,707.4	$1.7*10^{-3}$	£1.0 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£1,806.0	$1.2*10^{-3}$	£1.5 million	Nothing/ placebo	100%
	10	£1,629.7	$2.0*10^{-4}$	£0.8 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: PEG-G-CSF versus nothing/placebo	0.1	£1,622.2	$2.1*10^{-3}$	£0.8 million	Nothing/ placebo	100%
	0.95	£1,952.4	$2.6*10^{-4}$	£7.6 million	Nothing/ placebo	100%
SA6: Probability of self administrating PEG-G-CSF	0	£1,727.2	$1.7*10^{-3}$	£1.02 million	Nothing/ placebo	100%
	100%	£1,665.3	$41.7*10^{-3}$	£0.98 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£1,745.3	$1.7*10^{-3}$	£1.03 million	Nothing/ placebo	100%
	100%	£1,633.2	$1.7*10^{-3}$	£0.96 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£1,729.2	$1.6*10^{-3}$	£1.1 million	Nothing/ placebo	100%
	20%	£1,630.3	$1.9*10^{-3}$	£0.9 million	Nothing/ placebo	100%
SA9: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£1,800.9	$1.3*10^{-3}$	£1.4 million	Nothing/ placebo	100%
	6	£1,277.6	$3.4*10^{-3}$	£0.4 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£1,707.9	$1.7*10^{-3}$	£1.0 million	Nothing/ placebo	100%
	14	£1,614.9	$2.0*10^{-3}$	£0.8 million	Nothing/ placebo	100%
SA11: Cost per hospital bed day	£100	£1,878.4	$1.7*10^{-3}$	£1.1 million	Nothing/ placebo	100%
	£1000	£820.9	$1.7*10^{-3}$	£0.5 million	Nothing/ placebo	77.1%
SA12: Drug discounts of PEG-G-CSF	0% [3]	£1,696.3	$1.7*10^{-3}$	£1.0 million	Nothing/ placebo	100%
	82.1% [4]	£34.8	$1.7*10^{-3}$	£20,551.3	Nothing/ placebo	51.6%
	90% [5]	-£125.0	$-1.7*10^{-3}$	Dominate	Primary PEG-G-CSF [6]	97.7%
SA13: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£1,696.3	$9.2*10^{-4}$	£1.8 million	Nothing/ placebo	100%
	0.38	£1,696.3	$1.7*10^{-3}$	£1.0 million	Nothing/ placebo	100%
SA14: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£1,696.3	$1.2*10^{-3}$	£1.4 million	Nothing/ placebo	100%
	0.15	£1,696.3	$1.7*10^{-3}$	£1.0 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[3]: Corresponding price of PEG-G-CSF (when 0% discount is used): £686.38 per single subcutaneous injection (6mg).
[4]: Corresponding price of PEG-G-CSF (when 82.1% discount is used): £112.9 per single subcutaneous injection (6mg).
[5]: Corresponding price of PEG-G-CSF (when 90% discount is used): £68.6 per single subcutaneous injection (6mg).

[6:] Primary PEG-G-CSF = Primary prophylaxis with PEG-G-CSF.

Table A31 One-way sensitivity analyses results for solid tumour patients who can take quinolone: Nothing/ placebo v.s Primary prophylaxis with G(M)-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	1	£771.5	$4.7*10^{-4}$	£1.6 million	Nothing/ placebo	100%
	6	£4,733.9	$8.7*10^{-4}$	£5.5 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [2]	5%	£2,399.6	$7.4*10^{-4}$	£3.2 million	Nothing/ placebo	100%
	100%	£1,884.6	$1.5*10^{-3}$	£1.3 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£2,399.1	$7.1*10^{-4}$	£3.4 million	Nothing/ placebo	100%
	10	£2,374.8	$8.7*10^{-4}$	£2.7 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£2,442.9	$6.1*10^{-4}$	£4.0 million	Nothing/ placebo	100%
	10	£2,296.9	$1.1*10^{-3}$	£2.1million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: G(M)-CSF versus nothing/placebo	0.1	£2,141.1	$2.1*10^{-3}$	£1.0 million	Nothing/ placebo	100%
	0.95	£2,459.3	$2.6*10^{-4}$	£9.6 million	Nothing/ placebo	100%
SA6: Probability of self administrating G(M)-CSF	0%	£2,598.3	$9.2*10^{-4}$	£2.8 million	Nothing/ placebo	100%
	100%	£2,107.5	$9.2*10^{-4}$	£2.3 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£2,377.5	$9.2*10^{-4}$	£2.6 million	Nothing/ placebo	100%
	100%	£2,321.3	$9.2*10^{-4}$	£2.5 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£3,377.9	$8.3*10^{-4}$	£2.9 million	Nothing/ placebo	100%
	20%	£2,303.0	$1.1*10^{-3}$	£2.1 million	Nothing/ placebo	100%
SA9: Days of using G(M)-CSF for each cycle of chemotherapy	5 d	£1,397.0	$9.2*10^{-4}$	£1.5 million	Nothing/ placebo	100%
	11 d	£3,308.9	$9.2*10^{-4}$	£3.6million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£2,405.3	$7.0*10^{-4}$	£3.4 million	Nothing/ placebo	100%
	6	£2,143.3	$1.8*10^{-3}$	£1.2 million	Nothing/ placebo	100%
SA11: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£2,358.7	$8.9*10^{-4}$	£2.6 million	Nothing/ placebo	100%
	14	£2,312.2	$1.1*10^{-3}$	£2.1 million	Nothing/ placebo	100%
SA12: Cost per hospital bed day	£100	£2,454.4	$9.2*10^{-4}$	£2.7 million	Nothing/ placebo	100%
	£1000	£1,865.3	$9.2*10^{-4}$	£2.0 million	Nothing/ placebo	100%
SA13: Daily cost of G(M)-CSF per person	£60.69 [3]	£1,467.6	$9.2*10^{-4}$	£1.6 million	Nothing/ placebo	100%
	£98.57 [4]	£2,352.9	$9.2*10^{-4}$	£2.6 million	Nothing/ placebo	100%
SA14: Drug discounts of G(M)-CSF	0% [5]	£3,352.9	$9.2*10^{-4}$	£2.6 million	Nothing/ placebo	100%
	90% [6]	£279.5	$9.2*10^{-4}$	£0.3 million	Nothing/ placebo	100%

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA15: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£2,352.9	$4.9*10^{-4}$	£4.8 million	Nothing/ placebo	100%
	0.38	£2,352.9	$9.2*10^{-4}$	£2.6 million	Nothing/ placebo	100%
SA16: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£2,352.9	$6.8*10^{-4}$	£3.5 million	Nothing/ placebo	100%
	0.15	£2,352.9	$9.3*10^{-4}$	£2.5 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2:] In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[3:] Average cost of filgrastim and lenograstim assuming the daily dose of G(M)-CSF is 30 million-units for all adult patients regardless of weight.
[4:] Calculated from filgrastim and lenograstim based on patient weight distribution reported by: Green 2003, Romieu 2007 and Gigg 2003 (see Appendix A10).
[5]: Corresponding price of G(M)-CSF (when 0% discount is used):

- Filgrastim (30 million-unit syringe): £58.84.
- Filgrastim (48 million-unit syringe): £93.93.
- Lenograstim (13.4 million-unit syringe): £31.39.
- Lenograstim (33.6 million-unit syringe): £62.54.

[6]: Corresponding price of G(M)-CSF (when 90% discount is used):

- Filgrastim (30 million-unit syringe): £5.9.
- Filgrastim (48 million-unit syringe): £9.4.
- Lenograstim (13.4 million-unit syringe): £3.1.
- Lenograstim (33.6 million-unit syringe): £6.3.

A6.4 Probabilistic sensitivity analysis

A6.4.1 For patients who can take quinolones

For patients with a solid tumour who can take quinolones, the probability of primary prophylaxis with quinolone becoming cost-effective is always 100%, at a willingness to pay between £10,000 to £40,000 per QALY.

A6.4.2 For patients who cannot take quinolones

For patients with a solid tumour who cannot take quinolones, the probability of nothing/placebo becoming cost-effective is always 100%, at a willingness to pay between £10,000 to £40,000 per QALY.

A7 Results ─ Non-Hodgkin lymphoma sub group

The results for patients with adult non-Hodgkin lymphoma are presented below in the following order:

- base case analysis (section A7.1)
- structural sensitivity analysis (section A7.2)
- one-way sensitivity analysis (section A7.3)
- probabilistic sensitivity analysis (section A7.4)

Both strategies including quinolone are excluded from formal cost-effectiveness analysis, either because of no clinical evidence (quinolone alone) or prior dominated (more expensive and less effective) by other strategies (quinolone plus G(M)-CSF). The reasons for exclusion are detailed in section A7.1. As a result, no separate analyses were conducted for adult patients with non-Hodgkin lymphoma who can or cannot take quinolones.

A7.1 Base case analysis

For adult/elderly patients with non-Hodgkin lymphoma, no clinical evidence was identified for the use of quinolone alone for either primary or secondary prophylaxis therefore neither strategy was included in this analysis.

Compared to G(M)-CSF alone, G(M)-CSF + quinolone is more expensive and less effective in terms of preventing neutropenic sepsis (Table A4 and A9) so both primary and secondary prophylactic G(M)-CSF + quinolone strategies were excluded. As a result cost-effectiveness was only formally examined for the following five strategies:

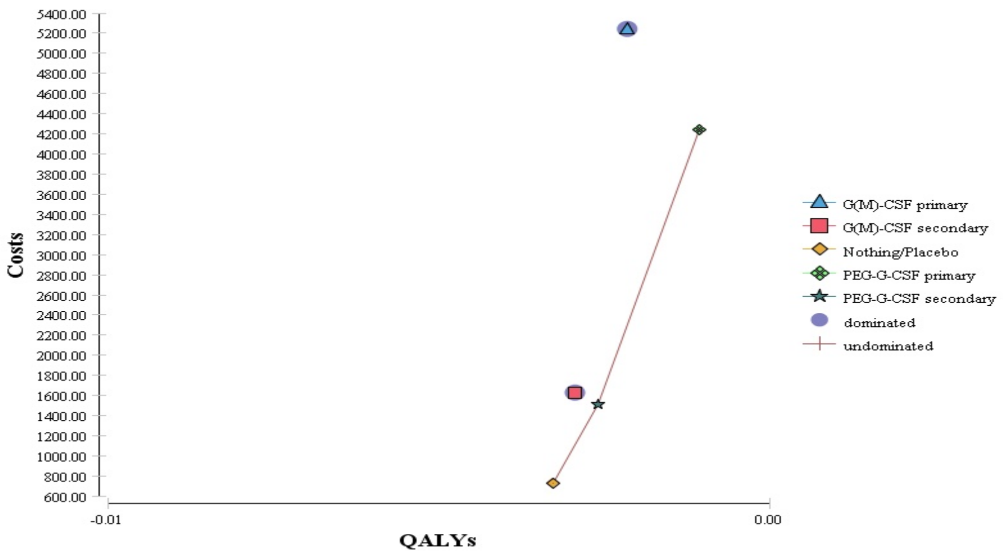
- Nothing/placebo
- Primary prophylaxis with G(M)-CSF
- Secondary prophylaxis with G(M)-CSF
- Primary prophylaxis with PEG-G-CSF
- Secondary prophylaxis with PEG-G-CSF

The incremental costs and incremental QALYs in the base case analysis for each of the five strategies are summarised in Table A32, and shown graphically in Figure A7. Taking nothing/placebo as the reference (least expensive) strategy, the other four strategies were shown to be more effective, but were each associated with a very high ICER (all > £1.2 million/QALY) and were not considered to be cost effective. Therefore at a WTP threshold of £20,000/QALY, nothing/placebo is the most cost-effective strategy.

Table A32 Incremental costs and effectiveness by treatment strategy for non-Hodgkin lymphoma patients (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 44.22%)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nothing/Placebo	£729.2	$-3.3*10^{-3}$	—	—	Comparator	Comparator
Secondary prophylaxis with PEG-G-CSF	£1,510.7	$-2.9*10^{-3}$	£781.4	$6.7*10^{-4}$	£1.2 million	£1.2 million
Secondary prophylaxis with G(M)-CSF	£1,629.0	$-2.6*10^{-3}$	£899.7	$3.2*10^{-4}$	£2.8 million	Dominated
Primary prophylaxis with PEG-G-CSF	£4,238.1	$-2.1*10^{-3}$	£3,508.9	$2.2*10^{-3}$	£1.6 million	£1.8 million
Primary prophylaxis with G(M)-CSF	£5,242.0	$-1.1*10^{-3}$	£4,512.8	$1.1*10^{-3}$	£4.1 million	Dominated

Figure A7 Incremental costs and effectiveness by treatment strategy for patients with non-Hodgkin lymphoma (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 44.22%)



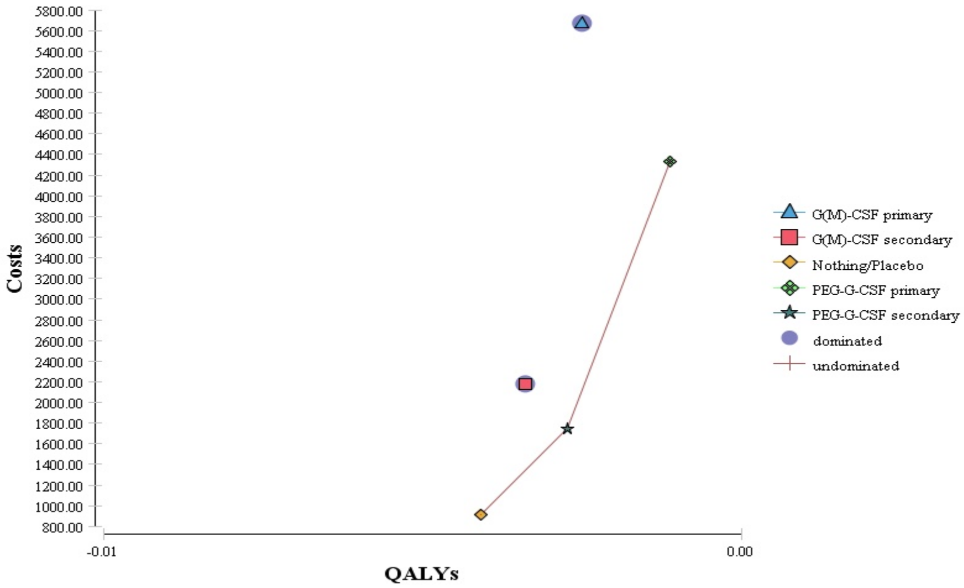
A7.2 Structural sensitivity analysis

For adult patients with non-Hodgkin lymphoma, the results of the structural sensitivity analysis are summarised in Table A33, and shown graphically in Figure A8. When using the high-risk model (Model A, 'carry on regardless'), nothing/placebo remains the most cost-effective strategy, at a WTP threshold of £20,000/QALY.

