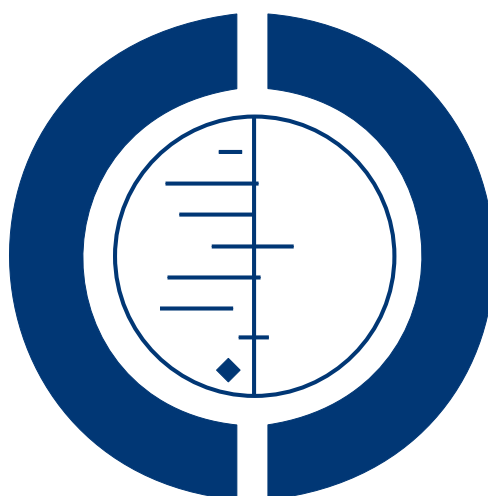


Prophylactic antibiotics or G(M)-CSF for the prevention of infections and improvement of survival in cancer patients receiving myelotoxic chemotherapy (Review)

Skoetz N, Bohlius J, Engert A, Monsef I, Blank O, Vehreschild JJ



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 12

<http://www.thecochranelibrary.com>

WILEY

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	4
BACKGROUND	6
OBJECTIVES	7
METHODS	7
RESULTS	10
Figure 1.	11
Figure 2.	13
Figure 3.	14
ADDITIONAL SUMMARY OF FINDINGS	15
DISCUSSION	18
AUTHORS' CONCLUSIONS	19
ACKNOWLEDGEMENTS	19
REFERENCES	19
CHARACTERISTICS OF STUDIES	27
DATA AND ANALYSES	36
APPENDICES	36
WHAT'S NEW	48
CONTRIBUTIONS OF AUTHORS	48
DECLARATIONS OF INTEREST	48
SOURCES OF SUPPORT	49
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	49
NOTES	49
INDEX TERMS	50

[Intervention Review]

Prophylactic antibiotics or G(M)-CSF for the prevention of infections and improvement of survival in cancer patients receiving myelotoxic chemotherapy

Nicole Skoetz¹, Julia Bohlius², Andreas Engert³, Ina Monsef¹, Oliver Blank¹, Jörg-Janne Vehreschild³

¹Cochrane Haematological Malignancies Group, Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany. ²Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. ³Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany

Contact address: Nicole Skoetz, Cochrane Haematological Malignancies Group, Department I of Internal Medicine, University Hospital of Cologne, Kerpener Str. 62, Cologne, 50937, Germany. nicole.skoetz@uk-koeln.de.

Editorial group: Cochrane Haematological Malignancies Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 12, 2015.

Review content assessed as up-to-date: 3 December 2015.

Citation: Skoetz N, Bohlius J, Engert A, Monsef I, Blank O, Vehreschild JJ. Prophylactic antibiotics or G(M)-CSF for the prevention of infections and improvement of survival in cancer patients receiving myelotoxic chemotherapy. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD007107. DOI: 10.1002/14651858.CD007107.pub3.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Febrile neutropenia (FN) and other infectious complications are some of the most serious treatment-related toxicities of chemotherapy for cancer, with a mortality rate of 2% to 21%. The two main types of prophylactic regimens are granulocyte (macrophage) colony-stimulating factors (G(M)-CSF) and antibiotics, frequently quinolones or cotrimoxazole. Current guidelines recommend the use of colony-stimulating factors when the risk of febrile neutropenia is above 20%, but they do not mention the use of antibiotics. However, both regimens have been shown to reduce the incidence of infections. Since no systematic review has compared the two regimens, a systematic review was undertaken.

Objectives

To compare the efficacy and safety of G(M)-CSF compared to antibiotics in cancer patients receiving myelotoxic chemotherapy.

Search methods

We searched *The Cochrane Library*, MEDLINE, EMBASE, databases of ongoing trials, and conference proceedings of the American Society of Clinical Oncology and the American Society of Hematology (1980 to December 2015). We planned to include both full-text and abstract publications. Two review authors independently screened search results.

Selection criteria

We included randomised controlled trials (RCTs) comparing prophylaxis with G(M)-CSF versus antibiotics for the prevention of infection in cancer patients of all ages receiving chemotherapy. All study arms had to receive identical chemotherapy regimes and other supportive care. We included full-text, abstracts, and unpublished data if sufficient information on study design, participant characteristics, interventions and outcomes was available. We excluded cross-over trials, quasi-randomised trials and post-hoc retrospective trials.

Prophylactic antibiotics or G(M)-CSF for the prevention of infections and improvement of survival in cancer patients receiving myelotoxic chemotherapy (Review)

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1

Data collection and analysis

Two review authors independently screened the results of the search strategies, extracted data, assessed risk of bias, and analysed data according to standard Cochrane methods. We did final interpretation together with an experienced clinician.

Main results

In this updated review, we included no new randomised controlled trials. We included two trials in the review, one with 40 breast cancer patients receiving high-dose chemotherapy and G-CSF compared to antibiotics, a second one evaluating 155 patients with small-cell lung cancer receiving GM-CSF or antibiotics.

We judge the overall risk of bias as high in the G-CSF trial, as neither patients nor physicians were blinded and not all included patients were analysed as randomised (7 out of 40 patients). We considered the overall risk of bias in the GM-CSF to be moderate, because of the risk of performance bias (neither patients nor personnel were blinded), but low risk of selection and attrition bias.

For the trial comparing G-CSF to antibiotics, all cause mortality was not reported. There was no evidence of a difference for infection-related mortality, with zero events in each arm. Microbiologically or clinically documented infections, severe infections, quality of life, and adverse events were not reported. There was no evidence of a difference in frequency of febrile neutropenia (risk ratio (RR) 1.22; 95% confidence interval (CI) 0.53 to 2.84). The quality of the evidence for the two reported outcomes, infection-related mortality and frequency of febrile neutropenia, was very low, due to the low number of patients evaluated (high imprecision) and the high risk of bias.

There was no evidence of a difference in terms of median survival time in the trial comparing GM-CSF and antibiotics. Two-year survival times were 6% (0 to 12%) in both arms (high imprecision, low quality of evidence). There were four toxic deaths in the GM-CSF arm and three in the antibiotics arm (3.8%), without evidence of a difference (RR 1.32; 95% CI 0.30 to 5.69; $P = 0.71$; low quality of evidence). There were 28% grade III or IV infections in the GM-CSF arm and 18% in the antibiotics arm, without any evidence of a difference (RR 1.55; 95% CI 0.86 to 2.80; $P = 0.15$, low quality of evidence). There were 5 episodes out of 360 cycles of grade IV infections in the GM-CSF arm and 3 episodes out of 334 cycles in the cotrimoxazole arm (0.8%), with no evidence of a difference (RR 1.55; 95% CI 0.37 to 6.42; $P = 0.55$; low quality of evidence). There was no significant difference between the two arms for non-haematological toxicities like diarrhoea, stomatitis, infections, neurologic, respiratory, or cardiac adverse events. Grade III and IV thrombopenia occurred significantly more frequently in the GM-CSF arm (60.8%) compared to the antibiotics arm (28.9%); (RR 2.10; 95% CI 1.41 to 3.12; $P = 0.0002$; low quality of evidence). Neither infection-related mortality, incidence of febrile neutropenia, nor quality of life were reported in this trial.

Authors' conclusions

As we only found two small trials with 195 patients altogether, no conclusion for clinical practice is possible. More trials are necessary to assess the benefits and harms of G(M)-CSF compared to antibiotics for infection prevention in cancer patients receiving chemotherapy.

PLAIN LANGUAGE SUMMARY

Prophylactic antibiotics or G(M)-CSF for the prevention of infections in cancer patients undergoing chemotherapy

Review question

We reviewed the existing literature examining the efficacy and safety of granulocyte (macrophage) colony-stimulating factors (G(M)-CSF) compared to antibiotics to prevent infections for cancer patients receiving chemotherapy.

Background

Cancer treatment with chemotherapy (anti-cancer drugs) disrupts the immune system and lowers white blood cell counts. This increases a person's risk of infection. Both G(M)-CSF and antibiotics can reduce the risk of infection associated with cancer treatments. The review compared the efficacy of antibiotics to G(M)-CSFs for the prevention of infection.

Study characteristics

We searched several medical databases and identified two randomised controlled trials (RCT) that met our inclusion criteria; no new trials were identified for this review update. One trial included 40 breast cancer patients receiving high-dose chemotherapy. Eighteen patients received G-CSF and 22 got antibiotics (ciprofloxacin and amphotericin) to prevent infection. Another trial evaluated GM-

CSF versus antibiotics in patients with small-cell lung cancer, with 78 patients in the GM-CSF arm and 77 patients in the antibiotics arm.

Key results

The study that analysed G-CSF versus antibiotics did not report all cause mortality, microbiologically or clinically documented infections, severe infections, quality of life, or adverse events. We found no evidence of a difference between the two prophylactic options for the outcomes of infection-related mortality (no patient died because of infection), or febrile neutropenia.

The trial that assessed GM-CSF versus antibiotics did not find any evidence of a difference in all cause mortality, trial mortality, infections, or severe infections. The only difference between the two arms was found for the adverse event thrombocytopenia, favouring patients receiving antibiotics. Quality of life was not reported in this trial.

More research is needed to determine the best prevention against infection in cancer patients.

Quality of the evidence

The quality of the evidence for infection-related mortality and frequency of febrile neutropenia in the G-CSF trial was very low, because of the small number of patients that were evaluated, and the study design (high risk of bias). The trial that analysed GM-CSF versus antibiotics reported overall survival, toxic deaths, infections, severe infections, and adverse events. Because of the very small number of patients included, we judged that the overall quality for all these outcomes was low.

The evidence is current to December 2015.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

G-CSF compared with antibiotics for the prevention of infections and improvement of survival in cancer patients receiving myelotoxic chemotherapy

Patient or population: cancer patients receiving myelotoxic chemotherapy

Intervention: G-CSF

Comparison: antibiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Antibiotics	G-CSF				
All cause mortality	see comment					not reported
Infection-related mortality	see comment			40 (1 RCT)	⊕○○○ ^{1,2} very low	no patient died of infectious causes during the 18-week duration of the trial
Quality of life	see comment					not reported
Incidence of febrile neutropenia	318 per 1000	388 per 1000 (169 to 904)	RR 1.22 (0.53 to 2.84)	40 (1 RCT)	⊕○○○ ^{1,2} very low	
Incidence of severe infections	see comment					not reported
Adverse events	see comment					not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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 quality: We are very uncertain about the estimate.

¹ due to the low number of very low number of events, the result is highly imprecise (downgraded by 2 points)

² high risk of performance bias (neither patients nor physicians blinded) and detection bias (no intention to treat analysis) (downgraded by 1 point)

BACKGROUND

Description of the condition

Cancer patients receiving myelosuppressive therapy or haematopoietic stem cell transplantation are at increased risk of febrile neutropenia and infectious complications. The risk of febrile neutropenia and subsequent infection is directly related to the duration and severity of neutropenia (Bodey 1966; Bodey 1986). Infectious complications constitute major dose-limiting side effects in patients undergoing myelosuppressive therapy. Special risk circumstances, such as patient age greater than 65 years or poor performance status, impact the associated morbidity and mortality (Kuderer 2006; Pizzo 1999). The mortality rate associated with febrile neutropenia in cancer patients is between 2% and 21% (Smith 2015). In addition, infectious complications are a common cause of dose reductions during chemotherapy treatment.

Febrile neutropenia (FN) can be prevented by a prophylactic regimen. Prophylaxis started at the beginning of the first chemotherapy cycle or in parallel with documented or anticipated neutropenia is called primary prophylaxis, whereas prophylaxis given to patients who had already experienced episodes of FN in an earlier chemotherapy cycle, is referred to as secondary prophylaxis. Effective prophylaxis, using either colony-stimulating factors (CSF) or antibiotics (or both), would decrease clinically relevant negative outcomes such as all cause mortality, infection-related mortality, and infectious complications. Given the high costs of the consequences of FN, and also of the colony-stimulating factors themselves, economic arguments are introduced into discussions on the best prophylactic strategy (Kuderer 2006; Leibovici 2006).

In clinical trials addressing the prevention of FN, granulocyte-macrophage colony-stimulating factors (GM-CSFs) have been reported to be effective in reducing the duration and severity of chemotherapy-induced febrile neutropenia (Johnston 2000; Holmes 2002). Prophylaxis, using antibiotics, has also been shown to be beneficial with reduced fever, incidence of infections and hospitalisations (Bucaneve 2005; Cullen 2005).

Description of the intervention

Colony-stimulating factors (CSF)

The current American Society of Clinical Oncology (ASCO) guidelines justify the administration of CSFs in clinical settings where the expected risk of suffering FN is approximately 20% (Smith 2015). In addition to the myelotoxicity of the planned chemotherapy regimen, patient-specific risk factors should be taken into account. Secondary prophylaxis with CSFs is recommended for patients who have developed a neutropenic complication in a

previous chemotherapy cycle, and in whom a reduced dose might compromise disease-free or overall survival, or treatment outcome. The guidelines from the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO) give similar recommendations (Vehreschild 2014).

Thus far, randomised controlled trials (Crawford 1991; Trillet-Lenoir 1993), and subsequent meta-analyses, have shown that primary prophylaxis with CSFs is effective in reducing FN in patients with both solid and haematological malignancies (Bohlius 2008; Hackshaw 2004; Lyman 2002; Sung 2004; Sung 2007; Wittman 2006). Furthermore, GM-CSFs may decrease hospitalisation and the use of intravenous therapeutic antibiotics (Crawford 1991; Trillet-Lenoir 1993). In a meta-analysis on the use of GM-CSFs in cancer patients hospitalised with established FN, the authors observed a possible benefit of adding GM-CSFs to antibiotic treatment on infection-related mortality and length of hospitalisation (Clark 2005). A meta-analysis by Kuderer 2006 showed that under certain standard dose chemotherapy regimens, early and infection-related mortality were also reduced with primary GM-CSF prophylaxis. However, none of the meta-analyses with less restrictive inclusion criteria were able to demonstrate that prophylactic administration of GM-CSFs improved overall survival when compared to placebo or no treatment. None of these analyses addressed the question of GM-CSFs versus antibiotics, which is a question closer to clinical reality. One group did a subgroup analysis of studies in which the published report mandated antibiotic prophylaxis compared to those that did not, and found no difference between the groups (Sung 2007). This may be due to the high number of trials where no information about antibiotic prophylaxis use is available. In addition, this meta-analysis included studies that analysed cycles of chemotherapy as opposed to patients. The distorting effect of such an analysis is difficult to estimate.