Table A33 Incremental costs and effectiveness by treatment strategy for non-Hodgkin lymphoma patients; Model A (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 44.22%)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nothing/Placebo	£913.1	$-4.1*10^{-3}$	—	—	Comparator	Comparator
Secondary prophylaxis with PEG-G-CSF	£1,746.0	$-2.7*10^{-3}$	£832.9	$1.4*10^{-3}$	£0.6 million	£0.6 million
Secondary prophylaxis with G(M)-CSF	£2,179.0	$-3.4*10^{-3}$	£1265.9	$7.0*10^{-4}$	£1.8 million	Dominated
Primary prophylaxis with PEG-G-CSF	£4,333.6	$-1.1*10^{-3}$	£3,420.5	$3.0*10^{-3}$	£1.1 million	£1.6 million
Primary prophylaxis with G(M)-CSF	£5,670.1	$-2.5*10^{-3}$	£4,757.1	$1.6*10^{-3}$	£3.0 million	Dominated

Figure A8 Incremental costs and effectiveness by treatment strategy for non-Hodgkin lymphoma patients, model A (baseline risk of neutropenic sepsis of one course of chemotherapy: 44.22%)



A7.3 One-way sensitivity analysis

Over sixteen scenarios were considered and tested using one-way sensitivity analysis (Section A4.2). The results of one-way sensitivity analyses for adult patients with a solid tumour who can take quinolones are presented below in the following order:

- Nothing/Placebo v.s Secondary prophylaxis with PEG-G-CSF (Table A34)
- Nothing/Placebo v.s Secondary prophylaxis with G(M)-CSF (Table A35)
- Nothing/Placebo v.s Primary prophylaxis with PEG-G-CSF (Table A36)
- Nothing/Placebo with quinolone v.s Primary prophylaxis with G(M)-CSF (Table A37)

For adult patients with non-Hodgkin lymphoma, the conclusion of the base case analysis (i.e. nothing/placebo being the most cost-effective prophylactic strategy) was robust to all of scenarios tested (Section A4.2), except for discounting the cost of PEG-G-CSF. At a WTP threshold of £20,000/QALY:

- When the discount to the cost of PEG-G-CSF was over 83.49% (corresponding price: £113.3 per single subcutaneous injection (6mg)), secondary prophylaxis with PEG-G-CSF became the most cost-effective strategy.
- When the discount to the cost of PEG-G-CSF was over 89.12% (corresponding price: £74.7 per single subcutaneous injection (6mg)), primary prophylaxis with PEG-G-CSF became the most cost-effective strategy.

Table A35 and A37 show that primary or secondary prophylaxis with G(M)-CSF is never the most cost-effective strategy, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount of G(M)-CSF, reduced days of using G(M)-CSF (5-day per cycle of chemotherapy), reduced daily dose (one vial of G(M)-CSF for all adult patients regardless of weight) etc.

Table A34 One-way sensitivity analyses results for non-Hodgkin lymphoma patients: Nothing/placebo v.s Secondary prophylaxis with PEG-G-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	3	£315.3	$7.2*10^{-4}$	£0.4 million	Nothing/ placebo	100%
	6	£781.4	$6.7*10^{-4}$	£1.2 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [2]	5%	£1,492.6	$6.6*10^{-4}$	£1.2 million	Nothing/ placebo	100%
	8.42%	£1,018.2	$1.0*10^{-3}$	£1.0 million	Nothing/ placebo	100%
	100%	£1,361.8	$8.2*10^{-4}$	£1.7 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£381.8	$4.7*10^{-4}$	£0.8 million	Nothing/ placebo	100%
	10	£1,247.6	$7.2*10^{-4}$	£1.7 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£1,580.6	$2.0*10^{-4}$	£5.2 million	Nothing/ placebo	100%
	10	£1,451.5	$6.8*10^{-4}$	£1.0 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: PEG-G-CSF versus nothing/placebo	0.1	£845.3	$1.1*10^{-3}$	£0.8 million	Nothing/ placebo	100%
	0.95	£665.0	$2.0*10^{-3}$	£3.3 million	Nothing/ placebo	100%
SA6: Probability of self administrating PEG-G-CSF	0	£795.5	$6.7*10^{-4}$	£1.2 million	Nothing/ placebo	100%
	100%	£767.4	$6.7*10^{-4}$	£1.1 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£795.4	$6.7*10^{-4}$	£1.2 million	Nothing/ placebo	100%
	100%	£761.9	$6.7*10^{-4}$	£1.1 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	10%	£820.8	$5.3*10^{-4}$	£1.5 million	Nothing/ placebo	100%
	35%	£755.2	$7.7*10^{-4}$	£1.0 million	Nothing/ placebo	100%
SA9: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£807.5	$5.7*10^{-4}$	£1.4 million	Nothing/ placebo	100%
	6	£677.1	$1.1*10^{-3}$	£0.6 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£790.1	$6.4*10^{-4}$	£1.2 million	Nothing/ placebo	100%
	14	£720.6	$9.2*10^{-4}$	£0.8 million	Nothing/ placebo	100%
SA11: Cost per hospital bed day	£100	£864.1	$6.7*10^{-4}$	£1.3 million	Nothing/ placebo	100%
	£1000	£384.1	$6.7*10^{-4}$	£0.6 million	Nothing/ placebo	100%
SA12: Drug discounts of PEG-G-CSF	0% [3]	£781.4	$6.7*10^{-4}$	£1.2 million	Nothing/ placebo	100%
	83.49%[4]	£13.5	$6.7*10^{-4}$	£20,089.4	Nothing/ placebo	54.0%
	90% [5]	-£46.4	$6.7*10^{-4}$	Dominate	Secondary PEG-G-CSF [6]	100%
SA13: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£781.4	$6.7*10^{-4}$	£1.2 million	Nothing/ placebo	100%
	0.38	£781.4	$3.2*10^{-4}$	£2.4 million	Nothing/ placebo	100%
SA14: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£781.4	$6.8*10^{-4}$	£1.1 million	Nothing/ placebo	100%
	0.15	£781.4	$5.6*10^{-4}$	£1.4 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[3]: Corresponding price of PEG-G-CSF (when 0% discount is used): £686.38 per single subcutaneous injection (6mg).
[4]: Corresponding price of PEG-G-CSF (when 83.49% discount is used): £113.3 per single subcutaneous injection (6mg).

[5]: Corresponding price of PEG-G-CSF (when 90% discount is used): £179.5 per single subcutaneous injection (6mg).
[6]: Secondary PEG-G-CSF = Secondary prophylaxis with PEG-G-CSF.

Table 35 One-way sensitivity analyses results for non-Hodgkin lymphoma patients: Nothing/placebo v.s Secondary prophylaxis with G(M)-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	3	£476.2	$3.6*10^{-4}$	£1.3 million	Nothing/ placebo	100%
	6	£899.7	$3.2*10^{-4}$	£2.8 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [2]	5%	£893.5	$3.2*10^{-4}$	£2.8 million	Nothing/ placebo	100%
	100%	£981.2	$5.6*10^{-4}$	£1.8 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£444.6	$2.3*10^{-4}$	£2.0 million	Nothing/ placebo	100%
	10	£1,494.5	$3.5*10^{-4}$	£4.2 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£1,327.4	$1.0*10^{-4}$	£12.8 million	Nothing/ placebo	100%
	10	£684.6	$3.2*10^{-4}$	£2.1 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: G(M)-CSF versus nothing/placebo	0.1	£1,121.4	$1.1*10^{-3}$	£1.0 million	Nothing/ placebo	100%
	0.95	£844.8	$2.0*10^{-4}$	£4.2 million	Nothing/ placebo	100%
SA6: Probability of self administrating G(M)-CSF	0%	£993.6	$3.2*10^{-4}$	£3.1 million	Nothing/ placebo	100%
	100%	£805.9	$3.2*10^{-4}$	£2.5 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£904.0	$3.2*10^{-4}$	£2.8 million	Nothing/ placebo	100%
	100%	£893.8	$3.2*10^{-4}$	£2.8 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	10%	£929.1	$2.1*10^{-4}$	£4.4 million	Nothing/ placebo	100%
	35%	£880.2	$4.0*10^{-4}$	£2.2 million	Nothing/ placebo	100%
SA9: Days of using G(M)-CSF for each cycle of chemotherapy	5 d	£534.1	$3.2*10^{-4}$	£1.7 million	Nothing/ placebo	100%
	11 d	£1,265.4	$3.2*10^{-4}$	£3.9 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£907.7	$2.9*10^{-4}$	£3.1 million	Nothing/ placebo	100%
	6	£868.0	$4.5*10^{-4}$	£1.9 million	Nothing/ placebo	100%
SA11: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£902.4	$3.1*10^{-4}$	£2.9 million	Nothing/ placebo	100%
	14	£881.2	$4.0*10^{-4}$	£2.2 million	Nothing/ placebo	100%
SA12: Cost per hospital bed day	£100	£942.5	$3.2*10^{-4}$	£2.9 million	Nothing/ placebo	100%
	£1000	£694.2	$3.2*10^{-4}$	£2.1 million	Nothing/ placebo	100%
SA13: Daily cost of G(M)-CSF per person	£60.69 [3]	£561.1	$3.2*10^{-4}$	£1.7 million	Nothing/ placebo	100%
	£98.57 [4]	£899.7	$3.2*10^{-4}$	£2.8 million	Nothing/ placebo	100%
SA14: Drug discounts of G(M)-CSF	0% [5]	£899.7	$3.2*10^{-4}$	£2.8 million	Nothing/ placebo	100%
	90% [6]	£106.6	$3.2*10^{-4}$	£0.3 million	Nothing/ placebo	100%

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA15: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£899.7	$1.4*10^{-4}$	£6.4 million	Nothing/ placebo	100%
	0.38	£899.7	$3.2*10^{-4}$	£2.8 million	Nothing/ placebo	100%
SA16: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£899.7	$2.9*10^{-4}$	£3.1 million	Nothing/ placebo	100%
	0.15	£899.7	$3.0*10^{-4}$	£2.8 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[3]: Average cost of filgrastim and lenograstim assuming the daily dose of G(M)-CSF is 30 million-units for all adult patients regardless of weight.
[4]: Calculated from filgrastim and lenograstim based on patient weight distribution reported by: Green 2003, Romieu 2007 and Gigg 2003 (see Appendix A10).
[5]: Corresponding price of G(M)-CSF (when 0% discount is used):

- Filgrastim (30 million-unit syringe): £58.84.
- Filgrastim (48 million-unit syringe): £93.93.
- Lenograstim (13.4 million-unit syringe): £31.39.
- Lenograstim (33.6 million-unit syringe): £62.54.

[6]: Corresponding price of G(M)-CSF (when 90% discount is used):

- Filgrastim (30 million-unit syringe): £5.9.
- Filgrastim (48 million-unit syringe): £9.4.
- Lenograstim (13.4 million-unit syringe): £3.1.
- Lenograstim (33.6 million-unit syringe): £6.3.