Of the many meta-analyses looking at GM-CSF versus placebo or no treatment, only one meta-analysis, restricted to patients with lymphoma, was published in *The Cochrane Library* (Bohlius 2008). This analysis found a reduction in the rate of infections (odds ratio (OR) 0.74; 95% CI 0.64 to 0.85) but no effect on infection-related mortality (OR 1.37 favouring control; 95% CI 0.66 to 2.82).

GM-CSF is usually well tolerated, with only a moderate number of adverse events, mostly bone pain and headaches, however, there are some hints of increased risk of acute myeloid leukaemia or myelodysplastic syndromes (Lyman 2010).

Antibiotics

During the last decade, prophylaxis with antibiotics was studied in a number of randomised clinical trials. The evidence provided was not considered to be entirely convincing, because none of the studies were sufficiently large to provide conclusive evidence on the real efficacy of prophylaxis (Bucaneve 2005; Cullen 2005; Karp 1987;

Lew 1995). Subsequent meta-analyses suggested that prophylaxis using antibiotics reduced the incidence of gram-negative bacterial infection, total infection, fever episodes, and hospitalisation (Cruciani 2003; Engels 1998). Moreover, a meta-analysis of data on antibiotic prophylaxis (or more specifically, fluoroquinolones) compared to placebo or no intervention demonstrated that not only infections were reduced, but all cause mortality, and infection-related mortality were too (Gafer-Gvili 2005; Gafer-Gvili 2012; Leibovici 2006). One important question which is still unanswered is whether prophylaxis should be considered for all patients with cancer and neutropenia. In another meta-analysis on antibiotic prophylaxis, the majority of patients were suffering from haematological malignancies and received high-dose chemotherapy and bone marrow transplantation, with only a few studies focusing on solid tumours (Cullen 2005; Gafer-Gvili 2012). Another factor possibly compromising the results of the main meta-analysis was that studies were included that randomised chemotherapy cycles and not patients, or reported cycle-based outcomes, as opposed to a true incidence (where the number of patients and not cycles are analysed). No information on GM-CSFs compared to antibiotics was available from these analyses.

How the intervention might work

Colony-stimulating factors

Granulocyte colony-stimulating factors (G-CSF) predominantly augment the proliferation, maturation, and release of neutrophils, resulting in a dose-dependent increase in circulating neutrophils (Bronchud 1988; Morstyn 1988). It is a growth factor for the myeloid lineage that stimulates the growth of granulocytes and eosinophil colonies; granulocyte (macrophage) colony-stimulating factors (GM-CSF) also stimulate the growth of macrophages (Griffin 1990). Both colony-stimulating factors have shown comparable results in decreasing the incidence and duration of neutropenia and fever after chemotherapy. However, there is a lack of formal comparisons between the two drugs. Probably due to the macrophage activation caused by GM-CSF, but not G-CSF, tolerability of GM-CSF has been reported to be inferior. Injection site reactions in particular, seem more frequent with GM-CSF (Alvarado 1999; Beveridge 1997; Beveridge 1998; Fischmeister 1999; Hovgaard 1992). Given the undesired additional effects of GM-CSF and concerns of tumour stimulation by GM-CSF, the drug has become more or less disregarded by recent clinical studies and guidelines (Smith 2015). Granulocyte (macrophage) colony-stimulating factors is no longer commercially available in several European countries for infection prophylaxis. It is licensed for mobilisation of stem cells, and after autologous or allogeneic stem cell transplantation (Smith 2015).

Antibiotics

Antibiotic prophylaxis, most often using fluoroquinolones, reduces infections by targeting potential pathogens, and in contrast to G-CSFs it does not provoke the dose-limiting effect of haematological toxicity. A major concern of a routine prophylactic use of antibiotics in patients with cancer and neutropenia is that it increases bacterial resistance to these agents. This, in turn, may compromise the treatment success of both current and future serious infections by expanding (multi)resistance. In addition, hypersensitivity reactions, gastrointestinal toxicities, and the promotion of fungal overgrowth after antibiotics put the patient at risk of potentially serious adverse events. These factors may limit their efficacy in reducing infection-related morbidity or mortality (Carratala 1995; Gafer-Gvili 2007; Somolinos 1992).

Why it is important to do this review

The best prophylactic treatment of febrile neutropenia and infections in cancer patients receiving antineoplastic therapy remains controversial, and in general, international guidelines concentrate on either antibiotics or G-CSFs. The evidence outlined above suggests that prophylaxis with an antibiotic might be as effective as with G-CSFs for reducing both infections and mortality.

The aim of this systematic review is to provide a comprehensive overview on the benefits and harms of G-CSF compared to antibiotics for infection prophylaxis in cancer patients. By systematically identifying all randomised trials conducted to date and by conducting a critical review of their reliability and validity, we will mitigate the statistical limitations of individual studies.

OBJECTIVES

To compare the efficacy and safety of G-CSF or GM-CSF compared to antibiotics in cancer patients receiving myelotoxic chemotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials (RCTs). We excluded cross-over trials and quasi-randomised trials. We included full-text, abstracts, and unpublished data if sufficient information on study design, participant characteristics, interventions and outcomes was available.

Types of participants

We planned to include paediatric and adult, male and female patients with a confirmed diagnosis of any type of cancer who were undergoing myelotoxic chemotherapy. Both solid and haematological malignancies were eligible.

Types of interventions

We included trials comparing G-CSF or GM-CSF to antibiotics in the primary prophylaxis of infection-related complications. Trials that examined pegylated G-CSF (pegfilgrastim) were eligible, provided pegfilgrastim was given once, 24 hours after the completion of chemotherapy.

Comparison 1

- G-CSF versus antibiotics

Comparison 2

- GM-CSF versus antibiotics

Trials looking at secondary prophylaxis, defined as prophylaxis in a patient who suffered from FN in an earlier course of chemotherapy, were also eligible, but a subgroup analysis was planned. However, we did not identify any trial evaluating secondary prophylaxis.

We included studies in which the intended chemotherapy regimen and supportive care did not differ between study arms. Therefore, we excluded studies that compared dose-intensified, dose-accelerated, or dose-dense regimens with standard chemotherapy, as this resulted in different chemotherapy protocols in the arm that received antibiotic prophylaxis and the arm that received CSF prophylaxis. Trials with more than two arms were included, provided at least two arms with the relevant comparison had the same chemotherapy protocol.

We excluded trials using G-CSF, GM-CSF, or antibiotics to treat febrile neutropenia, fever, or infections.

Types of outcome measures

Primary outcomes

- Overall survival
- All cause mortality (including infection-related, treatment-related, or on-trial mortality)
- Infection-related mortality

Studies focusing solely on the efficacy of prophylaxis will most likely have short-term follow-up only, mainly providing information on early mortality. Determining the cause of death in severely ill patients can be associated with measurement bias. Therefore, we extracted all cause mortality, comprising infection-related and treatment-related mortality.

Secondary outcomes

- Microbiologically or clinically documented infections, or both
 - We accepted any definition of clinically documented or microbiologically documented infections given by authors. If available, we extracted data on all, not only severe, clinically or microbiologically documented infections. Microbiologically documented infections were required to have some kind of cultural confirmation of the infection. Infections reported without information on microbiological confirmation were considered to be clinically documented infections.
- Severe infections
- Frequency of febrile neutropenia (FN; any definition of fever and neutropenia accepted)
- Quality of life (QoL; if measured with a validated QoL instrument)
- Adverse events

Search methods for identification of studies

For this updated review, we revised the search strategy used for the first review. We used search strategies based on those described in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We did not use any language constraints.

Electronic searches

We searched the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library*, December 2015; see [Appendix 1](#))
- MEDLINE (1980 to December 2015; for search strategy see [Appendix 2](#))
- EMBASE (1980 to January 2008; for search strategy see [Appendix 3](#))

Since we revised our searches, we re-ran them for CENTRAL and MEDLINE for the entire period, i.e. 1980 to 2015.

Searching other resources

We searched conference proceedings of the following annual meetings, which were not included in CENTRAL for abstracts:

- American Society of Hematology (ASH) from 2000 to 2015
- American Society of Clinical Oncology (ASCO) from 2000 to 2015
- European Hematology Association (EHA) from 2000 to 2015

We electronically searched the database of ongoing trials:

- [Metaregister of controlled trials](#)

We handsearched the following references:

- References of all identified trials, relevant review articles and current treatment guidelines

Data collection and analysis

Selection of studies

Two review authors (NS, OB) independently screened the results of the search strategies for eligibility by reading the abstracts. In the case of disagreement, we obtained the full-text publication. If no consensus could be reached, we consulted a third review author, in accordance with Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We documented the study selection process in a flow chart as recommended in the PRISMA statement (Moher 2009), showing the total numbers of retrieved references and the numbers of included and excluded studies.

Data extraction and management

Two review authors independently extracted the data according to the guidelines proposed by Higgins 2011b. If required, we contacted authors of individual studies for additional information. We used a standardised data extraction form containing the following items:

- General information: author; title; source; publication date; country; language; duplicate publications.
- Quality assessment ('Risk of bias' assessment): sequence generation; allocation concealment; blinding (participants, personnel, outcome assessors); incomplete outcome data; selective outcome reporting; other potential sources of bias.
- Study characteristics: trial design; aims; setting and dates; source of participants; inclusion and exclusion criteria; comparability of groups; subgroup analysis; statistical methods; power calculations; treatment cross-overs; compliance with assigned treatment; length of follow-up; time point of randomisation.
- Participant characteristics: age; diagnosis; stage of disease; prior treatments; number of participants recruited, allocated, and evaluated; participants lost to follow-up; noticeable differences in risk factors for developing FN.
- Interventions: duration; type; dose and timing of GM-CSF, G-CSF, antibiotics, and other infection prophylaxes (e.g. antimycotics); concomitant treatment (setting, duration, type of chemotherapy); and supportive care (e.g. type of empirical antibiotic therapy).
- Outcomes: all cause mortality; infection-related mortality; microbiologically or clinically documented infections, or both; severe infections; QoL; frequency of FN; adverse events.

Assessment of risk of bias in included studies

Two review authors (NS and OB) independently assessed the risk of bias for each study using the following criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

- Sequence generation
- Allocation concealment
- Blinding (participants, personnel, outcome assessors)
- Incomplete outcome data
- Selective outcome reporting
- Other potential sources of bias

We made a judgement for every criterion, using one of three categories.

1. 'Low risk': if the criterion was adequately fulfilled in the study, i.e. the study was at a low risk of bias for the given criterion.
2. 'High risk': if the criterion was not fulfilled in the study, i.e. the study was at high risk of bias for the given criterion.
3. 'Unclear': if the study report did not provide sufficient information to allow for a judgement of 'Yes' or 'No', or if the risk of bias was unknown for one of the criteria listed above.

Measures of treatment effect

We used intention-to-treat data. For binary outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs) for each comparison. We did not identify or extract time-to-event or continuous outcomes.

Unit of analysis issues

We evaluated the number of patients with events rather than number of episodes, as the second one could be biased (e.g. a patient with one episode of febrile neutropenia is at increased risk to have a second episode of febrile neutropenia).

Dealing with missing data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), there were many potential sources of missing data that had to be taken into account: at the study level, outcome level, and summary data level. It is important to distinguish between 'missing at random' and 'not missing at random'. As we only identified one trial without missing data, we did not contact the original investigators.

Assessment of heterogeneity

As we only found two trials, which we did not meta-analyse, we did not assess heterogeneity of treatment effects between trials.

Assessment of reporting biases

In meta-analyses with at least 10 trials included for one outcome, we would have explored potential publication bias by generating a funnel plot and statistically testing this by using a linear regression test (Sterne 2011). We would have considered a P value of less than 0.1 to be significant for this test. However, as we analysed two trials only, we did not generate a funnel plot.

Data synthesis

As we only identified one trial for each comparison, we could not pool data. However, to analyse data for individual studies we entered data into [Review Manager \(RevMan\)](#) 5.3. Moreover, we created 'Summary of findings' tables for each comparison on absolute risks in each group with the help of the GRADE approach, and will use it to summarise the evidence of all cause mortality, infection-related mortality, quality of life, incidence of febrile neutropenia, incidence of severe infections and adverse events.

Subgroup analysis and investigation of heterogeneity

We had considered performing subgroup analyses using the following characteristics:

- Different types of underlying malignant disease;
- Different baseline risk for febrile neutropenia or infection;
- Study setting (in-patients or out-patients);
- Different type of treatment (e.g. haematologic stem cell transplantation versus standard chemotherapy);
- Different types of G-CSFs used;
- Age (<18 versus \geq 18 years); and
- According to whether regimens included antimycotic prophylaxis.

However, as we had insufficient data to meta-analyse, we could not perform these analyses.

Sensitivity analysis

We had considered performing sensitivity analyses using the following quality criteria:

- Quality components with regard to low and high risk of bias;
- Fixed-effect modelling versus random-effects modelling;
- Duration of study; and
- full-text publication versus abstract publication only.

Again, as we identified only two trials, which were too heterogeneous to pool, we could not perform these analyses.

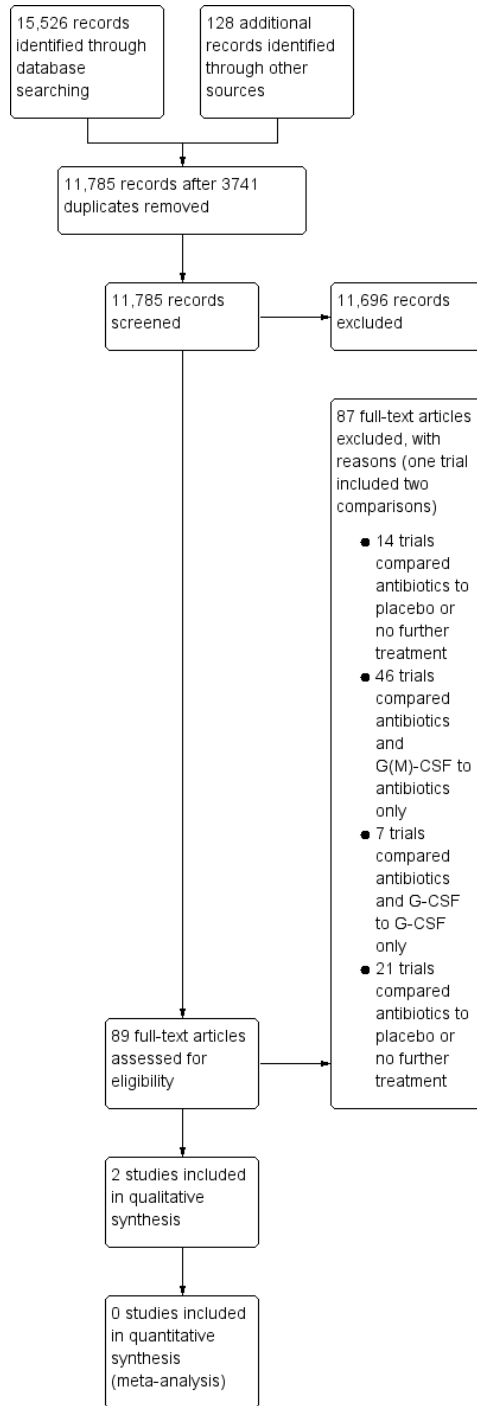
RESULTS

Description of studies

Results of the search

The literature search was designed to find all relevant articles where G-CSFs, GM-CSFs, or antibiotics were used as prophylactic agents. For this update, we set up a new search covering all time periods, i.e. after removing duplicates, we screened titles and abstracts of 11,785 references and excluded 11,696 at the initial stage. We assessed the full text of the remaining 89 references and excluded 87 references with reasons (see [Excluded studies](#)). As we identified no new trial fitting the inclusion criteria for this review update, we included the two already known trials in this review. See [Figure 1](#) for study flow diagram.