Table A36 One-way sensitivity analyses results for non-Hodgkin lymphoma patients: Nothing/placebo v.s Primary prophylaxis with PEG-G-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	3	£1,511.3	$2.4*10^{-3}$	£0.6 million	Nothing/ placebo	100%
	6	£3,508.9	$2.2*10^{-3}$	£1.6 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [2]	5%	£3,518.4	$2.2*10^{-3}$	£1.6 million	Nothing/ placebo	100%
	100%	£2,432.9	$2.1*10^{-3}$	£1.2 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£3,656.8	$1.7*10^{-3}$	£2.1 million	Nothing/ placebo	100%
	10	£3,468.3	$2.4*10^{-3}$	£1.4 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£3,752.4	$1.5*10^{-3}$	£2.6 million	Nothing/ placebo	100%
	10	£3,420.8	$2.4*10^{-3}$	£1.4 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: PEG-G-CSF versus nothing/placebo	0.1	£3,411.7	$3.0*10^{-3}$	£1.1 million	Nothing/ placebo	100%
	0.95	£3,545.8	$5.8*10^{-4}$	£6.2 million	Nothing/ placebo	100%
SA6: Probability of self administrating PEG-G-CSF	0	£3,569.2	$2.2*10^{-3}$	£1.61 million	Nothing/ placebo	100%
	100%	£3,448.5	$2.2*10^{-3}$	£1.56 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£3,558.4	$2.2*10^{-3}$	£1.61 million	Nothing/ placebo	100%
	100%	£3,439.7	$2.2*10^{-3}$	£1.56 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£3,622.8	$1.8*10^{-3}$	£2.0 million	Nothing/ placebo	100%
	20%	£3,432.9	$2.5*10^{-3}$	£1.4 million	Nothing/ placebo	100%
SA9: Days of inpatient treatment for neutropenic sepsis patients at	1	£3,601.1	$1.8*10^{-3}$	£2.0 million	Nothing/ placebo	100%

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
low-risk of serious adverse events	6	£3,139.9	$3.7*10^{-3}$	£0.8 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£3,539.6	$2.1*10^{-3}$	£1.7 million	Nothing/ placebo	100%
	14	£3,293.6	$3.1*10^{-3}$	£1.1 million	Nothing/ placebo	100%
SA11: Cost per hospital bed day	£100	£3,775.6	$2.2*10^{-3}$	£1.7 million	Nothing/ placebo	100%
	£1000	£2,226.9	$2.2*10^{-3}$	£1.0 million	Nothing/ placebo	77.1%
SA12: Drug discounts of PEG-G-CSF	0% [3]	£3,508.9	$2.2*10^{-3}$	£1.6 million	Nothing/ placebo	100%
	87.8% [4]	£44.9	$2.2*10^{-3}$	£20,328.8	Nothing/ placebo	51.3%
	90% [5]	-£41.9	$-2.2*10^{-3}$	Dominate	Primary PEG-G-CSF [6]	78.1%
SA13: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£3,508.9	$1.1*10^{-3}$	£3.3 million	Nothing/ placebo	100%
	0.38	£3,508.9	$2.2*10^{-3}$	£1.6 million	Nothing/ placebo	100%
SA14: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£3,508.9	$1.8*10^{-3}$	£2.0 million	Nothing/ placebo	100%
	0.15	£3,508.9	$2.2*10^{-3}$	£1.6 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[3]: Corresponding price of PEG-G-CSF (when 0% discount is used): £686.38 per single subcutaneous injection (6mg).
[4]: Corresponding price of PEG-G-CSF (when 87.8% discount is used): £83.7 per single subcutaneous injection (6mg).
[5]: Corresponding price of PEG-G-CSF (when 90% discount is used): £68.6 per single subcutaneous injection (6mg).
[6]: Primary PEG-G-CSF = Primary prophylaxis with PEG-G-CSF.

Table A37 One-way sensitivity analyses results for non-Hodgkin lymphoma patients: Nothing/placebo v.s Primary prophylaxis with G(M)-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	3	£2,230.6	$1.2*10^{-3}$	£1.8 million	Nothing/ placebo	100%
	6	£4,512.8	$1.1*10^{-3}$	£4.1 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [2]	5%	£4,525.4	$1.1*10^{-3}$	£4.1 million	Nothing/ placebo	100%
	100%	£1,972.0	$1.1*10^{-3}$	£1.7 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£4,708.8	$8.6*10^{-4}$	£5.4 million	Nothing/ placebo	100%
	10	£4,514.0	$1.2*10^{-3}$	£3.7 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£4,892.4	$7.3*10^{-4}$	£6.7 million	Nothing/ placebo	100%
	10	£4,331.4	$1.2*10^{-3}$	£3.7 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: G(M)-CSF versus nothing/placebo	0.1	£4,441.8	$3.0*10^{-3}$	£1.5 million	Nothing/ placebo	100%
	0.95	£4,474.4	$5.8*10^{-4}$	£7.8 million	Nothing/ placebo	100%
SA6: Probability of self administrating G(M)-CSF	0%	£4,971.8	$1.1*10^{-3}$	£4.5 million	Nothing/ placebo	100%
	100%	£4,053.7	$1.1*10^{-3}$	£3.6 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£4,531.8	$1.1*10^{-3}$	£4.1 million	Nothing/ placebo	100%
	100%	£4,486.2	$1.1*10^{-3}$	£4.0 million	Nothing/ placebo	100%

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	10%	£4,595.4	$8.1*10^{-4}$	£5.7 million	Nothing/ placebo	100%
	35%	£4,457.7	$1.3*10^{-3}$	£3.4 million	Nothing/ placebo	100%
SA9: Days of using G(M)-CSF for each cycle of chemotherapy	5 d	£3,320.6	$1.1*10^{-3}$	£3.0 million	Nothing/ placebo	100%
	11 d	£6,300.9	$1.1*10^{-3}$	£5.7 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£4,548.2	$9.7*10^{-4}$	£4.7 million	Nothing/ placebo	100%
	6	£4,370.8	$1.7*10^{-3}$	£2.6 million	Nothing/ placebo	100%
SA11: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£4,524.6	$1.1*10^{-3}$	£4.2 million	Nothing/ placebo	100%
	14	£4,429.9	$1.5*10^{-3}$	£3.1 million	Nothing/ placebo	100%
SA12: Cost per hospital bed day	£100	£4,654.7	$1.1*10^{-3}$	£4.2 million	Nothing/ placebo	100%
	£1000	£3,830.7	$1.1*10^{-3}$	£3.4 million	Nothing/ placebo	100%
SA13: Daily cost of G(M)-CSF per person	£60.69 [3]	£2,856.6	$1.1*10^{-3}$	£2.6 million	Nothing/ placebo	100%
	£98.57 [4]	£4,512.8	$1.1*10^{-3}$	£4.1 million	Nothing/ placebo	100%
SA14: Drug discounts of G(M)-CSF	0% [5]	£4,512.8	$1.1*10^{-3}$	£4.1 million	Nothing/ placebo	100%
	90% [6]	£634.2	$1.1*10^{-3}$	£0.6 million	Nothing/ placebo	100%
SA15: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£4,512.8	$5.1*10^{-4}$	£8.8 million	Nothing/ placebo	100%
	0.38	£4,512.8	$1.1*10^{-3}$	£4.1 million	Nothing/ placebo	100%
SA16: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£4,512.8	$9.5*10^{-4}$	£4.7 million	Nothing/ placebo	100%
	0.15	£4,512.8	$1.1*10^{-3}$	£4.0 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[3]: Average cost of filgrastim and lenograstim assuming the daily dose of G(M)-CSF is 30 million-units for all adult patients regardless of weight.
[4]: Calculated from filgrastim and lenograstim based on patient weight distribution reported by: Green 2003, Romieu 2007 and Gigg 2003 (see Appendix A10).
[5]: Corresponding price of G(M)-CSF (when 0% discount is used):

- Filgrastim (30 million-unit syringe): £58.84.
- Filgrastim (48 million-unit syringe): £93.93.
- Lenograstim (13.4 million-unit syringe): £31.39.
- Lenograstim (33.6 million-unit syringe): £62.54.

[6]: Corresponding price of G(M)-CSF (when 90% discount is used):

- Filgrastim (30 million-unit syringe): £5.9.
- Filgrastim (48 million-unit syringe): £9.4.
- Lenograstim (13.4 million-unit syringe): £3.1.
- Lenograstim (33.6 million-unit syringe): £6.3.

A7.4 Probabilistic sensitivity analysis

For patients with non-Hodgkin lymphoma, the probability for nothing/placebo becoming cost-effective is always 100%, at a willingness to pay between £10,000 to £40,000 per QALY.

A8 Results ─ Hodgkin lymphoma sub group

The results for adult patients with Hodgkin lymphoma are presented below in the following order:

- base case analysis (Section A8.1)
- one-way sensitivity analysis (Section A8.2)

- probabilistic sensitivity analysis (Section A8.3)

Structural sensitivity analysis was not conducted for this patient group. The reason for which is detailed in section A4.1. Both strategies including quinolone (quinolone alone and quinolone plus G(M)-CSF) were excluded from formal cost-effectiveness analysis, because of no clinical evidence. As a result, no separate analyses were conducted for adult patients with Hodgkin lymphoma who can or cannot take quinolones.

A8.1 Base case analysis

For adult patients with Hodgkin lymphoma, clinical evidence was only available for the use of G(M)-CSF for either primary or secondary prophylaxis. Therefore cost-effectiveness was only formally examined for the following three strategies:

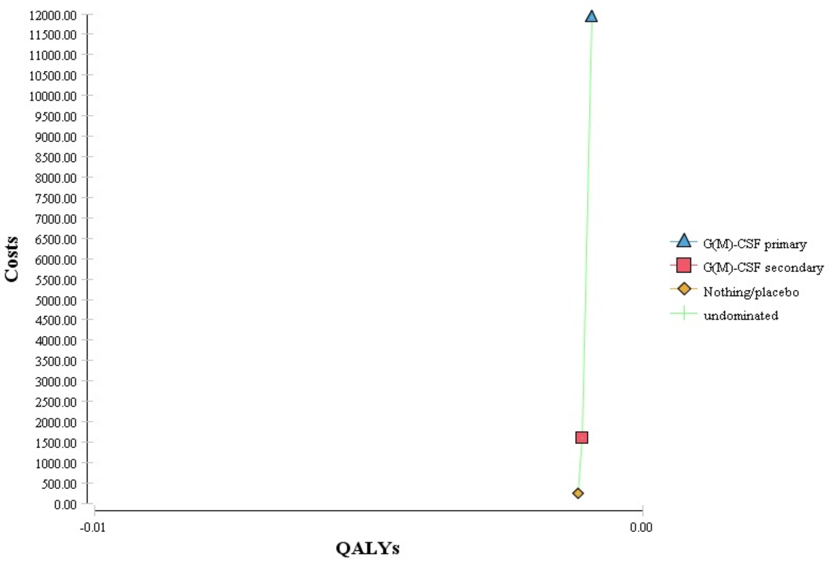
- Nothing/placebo
- Primary prophylaxis with G(M)-CSF
- Secondary prophylaxis with G(M)-CSF

The incremental costs and incremental QALYs in the base case analysis for each of the three strategies are summarised in Table A38, and shown graphically in Figure A9. Taking nothing/placebo as the reference (least expensive) strategy, the other two strategies were shown to be more effective, but were each associated with a very high ICER (both > £18.2 million/QALY) and were therefore not considered to be cost effective. Therefore at a WTP threshold of £20,000/QALY, nothing/placebo is the most cost-effective strategy.

Table A38 Incremental costs and effectiveness by treatment strategy for patients with Hodgkin lymphoma (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 20.27%)

Strategy	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Nothing/Placebo	£235.8	$-1.2*10^{-3}$	—	—	Comparator	Comparator
Secondary prophylaxis with G(M)-CSF	£1,608.8	$-1.1*10^{-3}$	£1,372.0	$7.5*10^{-5}$	£18.2 million	£18.2 million
Primary prophylaxis with G(M)-CSF	£11,921.8	$-9.3*10^{-4}$	£11,686.0	$2.5*10^{-4}$	£47.2 million	£59.9 million

Figure A9 Incremental costs and effectiveness by treatment strategy for patients with Hodgkin lymphoma (using a baseline risk of neutropenic sepsis for one course of chemotherapy of 20.27%)



A8.1.2 One-way sensitivity analysis

Over sixteen scenarios were considered and tested using one-way sensitivity analysis (Section A4.2). The results of one-way sensitivity analyses for adult patients with Hodgkin lymphoma are presented below in the following order:

- Nothing/Placebo v.s Secondary prophylaxis with G(M)-CSF (Table A39)
- Nothing/Placebo with quinolone v.s Primary prophylaxis with G(M)-CSF (Table A40)

For adult patients with Hodgkin lymphoma, the conclusion of the base case analysis (nothing/placebo being the most cost-effective prophylactic strategy) was robust to all scenarios tested (Section A4.2).

Table A39 and A40 show that primary or secondary prophylaxis with G(M)-CSF is never the most cost-effective strategy, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount, reduced days of using G(M)-CSF (5-day per cycle of chemotherapy), reduced daily dose (one vial of G(M)-CSF for all adult patients regardless of weight) etc.

Table A39 One-way sensitivity analyses results for Hodgkin lymphoma patients: Nothing/placebo v.s Secondary prophylaxis with G(M)-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	12	£771.0	$5.6*10^{-5}$	£10.2 million	Nothing/ placebo	100%
	16	£974.4	$7.0*10^{-5}$	£13.0 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [2]	5%	£2,977.0	$1.1*10^{-3}$	£2.65 million	Nothing/ placebo	100%
	16.56%	£4,769.2	$7.3*10^{-3}$	£0.65 million	Nothing/ placebo	100%
	100%	£5,279.1	$7.9*10^{-3}$	£0.67 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£572.4	$6.0*10^{-5}$	£9.7 million	Nothing/ placebo	100%
	10	£1,297.2	$8.0*10^{-5}$	£16.1 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic	1	£887.6	$1.0*10^{-5}$	£70.8 million	Nothing/	100%

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis					placebo	
	10	£863.5	$1.3*10^{-4}$	£6.9 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: G(M)-CSF versus nothing/placebo	0.1	£813.8	$3.8*10^{-4}$	£2.1 million	Nothing/ placebo	100%
	0.95	£880.1	$5.0*10^{-5}$	£19.3 million	Nothing/ placebo	100%
SA6: Probability of self administrating G(M)-CSF	0%	£1,007.9	$8.0*10^{-5}$	£13.4 million	Nothing/ placebo	100%
	100%	£740.6	$8.0*10^{-5}$	£9.8 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£875.2	$8.0*10^{-5}$	£11.62 million	Nothing/ placebo	100%
	100%	£871.7	$8.0*10^{-5}$	£11.58 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£877.9	$6.0*10^{-5}$	£14.4 million	Nothing/ placebo	100%
	15%	£870.6	$9.0*10^{-5}$	£9.7 million	Nothing/ placebo	100%
SA9: Days of using G(M)-CSF for each cycle of chemotherapy	5 d	£540.4	$8.0*10^{-5}$	£7.2 million	Nothing/ placebo	100%
	11 d	£1,208.1	$8.0*10^{-5}$	£16.0 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£877.6	$6.0*10^{-5}$	£14.2 million	Nothing/ placebo	100%
	6	£860.9	$1.3*10^{-4}$	£6.6 million	Nothing/ placebo	100%
SA11: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£874.6	$7.0*10^{-5}$	£11.9 million	Nothing/ placebo	100%
	14	£871.7	$9.0*10^{-5}$	£10.2 million	Nothing/ placebo	100%
SA12: Cost per hospital bed day	£100	£883.2	$8.0*10^{-5}$	£11.7 million	Nothing/ placebo	100%
	£1000	£831.1	$8.0*10^{-5}$	£11.0 million	Nothing/ placebo	100%
SA13: Daily cost of G(M)-CSF per person	£60.69 [3]	£756.3	$8.0*10^{-5}$	£10.0 million	Nothing/ placebo	100%
	£98.57 [4]	£1,238.3	$8.0*10^{-5}$	£16.4 million	Nothing/ placebo	100%
SA14: Drug discounts of G(M)-CSF	0% [5]	£874.2	$8.0*10^{-5}$	£11.6 million	Nothing/ placebo	100%
	90% [6]	£193.2	$8.0*10^{-5}$	£2.6 million	Nothing/ placebo	100%
SA15: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£874.2	$4.0*10^{-5}$	£23.5 million	Nothing/ placebo	100%
	0.38	£874.2	$8.0*10^{-5}$	£11.6 million	Nothing/ placebo	100%
SA16: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£874.2	$6.0*10^{-5}$	£14.5 million	Nothing/ placebo	100%
	0.15	£874.2	$8.0*10^{-5}$	£11.4 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[3]: Average cost of filgrastim and lenograstim assuming the daily dose of G(M)-CSF is 30 million-units for all adult patients regardless of weight.
[4]: Calculated from filgrastim and lenograstim based on patient weight distribution reported by: Green 2003, Romieu 2007 and Gigg 2003 (see Appendix A10).
[5]: Corresponding price of G(M)-CSF (when 0% discount is used):

- Filgrastim (30 million-unit syringe): £58.84.
- Filgrastim (48 million-unit syringe): £93.93.
- Lenograstim (13.4 million-unit syringe): £31.39.
- Lenograstim (33.6 million-unit syringe): £62.54.

[6]: Corresponding price of G(M)-CSF (when 90% discount is used):

- Filgrastim (30 million-unit syringe): £5.9.
- Filgrastim (48 million-unit syringe): £9.4.
- Lenograstim (13.4 million-unit syringe): £3.1.
- Lenograstim (33.6 million-unit syringe): £6.3.

Table A40 One-way sensitivity analyses results for Hodgkin lymphoma patients: Nothing/placebo v.s Primary prophylaxis with G(M)-CSF

Analysis	Value	Incremental costs (£)	Incremental QALYs	ICER (£) incremental (QALYs)	Optimal strategy	Probability CE [1]
SA1: Number of cycles of chemotherapy	12	£10,013.5	$2.5*10^{-4}$	£40.0 million	Nothing/ placebo	100%
	16	£13,358.5	$2.4*10^{-4}$	£54.6 million	Nothing/ placebo	100%
SA2: Baseline risk of neutropenic sepsis per chemotherapy cycle: Cycle 2 onwards [2]	5%	£11,328.9	$2.0*10^{-3}$	£5.8 million	Nothing/ placebo	100%
	100%	£9,910.2	$8.6*10^{-3}$	£1.2 million	Nothing/ placebo	100%
SA3: Relative risk of a neutropenic sepsis episode: Cycle 1 versus Cycle 2 onwards	1	£11,694.6	$2.1*10^{-4}$	£56.6 million	Nothing/ placebo	100%
	10	£11,679.3	$2.8*10^{-4}$	£41.9 million	Nothing/ placebo	100%
SA4: Relative risk of a neutropenic sepsis episode: Previous neutropenic sepsis versus no previous neutropenic sepsis	1	£11,706.8	$1.5*10^{-4}$	£79.5 million	Nothing/ placebo	100%
	10	£11,669.4	$3.3*10^{-4}$	£35.7 million	Nothing/ placebo	100%
SA5: Relative risk of a neutropenic sepsis episode: G(M)-CSF versus nothing/placebo	0.1	£11,522.5	$1.1*10^{-3}$	£10.7 million	Nothing/ placebo	100%
	0.95	£11,706.5	$1.4*10^{-4}$	£81.6 million	Nothing/ placebo	100%
SA6: Probability of self administrating G(M)-CSF	0%	£12,816.0	$2.5*10^{-4}$	£51.8 million	Nothing/ placebo	100%
	100%	£10,556.0	$2.5*10^{-4}$	£42.7 million	Nothing/ placebo	100%
SA7: Probability of using an ambulance for patients with neutropenic sepsis	0	£11,689.6	$2.5*10^{-4}$	£47.3 million	Nothing/ placebo	100%
	100%	£11,677.0	$2.5*10^{-4}$	£47.2 million	Nothing/ placebo	100%
SA8: Probability of patients with neutropenic sepsis who are at high risk of serious adverse events	5%	£11,696.7	$2.1*10^{-4}$	£56.6 million	Nothing/ placebo	100%
	20%	£11,675.4	$2.9*10^{-4}$	£40.5 million	Nothing/ placebo	100%
SA9: Days of using G(M)-CSF for each cycle of chemotherapy	5 d	£7,284.2	$2.5*10^{-4}$	£29.4 million	Nothing/ placebo	100%
	11 d	£16,087.9	$2.5*10^{-4}$	£65.0 million	Nothing/ placebo	100%
SA10: Days of inpatient treatment for neutropenic sepsis patients at low-risk of serious adverse events	1	£11,697.8	$2.0*10^{-4}$	£58.7 million	Nothing/ placebo	100%
	6	£11,639.0	$4.4*10^{-4}$	£26.5 million	Nothing/ placebo	100%
SA11: Days of inpatient treatment for neutropenic sepsis patients at high-risk of serious adverse events	6	£11,687.3	$2.4*10^{-4}$	£48.3 million	Nothing/ placebo	100%
	14	£11,676.9	$2.8*10^{-4}$	£41.0 million	Nothing/ placebo	100%
SA12: Cost per hospital bed day	£100	£11,714.9	$2.5*10^{-4}$	£47.4 million	Nothing/ placebo	100%
	£1000	£11,547.0	$2.5*10^{-4}$	£46.7 million	Nothing/ placebo	100%
SA13: Daily cost of G(M)-CSF per person	£60.69 [3]	£7,609.3	$2.5*10^{-4}$	£30.8 million	Nothing/ placebo	100%
	£98.57 [4]	£11,686.0	$2.5*10^{-4}$	£47.2 million	Nothing/ placebo	100%
SA14: Drug discounts of G(M)-CSF	0% [5]	£11,686.0	$2.5*10^{-4}$	£47.2 million	Nothing/ placebo	100%
	90% [6]	£2,138.6	$2.5*10^{-4}$	£8.6 million	Nothing/ placebo	100%
SA15: Utility decrement due to inpatient treatment of neutropenic sepsis)	0.14	£11,686.0	$1.2*10^{-4}$	£93.7 million	Nothing/ placebo	100%
	0.38	£11,686.0	$2.5*10^{-4}$	£47.2 million	Nothing/ placebo	100%
SA16: Utility decrement due to outpatient treatment of neutropenic sepsis	0	£11,686.0	$1.9*10^{-4}$	£60.1 million	Nothing/ placebo	100%
	0.15	£11,686.0	$2.5*10^{-4}$	£46.5 million	Nothing/ placebo	100%

[1]: CE = cost effective at a NICE WTP threshold of £20,000/QALY.
[2]: In the economic analysis, it is assumed that the relative risk of a neutropenic sepsis event in the first cycle of chemotherapy compared with cycle two onwards is 3.69 (Cullen, 2007). Therefore by testing a range of 5-100% risk of neutropenic sepsis (per cycle) for Cycle 2 onwards; we tested a range of 1.4-100% risk of neutropenic sepsis (per cycle) for the first cycle of chemotherapy.
[3]: Average cost of filgrastim and lenograstim assuming the daily dose of G(M)-CSF is 30 million-units for all adult patients regardless of weight.
[4]: Calculated from filgrastim and lenograstim based on patient weight distribution reported by: Green 2003, Romieu 2007 and Gigg 2003 (see Appendix A10).
[5]: Corresponding price of G(M)-CSF (when 0% discount is used):

- Filgrastim (30 million-unit syringe): £58.84.
- Filgrastim (48 million-unit syringe): £93.93.
- Lenograstim (13.4 million-unit syringe): £31.39.
- Lenograstim (33.6 million-unit syringe): £62.54.

[6]: Corresponding price of G(M)-CSF (when 90% discount is used):

- Filgrastim (30 million-unit syringe): £5.9.
- Filgrastim (48 million-unit syringe): £9.4.
- Lenograstim (13.4 million-unit syringe): £3.1.
- Lenograstim (33.6 million-unit syringe): £6.3.

A8.1.3 Probabilistic sensitivity analysis

For patients with Hodgkin lymphoma, the probability of nothing/placebo becoming cost-effective is always 100%, at a willingness to pay between £10,000 to £40,000 per QALY.

A9 Discussion

A9.1 Summary of results

The aim of this economic analysis was to determine which prophylactic strategy is the most cost-effective for cancer patients who are receiving chemotherapy.

The findings of the base-case analysis for all three patient sub–groups are summarised below.

At the NICE WTP threshold of £20,000 per QALY,

- For patients with a solid tumour and who can take quinolone, primary prophylaxis with quinolone is the most cost-effective prophylactic strategy.
- For patients with a solid tumour and who cannot take quinolone, 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,

The one-way sensitivity analysis that was conducted showed that the model was robust to all scenarios tested (Section A4.2), except for relative risk of neutropenic sepsis (quinolone versus nothing/placebo) and discounting the cost of PEG-G-CSF.

For patients with a solid tumour and who can take quinolone:

- When the relative risk of a neutropenic sepsis episode (quinolones versus nothing/placebo) was above 0.787, nothing/placebo became the most cost-effective strategy, at a WTP threshold of £20,000 per QALY.

For patients with a solid tumour and who cannot take quinolone:

- When the discount to the cost of PEG-G-CSF was over 73.85% (corresponding price: £179.5 per single subcutaneous injection (6mg)), secondary prophylaxis with PEG-G-CSF became the most cost-effective strategy.
- When the discount to the cost of PEG-G-CSF was over 84.13% (corresponding price: £108.9 per single subcutaneous injection (6mg)), primary prophylaxis with PEG-G-CSF became the most cost-effective strategy.

For patients with non-Hodgkin lymphoma:

- When the discount to the cost of PEG-G-CSF was over 83.49% (corresponding price: £113.3 per single subcutaneous injection (6mg)), secondary prophylaxis with PEG-G-CSF became the most cost-effective strategy.
- When the discount to the cost of PEG-G-CSF was over 89.12% (corresponding price: £74.7 per single subcutaneous injection (6mg)), primary prophylaxis with PEG-G-CSF became the most cost-effective strategy.

Primary or secondary prophylaxis with G(M)-CSF is never the most cost-effective strategy for any of the three patient groups of interest, even when extreme scenarios were considered, for example: 100% risk of neutropenic sepsis per cycle of chemotherapy, 90% drug discount of G(M)-CSF, reduced days of using G(M)-CSF (5-day per cycle of chemotherapy), reduced daily dose (one vial of G(M)-CSF for all adult patients regardless of weight) etc.

A9.2 Potential limitations within the model

A9.2.1 Relative risk of overall mortality

The volume of evidence that reported relative risk data for overall mortality obtained from the clinical evidence review was very sparse. What's more, of the studies that report this outcome their quality was assessed by GRADE as low since none were designed to investigate the effect of GCSF on short-term mortality and the death rate between different arms was low. Based on these two reaons, as well as the low short-term overall mortality rate for patients receiving chemotherapy (less than 1%) the GDG decided not to consider the survival difference of different prophylactic strategies in the base-case model.

The likely impact of this assumption is that for those prophylactic strategies that can improve short-term overall mortality, their effectiveness was underestimated in our analysis. However, since the baseline short-term overall mortality for the target population is assumed to be very low, the effect of this bias is likely to be small.

A9.2.2 Relative risk of neutropenic sepsis

A total of 202 RCTs were included for this topic. However only one of these studies directly compared the effectiveness of G(M)-CSF or PEG-G-CSF with quinolone (Herbst. *et al.,* 2009). Therefore in our economic analysis, each prophylactic strategy was only compared with nothing/placebo and not with each other. The direction of this bias is unknown.

As there was only one head-to-head trial directly comparing G-CSF with quinolone, a network meta-analysis was considered unfeasible for this economic model.