Figure 1. Study flow diagram.



Included studies

Two studies fulfilled the inclusion criteria of this review. One study involved adults with breast cancer receiving high-dose chemotherapy, and compared prophylaxis for at least six cycles (Schroder 1999). The other trial evaluated patients with small-cell lung cancer receiving accelerated chemotherapy (Sculier 2001). For more details see [Characteristics of included studies](#).

Design

Schroder 1999 was an open-label randomised (1:1) study. Sculier 2001 was a three-arm trial, two arms of which could be analysed in this review. The third arm evaluated standard chemotherapy without any infectious prophylaxis.

Sample sizes

Schroder 1999 included 40 patients, 18 in the G-CSF prophylaxis arm and 22 in the antibiotics arm. Sculier 2001 included 243 patients, 233 of whom were eligible. However, 78 of these patients received an intervention not applicable for this review, therefore 155 patients were analysed in this review.

Locations

Location is not reported by Schroder 1999, the Sculier 2001 trial took place in several European countries.

Participants

Schroder 1999 randomised chemotherapy-naïve patients with breast cancer who received three, three-week courses of intravenous cyclophosphamide (1500 mg/m²), epirubicin (80 mg/m²), and 5-fluouracil (1500 or 1000 mg/m²) given on day one; followed by three cycles of intravenous cyclophosphamide (1500 mg/m²), 5-fluouracil (600 mg/m²) on day one and intravenous methotrexate (1500 mg/m²) on day two. Sculier 2001 included patients with small-cell lung cancer receiving six courses of EVI (epirubicin 90 mg/m², vindesine 3 mg/m² and ifosfamide 5 g/m²) every 14 days.

Interventions

In the G-CSF arm in the Schroder 1999 trial, patients received 263 µg subcutaneous of G-CSF (lenograstim) on days 3 through to day 12 of each cycle. Patients in the antibiotics arm received two oral prophylactic agents, a combination of ciprofloxacin (250 mg twice daily) and amphotericin B (500 mg four times per day) on days 3 through to day 17 of each cycle, without blinding of the study participants. Patients in the Sculier 2001 study received

either GM-CSF as a daily subcutaneous dose of 5 µg/kg, from day 3 through to day 13 or until the neutrophil count reached ≥ 4000 mm³ after nadir, or cotrimoxazole (160 mg trimethoprim plus 800 mg sulfamethoxazole). This was administered orally every 12 hours from day three until the end of the courses of chemotherapy.

Outcomes

Schroder 1999 evaluated infection-related mortality, episodes of hospitalisation for febrile neutropenia, duration of hospitalisation for febrile neutropenia, grade IV leucopenia, and analysed costs of prophylaxis. Sculier 2001 assessed overall survival, tumour response, absolute and relative dose intensity, incidence of infections and severe infection, and adverse events. None of the trials evaluated quality of life.

Conflict of interest

Funding not reported.

Excluded studies

We excluded 87 trials with reasons (one trial included two comparisons (Tjan-Heijnen 2003):

- 14 trials compared antibiotics to placebo or no further treatment (Attal 1991; Carlson 1997; Cullen 2005; Dickgreber 2009; Karp 1986; Lamy 1993; Lee 2002; Petersen 1988; Pignon 1990; Rafecas 1989; Schuette 2011; Talbot 1993; Tjan-Heijnen 2003; Yamada 1993).
- 46 trials compared antibiotics and G-CSF or GM-CSF to antibiotics only (Aarts 2013; Alonzo 2002; Altman 1996; Ardizzone 1994; Bishop 2000; Bradstock 2001; Burton 2006; Clarke 1999; Dibenedetto 1995; Ernst 2008; Faber 2006; Garcia 2000; Garcia-Saenz 2002; Geissler 1997; Gonzalez-Vicent 2004; Greenberg 1996; Gulati 1992; Heath 2003; Hecht 2010; Heil 1997; Joshi 2003; Ladenstein 2010; Lee 1998; Lehrnbecher 2007; Little 2002; Maiche 1993; McQuaker 1997; Michel 2000; Miles 1994; Nemunaitis 1995; Nolan 2007; Ojeda 1999; Ottmann 1995; Pettengell 1992; Piccirillo 1999; Przepiorka 2001; Pui 1997; Schmitz 2004; Spitzer 1994; Stahel 1994; Timmer-Bonte 2005; Trigg 2000; Welte 1996; Witz 1998; Yau 1996; Zinzani 1997a).
- 7 trials compared antibiotics and G-CSF to G-CSF only (Eleutherakis-Papaikovou 2010; Feng 2014; Kim 2005; Lalami 2004; Lee 1998; Suh 2008; Tjan-Heijnen 2003).
- 21 trials compared G-CSF to placebo or no further treatment (Bennett 2001; Björkholm 1999; Brugger 2009; Chevallier 1995; Crawford 1997; Doorduijn 2005; Dunlop 1996; Fridrik 1997; Godwin 1998; Hartmann 1997;

Holowiecki 2002; Kosaka 2015; Larson 1998; Michon 1998;
 Osby 2003; Patte 2002; Romieu 2007; Seymour 1995;
 Trillet-Lenoir 1993; Veyret 2006; Vogel 2005).

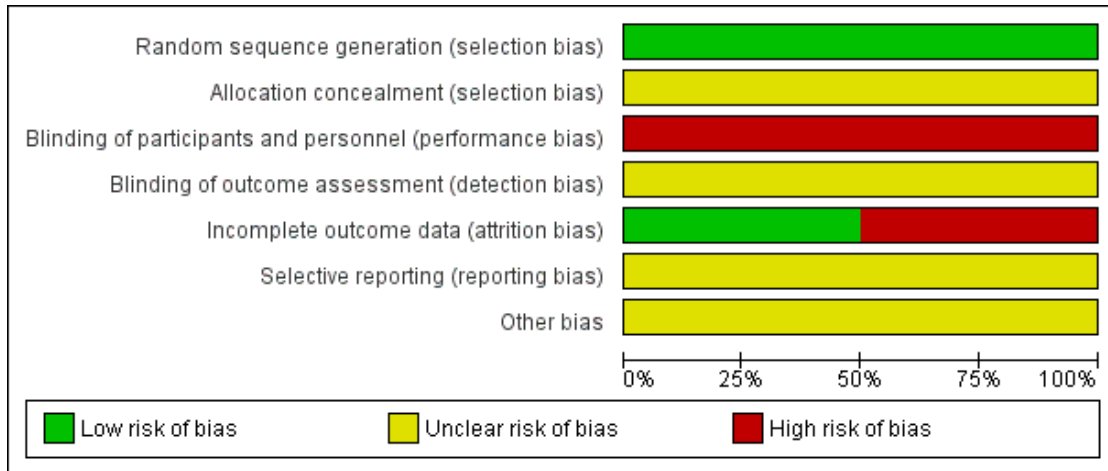
Risk of bias in included studies

See Figure 2 and Figure 3 for risk of bias summary.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Schroder 1999	+	?	-	?	-	?	?
Sculier 2001	+	?	-	?	+	?	?

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Both trials were described as randomised, but the randomisation procedure was not reported. Therefore, we judged the risk of selection bias as unclear.

Blinding

There was no blinding of the participants or personnel due to the use of either an oral antibiotic or subcutaneous injections of GM-CSF; no information was given about whether or not the assessors were blinded. Therefore we judged potential risk of performance bias as high and of detection bias as unclear.

Incomplete outcome data

As 23 courses from seven patients from the antibiotics group, who switched to rhG-CSF, were not included in the analysis by Schroder 1999, we judged the risk of attrition bias as high in this trial. All patients in the Sculier 2001 trial were evaluated as randomised, reasons for ten patients not being eligible after randomisation were given. Therefore, we judged risk of attrition bias for this trial as low.

Selective reporting

As we did not identify study protocols; it is unclear if all the planned outcomes are reported. We judged the risk of reporting bias as unclear.

Other potential sources of bias

As no other potential source of bias was reported, we judged this bias as “unclear”.

Effects of interventions

See: [Summary of findings for the main comparison; Summary of findings 2](#)

Comparison 1: G-CSF versus antibiotics

Overall survival

Not reported by Schroder 1999.

All cause mortality (including infection-related, treatment-related, or on-trial mortality)

Not reported by Schroder 1999.

Infection-related mortality

Infection-related mortality was the same in both groups of the Schroder 1999 trial: no patient died of infectious causes during the 18-week duration of the trial.

Microbiologically or clinically documented infections

Not reported.

Incidence of severe infections

Not reported

Quality of life (QoL)

Not reported.

Incidence of febrile neutropenia (FN)

[Schroder 1999](#) reported febrile neutropenia in 7/18 patients receiving G-CSF and in 7/22 patients receiving ciprofloxacin and amphotericin B (relative risk (RR) 1.22; 95% confidence interval (CI) 0.53 to 2.84).

Adverse events

Not reported.

Comparison 2: GM-CSF versus antibiotics**Overall survival**

There was no evidence of a difference in median survival time, with 264 (95% CI 220 to 308) days for patients in the GM-CSF arm and 264 (95% CI 223 to 305 days) in the antibiotics arm ([Sculier 2001](#)). Two-year survival times were 6% (0 to 12%) in both arms.

All cause mortality (including infection-related, treatment-related, or on-trial mortality)

There were four toxic deaths in the GM-CSF arm (5.1%) and three in the antibiotics arm (3.8%), without evidence for a difference (RR 1.32; 95% CI 0.30 to 5.69; P = 0.71).

Infection-related mortality

This outcome was not reported in [Sculier 2001](#).

Microbiologically or clinically documented infections

There were 22 grade III or IV infections (28%) in the GM-CSF arm in the [Sculier 2001](#) trial and 14 infections (18%) in the antibiotics arm, without any evidence of a difference (RR 1.55; 95% CI 0.86 to 2.80; P = 0.15).

Incidence of severe infections

There were 5 episodes out of 360 cycles (1.3%) of grade IV infections in the GM-CSF arm and 3 episodes out of 334 cycles in the cotrimoxazole arm (0.8%), without evidence of a difference (RR 1.55; 95% CI 0.37 to 6.42; P = 0.55).

Quality of life (QoL)

Not reported.

Incidence of febrile neutropenia (FN)

Not reported.

Adverse events

There was no significant difference between the two arms for non-haematological toxicities like diarrhoea, stomatitis, infections, neurologic, respiratory or cardiac adverse events. Grade III and IV thrombopenia occurred significantly more frequently in the GM-CSF arm (60.8%) compared to the antibiotics arm (28.9%); with a RR 2.10; 95% CI 1.41 to 3.12; P = 0.0002.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

GM-CSF compared with antibiotics for the prevention of infections and improvement of survival in cancer patients receiving myelotoxic chemotherapy

Patient or population: cancer patients receiving myelotoxic chemotherapy

Intervention: GM-CSF

Comparison: antibiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Antibiotics	GM-CSF				
All cause mortality	see comment			115 (1 RCT)	⊕⊕○○ ¹ low	Two-year survival times were 6% (0 to 12%) in both arms
Infection-related mortality	see comment					not reported
Quality of life	see comment					not reported
Incidence of febrile neutropenia	see comment					not reported
Incidence of severe infections (Grade III or IV)	182 per 1000	282 per 1000 (156 to 509)	RR 1.55 (0.86 to 2.80)	115 (1 RCT)	⊕⊕○○ ¹ low	not reported
Adverse events Toxic deaths	39 per 1000	51 per 1000 (12 to 222)	RR 1.32 (0.30 to 5.69)	115 (1 RCT)	⊕⊕○○ ¹ low	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: 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 quality: We are very uncertain about the estimate.

¹ due to the low number of very low number of events, the result is highly imprecise (downgraded by 2 points)

DISCUSSION

Summary of main results

The striking finding of this review is that there is only one very small study comparing granulocyte colony-stimulating factors (G-CSF) to antibiotics for infection prophylaxis in cancer patients receiving myelosuppressive chemotherapy, and one trial with 155 patients evaluating granulocyte macrophage colony-stimulating factors (GM-CSF) versus antibiotics. The trial evaluating G-CSF did not report all cause mortality, incidence of documented or severe infections, quality of life, or adverse events. We did not find evidence of a difference in infection-related mortality (none of the 40 included patients died because of infection), or in incidence of febrile neutropenia.

The trial that evaluated GM-CSF reported overall survival, toxic deaths, infections and severe infections and non-haematological adverse events, without any evidence of a difference between the GM-CSF arm and the antibiotics arm. Patients in the antibiotics arm had fewer thrombopenic adverse events. Quality of life was not reported.

Overall completeness and applicability of evidence

As only two small trials were identified, it is not possible to come to a final conclusion regarding the best prophylactic regimen in cancer patients at risk of neutropenia. Therefore, this clinically important question remains unanswered. Moreover, the trial assessing G-CSF evaluated only a few of the outcomes of interest (incidence of febrile neutropenia and infection-related mortality), but all cause mortality, incidence of documented or severe infections, quality of life, and adverse events were not assessed.

The trial evaluating GM-CSF versus antibiotics reported more of the outcomes of interest (overall survival, toxic deaths, infections and severe infections and adverse events), however, due to the small sample size, there was no evidence of a difference, except for the adverse event, thrombocytopenia.

The 41 trials that were excluded because they evaluated the influence of the combination of GM-CSF and antibiotics compared to GM-CSF or antibiotics only, underline the huge imbalance between the number of direct comparisons of the two drugs we evaluated in this review, and the number of trials that were conducted in this field.

Quality of the evidence

The risk of bias in [Schroder 1999](#) was high, as this trial was not blinded and not all patients of the included 40 patients were analysed as randomised (seven of 22 patients from the antibiotics arm crossed-over to G-CSF and were excluded from analysis). The risk

of bias for [Sculier 2001](#) could be considered to be moderate, as risk of performance bias was high, but risk of selection and attrition bias was low.

As only two trials could be included in this review, one evaluating G-CSF, the other evaluating GM-CSF, no meta-analysis was possible. The trial evaluating G-CSF reported infection-related mortality and incidence of febrile neutropenia. We judged the quality of evidence for both outcomes to be very low, due to the small number of events, which lead to high imprecision (downgraded by two levels), and the high risk of bias (downgraded by one level). The trial that analysed GM-CSF versus antibiotics reported overall survival, toxic deaths, infections, severe infections and adverse events. Because of the very small number of patients included, we downgraded overall quality of the evidence for all outcomes by two levels (high imprecision). As risk of bias was moderate in this trial, we did not downgrade the quality of evidence for this reason. Therefore, overall quality for all the outcomes mentioned above was considered to be low.

Potential biases in the review process

To prevent bias within the review, we considered only RCTs and performed all relevant processes in duplicate. We developed a sensitive search strategy, and searched all relevant data from international cancer congresses by hand to minimise potential publication bias. We are not aware of any obvious deficiencies in our review process. The small number of trials included in this review could lead to publication bias as a funnel plot could not be generated.

Agreements and disagreements with other studies or reviews

One comprehensive meta-analysis of GM-CSF versus control includes 148 trials with more than 16,000 patients ([Sung 2007](#)). However, in this publication it is not reported how many patients received additional antibiotics, and how many patients received either G-CSF or GM-CSF. Similarly, the most comprehensive antibiotics versus control meta-analysis includes 49 trials with more than 6000 patients (for the outcome all cause mortality; [Gafer-Gvili 2005](#)). The low number of trials directly comparing antibiotics to G-CSFs is surprising, considering the higher cost of GM-CSFs compared to standard antibiotics. However, a high number of trials comparing GM-CSFs to control received funding from pharmaceutical companies that produce GM-CSFs. As there are only two small trials directly comparing G-CSF or GM-CSF versus antibiotics, no final conclusion on the best prophylactic regimen is possible. Clearly, more trials with larger numbers of patients are required to answer this question, in particular, with regard to early all cause and infection-related mortality. In addition, GM-CSF is no longer commercially available for infection prophylaxis in several European countries; it is licensed instead for

mobilisation of stem cells or after autologous or allogeneic stem cell transplantation (Smith 2015).

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient direct evidence from randomised controlled trials to recommend one prophylaxis (G-CSFs, GM-CSFs, or antibiotics) over the other for cancer patients receiving myelotoxic chemotherapy.

Implications for research

Large high quality trials comparing antibiotic prophylaxis to in-

fection prophylaxis using G-CSFs or GM-CSFs are necessary in a wide range of cancer patients, to evaluate clinically important outcomes, like all cause and infection-related mortality, incidence of febrile neutropenia, quality of life and adverse events.

ACKNOWLEDGEMENTS

We would like to thank the authors of the first published version of this review, Christine Herbst, Frauke Naumann-Winter, Eva-Brigitta Kruse, Julia Bohlius and Holger Schulz. We also thank Olaf Weingart and Andrea Will of the Cochrane Haematological Malignancies Group (CHMG) Editorial Base as well as the Content Editor and the Statistic Editor for commenting on this review. We also thank the Copy-Editors Janet Wale and Vicki Pennick.

REFERENCES

References to studies included in this review

Schroder 1999 *{published data only}*

Schroder CP, de Vries EG, Mulder NH, Willemse PH, Sleijfer DT, Hospers GA, et al. Prevention of febrile leucopenia after chemotherapy in high-risk breast cancer patients: no significant difference between granulocyte-colony stimulating growth factor or ciprofloxacin plus amphotericin B. *Journal of Antimicrobial Chemotherapy* 1999;**43**(5):741–3.

Sculier 2001 *{published data only}*

Sculier JP, Paesmans M, Lecomte J, Van Cutsem O, Lafitte JJ, Berghmans T, et al. A three-arm phase III randomised trial assessing, in patients with extensive-disease small-cell lung cancer, accelerated chemotherapy with support of haematological growth factor or oral antibiotics. *British Journal of Cancer* 2001;**85**(10):1444–51.

References to studies excluded from this review

Aarts 2013 *{published data only}*

Aarts MJ, Peters FP, Mandigers CM, Dercksen MW, Stouthard JM, Nortier HJ, et al. Primary granulocyte colony-stimulating factor prophylaxis during the first two cycles only or throughout all chemotherapy cycles in patients with breast cancer at risk for febrile neutropenia. *Journal of Clinical Oncology* 2013;**31**(34):4290–6. [DOI: 10.1200/JCO.2012.44.6229.]

Alonzo 2002 *{published data only}*

Alonzo TA, Kobrinsky NL, Aledo A, Lange BJ, Buxton AB, Woods WG. Impact of granulocyte colony-stimulating factor use during induction for acute myelogenous leukemia in children: a report from the Children's Cancer Group. *Journal of Pediatric Hematology/Oncology* 2002;**24**(8): 627–35.

Altman 1996 *{published data only}*

Altman A, Steinherz P, Trigg M, Halpern S, Jhanwar S, Pieters R, et al. A prospective randomized trial of granulocyte colony-stimulating factor (G-CSF) during induction or consolidation phases of intensive chemotherapy for acute lymphocytic leukemia (ALL) [abstract]. *Journal of Clinical Oncology*. 1996;542, Abstract 1760.

Ardizzoni 1994 *{published data only}*

Ardizzoni A, Venturini M, Sertoli MR, Giannesi PG, Brema F, Danova M, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) allows acceleration and dose intensity increase of CEF chemotherapy: a randomised study in patients with advanced breast cancer. *British Journal of Cancer* 1994;**69**(2):385–91.

Attal 1991 *{published data only}*

Attal M, Schlaifer D, Rubie H, Huguier F, Charlet JP, Bloom E, et al. Prevention of gram-positive infections after bone marrow transplantation by systemic vancomycin: a prospective, randomized trial. *Journal of Clinical Oncology* 1991;**9**(5):865–70.

Bennett 2001 *{published data only}*

Bennett CL, Hynes D, Godwin J, Stinson TJ, Golub RM, Appelbaum FR, et al. Economic analysis of granulocyte colony stimulating factor as adjunct therapy for older patients with acute myelogenous leukemia (AML): estimates from a Southwest Oncology Group clinical trial. *Cancer Investigation* 2001;**19**(6):603–10.

Bishop 2000 *{published data only}*

Bishop MR, Tarantolo SR, Geller RB, Lynch JC, Bierman PJ, Pavletic ZS, et al. A randomized, double-blind trial of filgrastim (granulocyte colony-stimulating factor) versus placebo following allogeneic blood stem cell transplantation. *Blood* 2000;**96**(1):80–5.

Björkholm 1999 *{published data only}*

Björkholm M, Osby E, Hagberg H, Kvaloy S, Teerenhovi L, Myhre J. Randomized trial of r-metHu granulocyte colony-stimulating factor (G-CSF) as adjunct to CHOP or CNOP treatment of elderly patients with aggressive non-Hodgkin's lymphoma [abstract]. *Blood*. 1999;599a.

Bradstock 2001 *{published data only}*

Bradstock K, Matthews J, Young G, Lowenthal R, Baxter H, Cetal A. Effects of glycosylated recombinant human granulocyte colony-stimulating factor after high-dose cytarabine-based induction chemotherapy for adult acute myeloid leukaemia. *Leukemia* 2001;15(9):1331–8.

Brugger 2009 *{published data only}*

Brugger W, Bacon P, Lawrinson S, Romieu G. Neutrophil recovery in elderly breast cancer patients receiving adjuvant anthracycline-containing chemotherapy with pegfilgrastim support. *Critical Reviews in Oncology/Hematology* 2009;72(3):265–9.

Burton 2006 *{published data only}*

Burton C, Linch D, Hoskin P, Milligan D, Dyer MJ, Hancock B, et al. A phase III trial comparing CHOP to PMitCEBO with or without G-CSF in patients aged 60 plus with aggressive non-Hodgkin's lymphoma. *British Journal of Cancer* 2006;94(6):806–13.

Carlson 1997 *{published data only}*

Carlson JW, Fowler JM, Mitchell SK, Carson LF, Mayer AR, Copeland LJ. Chemoprophylaxis with ciprofloxacin in ovarian cancer patients receiving paclitaxel: a randomized trial. *Gynecologic Oncology* 1997;65(2):325–9.

Chevallier 1995 *{published data only}*

Chevallier B, Chollet P, Merrouche Y, Roche H, Fumoleau P, Kerbrat P, et al. Lenograstim prevents morbidity from intensive induction chemotherapy in the treatment of inflammatory breast cancer. *Journal of Clinical Oncology* 1995;13(7):1564–71.

Clarke 1999 *{published data only}*

Clarke V, Dunstan FD, Webb DK. Granulocyte colony-stimulating factor ameliorates toxicity of intensification chemotherapy for acute lymphoblastic leukemia. *Medical & Pediatric Oncology* 1999;32(5):331–5.

Crawford 1997 *{published data only}*

Crawford J, Kreisman H, Garewal H, Jones SE, Shoemaker D, Pupa MR, et al. The impact of filgrastim schedule variation on hematopoietic recovery post-chemotherapy. *Annals of Oncology* 1997;8(11):1117–24.

Cullen 2005 *{published data only}*

Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *New England Journal of Medicine* 2005;353(10):988–98.

Dibenedetto 1995 *{published data only}*

Dibenedetto SP, Ragusa R, Ippolito AM, Lo NL, Di Cataldo A, D'Amico S, et al. Assessment of the value of treatment with granulocyte colony-stimulating factor in children with

acute lymphoblastic leukemia: a randomized clinical trial. *European Journal of Haematology* 1995;55(2):93–6.

Dickgreber 2009 *{published data only}*

Dickgreber N, Nagel S, Roscher K, Schuette W. Randomised, placebo-controlled phase III trial of docetaxel plus carboplatin with or without levofloxacin prophylaxis in elderly patients with advanced non-small cell lung cancer: The APRONTA Trial. [19th European Congress of Clinical Microbiology and Infectious Diseases]. *Clinical Microbiology and Infection* 2009;15:S519.

Doorduijn 2005 *{published data only}*

Doorduijn J, Buijt I, Holt B, Steijaert M, Uyl-de Groot C, Sonneveld P. Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy. *European Journal of Haematology* 2005;75(2):116–23.

Dunlop 1996 *{published data only}*

Dunlop DJ, Andersen S, Paul J, Soukop M, Ellis D, Tansey P. Filgrastim as an adjunct to combination chemotherapy in Hodgkin's disease. *Annals of Oncology* 1996:51.

Eleutherakis-Papaiaikovou 2010 *{published data only}*

Eleutherakis-Papaiaikovou E, Kostis E, Migkou M, Christoulas D, Terpos E, Gavriatopoulou M, et al. Prophylactic antibiotics for the prevention of neutropenic fever in patients undergoing autologous stem-cell transplantation: results of a single institution, randomized phase 2 trial. *American Journal of Hematology* 2010;85(11):863–7.

Ernst 2008 *{published data only}*

Ernst P, Bacigalupo A, Ringden O, Ruutu T, Kolb HJ, Lawrinson S, et al. A phase 3, randomized, placebo-controlled trial of filgrastim in patients with haematological malignancies undergoing matched-related allogeneic bone marrow transplantation. *Archives of Drug Information* 2008;1(3):89–96.

Faber 2006 *{published data only}*

Faber E, Pytlík R, Slaby J, Zapletalova J, Kozak T, Raida L, et al. Individually determined dosing of filgrastim after autologous peripheral stem cell transplantation in patients with malignant lymphoma—results of a prospective multicentre controlled trial. *European Journal of Haematology* 2006;77(6):493–500.

Feng 2014 *{published data only}*

Feng X, Ruan Y, He Y, Zhang Y, Wu X, Liu H, et al. Prophylactic first-line antibiotics reduce infectious fever and shorten hospital stay during chemotherapy-induced agranulocytosis in childhood acute myeloid leukemia. *Acta Haematologica* 2014;132(1):112–7.

Fridrik 1997 *{published data only}*

Fridrik MA, Greil R, Hausmaninger H, Krieger O, Oppitz P, Stoger M, et al. Randomized open label phase III trial of CEOP/IMVP-Dexa alternating chemotherapy and filgrastim versus CEOP/IMVP-Dexa alternating chemotherapy for aggressive non-Hodgkin's lymphoma (NHL). A multicenter trial by the Austrian Working Group for Medical Tumor Therapy.[Erratum appears in Ann