A9.2.3 Impact of prophylactic strategy on subsequent chemotherapy

Although our systematic review of cost-effectiveness studies did identify several studies trying to model the impact of using G-CSF on patients long-term survival for patients with stage II breast cancer by maintaining chemotherapy dose (Borget, *et al*., (2009); Danova, *et al.*, (2008); Liu, *et al*., (2009); Lyman, (2009 (a)); Lyman, (2009 (b)); Ramsey, (2009); Whyte, *et al*., (2011)), none of these studies used any direct clinical data. Instead, these studies were trying to build an indirect relationship between use of G-CSF and patient long-term survival. They stated that G-CSF could prevent neutropenic sepsis; neutropenic sepsis is a risk factor of receiving dose-reduction chemotherapy and dose-reduction chemotherapy is a risk factor for patient long-term survival. Then based on this hypothesis, the authors claimed that G-CSF could improve patient long-term survival. However, these assumptions are in contrast with more direct evidence:

- Papaldo *et al* (2005) shows that the addition of varying intensity schedules of open-label G-CSF to high-dose epirubicin/cyclophosphamide chemotherapy in patients with stage I and II breast cancer had no significant impact on the delivered dose-intensity compared with the non-G-CSF arms.
- Results from the Impact of Neutropenia in Chemotherapy Euroopean study group (INC-EU) prospective obervational study shows that the impact of primary prophylaxis with G-CSF on relative dose intensity is not significant (Pettengell 2008).
- A recent meta-analysis (Shitara, *et al.,* 2011) shows that neutropenia experienced during chemotherapy is actually associated with improved survival in patients with advanced cancer or haematological malignancies undergoing chemotherapy. This implies that experiencing side effects of chemotherapy might not be associated with impaired long term survival.

In order to investigate the impact of prophylactic strategy on subsequent chemotherapy we would need to conduct a systematic review to identify which specific patient group(s) were likely to benefit from dose-intense/dense chemotherapy. Having identified these patient group(s) we would then need to search for and appraise RCTs comparing dose-intense chemotherapy + GCSF with normal chemotherapy + no GCSF. Data would be needed on overall survival/relapse free survival, the cost of chemotherapy regimes and patients future quality of life. Given that the guideline covers all cancer patients, from paediatric to adult, and the multitude of different chemotherapy regimens used in these different groups, it would be extremely complicated to model and a vast amount of data would be required.

This bias works against any prophylactic strategies that could potentially improve patient long-term survival or relapse free survival by maintaining chemotherapy dose.

A9.3 Compared with published studies

A total of 10 studies were identified in the systematic review of economic evidence for this topic (Full evidence review). However, none of these studies include all of the interventions that the GDG considered relevant for the topic (Section A2.1).

A9.3.1 Different types of G(M)-CSF versus each other

Six out of 10 studies compared different types of G-CSF with each other. All six studies considered two efficacies of G-CSF (i) preventing neutropenic sepsis and (ii) improving patient long-term survival by facilitating chemotherapy. The conclusions of these six studies are as follows:

For patients with at least 20% risk of febrile neutropenia:

- Primary prophylaxis with PEG-G-CSF is more effective and less expensive than primary prophylaxis with 11-day G-CSF (Borget, 2009; Liu, 2009; Lyman, 2009(b))
- Primary prophylaxis with PEG-G-CSF is more effective and more expensive than primary prophylaxis with 6-day G-CSF; and the ICER of PEG-G-CSF is less than the NICE WTP threshold of £20,000 per QALY (Borget, 2009; Danova, 2008; Liu, 2009; Lyman, 2009(a); Lyman, 2009(b))
- Primary prophylaxis with PEG-G-CSF is more effective and more expensive than secondary prophylaxis with PEG-G-CSF; and the ICER of primary prophylaxis with PEG-G-CSF is 3.3 times higher than the NICE WTP threshold of £20,000 per QALY (Ramsey, 2009).

Our analysis only considered the efficacy of G(M)-CSF in preventing neutropenic sepsis (Section A9.1.3); and didn't differentiate between 6 or 11-day G(M)-CSF. Despite these differences, the conclusions of our analysis (Section A6) are consistent with the conclusions of the six included papers above:
At the NICE WTP threshold of £20,000 per QALY

- Primary prophylaxis with PEG-G-CSF is more cost-effective than primary prophylaxis with G(M)-CSF.
- Secondary prophylaxis with PEG-G-CSF is more cost effective than primary prophylaxis with PEG-G-CSF.

A9.3.2 G(M)-CSF versus nothing/placebo

Two of the 10 studies (Lathia, 2009; Whyte, et al., (2011)) compared G-CSF with placebo. Lathia, (2009) considered G-CSF's efficacy in preventing neutropenic sepsis only (same as our analysis), and reported that compared to nothing, the ICER for primary prophylaxis with G(M)-CSF and primary prophylaxis with PEG-G-CSF are £0.94 million/QALY and £2.39 million/QALY respectively (converted to 2011 UK pounds), for patients with at least 20% risk of febrile neutropenia. This conclusion is consistent with our results.

Whyte (2011) considered primary and secondary prophylaxis with all different types of G-CSF and compared them with nothing/placebo. Their study concluded that at NICE willingness-to-pay threshold of £20,000 per QALY:

- for patients with a febrile neutropenia risk level of 11% -37%, secondary PEG-G-CSF is the most cost-effective strategy.
- for patients with a febrile neutropenia risk greater than 38%, primary PEG-G-CSF is the the most cost-effective strategy.

However Whyte (2011) considered three efficacies of G-CSF (i) preventing neutropenic sepsis; (ii) improving patient short-term survival (by preventing febrile neutropenia); and (iii) improving patient long-term survival by facilitating chemotherapy, whilst our analysis only considered the efficacy of G(M)-CSF in preventing neutropenic sepsis (Section A9.1.3). What's more, it is acknowledged that the efficacy data of G-CSF in terms of improving short-term and long-term survival estimated by Whyte *et al*., (2011) differ substantively from the data reported by best available evidence (Note 28, Table 5.10)

A9.3.3 G(M)-CSF plus quinolone versus quinolone alone

Two of 10 studies compared G(M)-CSF plus quinolone with quinolone alone, for patients with at least 20% risk of febrile neutropenia. Timmer-Bonte, (2006) compared primary prophylaxis with G(M)-CSF plus quinolone to primary prophylaxis with quinolone alone and Timmer-Bonte, (2008) compared secondary prophylaxis with G(M)-CSF plus quinolone to secondary prophylaxis with quinolone alone. Both papers considered G-CSF's efficacy in preventing neutropenic sepsis only (same as our analysis), and found out that G-CSF plus quinolone is more clinically effective than quinolone alone but is associated with a very high ICER (£0.27 million per febrile neutropenia-free cycle of chemotherapy (Timmer-Bonte, 2008) and £4149 per one percent decrease of the probability of febrile neutropenia (Timmer-Bonte, 2006). Neither study reported an ICER in terms of incremental cost per QALY, so it was very difficult to compare their results with ours.

A9.4 Implications for future research

Further research that could improve the model for this topic would include collecting the following additional data/information:

- A head-to-head RCT which directly compares G-CSF with quinolone

- The impact of the prophylactic strategy of neutropenic sepsis on patients' long-term survival
- The impact of prophylactic quinolone on antibiotic resistance

A10 Cost of different types of G(M)-CSF

Two types of G(M)-CSF are currently used in the U.K practice: filgrastim and lenograstim. The daily drug cost of filgrastim and lenograstim are presented in Table A41 and A42 separately. In our economic anlayisis, the daily cost of G(M)-CSF is the average cost of filgrastim and lenograstim (Table 43).

The unit cost of G(M)-CSF per day was calculated based on the average cost of all G(M)-CSF brands listed by British National Formulary 62.

Table A41 Daily cost of filgrastim

Weight [1:]	Percentage	Syringe of filgrastim required (per day)	Daily cost of filgrastim
<60kg	20.04%	One single 30 million-unit syringe [2]	£58.84
60<X<96 kg	74.59%	One single 48 million-unit syringe [3]	£93.93
>96 kg	5.37%	Two 30 million-unit syringes	£117.68
Weighted daily cost			**£88.17**

[1] The weight distribution of cancer patients was obtained from: Green 2003, Romieu 2007, and Gigg 2003.
[2] The cost of a single 30-million-unit syringe of filgrastim is caclculated as £58.84. This is an average cost of the following brands: Neupogen Nivestim, Ratiograstim, Tevagrastim and Zarzio. The costs of all brands were obtained from BFN 62.
[3] The cost of a single 48-million-unit syringe of filgrastim is caclculated as £93.93. This is an average cost of the following brands: Neupogen Nivestim, Ratiograstim, Tevagrastim and Zarzio. The costs of all brands were obtained from BFN 62.

Table A42 Daily cost of Lenograstim

Weight [1]	Percentage	Syringe of filgrastim required (per day)	Daily cost of Lenograstim
<53kg	9.51%	One single 33.6 million-unit syringe [2]	£62.54
53<X<74 kg	45.29%	One single 33.6 million-unit syringe + One single 13.4 million-unit syringe [3]	£93.93
>74 kg	45.20%	Two 33.6 million-unit syringes	£125.08
Weighted daily cost			£108.97

[1] The weight distribution of cancer patients was obtained from: Green 2003, Romieu 2007, and Gigg 2003.
[2] The cost of a single 33.6-million-unit syringe of Lenograstim is caclculated as £62.54. This is the cost of Granocyte reported by BFN 62.
[3] The cost of a single 13.4-million-unit syringe of Lenograstim is caclculated as £40.11. This is the cost of Granocyte reported by BFN 62.

Table A43 Daily cost of G(M)-CSF used in economic analysis

	Daily cost of different types of G(M)-CSF
Daily cost of filgrastim	£88.17
Daily cost of Lenograstim	£108.97
Average cost of daily G(M)-CSF	£98.57

A11 Cost of ambulance for each patient subgroup

According to the recent report ‘Accident and Emergency Attendances in England (Experimental Statistics) 2009-10’ (Health and Social Care Information Centre, 2011), the use of an ambulance is positively associated with age (Figure A10). Therefore the ambulance use for each patient subgroup was calculated based on their age distribution (Table A44).

Figure A10 Use of ambulance by all A & E attendances by age (2009-10)

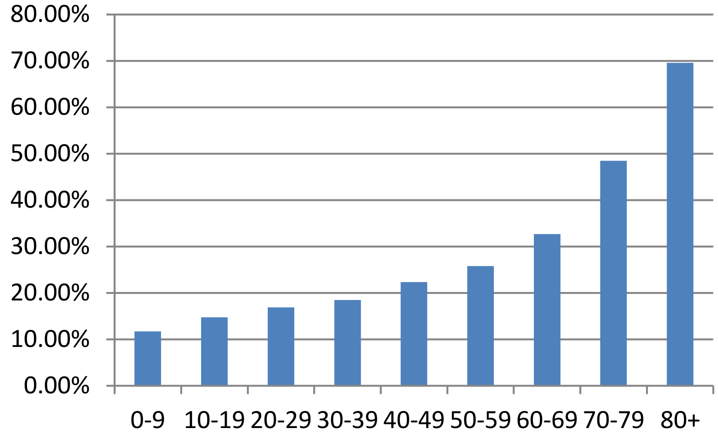


Table A44 Age distribution and estimated ambulance use for each patient subgroup

Age (y)	Solid tumour (adult)		Non-Hodgkin lymphoma (adult)		Hodgkin lymphoma (adult)	
	Age distribution	Ambulance use	Age distribution	Ambulance use	Age distribution	Ambulance use
20-29	0.21%	0.04%	1.71%	0.29%	22.30%	3.77%
30-39	1.47%	0.27%	3.58%	0.66%	18.99%	3.51%
40-49	5.87%	1.31%	7.86%	1.76%	15.09%	3.37%
50-59	13.91%	3.59%	14.96%	3.86%	12.24%	3.16%
60-69	26.64%	8.71%	24.45%	8.00%	12.77%	4.18%
70-79	29.74%	14.42%	27.69%	13.42%	12.84%	6.22%
80+	22.15%	15.41%	19.75%	13.74%	5.76%	4.01%
Total use of ambulance		**43.75%**		**41.73%**		**28.22%**

A12 Average cost of oral antibiotics

The cost of oral antibiotics was calculated based on cost data obtained from the British National Formulary assuming no wastage.

Table A45 Average cost of oral antibiotics for patients with neutropenic sepsis

Oral antibiotics	Component	Daily dose	Cost per vial/unit	Daily cost	Total daily cost
Ciprofloxacin + Clindamycin	Ciprofloxacin	1 g/ day	500 mg (scored), 10-tab pack = £12.49	£2.50	£7.07 /day
	Clindamycin	1200 mg/d	21-tab pack = £4.19	£4.57	

A13 References

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Appendix B

Abbreviations

ANC
Absolute Neutrophil Count

CRP
C-Reactive Protein

EORTC
European Organisation for Research and treatment of Cancer

ESR
Erythrocyte Sedimentation Rate

G-CSF
Granulocyte Colony Stimulating Factor

GM-CSF
Granulocyte Macrophage Colony Stimulating Factor

CXR
Chest X-Ray

MASCC
Multinational Association for Supportive Care in Cancer

NPV
Negative Predictive Value

GRADE
Grading of Recommendations Assessment, Development and Evaluation

CVAD
Central Venous Access Device

GDG
Guideline Development Group

NCAT
National Cancer Action Team

NCAG
National Chemotherapy Advisory Group

NCEPOD
National Confidential Enquiry into Patient Outcome and Death

PPV
Positive Predicated Value

Appendix C

Glossary

Acute Leukaemia
Progressive, malignant disease of the blood-forming tissue in the bone marrow, usually characterised by the production of abnormal white blood cells, which may be present in the bone marrow and blood.