- Hematol. 2014 Mar;93(3):539-40]. *Annals of Hematology* 1997;75(4):135-40.
- Garcia 2000** *{published data only}*
Garcia G. Immediate vs. delayed imipenem treatment in cancer patients with profound neutropenia induced by high-dose chemotherapy: Results of a randomized study. *Revista Espanola de Quimioterapia* 2000; Vol. 15:257-63.
- Garcia-Saenz 2002** *{published data only}*
Garcia-Saenz JA, Martin M, Casado A, Perez-Segura P, Manrique I, Flores L, et al. Immediate vs. delayed imipenem treatment in cancer patients with profound neutropenia induced by high-dose chemotherapy: results of a randomized study. *Revista Espanola de Quimioterapia* 2002;15(3):257-63.
- Geissler 1997** *{published data only}*
Geissler K, Koller E, Hubmann E, Niederwieser D, Hinterberger W, Geissler D, et al. Granulocyte colony-stimulating factor as an adjunct to induction chemotherapy for adult acute lymphoblastic leukemia--a randomized phase-III study. *Blood* 1997;90(2):590-6.
- Godwin 1998** *{published data only}*
Godwin JE, Kopecky KJ, Head DR, Willman CL, Leith CP, Hynes HE, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest oncology group study (9031). *Blood* 1998;91(10):3607-15.
- Gonzalez-Vicent 2004** *{published data only}*
Gonzalez-Vicent M, Madero L, Sevilla J, Ramirez M, Diaz MA. A prospective randomized study of clinical and economic consequences of using G-CSF following autologous peripheral blood progenitor cell (PBPC) transplantation in children. *Bone Marrow Transplantation* 2004;34(12):1077-81.
- Greenberg 1996** *{published data only}*
Greenberg P, Advani R, Keating A, Gulati SC, Nimer S, Champlin R, et al. GM-CSF accelerates neutrophil recovery after autologous hematopoietic stem cell transplantation. *Bone Marrow Transplantation* 1996;18(6):1057-64.
- Gulati 1992** *{published data only}*
Gulati SC, Bennett CL. Granulocyte-macrophage colony-stimulating factor (GM-CSF) as adjunct therapy in relapsed Hodgkin disease. *Annals of Internal Medicine* 1992;116(3):177-82.
- Hartmann 1997** *{published data only}*
Hartmann LC, Tschetter LK, Habermann TM, Ebbert LP, Johnson PS, Mailliard JA, et al. Granulocyte colony-stimulating factor in severe chemotherapy-induced afebrile neutropenia. *New England Journal of Medicine* 1997;336(25):1776-80.
- Heath 2003** *{published data only}*
Heath JA, Steinherz PG, Altman A, Sather H, Jhanwar S, Halpern S, et al. Human granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia: a Children's Cancer Group Study. *Journal of Clinical Oncology* 2003;21(8):1612-7.
- Hecht 2010** *{published data only}*
Hecht JR, Pillai M, Gollard R, Heim W, Swan F, Patel R, et al. A randomized, placebo-controlled phase II study evaluating the reduction of neutropenia and febrile neutropenia in patients with colorectal cancer receiving pegfilgrastim with every-2-week chemotherapy. *Clinical Colorectal Cancer* 2010;9(2):95-101.
- Heil 1997** *{published data only}*
Heil G, Hoelzer D, Sanz MA, Lechner K, Liu Yin JA, Papa G, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group. *Blood* 1997;90(12):4710-8.
- Holowiecki 2002** *{published data only}*
Holowiecki J, Giebel S, Krzemien S, Krawczyk-Kulis M, Jagoda K, Kopera M, et al. G-CSF administered in time-sequenced setting during remission induction and consolidation therapy of adult acute lymphoblastic leukemia has beneficial influence on early recovery and possibly improves long-term outcome: a randomized multicenter study. *Leukemia & Lymphoma* 2002;43(2):315-25.
- Jones 1996** *{published data only}*
Jones SE, Schottstaedt MW, Duncan LA, Kirby RL, Good RH, Mennel RG, et al. Randomized double-blind prospective trial to evaluate the effects of sargramostim versus placebo in a moderate-dose fluorouracil, doxorubicin, and cyclophosphamide adjuvant chemotherapy program for stage II and III breast cancer. *Journal of Clinical Oncology* 1996;14(11):2976-83.
- Joshi 2003** *{published data only}*
Joshi SS, Bishop MR, Lynch JC, Tarantolo SR, Abhyankar S, Bierman PJ, et al. Immunological and clinical effects of post-transplant G-CSF versus placebo in T-cell replete allogeneic blood transplant patients: results from a randomized double-blind study. *Cytotherapy* 2003;5(6):542-52.
- Karp 1986** *{published data only}*
Karp JE, Merz WG, Hendricksen C, Laughon B, Redden T, Bamberger BJ, et al. Infection management during antileukemia treatment-induced granulocytopenia: the role for oral norfloxacin prophylaxis against infections arising from the gastrointestinal tract. *Scandinavian Journal of Infectious Diseases Supplement* 1986;48:66-78.
- Kim 2005** *{published data only}*
Kim S, Cho YH, Ko OB, Koo JE, Lee D, Chong YP, et al. Beneficial prophylactic antimicrobial use against infectious complications during autologous stem cell transplantation: a result of randomized phase II study in multiple myeloma and non-Hodgkin's lymphoma patients. *Blood*. 2005; Vol. 11.
- Kosaka 2015** *{published data only}*
Kosaka Y, Rai Y, Masuda N, Takano T, Saeki T, Nakamura S, et al. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/

- cyclophosphamide chemotherapy. *Support Care Cancer* 2015;**23**(4):1137–43.
- Ladenstein 2010** *{published data only}*
Ladenstein R, Valteau-Couanet D, Brock P, Yaniv I, Castel V, Laureys G, et al. Randomized Trial of prophylactic granulocyte colony-stimulating factor during rapid COJEC induction in pediatric patients with high-risk neuroblastoma: the European HR-NBL1/SIOPEN study. *Journal of Clinical Oncology* 2010;**28**(21):3516–24.
- Lalami 2004** *{published data only}*
Lalami Y, Paesmans M, Aoun M, Munoz-Bermeo R, Reuss K, Cherif S, et al. A prospective randomised evaluation of G-CSF or G-CSF plus oral antibiotics in chemotherapy-treated patients at high risk of developing febrile neutropenia. *Supportive Care in Cancer* 2004;**12**(10): 725–30.
- Lamy 1993** *{published data only}*
Lamy T, Michelet C, Dauriac C, Grulois I, Donio PY, Pris e PY. Benefit of prophylaxis by intravenous systemic vancomycin in granulocytopenic patients: a prospective, randomized trial among 59 patients. *Acta Haematologica* 1993;**90**(3):109–13.
- Larson 1998** *{published data only}*
Larson RA, Dodge RK, Linker CA, Stone RM, Powell BL, Lee EJ, et al. A randomized controlled trial of filgrastim during remission induction and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. *Blood* 1998;**92**(5):1556–64.
- Lee 1998** *{published data only}*
Lee SM, Radford JA, Dobson L, Huq T, Ryder WD, Pettengell Retal. Recombinant human granulocyte colony-stimulating factor (filgrastim) following high-dose chemotherapy and peripheral blood progenitor cell rescue in high-grade non-Hodgkin's lymphoma: clinical benefits at no extra cost. *British Journal of Cancer* 1998;**77**(8):1294–9.
- Lee 2002** *{published data only}*
Lee DG, Choi SM, Choi JH, Yoo JH, Park YH, Kim YJ, et al. Selective bowel decontamination for the prevention of infection in acute myelogenous leukemia: a prospective randomized trial. *Korean Journal of Internal Medicine* 2002; **17**(1):38–44.
- Lehrnbecher 2007** *{published data only}*
Lehrnbecher T, Zimmermann M, Reinhardt D, Dworzak M, Stary J, Creutzig U. Prophylactic human granulocyte colony-stimulating factor after induction therapy in pediatric acute myeloid leukemia. *Blood* 2007;**109**(3): 936–43.
- Little 2002** *{published data only}*
Little MA, Morland B, Chisholm J, Hole A, Shankar A, Devine T, et al. A randomised study of prophylactic G-CSF following MRC UKALL XI intensification regimen in childhood ALL and T-NHL. *Medical & Pediatric Oncology* 2002;**38**(2):98–103.
- Maiche 1993** *{published data only}*
Maiche AG, Muhonen T. Granulocyte colony-stimulating factor (G-CSF) with or without a quinolone in the prevention of infection in cancer patients. *European Journal of Cancer* 1993;**29A**(10):1403–5.
- McQuaker 1997** *{published data only}*
McQuaker IG, Hunter AE, Pacey S, Haynes AP, Iqbal A, Russell NH. Low-dose filgrastim significantly enhances neutrophil recovery following autologous peripheral-blood stem-cell transplantation in patients with lymphoproliferative disorders: evidence for clinical and economic benefit (Structured abstract). *Journal of Clinical Oncology* 1997;**15**(2):451–7.
- Michel 2000** *{published data only}*
Michel G, Landman-Parker J, Auclerc MF, Mathey C, Leblanc T, Legall E, et al. Use of recombinant human granulocyte colony-stimulating factor to increase chemotherapy dose-intensity: a randomized trial in very high-risk childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology* 2000;**18**(7):1517–24.
- Michon 1998** *{published data only}*
Michon JM, Hartmann O, Bouffet E, Meresse V, Coze C, Rubie H, et al. An open-label, multicentre, randomised phase 2 study of recombinant human granulocyte colony-stimulating factor (filgrastim) as an adjunct to combination chemotherapy in paediatric patients with metastatic neuroblastoma. *European Journal of Cancer* 1998;**34**(7): 1063–9.
- Miles 1994** *{published data only}*
Miles DW, Fogarty O, Ash CM, Rudd RM, Trask CW, Spiro SG, et al. Received dose-intensity: a randomized trial of weekly chemotherapy with and without granulocyte colony-stimulating factor in small-cell lung cancer. *Journal of Clinical Oncology* 1994;**12**(1):77–82.
- Nemunaitis 1995** *{published data only}*
Nemunaitis J, Rosenfeld CS, Ash R, Freedman MH, Deeg HJ, Appelbaum F, et al. Phase III randomized, double-blind placebo-controlled trial of rhGM-CSF following allogeneic bone marrow transplantation. *Bone Marrow Transplantation* 1995;**15**(6):949–54.
- Nolan 2007** *{published data only}*
Nolan L, Lorigan P, Chilton S, Newman J, Else R, Smith P, et al. Low-dose lenograstim is as effective as standard dose in shortening neutrophil engraftment time following myeloablative chemotherapy and peripheral blood progenitor cell rescue. *British Journal of Haematology* 2007; **137**(5):436–42.
- Ojeda 1999** *{published data only}*
Ojeda E, Garcia-Bustos J, Aguado M, Arrieta R, Quevedo E, Yuste VJ, et al. A prospective randomized trial of granulocyte colony-stimulating factor therapy after autologous blood stem cell transplantation in adults. *Bone Marrow Transplantation* 1999;**24**(6):601–7.
- Osby 2003** *{published data only}*
Osby E, Hagberg H, Kvaløy S, Teerenhovi L, Anderson H, Cavallin-Stahl E, et al. CHOP is superior to CNOP in elderly patients with aggressive lymphoma while outcome is unaffected by filgrastim treatment: results of a Nordic

- Lymphoma Group randomized trial. *Blood* 2003;**101**(10):3840–8.
- Ottmann 1995** *{published data only}*
Ottmann OG, Hoelzer D, Gracien E, Ganser A, Kelly K, Reutzel R, et al. Concomitant granulocyte colony-stimulating factor and induction chemoradiotherapy in adult acute lymphoblastic leukemia: a randomized phase III trial. *Blood* 1995;**86**(2):444–50.
- Patte 2002** *{published data only}*
Patte C, Laplanche A, Bertozzi AI, Baruchel A, Frappaz D, Schmitt C, et al. Granulocyte colony-stimulating factor in induction treatment of children with non-Hodgkin's lymphoma: a randomized study of the French Society of Pediatric Oncology. *Journal of Clinical Oncology* 2002;**20**(2):441–8.
- Petersen 1988** *{published data only}*
Petersen F, Thornquist M, Buckner C, Counts G, Nelson N, Meyers J, et al. The effects of infection prevention regimens on early infectious complications in marrow transplant patients: a four arm randomized study. *Infection* 1988;**16**(4):199–208.
- Pettengell 1992** *{published data only}*
Pettengell R, Gurney H, Radford JA, Deakin DP, James R, Wilkinson PM, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992;**80**(6):1430–6.
- Piccirillo 1999** *{published data only}*
Piccirillo N, Sica S, Laurenti L, Chiusolo P, La Barbera EO, Sora F, et al. Optimal timing of G-CSF administration after CD34+ immunoselected peripheral blood progenitor cell transplantation. *Bone Marrow Transplantation* 1999;**23**(12):1245–50.
- Pignon 1990** *{published data only}*
Pignon B, Thiriet L, Aubert D, Pennaforte JL, Vilque JP, Lartigue B, et al. Evaluation of the efficacy of prophylactic intravenous antibiotherapy with ceftriaxone in post-chemotherapy agranulocytic patients. *Nouvelle Revue Française d'Hématologie* 1990;**32**(4):249–52.
- Przepiorka 2001** *{published data only}*
Przepiorka D, Smith TL, Folloder J, Anderlini P, Chan KW, Korbling M, et al. Controlled trial of filgrastim for acceleration of neutrophil recovery after allogeneic blood stem cell transplantation from human leukocyte antigen-matched related donors. *Blood* 2001;**97**(11):3405–10.
- Pui 1997** *{published data only}*
Pui CH, Boyett JM, Hughes WT, Rivera GK, Hancock ML, Sandlund JT, et al. Human granulocyte colony-stimulating factor after induction chemotherapy in children with acute lymphoblastic leukemia. *New England Journal of Medicine* 1997;**336**(25):1781–7.
- Rafecas 1989** *{published data only}*
Rafecas FJ, Gil E, Martín G, Martínez J, Sanz G, Sempere A, et al. Oral ciprofloxacin in the prophylaxis of bacterial infection in neutropenic patients. A randomized, double-blind, comparative clinical study. *Revista Española de Quimioterapia* 1989;**2**:174–7.
- Romieu 2007** *{published data only}*
Romieu G, Clemens M, Mahlberg R, Fargeot P, Constenla M, Schutte M, et al. Pegfilgrastim supports delivery of FEC-100 chemotherapy in elderly patients with high risk breast cancer: a randomized phase 2 trial. *Critical Reviews in Oncology/hematology* 2007;**64**(1):64–72.
- Schmitz 2004** *{published data only}*
Schmitz N, Ljungman P, Cordonnier C, Kempf C, Linkesch W, Alegre A, et al. Lenograstim after autologous peripheral blood progenitor cell transplantation: results of a double-blind, randomized trial. *Bone Marrow Transplantation* 2004;**34**(11):955–62.
- Schuette 2011** *{published data only}*
Schuette W, Nagel S, von Weikersthal LF, Pabst S, Schumann C, Deuss B, et al. Randomized phase III trial of docetaxel plus carboplatin with or without levofloxacin prophylaxis in elderly patients with advanced non-small cell lung cancer: the APRONTA trial. *Journal of Thoracic Oncology* 2011;**6**(12):2090–6.
- Seymour 1995** *{published data only}*
Seymour AM, de Campos E, Thatcher N, De Greve J, Cunningham D, Howell A, et al. A single-blind, randomised, vehicle-controlled dose-finding study of recombinant human granulocyte colony-stimulating factor (lenograstim) in patients undergoing chemotherapy for solid cancers and lymphoma. *European Journal of Cancer* 1995;**31A**(13-14):2157–63.
- Spitzer 1994** *{published data only}*
Spitzer G, Adkins DR, Spencer V, Dunphy FR, Petruska PJ, Velasquez WS, et al. Randomized study of growth factors post-peripheral-blood stem-cell transplant: neutrophil recovery is improved with modest clinical benefit. *Journal of Clinical Oncology* 1994;**12**(4):661–70.
- Stahel 1994** *{published data only}*
Stahel RA, Jost LM, Cerny T, Pichert G, Honnegger H, Tobler A, et al. Randomized study of recombinant human granulocyte colony-stimulating factor after high-dose chemotherapy and autologous bone marrow transplantation for high-risk lymphoid malignancies. *Journal of Clinical Oncology* 1994;**12**(9):1931–8.
- Suh 2008** *{published data only}*
Suh Y, Chun C, Oh S. Prevention of infection after TAC chemotherapy for node-positive breast cancer as an adjuvant therapy with or without ciprofloxacin. *Annals of Oncology* 2008;**26**(155):81.
- Talbot 1993** *{published data only}*
Talbot GH, Cassileth PA, Paradiso L, Correa-Coronas R, Bond L. Oral enoxacin for infection prevention in adults with acute nonlymphocytic leukemia. The Enoxacin Prophylaxis Study Group. *Antimicrobial Agents & Chemotherapy* 1993;**37**(3):474–82.
- Timmer-Bonte 2005** *{published data only}*
Timmer-Bonte JN, de Boo TM, Smit HJ, Biesma B, Wilschut FA, Cheragwandi SA, et al. Prevention of

chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch Randomized Phase III Study. *Journal of Clinical Oncology* 2005;**23**(31): 7974–84.

Tjan-Heijnen 2003 {published data only}

Tjan-Heijnen VC, Caleo S, Postmus PE, Ardizzoni A, Burghouts JT, Buccholz E, et al. Economic evaluation of antibiotic prophylaxis in small-cell lung cancer patients receiving chemotherapy: an EORTC double-blind placebo-controlled phase III study (08923). *Annals of Oncology* 2003;**14**(2):248–57.

Trigg 2000 {published data only}

Trigg ME, Peters C, Zimmerman MB. Administration of recombinant human granulocyte-macrophage colony-stimulating factor to children undergoing allogeneic marrow transplantation: a prospective, randomized, double-masked, placebo-controlled trial. *Pediatric Transplantation* 2000;**4**(2):123–31.

Trillet-Lenoir 1993 {published data only}

Trillet-Lenoir V, Green J, Manegold C, Von Pawel J, Gatzemeier U, Lebeau B, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *European Journal of Cancer* 1993;**29A**(3):319–24.

Veyret 2006 {published data only}

Veyret C, Levy C, Chollet P, Merrouche Y, Roche H, Kerbrat P, et al. Inflammatory breast cancer outcome with epirubicin-based induction and maintenance chemotherapy: ten-year results from the French Adjuvant Study Group GETIS 02 Trial. *Cancer* 2006;**107**(11):2535–44.

Vogel 2005 {published data only}

Vogel CL, Wojtukiewicz MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ, Wiens BL, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *Journal of Clinical Oncology* 2005;**23**(6):1178–84.

Welte 1996 {published data only}

Welte K, Reiter A, Mempel K, Pfetsch M, Schwab G, Schrappe M, et al. A randomized phase-III study of the efficacy of granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia. Berlin-Frankfurt-Munster Study Group. *Blood* 1996;**87**(8): 3143–50.

Witz 1998 {published data only}

Witz F, Sadoun A, Perrin MC, Berthou C, Briere J, Cahn JY, et al. A placebo-controlled study of recombinant human granulocyte-macrophage colony-stimulating factor administered during and after induction treatment for de novo acute myelogenous leukemia in elderly patients. Groupe Ouest Est Leucemies Aigues Myeloblastiques (GOELAM). *Blood* 1998;**91**(8):2722–30.

Yamada 1993 {published data only}

Yamada T, Dan K, Nomura T. Prevention of bacterial and fungal infections in acute leukemia patients: a new and

potent combination of oral norfloxacin and amphotericin B. *Internal Medicine (Tokyo, Japan)* 1993;**32**(9):710–5.

Yau 1996 {published data only}

Yau JC, Neidhart JA, Triozzi P, Verma S, Nemunaitis J, Quick DP, et al. Randomized placebo-controlled trial of granulocyte-macrophage colony-stimulating-factor support for dose-intensive cyclophosphamide, etoposide, and cisplatin. *American Journal of Hematology* 1996;**51**(4): 289–95.

Additional references

Alvarado 1999

Alvarado Ibarra ML, Borbolla Escoboza JR, Lopez-Hernandez MA, Gonzalez-Avante CM, FloresChapa JD, Trueba Christy E, et al. Neutrophil recovery time and adverse side effects in acute leukemia patients treated with intensive chemotherapy and concomitant G or GM-CSF. *Revista de Investigacion Clinica* 1999;**51**(2):77–80. [PUBMED: 10410585]

Beveridge 1997

Beveridge RA, Miller JA, Kales AN, Binder RA, Robert NJ, Heisrath-Evans J, et al. Randomized trial comparing the tolerability of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in cancer patients receiving myelosuppressive chemotherapy. *Supportive Care in Cancer* 1997;**5**(4):289–98. [PUBMED: 9257425]

Beveridge 1998

Beveridge RA, Miller JA, Kales AN, Binder RA, Robert NJ, Harvey JH, et al. A comparison of efficacy of sargramostim (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression. *Cancer Investigation* 1998;**16**(6):366–73. [PUBMED: 9679526]

Bodey 1966

Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Annals of Internal Medicine* 1966;**64**(2):328–40.

Bodey 1986

Bodey GP. Infection in cancer patients. A continuing association. *American Journal of Medicine* 1986;**81**(1A): 11–26.

Bohlius 2008

Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD003189.pub4]

Bronchud 1988

Bronchud MH, Potter MR, Morgenstern G, Blasco MJ, Scarffe JH, Thatcher N, et al. In vitro and in vivo analysis of the effects of recombinant human granulocyte colony-stimulating factor in patients. *British Journal of Cancer* 1988;**58**(1):64–9.

Bucaneve 2005

Bucaneve G, Micozzi A, Menichetti F, Martino P, Dionisi MS, Martinelli G, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *New England Journal of Medicine* 2005;**353**(10):977–87.

Carratala 1995

Carratala J, Fernandez-Sevilla A, Tubau F, Callis M, Gudiol F. Emergence of quinolone-resistant *Escherichia coli* bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clinical Infectious Diseases* 1995;**20**(3):557–60.

Clark 2005

Clark OA, Lyman GH, Castro AA, Clark LG, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. *Journal of Clinical Oncology* 2005;**23**(18):4198–214.

Crawford 1991

Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *New England Journal of Medicine* 1991;**325**(3):164–70.

Cruciani 2003

Cruciani M, Malena M, Bosco O, Nardi S, Serpelloni G, Mengoli C. Reappraisal with meta-analysis of the addition of Gram-positive prophylaxis to fluoroquinolone in neutropenic patients. *Journal of Clinical Oncology* 2003;**21**(22):4127–37.

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.* 2011.

Engels 1998

Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. *Journal of Clinical Oncology* 1998;**16**(3):1179–87.

Fischmeister 1999

Fischmeister G, Kurz M, Haas OA, Micksche M, Buchinger P, Printz D, et al. G-CSF versus GM-CSF for stimulation of peripheral blood progenitor cells (PBPC) and leukocytes in healthy volunteers: comparison of efficacy and tolerability. *Annals of Hematology* 1999;**78**(3):117–23. [PubMed: 10211753]

Gafer-Gvili 2005

Gafer-Gvili A, Fraser A, Paul M, Leibovici L. Meta-Analysis: Antibiotic prophylaxis reduces mortality in neutropenic patients. *Annals of Internal Medicine* 2005;**142** (12 Pt 1):979–95.

Gafer-Gvili 2007

Gafer-Gvili A, Paul M, Fraser A, Leibovici L. Effect of quinolone prophylaxis in afebrile neutropenic patients on

microbial resistance: systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy* 2007;**59**(1):5–22.

Gafer-Gvili 2012

Gafer-Gvili A, Fraser A, Paul M, Vidal L, Lawrie TA, van de Wetering M D, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database of Systematic Reviews* 2012, Issue 1. [DOI: 10.1002/14651858.CD004386.pub3]

Griffin 1990

Griffin JD, Cannistra SA, Sullivan R, Demetri GD, Ernst TJ, Kanakura Y. The biology of GM-CSF: regulation of production and interaction with its receptor. *International Journal of Cell Cloning* 1990;**8 Suppl 1**:35–44.

Hackshaw 2004

Hackshaw A, Sweetenham J, Knight A. Are prophylactic haematopoietic growth factors of value in the management of patients with aggressive non-Hodgkin's lymphoma?. *British Journal of Cancer* 2004;**90**(7):1302–5.

Higgins 2011

Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.* 2011.

Higgins 2011a

Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.* 2011.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.* 2011.

Holmes 2002

Holmes FA, Jones SE, O'Shaughnessy J, Vukelja S, George T, Savin M, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. *Annals of Oncology* 2002;**13**(6):903–9.

Hovgaard 1992

Hovgaard DJ, Nissen NI. Effect of recombinant human granulocyte-macrophage colony-stimulating factor in patients with Hodgkin's disease: a phase I/II study. *Journal of Clinical Oncology* 1992;**10**(3):390–7. [PubMed: 1740678]

Johnston 2000

Johnston E, Crawford J, Blackwell S, Bjurström T, Lockbaum P, Roskos L, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. *Journal of Clinical Oncology* 2000; **18**(13):2522–8.

Karp 1987

Karp JE, Merz WG, Hendricksen C, Laughon B, Redden T, Bamberger BJ, et al. Oral norfloxacin for prevention of gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1987; **106**(1):1–7.

Kuderer 2006

Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006; **106**(10): 2258–66.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, Available from www.cochrane-handbook.org. 2011.

Leibovici 2006

Leibovici L, Paul M, Cullen M, Bucaneve G, Gafter-Gvili A, Fraser A, et al. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. *Cancer* 2006; **107**(8):1743–51.

Lew 1995

Lew MA, Kehoe K, Ritz J, Antman KH, Nadler L, Kalish LA, et al. Ciprofloxacin versus trimethoprim/sulfamethoxazole for prophylaxis of bacterial infections in bone marrow transplant recipients: a randomized, controlled trial. *Journal of Clinical Oncology* 1995; **13**(1): 239–50.

Lyman 2002

Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: A meta-analysis. *American Journal of Medicine* 2002; **112**(5):406–11.

Lyman 2010

Lyman GH, Dale DC, Wolff DA, Culakova E, Poniewierski MS, Kuderer NM, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. *Journal of Clinical Oncology* 2010; **28**(17):2914–24. [PUBMED: 20385991]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-Analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009; **62**(10):1006–12. [PUBMED: 19631508]

Morstyn 1988

Morstyn G, Campbell L, Souza LM, Alton NK, Keech J, Green M, et al. Effect of granulocyte colony stimulating

factor on neutropenia induced by cytotoxic chemotherapy. *Lancet* 1988; **1**(8587):667–72.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998; **17**(24): 2815–34.

Pizzo 1999

Pizzo PA. Fever in immunocompromised patients. *New England Journal of Medicine* 1999; **341**(12):893–900.

Review Manager (RevMan) [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Smith 2015

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of Clinical Oncology* 2015; **33**(28):3199–212.

Somolinos 1992

Somolinos N, Arranz R, Del Rey MC, Jimenez ML. Superinfections by *Escherichia coli* resistant to fluoroquinolones in immunocompromised patients. *Journal of Antimicrobial Chemotherapy* 1992; **30**(5):730–1.

Sterne 2011

Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, Available from www.cochrane-handbook.org. 2011.

Sung 2004

Sung L, Nathan PC, Lange B, Beyene J, Buchanan JR. Prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor decrease febrile neutropenia after chemotherapy in children with cancer: A meta-analysis of randomized controlled trials. *Journal of Clinical Oncology* 2004; **22**(16):3350–6.

Sung 2007

Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. *Annals of Internal Medicine* 2007; **147**(6):400–11.

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; **8**(8):16.

Vehreschild 2014

Vehreschild JJ, Bohme A, Cornely OA, Kahl C, Karthaus M, Kreuzer KA, et al. Prophylaxis of infectious complications with colony-stimulating factors in adult cancer patients undergoing chemotherapy-evidence-based guidelines from the Infectious Diseases Working Party AGIHO of the

German Society for Haematology and Medical Oncology (DGHO). *Annals of Oncology* 2014;**25**(9):1709–18. [PUBMED: 24631945]

Wittman 2006

Wittman B, Horan J, Lyman GH. Prophylactic colony-stimulating factors in children receiving myelosuppressive chemotherapy: a meta-analysis of randomized controlled trials. *Cancer Treatment Reviews* 2006;**32**(4):289–303.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Schroder 1999

Methods	<p>Randomisation</p> <ul style="list-style-type: none"> • 1:1 ratio • Intervention arm: G-CSF for prevention of infection • Control arm: ciprofloxacin and amphotericin <p>Recruitment Period</p> <ul style="list-style-type: none"> • Not reported <p>Median follow-up time</p> <ul style="list-style-type: none"> • Not reported
Participants	<p>40 patients randomised</p> <ul style="list-style-type: none"> • 18 patients G-CSF • 22 patients antibiotics <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients with metastatic breast cancer • Age \leq 65 years • Chemotherapy-naive <p>Mean age in years</p> <ul style="list-style-type: none"> • G-CSF arm: 39 years (range: 28 to 50) • Antibiotics arm: 42 years (range: 29 to 51) <p>Metastases</p> <ul style="list-style-type: none"> • G-CSF arm: <ul style="list-style-type: none"> ○ 8 single metastases ○ 10 multiple metastases • Antibiotics arm <ul style="list-style-type: none"> ○ 14 single metastases ○ 8 multiple metastases <p>Country</p> <ul style="list-style-type: none"> • Not reported
Interventions	<p>All patients</p> <ul style="list-style-type: none"> • 3 courses of IV cyclophosphamide (1500 mg/m²), epirubicin (80 mg/m²) and 5-fluorouracil (5-FU; 1500 or 1000 mg/m²) on day 1 • 3 courses of IV cyclophosphamide (1500 mg/m²) and 5-FU (600mg/m²) on day 1 and IV methotrexate (1500 mg/m²) on day 2 <p>G-CSF arm</p> <ul style="list-style-type: none"> • 263 μg subcutaneously on days 3 to 12 <p>Antibiotics arm</p> <ul style="list-style-type: none"> • Oral ciprofloxacin 2 x 250 mg daily, and oral amphotericin B suspension 100 mg/mL, 4 x 5 mL daily; both on days 3 to 17
Outcomes	<ul style="list-style-type: none"> • Episodes of hospitalisation for febrile neutropenia • Duration of hospitalisation for febrile neutropenia • Grade IV leucopenia • Cost analyses

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Before chemotherapy, patients were randomized to group I or II."
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial (subcutaneous injection of G-CSF versus oral antibiotics)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessor not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	"Not included in the analyses were 23 courses from seven patients from group II (antibiotics), who switched to rhG-CSF. Of these seven patients, three patients stopped, because of disease progression or death from the disease, after having received a total of nine courses; therefore 11 more courses were not administered and not included in the analyses."
Selective reporting (reporting bias)	Unclear risk	No study protocol identified, therefore unclear, if all the planned outcomes are reported
Other bias	Unclear risk	Not reported