Adverse Event
Detrimental change in health, or side effect, occurring in a patient receiving the treatment.

Adverse Clinical Outcome
Detrimental change in health that occurs in a patient; in this guideline a patient with an episode of suspected or proven neutropenic sepsis.

Afebrile
No fever, normal body temperature.

Albumin
Main protein of plasma - protein that is water soluble.

Ambulatory Care
Care that can provided on an outpatient basis

Aminoglycoside
A group of antibiotics that are effective against certain types of bacteria, but which need careful monitoring of the levels in the body to reduce the chance of side effects, particularly kidney damage and hearing impairment. For example gentamicin and tobramicin.

Anti Cancer Treatment
Treatment which is given with the intent to reduce the level of cancer cells in a patient. This includes, but is not limited to, chemotherapy and radiotherapy.

Anti microbial Therapy
Treatment of infectious disease using agents that either kill microbes or otherwise interfere with microbial growth.

Antibiotic Resistance
Resistance of a microorganism to an antimicrobial medicine to which it was previously sensitive.

Appropriately Trained
Having achieved recognised professional competence in dealing with a specific area of clinical practice.

Bacterial Infection
Occurs when harmful bacteria enters the body and multiply, causing unpleasant symptoms and/or an adverse event.

Beta Lactam Antibiotic
Beta-Lactams are a broad class of antibiotics that work by inhibiting cell wall synthesis by the bacterial organism and are the most widely used group of antibiotics. They include

penicillin derivatives (penams), cephalosporins (cephems), monobactams, and carbapenems.

Biochemical Profile
Laboratory tests performed upon a blood sample to indicate how well the kidneys and liver are working.

Blood culture
Blood obtained to be analaysed for the growth of a microbiological culture.

Blood Gases
A blood test that is performed to show the level of acid, oxygen and carbon dioxide in the blood.

Broad Spectrum Antibiotic
An antibiotic that is effective against a wide range of infectious bacteria, both Gram-positive and Gram-negative

Carer
Someone who provides support to the patient who could not manage without this help.

Central Venous Access Device (CVAD)
Central venous access devices are small, flexible tubes placed in large veins of patients who are likely to require frequent blood tests or venous access for treatment. They may be fully implanted under the skin or emerge from a tunnel through the skin.

Cephalosporins
A class of beta lactam antibiotics (See Beta Lactam Antibiotic)

Chemotherapy
Drug(s) that kill cells dividing faster than normal. These drugs are usually used in the treatment of cancer.

Chest X-Ray
A photographic or digital image of the chest produced by the use of ionising radiation.

Clinical effectiveness
The extent to which an intervention produces an overall health benefit in routine clinical practice.

Clinical Question
This term is sometimes used in guideline development work to refer to the questions about treatment and care that are formulated in order to guide the search for research evidence. When a clinical question is formulated in a precise way, it is called a focused question.

Clinical Population
A group of people that are studied for health reasons.

Clinically documented infection
An infection which has been diagnosed by the use of careful observation and physical examination of a patient.

Clinically Relevant
An outcome or event which has a direct relevance to a patient's health status, or which is important in modifying which treatment is received or how it is delivered.

Clostridium Difficile
A type of bacteria that lives within the gut which can produce toxins (poisons), which cause illness such as diarrhoea and fever.

Combination Therapy
The simultaneous use of more than one drug.

Complications
Adverse clinical outcomes after an event, treatment or procedure.

Cost Benefit Analysis
A type of economic evaluation where both costs and benefits of healthcare treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost Effectiveness Analysis
A type of economic evaluation comparing the costs and the effects on health of different treatments. Health effects are measured in health-related units, for example the cost of preventing one additional heart attack.

Cost Effectiveness
Value for money. A specific healthcare treatment is said to be cost effective if it gives a greater health gain than could be achieved by using the resources in other ways.

Cost-effectiveness model
An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.

C-Reactive Protein (CRP)
A protein that is produced by the liver and found in the blood. May be raised by a variety of problems, including infection.

Critical Care
Facilities within a hospital to look after patients whose conditions are life-threatening and need constant close monitoring and support from equipment and medication to keep normal body functions.

Diagnosis
The process of identifying or determining the cause of a disease. The decision reached at the conclusion of such a process.

Deterioration
To become worse.

Dip Stick Urinalysis
A technical procedure where a plastic strip with pre-formed chemical reagents is placed in urine, removed, and the results of the various tests examined.

Documented Infection
An infection which has been diagnosed by clinical examination, or by the detection of pathogenic organisms.

Dominance
An intervention is said to be dominated if there is an alternative intervention that is both less costly and more effective.

Door to needle time
A phrase used to describe the duration between the arrival of a patient in a healthcare facility and the delivery of a particular intervention (which may not necessarily be delivered by a needle).

Dose Intensity
The total amount of chemotherapy delivered per time unit.

Dual Therapy
The simultaneous use of two drugs in treating one condition.

Escherichia coli (E-Coli)
A Gram-negative, rod-shaped bacterium that is commonly found in the lower intestine and can cause severe illness, including death.

Emergency Care
A hospital facility which provides immediate diagnosis and management of severe, life or limb threatening health problems.

Empiric
An action undertaken prior to determination of the underlying cause of a problem.

Empiric Therapy
Treatment undertaken prior to determination of the underlying cause of a problem.

Empiric Antibiotic
An empiric antibiotic is given to a person before a specific microorganism or source of the potential infection is known. It is usually a broad-spectrum antibiotic and the treatment may change if the microorganism or source is confirmed.

Endocarditis
An inflammation of the inside lining of the heart chambers and heart valves.

Epidermis
The outer layer of the skin.

EQ-5D (EuroQol-5D)
A standardised instrument used to measure a health outcome. It provides a single index value for health status.

Evidence Table
A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Extrapolation
In data analysis, predicting the value of a parameter outside the range of observed values.

False negative
A result that appears negative but should have been positive, i.e. a test failure

False positive
A result that appears positive but should have been negative, i.e. a test failure.

Febrile Neutropenia
The development of fever, often with other signs of infection, in a patient with neutropenia.

Fever
A raise in body temperature above normal range.

Fluoroquinolones
A class of antimicrobial medicines used to treat infections caused by many bacteria.

Glycopeptide Antibiotic
A class of antibiotic that inhibits cell wall synthesis. Examples include vancomycin and teicoplanin.

GRADE
The GRADE approach is a method of grading the quality of evidence and strength of recommendations in healthcare guidelines. It is developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (www.gradeworkinggroup.org)."

Gram Negative
A primary method of characterising organisms in microbiology.

Gram Positive
A primary method of characterising organisms in microbiology.

Granulocyte Colony Stimulating Factor
A type of protein that stimulates the bone marrow to make white blood cells (granulocytes).

Granulocyte Macrophage Colony Stimulating Factor
A type of protein that stimulates the bone marrow to make white blood cells (granulocytes and monocytes).

Growth Factors
A protein molecule to regulate cell division & cell survival. Often used in this context to refer to G-CSF and GM-CSF.

Healthcare professional
An individual who provides health services within a nationally accredited framework of training and regulation.

Health Economics
A branch of economics which studies decisions about the use and distribution of healthcare resources.

Heterogeneity
A term used to describe the amount of difference of results or effects.

Homogeneity

A term used to describe the amount of similarity of results or effects**.**

Hospital Acquired infection
Infections that are not present and without evidence of incubation at the time of admission to a hospital.

Immuno compromise
The body's ability to fight infections is reduced due to a weakened immune system.

Incremental analysis
The analysis of additional costs and additional clinical outcomes with different interventions.

Incremental cost
The mean cost per patient associated with an intervention minus the mean cost per patient associated with a comparator intervention.

Incremental cost-effectiveness ratio (ICER)
The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.

Incremental net benefit (INB)
The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.

Infection
The growth of a parasitic organism within the body.

Inflammatory Markers
Proteins or other molecules which are raised by inflammatory processes in the body and can be measured, usually by blood tests.

Inpatient
The care of patients whose condition requires admission to a hospital.

Intravenous
Infusion or injection into a vein.

Intraluminal infection
A device-related infection seen in central venous access devices, related to the inside of the tube of the device.

Lactate
A naturally produced acid which rises when energy expenditure outstrips oxygen supply, as can happen in severe sepsis.

Life threatening infection
An infection which may cause death.

Linezolid
Antibiotic used for the treatment of serious infections caused by Gram-positive bacteria.

Liver Function Test
A series of biochemical tests performed on a blood sample to indicate how well a patient's liver is working.

Local microbiological contraindications
Knowledge of the antibiotic resistance patterns in the community in and around a health care setting which demonstrate which antibiotics should not be used empirically.

Local microbiological indications
Knowledge of microbiological enviroment in the community in and around a health care setting which demonstrate which antibiotics should be used empirically.

Low Risk
To be safe or without problems.
To have a very low chance of problems occurring.

Lymphocyte Count
This test measures the amount of lymphocytes in blood. Lymphocytes are a type of white blood cell.

Markov model
A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).

MASCC
A scoring system used to determine risk of serious complications.

Meta-analysis
A method of summarising previous research by reviewing and combining the results of a number of different clinical studies.

Microbiological
The effects that microorganisms have on other living organisms.

Mixed Treatment Comparisons
A type of meta-analysis which allows simultaneous comparisons of greater than two treatment options.

Monocyte Count
This test measures the amount of monocytes in blood. Monocytes are a type of white blood cell.

Monotherapy
The use of a single drug for treatment.

Morbidity
A diseased condition or state.

Mortality
Death.

Multi Resistant Organism
A microbe which is resistant to a number of different classes of antibiotic.

Myelo suppressive Anti Cancer Treatment
Treatment that causes bone marrow suppression.

Nephrotoxicity
The poisonous effect of medication, on the kidneys.

Neutropenia
An abnormally low number of neutrophils, the most important type of white blood cell to fight off bacterial infections.

Neutropenic Sepsis
An abnormal decrease in the number of neutrophils in the blood together with infection.

Neutrophil
A type of white blood cell, important in fighting off particularly bacterial infections.

Neutrophil Count
This test measures the number of neutrophils in blood. Neutrophils are a type of white blood cell.

Odds ratio
A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

One-way simple sensitivity analysis (univariate analysis)
Each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.

Oncologist
A doctor who specialises in managing cancer.

Oncology team
A team of healthcare professionals who specialise in looking after patients with malignant disease.

Opportunity cost
The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.

Optimal Duration
The best possible, most desirable period of time.

Oral Antibiotic Therapy
Antibiotics taken by mouth.

Organism
An individual form of life; such as bacterium in the context of this guideline.

Outcome
An end result; a consequence.

Outpatient
The care of patients whose condition does not require admission to a hospital.

Overall survival
Time lived after a diagnosis of cancer. Often quoted as a percentage chance of living a number of years (e.g. 5 or 10).

Overtreatment
Excessive treatment.

Peripheral Blood Culture
Blood obtained from a peripheral venous site to be analaysed for the growth of a microbiological culture.

Pocket Infection
A device-related infection seen in central venous access devices, related to the access port in a fully implanted device

Primary care
Health care delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other healthcare professionals, dentists, pharmacists and opticians.

Primary prophylaxis
A preventative intervention administered in all cycles of chemotherapy.

Primary treatment
Initial treatment used.

Probabilistic sensitivity analysis
Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques.

Prognostic study
A study that examines selected predictive variables, or risk factors, and assesses their influence on the outcome of a disease.

Prophylactic Treatment
Treatment used to protect a person from a disease.

Prophylaxis
Prevention of a disease or complication

Prospective diagnostic study
A study that looks at a new diagnostic method to see if it is as good as the current 'gold standard' method of diagnosing a disease.

Prospective Study
A study in which people are entered into research and then followed up over a period of time with future events recorded as they happen.

Publication bias
Also known as reporting bias. A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found.

Qualitative Study
A study used to explore and understand peoples' beliefs, experiences, attitudes, behaviour and interactions.

Quality adjusted life years (QALYs)
A measure of health outcome which looks at both length of life and quality of life. QALYS are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a 0 to 1 scale). One QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on.

Quality of life
An overall appraisal of well being.

Radiotherapy
A treatment for cancer that uses high energy ionising radiation to kill cells.

Randomised controlled trials (RCTs)
A clinical trial in which subjects are randomised to different groups for the purpose of studying the effect of a new intervention, for example a drug or other therapy.

Relative risk (also known as risk ratio)
The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk (RR) of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Retrospective Data
Data that deals with the present/past and does not involve studying future events.

Risk
The chance of an adverse outcome happening.

Risk Assessment Tool
A tool, usually a score from pieces of information given by patients, blood tests and examination finding, which is used to assess a patient's risk of a particular outcome. In this setting, it refers to a tool used to assess the risk of serious complications of infection. For example MASCC.

Secondary care
Services provided by the hospital, as opposed to the General Practitioner and the primary care team.

Secondary prophylaxis
Prophylaxis are administered in all remaining cycles of chemotherapy after one episode of neutropenic sepsis.

Sensitivity
The proportion of individuals who have disease correctly identified by the study test.

Sensitivity analysis
A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

Structural sensitivity analysis
Different structures of economic model are used to test the impact of model structure on the results of the study.

Sepsis
The body's response to an infection.