Methods	<p>Randomisation</p> <ul style="list-style-type: none"> • 1:1:1 ratio • Standard chemotherapy arm (6 courses of EVI (epirubicin 90 mg/m², vindesine 3 mg/m² and ifosfamide 5 g/m²; all drugs given IV on day 1); no infection prophylaxis given (therefore not evaluated in this review) • Intervention arm: accelerated chemotherapy (the same as above, given every 14 days) and GM-CSF for prevention of infection • Control arm: accelerated chemotherapy (the same as above, given every 14 days) and cotrimoxazole prophylaxis <p>Recruitment Period</p> <ul style="list-style-type: none"> • April 1993 to April 2000 <p>Median follow-up time</p> <ul style="list-style-type: none"> • Not reported
Participants	<p>243 patients randomised, 233 eligible</p> <ul style="list-style-type: none"> • 78 standard arm (not evaluated in this review) • 78 patients GM-CSF • 77 patients antibiotics <p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients with small-cell lung cancer and extensive disease (with metastases or as a locoregional disease that could not be locally treated in a single radiotherapy field) • Age ≤ 75 years • Patients should not have had prior therapy (radiotherapy, chemotherapy, surgery) <p>Mean age in years</p> <ul style="list-style-type: none"> • GM-CSF arm: 64 years (range: 35 to 74) • Antibiotics arm: 61 years (range: 37 to 74) <p>Stage</p> <ul style="list-style-type: none"> • GM-CSF arm: <ul style="list-style-type: none"> ◦ Stage III: 7 patients ◦ Stage IV: 71 patients • Antibiotics arm <ul style="list-style-type: none"> ◦ Stage III: 7 patients ◦ Stage IV: 70 patients <p>Brain metastases</p> <ul style="list-style-type: none"> • GM-CSF arm: <ul style="list-style-type: none"> ◦ 14 patients • Antibiotics arm <ul style="list-style-type: none"> ◦ 17 patients <p>Countries</p> <ul style="list-style-type: none"> • Several countries in Europe
Interventions	<p>All patients</p> <ul style="list-style-type: none"> • 6 courses of EVI (epirubicin 90 mg/m², vindesine 3 mg/m² and ifosfamide 5 g/m²; all drugs given IV on day 1, in the accelerated arms every 14 days <p>GM-CSF arm</p> <ul style="list-style-type: none"> • GM-CSF was given, as a daily subcutaneous dose of 5 µg/kg, from day 3 through day 13, or until neutrophil count reached ≥ 4000 mm³ after nadir. <p>Antibiotics arm</p> <ul style="list-style-type: none"> • Cotrimoxazole (160 mg trimethoprim plus 800 mg sulfamethoxazole) was administered orally every 12 hours from day 3 until the end of the course of

	chemotherapy	
Outcomes	<ul style="list-style-type: none"> ● Overall survival ● Tumour response ● Absolute and relative dose intensity ● Incidence of infections and severe infection ● Adverse events 	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"eligible patients were randomised"
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label trial (subcutaneous injection of GM-CSF versus oral antibiotics)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessor not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"In the 233 eligible patients, 14 were nonassessable for response (2 in arm A, 6 in arm B, and 6 in arm C) for the following reasons: too long delay between 2 courses of chemotherapy (1), early death unrelated to cancer or treatment complications (9), protocol violation (2), death prior to starting treatment (1), no work-up at evaluation (1)"
Selective reporting (reporting bias)	Unclear risk	No study protocol identified, therefore unclear if all the planned outcomes are reported
Other bias	Unclear risk	Not reported

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aarts 2013	Comparison of G-CSF plus antibiotics versus antibiotics alone
Alonzo 2002	Comparison of G-CSF plus antibiotics versus antibiotics alone
Altman 1996	Comparison of G-CSF plus antibiotics versus antibiotics alone
Ardizzoni 1994	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Attal 1991	Comparison of antibiotics versus placebo
Bennett 2001	Comparison of G-CSF versus placebo
Bishop 2000	Comparison of G-CSF plus antibiotics versus antibiotics alone
Björkholm 1999	Comparison of G-CSF versus placebo
Bradstock 2001	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Brugger 2009	Comparison of G-CSF versus placebo
Burton 2006	Comparison of G-CSF plus antibiotics versus antibiotics alone
Carlson 1997	Comparison of antibiotics versus placebo
Chevallier 1995	Comparison of G-CSF versus placebo
Clarke 1999	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Crawford 1997	Comparison of G-CSF versus placebo
Cullen 2005	Comparison of antibiotics versus placebo
Dibenedetto 1995	Comparison of G-CSF plus antibiotics versus antibiotics alone
Dickgreber 2009	Comparison of antibiotics versus placebo
Doorduijn 2005	Comparison of G-CSF versus placebo
Dunlop 1996	Comparison of G-CSF versus placebo
Eleutherakis-Papaiakovou 2010	Comparison of G-CSF plus antibiotics versus G-CSF alone
Ernst 2008	Comparison of G-CSF plus antibiotics versus antibiotics alone

(Continued)

Faber 2006	Comparison of G-CSF plus antibiotics versus antibiotics alone
Feng 2014	Comparison of G-CSF plus antibiotics versus G-CSF alone
Fridrik 1997	Comparison of G-CSF versus placebo
Garcia 2000	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Garcia-Saenz 2002	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Geissler 1997	Comparison of G-CSF plus antibiotics versus antibiotics alone
Godwin 1998	Comparison of G-CSF versus placebo
Gonzalez-Vicent 2004	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Greenberg 1996	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Gulati 1992	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Hartmann 1997	Comparison of G-CSF versus placebo
Heath 2003	Comparison of G-CSF plus antibiotics versus antibiotics alone
Hecht 2010	Comparison of G-CSF plus antibiotics versus antibiotics alone
Heil 1997	Comparison of G-CSF plus antibiotics versus antibiotics alone
Holowiecki 2002	Comparison of G-CSF versus placebo
Jones 1996	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Joshi 2003	Comparison of G-CSF plus antibiotics versus antibiotics alone
Karp 1986	Comparison of antibiotics versus placebo
Kim 2005	Comparison of G-CSF plus antibiotics versus G-CSF alone
Kosaka 2015	Comparison of G-CSF versus placebo
Ladenstein 2010	Comparison of G-CSF plus antibiotics versus antibiotics alone
Lalami 2004	Comparison of GM-CSF plus antibiotics versus GM-CSF alone
Lamy 1993	Comparison of antibiotics versus placebo

(Continued)

Larson 1998	Comparison of G-CSF versus placebo
Lee 1998	Comparison of G-CSF plus antibiotics versus antibiotics alone
Lee 2002	Comparison of antibiotics versus placebo
Lehrnbecher 2007	Comparison of G-CSF plus antibiotics versus antibiotics alone
Little 2002	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Maiche 1993	Comparison of GM-CSF plus antibiotics versus GM-CSF alone
McQuaker 1997	Comparison of G-CSF plus antibiotics versus antibiotics alone
Michel 2000	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Michon 1998	Comparison of G-CSF versus placebo
Miles 1994	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Nemunaitis 1995	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Nolan 2007	Comparison of G-CSF plus antibiotics versus antibiotics alone
Ojeda 1999	Comparison of G-CSF plus antibiotics versus antibiotics alone
Osby 2003	Comparison of G-CSF versus placebo
Ottmann 1995	Comparison of G-CSF plus antibiotics versus antibiotics alone
Patte 2002	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Petersen 1988	Comparison of antibiotics versus placebo
Pettengell 1992	Comparison of G-CSF plus antibiotics versus antibiotics alone
Piccirillo 1999	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Pignon 1990	Comparison of antibiotics versus placebo
Przepiorka 2001	Comparison of G-CSF plus antibiotics versus antibiotics alone
Pui 1997	Comparison of G-CSF plus antibiotics versus antibiotics alone
Rafecas 1989	Comparison of antibiotics versus placebo

(Continued)

Romieu 2007	Comparison of G-CSF versus placebo
Schmitz 2004	Comparison of G-CSF plus antibiotics versus antibiotics alone
Schuette 2011	Comparison of antibiotics versus placebo
Seymour 1995	Comparison of G-CSF versus placebo
Spitzer 1994	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Stahel 1994	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Suh 2008	Comparison of G-CSF plus antibiotics versus G-CSF alone
Talbot 1993	Comparison of antibiotics versus placebo
Timmer-Bonte 2005	Comparison of G-CSF plus antibiotics versus antibiotics alone
Tjan-Heijnen 2003	Comparison of G-CSF plus antibiotics versus antibiotics alone
Trigg 2000	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Trillet-Lenoir 1993	Comparison of G-CSF versus placebo
Veyret 2006	Comparison of G-CSF versus placebo
Vogel 2005	Comparison of G-CSF versus placebo
Welte 1996	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Witz 1998	Comparison of GM-CSF plus antibiotics versus antibiotics alone
Yamada 1993	Comparison of antibiotics versus placebo
Yau 1996	Comparison of GM-CSF plus antibiotics versus antibiotics alone

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. CENTRAL search strategy

January 2008

- #1 MeSH descriptor Anti-Bacterial Agents explode all trees
- #2 (antibacterial*) OR (anti-bacterial*)
- #3 (antibio*)
- #4 (antimicrobial*) OR (anti-microbial*) OR (anti-mycobacterial*) OR (antimycobacterial*) OR (bacteriocid*) OR (selective NEAR/3 decontaminat*)
- #5 MeSH descriptor Antibiotic Prophylaxis explode all trees
- #6 MeSH descriptor Quinolones explode all trees
- #7 (fluoroquinilones) OR (ciprofloxa*in*) OR (ofloxa*in*) OR (norfloxa*in*) OR (enoxa*in*) OR (pefloxa*in*)
- #8 MeSH descriptor Trimethoprim explode all trees
- #9 (trimethoprim) OR (sulfamethoxazol*) OR (trimethoprim-sulfamethoxazol*, (trimethoprim NEAR/3 sulfamethoxazol*)) OR (tmp-smz*)
- #10 MeSH descriptor Polymyxins explode all trees
- #11 (colistin) OR (nalidixic NEAR/3 acid) OR (polymyxin)
- #12 MeSH descriptor Aminoglycosides explode all trees
- #13 MeSH descriptor Gentamicins explode all trees
- #14 MeSH descriptor Nebramycin explode all trees
- #15 MeSH descriptor Neomycin explode all trees
- #16 MeSH descriptor Vancomycin explode all trees
- #17 (gentami*in) OR (tobramy*in) OR (meomy*in)
- #18 MeSH descriptor Roxithromycin explode all trees
- #19 MeSH descriptor Rifampin explode all trees
- #20 (vancomy*in) OR (roxithromy*in) OR (rifampin*,rifampicin*)
- #21 MeSH descriptor beta-Lactams explode all trees
- #22 MeSH descriptor Penicillins explode all trees
- #23 MeSH descriptor Amoxicillin explode all trees
- #24 MeSH descriptor Cephalothin explode all trees
- #25 MeSH descriptor Ceftriaxone explode all trees
- #26 MeSH descriptor Ticarcillin explode all trees
- #27 (beta-lactam*) OR (peni*illin) OR (amoxi*illin*) OR (cephalot*in*,cefalot*in*) OR (ceftriaxone*)
- #28 (tica*illin*) OR (framycetin)
- #29 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)
- #30 MeSH descriptor Colony-Stimulating Factors explode all trees
- #31 MeSH descriptor Colony-Stimulating Factors, Recombinant explode all trees
- #32 MeSH descriptor Granulocyte Colony Stimulating Factor, Recombinant explode all trees
- #33 MeSH descriptor Granulocyte Colony-Stimulating Factor explode all trees
- #34 MeSH descriptor Macrophage Colony-Stimulating Factor explode all trees
- #35 MeSH descriptor Granulocyte-Macrophage Colony-Stimulating Factor explode all trees
- #36 (rhg*csf*,rhgm*csf*) OR (rmethug*,rhmethug*) OR (rhug*,rhugm*) OR (gcsf*,g-csf*) OR (gm-csf*,gmcsf*)
- #37 (granulo*yt* NEAR/3 fa*tor*) OR (ma*rophag* NEAR/5 fa*tor*) OR (csf.ti) OR (filgrastim*) OR (neupogen*)

- #38 (lenograstim*) OR (euprotin*) OR (peg*filgrastim*) OR (neulasta*) OR (leukine)
- #39 (molgramostine*) OR (mielogen*) OR (leucomax*) OR (granocyte)
- #40 MeSH descriptor Filgrastim explode all trees
- #41 (#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40)
- #42 MeSH descriptor Leukopenia, this term only
- #43 .MeSH descriptor Agranulocytosis explode all trees
- #44 (granulocytopen*) OR (agranulocyto*) OR (neutropen*) OR (leu*open*) OR (aplasia, aplastic, aplasion)
- #45 (leukocyt* NEAR/5 nadir) OR (neutrophil NEAR/5 nadir)
- #46 MeSH descriptor Infection explode all trees
- #47 (infect*)
- #48 MeSH descriptor Sepsis explode all trees
- #49 (septicemia, septicaemia) OR (bacteraem*, bacterem*) OR (fever*) OR (pyrexia) OR (fever NEAR/4 (unknown NEAR/3 origin))
- #50 MeSH descriptor Fever explode all trees
- #51 MeSH descriptor Fever of Unknown Origin, this term only
- #52 (pneumonia) OR (lung inflammation) OR (pulmonary inflammation) OR (pneumonitis)
- #53 (#42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52)
- #54 MeSH descriptor Neoplasms by Histologic Type explode all trees
- #55 MeSH descriptor Neoplasms by Site explode all trees
- #56 (neoplas*) OR (krebs,cancer*) OR (malignan*)
- #57 (leukaem*,leukem*) OR (lymphom*) OR (melano*) OR (metastas*) OR (mesothelio*,mesotelio*)
- #58 (gliom,glioblastom*) OR (osteo*sarcom*) OR (carcinomatos*) OR (blastom*) OR (neuroblastom*)
- #59 MeSH descriptor Pneumonia explode all trees
- #60 (#54 OR #55 OR #56 OR #57 OR #58 OR #59)
- #61 (#53 OR #59)
- #62 (#29 AND #41 AND #61)