Septic Shock
Septic shock is a medical emergency caused by decreased tissue perfusion and oxygen delivery as a result of severe infection and sepsis.

Severe Sepsis
A life-threatening form of sepsis.

Short-term mortality
Death within a short period of time, for instance 30 days from onset of fever.

Signs
Physical changes noted in patients by healthcare providers or patients themselves.

Solid Tumours
Cancer of body tissues other than blood, bone marrow, or lymphatic system.

Specialist Centre
A healthcare facility which has been designated by an approved national process for the treatment of patients (in the present context) with cancer, leukaemia or lymphoma.

Specialist Oncology Advice
Advice given from a healthcare professional with appropriate training in the treatment of cancer, leukaemia or lymphoma.

Specificity
The proportion of individuals who do not have a disease and who are correctly identified by the study test.

Staphylococci
A group of bacteria that can cause a number of diseases as a result of infection of various tissues of the body.

Stem Cell Transplant
A procedure that replaces the cells in a patient which make blood. (Accurately described as a haemopoietic stem cell transplant).

Step Down
Decrease or reduction in treatment or medication.

Super-infection
An infection following a previous infection, especially when caused by microorganisms that have become resistant to the antibiotics used earlier.

Symptoms
The feelings and problems experienced by a patient relating to their illness.

Systematic review
A review of the literature done to answer a defined question often using quantitative methods to summarise the results.

Teicoplanin
Antibiotic used for the treatment of serious infections caused by some Gram-positive bacteria.

Tertiary Care
A major healthcare/medical centre providing complex treatments which receives referrals from both primary and secondary care. Sometimes called a tertiary referral centre.

Time horizon
The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.

Tissue diagnosis
Diagnosis based on the microscopic examination of biopsies from tissues in the body.

Toxicity
Undesirable and harmful side effects of a drug or other treatment.

Treatment Failure
Unsuccessful results or consequences of treatments used in combating disease.

Treatment Regimen
A plan of treatment.

True negative
When testing for a condition or disease, this result confirms the absence of the condition in an individual who genuinely does not have the condition in question. (Contrast with false negative (see above) where the test may incorrectly indicate that the individual is free from the condition being investigated. The condition is present but not detected by the test).

True positive
When testing for a condition or disease, this result confirms the presence of the condition in question in individuals who have it. (Compare with false positive where the test may incorrectly indicate that the individual has a condition, but in fact they do not).

Tunnel infection
A device-related infection seen in central venous access devices, related to the tube as it passes beneath the skin.

Urinalysis
The examination of urine, often by microscope or dip-stick.

Utility
A measure of the strength of an individual's preference for a specific health state in relation to alternative health states. The utility scale assigns numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health). Health states can be considered worse than death and thus have a negative value.

Vancomycin
Antibiotic used for the treatment of serious infections caused by Gram-positive bacteria.

Vesicant & Irritant Cytotoxic Infusions
Types of chemotherapy which can cause local tissue damage if they escape from the vein.

Appendix D

Guideline scope

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

Short title
Neutropenic Sepsis

The Remit
The Department of Health has asked NICE: 'To produce a clinical guideline on the prevention and management of neutropenic sepsis in cancer patients'.

Clinical need for the guideline
Neutropenic sepsis is a recognised and potentially fatal complication of anticancer treatment (particularly chemotherapy), although there are no accurate data available for morbidity and mortality in adults. For example, mortality rates have variously been reported as between 2 and 21%. Neutropenic sepsis is the second most common reason for hospital admission among children and young people with cancer, with approximately 4000 episodes occurring annually in the UK.

The consequences of an episode of infection in a neutropenic person can be described in descending order of adversity as: death, intensive care admission, medical complication (for example, need for supplemental oxygen, worsening renal function or hepatic impairment), bacteremia (bacteria in the bloodstream), significant bacterial infection, or no adverse after effects. It may also lead to delay or modification of subsequent courses of chemotherapy.

Adopting a policy of aggressive use of inpatient intravenous antibiotics in such episodes has reduced the mortality rate dramatically, for example in children and young adults from 30% in Europe in the 1970s to 1% in the late 1990s. Intensive care management is needed in fewer than 5% of cases in England.

Current practice
Systemic therapies to treat cancer have a risk of reducing the bone marrow's ability to respond to infection by reducing its ability to produce a type of white blood cell known as a neutrophil. This is particularly the case with systemic chemotherapy, although radiotherapy may also cause such suppression.

Most chemotherapy is given in a day-case or outpatient setting so episodes of fever in a potentially neutropenic person, and obvious sepsis, will predominantly present in the community. People receiving chemotherapy and their carers are informed of 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 report ('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 with 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 trust-level policies for dealing with neutropenic fever. It also highlighted variation in the provision of information on treatment of side effects and access to a 24-hour telephone advice.

There is national variation in the use of:

- primary and secondary prophylaxis
- risk stratification in episodes of febrile neutropenia
- oral or intravenous antibiotics
- growth factors
- in- or outpatient management policies.

Evidence-based recommendations on the prevention, identification and management of this life threatening complication of cancer treatment are expected to improve outcomes.

The guideline

The guideline development process is described in detail on the NICE website (Section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections. The guideline will define febrile neutropenia/neutropenic fever and neutropenic sepsis.

Population

Groups that will be 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 will not be covered

- Neutropenia or neutropenic sepsis not caused by anti-cancer treatment.

Healthcare setting

All settings in which NHS care is received.

Clinical management

Key clinical issues that will be covered

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug’s summary of product characteristics to inform decisions made with individual patients.

- Signs and symptoms in people with suspected neutropenic sepsis in the community that necessitate referral to secondary/tertiary care.
- Education and support for patients and carers on the identification of neutropenic sepsis.
- Emergency assessment in secondary/tertiary care of a person with suspected neutropenic sepsis.
- Appropriate initial investigations of suspected infection in a neutropenic patient in secondary care:
- Definition of neutropenia and fever.

- Investigations appropriate for risk stratification and management.
- Risk stratification and management of suspected bacterial infection:
    - Clinically applied risk stratification scores or algorithms.
    - Inpatient versus ambulatory (non-hospitalised) management strategies.
    - Oral antibiotic therapy, intravenous antibiotic monotherapy or intravenous antibiotic dual therapy.
    - Timing of initial antibiotic therapy.
    - Switching from intravenous to oral antibiotic therapy.
    - Management of unresponsive fever.
    - Duration of empiric antibiotic therapy (antibiotics chosen in the absence of an identified bacterium).
    - Duration of inpatient care.
- Primary and secondary prophylaxis in people at risk of neutropenic sepsis during anti-cancer treatment:
    - Primary prophylaxis with growth factors (for example granulocyte colony stimulating factor) and/or antibiotics (for example fluoroquinolones).
    - Secondary prophylaxis with growth factors, granulocyte infusion and/or antibiotics.
- Role of empiric glycopeptide antibiotics (antibiotics chosen in the absence of an identified bacterium) in patients with central lines and neutropenia or neutropenic sepsis.
- Indications for removing central lines in patients with neutropenia or neutropenic sepsis.
- Information and support for patients and carers.
- Training of all healthcare professionals on the identification and management of neutropenic sepsis.

Clinical issues that will not be covered

- Prophylaxis, investigation and management of non-bacterial infection
- Investigation and management of graft versus host disease
- Treatment of specific bacterial infections (for example bacterial pneumonia)
- Management of severe sepsis by intensive/critical care units
- Effect of neutropenic sepsis on subsequent chemotherapy scheduling and dose.
- Routine management of central lines and prevention of central line infection.

Main outcomes

- Mortality rate.
- Morbidity (for example renal impairment).
- Hospitalisation rates and length of hospital stay.
- Recurrence rate.
- Time to treatment of neutropenic sepsis.
- Health-related quality of life assessments (or surrogates, such as 'acceptability' or 'preference').

Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

Status

Scope
This is the final scope.

Timing
The development of the guideline recommendations will begin in September 2010.

Related NICE guidance
Published guidance

- Metastatic malignant disease of unknown primary origin (2010). NICE clinical guideline 104. Available from www.nice.org.uk/guidance/CG104
- Advanced breast cancer. NICE clinical guideline 81 (2009). Available from www.nice.org.uk/guidance/CG81
- Early and locally advanced breast cancer. NICE clinical guideline 80 (2009). Available from www.nice.org.uk/guidance/CG80
- Medicines adherence. NICE clinical guideline 76 (2009). Available from www.nice.org.uk/guidance/CG76
- Prostate cancer. NICE clinical guideline 58 (2008). Available from www.nice.org.uk/guidance/CG58
- Acutely ill patients in hospital. NICE clinical guideline 50 (2007). Available from www.nice.org.uk/guidance/CG50
- Improving outcomes for people with brain and other CNS tumours. NICE cancer service guidance (2006). Available from www.nice.org.uk/CSGBraincns
- Improving outcomes for people with sarcoma. NICE cancer service guidance (2006). Available from www.nice.org.uk/CSGSarcoma
- Improving outcomes for people with skin tumours including melanoma. NICE cancer service guidance (2006). Available from www.nice.org.uk/CSGSTIM
- Improving outcomes in children and young people with cancer. NICE cancer service guidance (2005). Available from www.nice.org.uk/CSGCYP
- Lung cancer. NICE clinical guideline 24 (2005). Available from www.nice.org.uk/guidance/CG24
- Improving outcomes in colorectal cancers. NICE cancer service guidance (2004). Available from www.nice.org.uk/CSGCC
- Improving outcomes in head and neck cancers. NICE cancer service guidance (2004). Available from www.nice.org.uk/CSGHN
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004). Available from www.nice.org.uk/CSGSP
- Improving outcomes in haematological cancers. NICE cancer service guidance (2003). Available from www.nice.org.uk/CSGHO
- Improving outcomes in breast cancer. NICE cancer service guidance (2002). Available from www.nice.org.uk/CSGBC
- Improving outcomes in urological cancers. NICE cancer service guidance (2002). Available from www.nice.org.uk/CSGUC
- Improving outcomes in upper gastro intestinal cancers. Service guidance (2001). Available from www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4010025
- Improving outcomes in gynaecological cancers. Service guidance (1999). Available from www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005385

- Improving outcomes in lung cancer. Service guidance (1998). Available from www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4009184

Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website).

- Lung cancer (update). NICE clinical guideline. Publication expected March 2011.
- Ovarian cancer. NICE clinical guideline. Publication expected April 2011.
- Colorectal cancer. NICE clinical guideline. Publication expected October 2011.

Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/GuidelinesManual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix E

People and organisations involved in production of the guideline

E1.1 Members of the Guideline Development Group

E1.2 Organisations invited to comment on the guideline

E1.3 Individuals carrying out literature reviews and complementary work

E1.4 Members of the NICE project team

Appendix E.1

Members of the Guideline Development Group (GDG)

GDG Chair

Professor Barry W Hancock OBE	Emeritus Professor of Oncology University of Sheffield

GDG Lead Clinician

Dr Robert S Phillips	Consultant Paediatric & Teenage/Young Adult Oncologist (Locum), Leeds General Infirmary, Leeds

Group Members

Mrs Wendy King	Macmillan Paediatric Oncology Clinical Nurse Specialist[24], Whittington Health
Dr Barbara Anne Crosse	Consultant Medical Oncologist, Calderdale and Huddersfield NHS Foundation Trust
Dr Mark Holland	Consultant Physician in Acute Medicine, University Hospital of South Manchester NHS Foundation Trust[25]
Catherine Oakley	Chemotherapy Nurse Consultant, Guy's and St Thomas' NHS Foundation Trust
Professor Rosemary A Barnes	Professor/Honorary Consultant Medical Microbiologist, Cardiff University, School of Medicine/University Hospital of Wales
Mrs Anne Higgins	Haemato-oncology Clinical Nurse Specialist and South West London Cancer Network Lead Chemotherapy Nurse. Epsom and St Helier University NHS Trust[26]
Dr Peter Jenkins	Consultant Clinical Oncologist, Cheltenham General Hospital
Dr Anton Kruger	Consultant Haematologist, Royal Cornwall Hospital
Dr Paul D Wallman	Consultant Emergency Physician & Clinical Director of Medicine, Trafford Healthcare NHS Trust[27]
Mrs Jeanette Hawkins	Lead Cancer Nurse, Birmingham Children's Hospital NHS Foundation Trust

[24] From March 2012, Macmillan Paediatric Oncology Nurse Consultant, Whittington Health
[25] From May 2012, Consultant Physician in Acute Medicine, University Salford Royal NHS Foundation Trust
[26] From April 2012, Lead nurse for acute oncology service, Heamatology/Oncology & Chemotherapy SWCLN, Lead Chemothereapy Nurse, St George'e Healthcare NHS Trust
[27] From September 2011, Consultant in Emergency Medicine, Brighton and Sussex University Hospitals

Dr Helen Clayson	Medical Director, St Mary's Hospice, Cumbria[28]
Miss Miranda Holmes	Service Improvement, East Midlands Cancer Network
Dr Anne Davidson	Consultant Paediatrician with an interest in Oncology, Royal Alexandra Children's Hospital
Ms Janie Thomas[29]	Patient/Carer Member
Dr Nicola Harris	Patient/Carer Member
Miss Rachel Drew	Patient/Carer Member

[28] GP principal from 1980 to 2005 Retired March 2011
[29] September 2010 – RIP December 2011

Declarations of interest

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline. The interests that were declared are as follows:

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Professor Barry Hancock	Honorarium from GlaxoSmithKline to lecture at an advisory group meeting on renal cancer	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Local principal investigator for GlaxoSmithKline renal cancer study.	Non-Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the subject area not being investigated by the guideline
	Chaired educational meetings, supported by grants from Pfizer and Chugai, on trophoblastic disease	Non-Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Honorarium from Oxford Outcomes Consultancy/Millenium for advising on the treatment of relapsed Hodgkin Lymphoma	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Dr Robert S Phillips	Member of Children's Cancer & Leukaemia Group (CCLG) Supportive Care Group	Personal Non-Pecuniary	Declare and chairperson's action taken that can participate in discussion on all topics
	Undertaking research funded by MRC to develop/refine risk stratification criteria for febrile neutropenic episodes in children/young people undergoing cancer treatment	Non-Personal Pecuniary Specific	Declare and must withdraw from discussions on all topics that include risk stratification criteria in children/young people with cancer. Chairperson's action taken that can be asked specific technical questions about this topic
Mrs Jeanette Hawkins	Managerial responsibility for service providing care for patients with neutropenic sepsis	Non-Personal Pecuniary Specific	Declare and can participate in discussions on all topics as payments are not outside normal NHS funding or from drug companies
	Line manage delivery of paediatric practical oncology programme: supportive care module (accredited by Birmingham City University)	Non-Personal Pecuniary Specific	Declare and can participate in discussions on all topics as payments are student course fees
	Hand out free digital thermometers supplied by Chugai at Birmingham Childrens Hospital.	Non-Personal Pecuniary Specific	Declare and must withdraw from discussions on all topics that include thermometers. Chairperson's action taken that can be asked specific questions about this topic

Dr Anton Kruger	Attended the European Haematology Society meeting in June 2010. Travelling expenses and subsistence reimbursed by drug company	Personal Pecuniary Non-specific	Declare and can participate in discussion of all topics as reimbursement of expenses not beyond reasonable amounts
Catherine Oakley	Board member of UK Oncology Nursing Society	Personal Non-Pecuniary	Declare and chairperson's action taken that can take participate in discussion on all topics as not specific to neutropenic sepsis
	Attended a Britain Against Cancer Conference in December 2010, conference place was funded by Amgen.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Honorarium received from Amjen to participate in a workshop to look at home delivery of Denosumab.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Participated in a specialist nurse advisory board for Afinitor and received an honoraria from Novartis.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Dr Peter Jenkins	Funding received from Sanofi Aventis regarding review written on TAC Chemotherapy in Breast Cancer	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics. Topic reviewed did not relate to Neutropenic sepsis.
	Honorarium to lecture to Pharmaceutical Reps for Sanofi Aventis on the Risk of febrile neutropenia with docetaxel based chemotherapy	Personal Pecuniary Specific	Declare and must withdraw from discussion on all topics that include febrile neutropenia with doxetaxel. However subject area is not being investigated by the guideline
	Honorarium from Astra-Zeneca to attend advisory board for market research with regards to hormonal treatment Faslodex	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Travel grant received from Boehringer Ingelheim to present paper to ECCO meeting in Berlin.	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Payment received from Succinct Communications sponsored by Sanofi Aventis to write a short article for Medical matters magazine for Oncologists	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Attended a UKCC Cancer Convention on Breast Cancer sponsored by Sanofi. Travel expenses and accommodation were reimbursed.	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the expenses were not beyond a reasonable amount
	Attended an update meeting on the new developments in the diagnosis and	Personal Pecuniary	Declare and can participate in discussions on all topics as the

	management of prostate and breast cancer, sponsored by Sanofi. Travel expenses and accommodation were reimbursed.	Non specific	expenses were not beyond a reasonable amount
	Attended a UKCC Cancer Convention on Prostate Cancer sponsored by Sanofi. Travel expenses and accommodation were reimbursed.	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the expenses were not beyond a reasonable amount
	Attended an update meeting on the new developments in the diagnosis and management of prostate and breast cancer, sponsored by Sanofi. Travel expenses and accommodation were reimbursed.	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the expenses were not beyond a reasonable amount
	Paper accepted for publication in Annals Oncology, on a validation study of a model for predicting the risk of febrile neutropenia with chemotherapy. No payment was received.	Personal non-pecuniary	Declare and can participate in discussions on all topics as no payment was received for study
	Attended a Prostate Cancer UK summit, sponsored by Janseen. Travel expenses were reimbursed.	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as no payment was received for study
	Attended a local department meeting on metastatic breast cancer. Book donation received from Eribulin.	Personal Pecuniary Non specific	Declare and can participate in discussion on all topics as the expenses were not beyond reasonable amounts.
	Attended the San Antonio Cancer Symposium sponsored by Roche. Travel expenses and accommodation were reimbursed.	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the expenses were not beyond a reasonable amount
Dr Mark Holland	Attended meeting sponsored by Sanofi Aventis on new anti-arrhythmic drug. Dinner and accommodation were paid.	Personal Pecuniary Non specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Appraisal made and report written of Christie Hospital Acute Medical Services. Christie paid locum fees.	Non-Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline.
	Member of hospital chemotherapy group and North West acute cancer network.	Personal Non-Pecuniary	Declare and chairperson's action taken that can participate in discussion on all topics
Professor Rosemary A Barnes	Participated on advisory board for MSD Caspofungin and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
	Participated on advisory board for Gilead (Ambisome) and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being

		investigated by the guideline
Participated on advisory board for Prizer Anidulafungin and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Participated on advisory board for Prizer (Voriconazole) and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Participated on advisory board for Gilead (Ambisome) and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Participated on advisory board for Prizer (Voriconazole) and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Participated on advisory board for Gilead (Ambisome) and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Participated on advisory board for Prizer Anidulafungin and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Participated on advisory board for Astellas (Micafungin) and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Participated on advisory board for Gilead (Ambisome) and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Participated on advisory board for Gilead (Ambisome) and received an honoraria.	Personal Pecuniary Non-specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Received an educational grant and scientific fellowship award from Gilead Sciences for Audit of effect of antifungal prophylaxis and enhanced diagnostics on the incidence and management of invasive fungal disease in high risk haematology and transplant recipients	Non-Personal Non-Specific	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline
Received an educational grant and scientific fellowship award from Pfizer for Artemis Study: prospective study of azole sensitivity using novel methodology	Personal Non-Pecuniary	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline

	Received an educational grant and scientific fellowship award from Pfizer for Molecular diagnosis in aspergillosis	Personal Non-Pecuniary	Declare and can participate in discussions on all topics as the subject area is not being investigated by the guideline

Appendix E.2

Organisations invited to comment on guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline

- Airedale NHS Foundation Trust
- Alder Hey Children's NHS Foundation Trust
- Association of Cancer Physicians
- Association of Chartered Physiotherapists in Oncology and Palliative Care
- Astrazeneca UK Ltd
- Barnsley Hospital NHS Foundation Trust
- Bradford District Care Trust
- Breakthrough Breast Cancer
- Breast Cancer Care
- British Medical Association
- British Medical Journal
- British National Formulary
- British Nuclear Medicine Society
- British Paediatric Allergy, Immunity & Infection Group
- British Psychological Society
- British Society for Antimicrobial Chemotherapy
- British Society for Haematology
- British Society for Immunology
- British Thoracic Society
- Cambridge University Hospitals NHS Foundation Trust
- Camden Link
- Cancer Network Pharmacists Forum
- Cancer Research UK
- Cancer Services Co-ordinating Group
- Care Quality Commission (CQC)
- Central South Coast Cancer Network
- Children and Young People's Cancer Nurses Community
- Chugai Pharma Europe Ltd
- Commission for Social Care Inspection
- Cumberland Infirmary
- Department for Communities and Local Government
- Department of Health
- Department of Health, Social Services and Public Safety - Northern Ireland
- Dorset Cancer Network
- Dorset Primary Care Trust
- East Lancashire Hospitals NHS Trust
- East Midlands Cancer Network

- Faculty of Intensive Care Medicine
- George Eliot Hospital NHS Trust
- Gilead Sciences Ltd
- Gloucestershire Hospitals NHS Foundation Trust
- Gloucestershire LINk
- Great Western Hospitals NHS Foundation Trust
- Greater Manchester and Cheshire Cancer Network
- Greater Midlands Cancer Network
- Guy's and St Thomas' NHS Foundation Trust
- Health Protection Agency
- Health Quality Improvement Partnership
- Healthcare Improvement Scotland
- Hospira UK Limited
- Institute of Biomedical Science
- Intensive Care Society
- Joint Collegiate Council for Oncology
- Jo's Trust
- Kidney Research UK
- Lancashire Care NHS Foundation Trust
- Letterkenny General Hospital
- Leukaemia CARE
- Leukemia Research Fund
- Liverpool Community Health
- Liverpool Primary Care Trust
- Luton and Dunstable Hospital NHS Trust
- Macmillan Cancer Support
- Maidstone and Tunbridge Wells NHS Trust
- Medicines and Healthcare products Regulatory Agency
- Medway NHS Foundation Trust
- Merseyside & Cheshire Cancer Network
- Ministry of Defence
- Myeloma UK
- National Alliance of Childhood Cancer Patient Organisations
- National Cancer Research Institute
- National Clinical Guideline Centre
- National Collaborating Centre for Mental Health
- National Institute for Health Research Health Technology Assessment Programme
- National Lung Cancer Forum for Nurses
- National Patient Safety Agency
- National Public Health Service for Wales
- National Treatment Agency for Substance Misuse
- Neonatal & Paediatric Pharmacists Group
- NHS Bournemouth and Poole

- NHS Clinical Knowledge Summaries
- NHS Connecting for Health
- NHS Direct
- NHS Plus
- NHS Sheffield
- NHS Worcestershire
- NICE
- NICE – CPHE
- NICE - CPHE Methodology
- NICE - Guidelines HE
- NICE - IMPLEMENTATION CONSULTANT Region – East
- NICE - IMPLEMENTATION CO-ORDINATION
- NICE – PPIP
- NICE - R&D
- NICE - Technical Appraisals
- North East London Cancer Network
- North Essex Mental Health Partnership Trust
- North of England Cancer Network
- North Tees and Hartlepool NHS Foundation Trust
- North West London Cancer Network
- Northamptonshire Primary Care Trust
- Northern Ireland Cancer Network
- Nottingham City Hospital
- Oxfordshire Primary Care Trust
- Paediatric Intensive Care Society
- PERIGON Healthcare Ltd
- Pfizer
- Pilgrims Hospices in East Kent
- Public Health Wales NHS Trust
- Roche Diagnostics
- Royal Berkshire NHS Foundation Trust
- Royal College of Anaesthetists
- Royal College of General Practitioners
- Royal College of General Practitioners in Wales
- Royal College of Midwives
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists
- Royal College of Paediatrics and Child Health
- Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition
- Royal College of Pathologists
- Royal College of Physicians
- Royal College of Psychiatrists
- Royal College of Radiologists
- Royal College of Surgeons of England
- Royal Marsden NHS Foundation Trust

- Royal Pharmaceutical Society
- Royal Society of Medicine
- Royal United Hospital Bath NHS Trust
- Sacyl
- Scarborough and North Yorkshire Healthcare NHS Trust
- Scottish Intercollegiate Guidelines Network
- Sheffield Teaching Hospitals NHS Foundation Trust
- SNDRi
- Social Care Institute for Excellence
- Society for Acute Medicine
- South Asian Health Foundation
- South East Coast Ambulance Service
- South East Wales Cancer Network
- South Staffordshire Primary Care Trust
- South Tees Hospitals NHS Trust
- South West Midlands Newborn Network
- Southampton University Hospitals Trust
- Takeda UK Ltd
- Teenage Cancer Trust
- Teenagers and Young Adults with Cancer
- The Association for Clinical Biochemistry
- The British In Vitro Diagnostics Association
- The Lymphoma Association
- The Rotherham NHS Foundation Trust
- UCL Partners
- UK Clinical Pharmacy Association
- United Kingdom Chemotherapy Redesign Group
- United Kingdom Oncology Nursing Society
- University College London Hospital NHS Foundation Trust
- University Hospital Birmingham NHS Foundation Trust
- Welsh Government
- Welsh Scientific Advisory Committee
- Western Cheshire Primary Care Trust
- Western Health and Social Care Trust
- Whipps Cross University Hospital NHS Trust
- Wirral University Teaching Hospital NHS Foundation Trust
- York Hospitals NHS Foundation Trust

Appendix E.3

Individuals carrying out literature reviews and complementary work

Dr John Graham	Director, National Collaborating Centre for Cancer, Cardiff

Overall Co-ordinators

Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Angela Bennett	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff

Project Manager

Lianne Gwillim	National Collaborating Centre for Cancer, Cardiff

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Dr Mia Schmidt-Hansen	National Collaborating Centre for Cancer, Cardiff
Dr Catrin Lewis	National Collaborating Centre for Cancer, Cardiff

Information Specialists

Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Stephanie Arnold	National Collaborating Centre for Cancer, Cardiff

Health Economists

Huajie Jin	National Collaborating Centre for Cancer, Cardiff

Senior Health Economic Advice

Dr Alec Miners	Lecturer in Health Economics, London School of Hygiene & Tropical Medicine

Mixed treatment comparison and meta-regression analyses

Dr Robert S Phillips	Consultant Paediatric & Teenage/Young Adult Oncologist (Locum), Leeds General Infirmary, Leeds

Needs Assessment

Dr Timothy Simmons	SpR Clinical Oncology, Weston Park Hospital, Sheffield

[30] Retired June 2011

Appendix E.4

Members of the NICE project team

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