December 2015

ID Search

- #1 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
- #2 (antibacterial* or anti-bacterial*)
- #3 antibio*
- #4 (antimicrobial* or anti-microbial*)
- #5 (anti-Mycobacterial* or antimycobacterial*)
- #6 bacteriocid*
- #7 (selective* near/3 decontaminat*)
- #8 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees
- #9 MeSH descriptor: [Quinolones] explode all trees
- #10 Fluoroquinolones*
- #11 ciprofloxa*in*
- #12 ofloxa*in*
- #13 norfloxa*in*
- #14 Enox*in*
- #15 pefloxa*in*
- #16 MeSH descriptor: [Trimethoprim] explode all trees
- #17 trimethoprim*
- #18 sulfamethoxazol*
- #19 Trimethoprim-Sulfamethoxazol*
- #20 tmp-smz*
- #21 MeSH descriptor: [Polymyxins] explode all trees
- #22 colistin*
- #23 (Nalidixic* near/3 acid*)
- #24 Polymyxin*
- #25 MeSH descriptor: [Aminoglycosides] explode all trees

#26 MeSH descriptor: [Gentamicins] explode all trees
 #27 Gentami*in*
 #28 MeSH descriptor: [Nebramycin] explode all trees
 #29 Tobramy*in*
 #30 MeSH descriptor: [Neomycin] explode all trees
 #31 Neomy*in*
 #32 MeSH descriptor: [Vancomycin] explode all trees
 #33 Vancomy*in*
 #34 MeSH descriptor: [Roxithromycin] explode all trees
 #35 Roxithromy*in*
 #36 MeSH descriptor: [Rifampin] explode all trees
 #37 (rifampin* or rifampicin*)
 #38 MeSH descriptor: [beta-Lactams] explode all trees
 #39 MeSH descriptor: [Penicillins] explode all trees
 #40 MeSH descriptor: [Amoxicillin] explode all trees
 #41 MeSH descriptor: [Cephalothin] explode all trees
 #42 MeSH descriptor: [Ceftriaxone] explode all trees
 #43 MeSH descriptor: [Ticarcillin] explode all trees
 #44 (beta-lactam* or beta* lactam*)
 #45 Peni*illin*
 #46 Amoxi*illin*
 #47 (Cephalot*in* or cefalot*in*)
 #48 Ceftriaxone*
 #49 Ticar*illin*
 #50 framycetin*
 #51 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
 #52 MeSH descriptor: [Colony-Stimulating Factors] explode all trees
 #53 MeSH descriptor: [Granulocyte Colony-Stimulating Factor] explode all trees
 #54 MeSH descriptor: [Granulocyte-Macrophage Colony-Stimulating Factor] explode all trees
 #55 MeSH descriptor: [Macrophage Colony-Stimulating Factor] explode all trees
 #56 RHG*CSF* or RH-G*CSF* or RHGM*CSF* or RH-GM*CSF*
 #57 RMETHUG* or RHMETHUG* or R-METHUG* or RH-METHUG*
 #58 RHUG* or RHUGM*
 #59 GCSF* or G-CSF*
 #60 GM-CSF* or GMCSF*
 #61 GRANULO*YT* near/3 FA*TOR*
 #62 MA*ROPHAG* near/5 FA*TOR*
 #63 FILGRASTIM*
 #64 neupogen*
 #65 religrast*
 #66 nugraf*
 #67 LENOGRASTIM*
 #68 Granocyte*
 #69 Euprotin*
 #70 PEG*FILGRASTIM*
 #71 Neulasta*
 #72 LEUKINE*
 #73 sagramostim*
 #74 MOLGRAMOSTIN*
 #75 macrogen*
 #76 Mielogen*

#77 Leucomax*
 #78 nartograstim*
 #79 pegnartograstim*
 #80 ecogramostim*
 #81 regramostim*
 #82 leridistim*
 #83 #52 or #53 or #54 or #55 or #56 or #57 or #58 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70
 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82
 #84 biograstim*
 #85 radiograstim*
 #86 XM02*
 #87 immunex*
 #88 granulokin*
 #89 nivestim*
 #90 tevagrastim*
 #91 zarzio*
 #92 #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91
 #93 #83 or #92
 #94 #51 or #93
 #95 MeSH descriptor: [Neoplasms by Histologic Type] explode all trees
 #96 MeSH descriptor: [Neoplasms by Site] explode all trees
 #97 neoplas*
 #98 tumor* or tumour*
 #99 (Krebs* or cancer*)
 #100 malignan*
 #101 (carcino* or karzino*)
 #102 karzinom*
 #103 sarcom*
 #104 leukem* or leukaem*
 #105 lymphom*
 #106 melano*
 #107 metastas*
 #108 (mesothelio* or mesotelio*)
 #109 carcinomatos*
 #110 osteo*sarcom*
 #111 (blastom* or neuroblastom*)
 #112 carcinomatos*
 #113 (gliom* or glioblastom*)
 #114 osteo*sarcom*
 #115 (blastom* or neuroblastom*)
 #116 #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #108 or #112 or #113 or #114
 or #115
 #117 #94 and #116
 #118 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #17 or #18 or #19 or #20 or #
 22 or #23 or #24 or #25 or #27 or #28 or #29 or #31 or #33 or #35 or #37 or #43 or #44 or #45 or #46 or #47 or #48 or #50
 #119 #118 or #93
 #120 #116 and #119 Publication Date from 1985 to 2014, in Trials
 #121 #118 and #93
 #122 #116 and #121 Publication Date from 1985 to 2015

Appendix 2. MEDLINE search strategy

From 1980 to 20 January 2008

- 1 exp ANTI-BACTERIAL AGENTS/
- 2 (antibacterial\$ or anti-bacterial\$).tw,kf,ot.
- 3 antibio\$.tw,kf,ot.
- 4 (antimicrobial\$ or anti-microbial\$).tw,kf,ot.
- 5 (anti-mycobacterial\$ or antimycobacterial\$).tw,kf,ot.
- 6 bacteriocid\$.tw,kf,ot.
- 7 (selective\$ adj3 decontaminat\$).tw,kf,ot.
- 8 ANTIBIOTIC PROPHYLAXIS/
- 9 exp QUINOLONE/
- 10 fluoroquinolones\$.tw,kf,ot.
- 11 ciprofloxacin\$.tw,kf,ot.
- 12 ofloxacin\$.tw,kf,ot.
- 13 norfloxacin\$.tw,kf,ot.
- 14 enoxacin\$.tw,kf,ot.
- 15 pefloxacin\$.tw,kf,ot.
- 16 exp TRIMETHOPRIM/
- 17 trimethoprim\$.tw,kf,ot.
- 18 sulfamethoxazole\$.tw,kf,ot.
- 19 trimethoprim-sulfamethoxazole\$.tw,kf,ot.
- 20 tmp-smz\$.tw,kf,ot.
- 21 exp POLYMYXINS/
- 22 colistin\$.tw,kf,ot.
- 23 (nalidixic\$ adj3 acid\$).tw,kf,ot.
- 24 polymyxin\$.tw,kf,ot.
- 25 AMINOGLYCOSIDES/
- 26 GENTAMICINS/
- 27 gentamicin\$.tw,kf,ot.
- 28 exp NEBRAMYCIN/
- 29 tobramycin\$.tw,kf,ot.
- 30 NEOMYCIN/
- 31 neomycin\$.tw,kf,ot.
- 32 VANCOMYCIN/
- 33 vancomycin\$.tw,kf,ot.
- 34 ROXITHROMYCIN/
- 35 roxithromycin\$.tw,kf,ot.
- 36 RIFAMPIN/
- 37 (rifampin\$ or rifampicin\$).tw,kf,ot.
- 38 BETA-LACTAMS/
- 39 beta-lactam\$.tw,kf,ot.
- 40 PENICILLINS/
- 41 penicillin\$.tw,kf,ot.
- 42 AMOXICILLIN/
- 43 amoxicillin\$.tw,kf,ot.
- 44 CEPHALOTHIN/
- 45 (cephalothin\$ or cefalothin\$).tw,kf,ot.
- 46 CEFTRIAXONE/
- 47 ceftriaxone\$.tw,kf,ot.
- 48 TICARCILLIN/
- 49 ticarcillin\$.tw,kf,ot.
- 50 framycetin\$.tw,kf,ot.

51 or/1-50
 52 COLONY-STIMULATING FACTORS/
 53 exp COLONY-STIMULATING FACTORS, RECOMBINANT/
 54 exp GRANULOCYTE COLONY STIMULATING FACTOR, RECOMBINANT/
 55 exp GRANULOCYTE COLONY-STIMULATING FACTOR/
 56 exp GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR/
 57 MACROPHAGE COLONY-STIMULATING FACTOR/
 58 (rhg?csf\$ or rhgm?csf\$).tw,kf,ot.
 59 (rmethug\$ or rhmethug\$).tw,kf,ot.
 60 (rhug\$ or rhugm\$).tw,kf,ot.
 61 (gcsf\$ or g-csf\$).tw,kf,ot.
 62 (gm-csf\$ or gmcsf\$).tw,kf,ot.
 63 (granulo?yt\$ adj3 fa#tor\$).tw,kf,ot.
 64 (ma#rophag\$ adj5 fa#tor\$).tw,kf,ot.
 65 csf.ti.
 66 FILGRASTIM\$.tw,hw,nm,kf.
 67 NEUPOGEN\$.tw,hw,nm,kf.
 68 LENOGRASTIM\$.tw,hw,nm,kf.
 69 GRANOCYTE\$.tw,hw,nm,kf.
 70 EUPROTIN\$.tw,hw,nm,kf.
 71 PEG?FILGRASTIM\$.tw,hw,nm,kf.
 72 NEULASTA\$.tw,hw,nm,kf.
 73 LEUKINE\$.tw,hw,nm,kf.
 74 MOLGRAMOSTIN\$.tw,hw,nm,kf.
 75 Mielogen\$.tw,kf,ot.
 76 LEUCOMAX\$.tw,hw,nm,kf.
 77 or/52-76
 78 51 or 77
 79 *LEUKOPENIA/
 80 exp AGRANULOCYTOSIS/
 81 granulocytopen\$.tw,kf,ot.
 82 agranulocyto\$.tw,kf,ot.
 83 neutropen\$.tw,kf,ot.
 84 leu#open\$.tw,kf,ot.
 85 (aplasia or aplastic or aplasion).tw,kf,ot.
 86 (leukocyt\$ adj5 nadir).tw,ot.
 87 (neutrophil\$ adj5 nadir).tw,ot.
 88 INFECTION/
 89 infect\$.tw,kf,ot.
 90 SEPSIS/
 91 (septicem\$ or septicaem\$).tw,kf,ot.
 92 (bacteraem\$ or bacterem\$).tw,kf,ot.
 93 FEVER/
 94 fever\$.tw,kf,ot.
 95 pyrexia\$.tw,kf,ot.
 96 "Fever of Unknown Origin"/
 97 (fever adj4 (unknown adj3 origin)).tw,kf,ot.
 98 PNEUMONIA/
 99 (lung\$ or pulmon\$) and inflammation\$.tw,kf,ot.
 100 pneumonit\$.tw,kf,ot.
 101 engraftment\$.tw,kf,ot.
 102 (neutrophil\$ adj3 recover\$).tw,kf,ot.
 103 (haematolog\$ adj3 recover\$).tw,kf,ot.

104 (hematolog\$ adj3 recover\$).tw,kf,ot.
 105 or/79-104
 106 exp NEOPLASMS BY HISTOLOGIC TYPE/
 107 exp NEOPLASMS BY SITE/
 108 neoplas\$.tw,kf,ot.
 109 tumo:r\$.tw,kf,ot.
 110 (krebs\$ or cancer\$).tw,kf,ot.
 111 malignan\$.tw,kf,ot.
 112 (carcino\$ or karzino\$).tw,kf,ot.
 113 karzinom\$.tw,kf,ot.
 114 sarcom\$.tw,kf,ot.
 115 leuk#?m\$.tw,kf,ot.
 116 lymphom\$.tw,kf,ot.
 117 melano\$.tw,kf,ot.
 118 metastas\$.tw,kf,ot.
 119 (mesothelio\$ or mesotelio\$).tw,kf,ot.
 120 carcinomatos\$.tw,kf,ot.
 121 (gliom\$ or glioblastom\$).tw,kf,ot.
 122 osteo?sarcom\$.tw,kf,ot.
 123 (blastom\$ or neuroblastom\$).tw,kf,ot.
 124 or/106-123
 125 105 and 124
 126 78 and 125
 127 randomized controlled trial.pt.
 128 controlled clinical trial.pt.
 129 RANDOMIZED CONTROLLED TRIALS/
 130 RANDOM ALLOCATION/
 131 DOUBLE BLIND METHOD/
 132 SINGLE BLIND METHOD/
 133 or/127-132
 134 (ANIMALS not HUMANS)/
 135 133 not 134
 136 clinical trial.pt.
 137 exp CLINICAL TRIALS/
 138 (clin\$ adj25 trial\$).ti,ab.
 139 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
 140 PLACEBOS/
 141 placebo\$.ti,ab.
 142 random\$.ti,ab.
 143 RESEARCH DESIGN/
 144 or/136-143
 145 144 not 134
 146 145 not 135
 147 COMPARATIVE STUDY/
 148 exp EVALUATION STUDIES/
 149 FOLLOW UP STUDIES/
 150 PROSPECTIVE STUDIES/
 151 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
 152 or/143-147
 153 152 not 134
 154 153 not (135 or 146)
 155 135 or 146 or 154
 156 126 and 155

Update search January 2008 to 3 December 2015

- 1 exp ANTI-BACTERIAL AGENTS/
- 2 (antibacterial\$ or anti-bacterial\$).tw,kf,ot.
- 3 Antibio\$.tw,kf,ot.
- 4 (antimicrobial\$ or anti-microbial\$).tw,kf,ot.
- 5 (Anti-Mycobacterial\$ or antimycobacterial\$).tw,kf,ot.
- 6 Bacteriocid\$.tw,kf,ot.
- 7 (selective adj3 decontaminat\$).tw,kf,ot.
- 8 Antibiotic Prophylaxis/
- 9 exp QUINOLONE/
- 10 Fluoroquinolones\$.tw,kf,ot.
- 11 ciprofloxa#in\$.tw,kf,ot.
- 12 ofloxa#in\$.tw,kf,ot.
- 13 norfloxa#in\$.tw,kf,ot.
- 14 Enoxa#in.tw,kf,ot.
- 15 pefloxa#in\$.tw,kf,ot.
- 16 exp TRIMETHOPRIM/
- 17 trimethoprim.tw,kf,ot.
- 18 sulfamethoxazol\$.tw,kf,ot.
- 19 Trimethoprim-Sulfamethoxazol\$.tw,kf,ot.
- 20 tmp-smz\$.tw,kf,ot.
- 21 exp POLYMYXINS/
- 22 colistin\$.tw,kf,ot.
- 23 (Nalidixic\$ adj3 acid\$).tw,kf,ot.
- 24 Polymyxin\$.tw,kf,ot.
- 25 AMINOGLYCOSIDES/
- 26 GENTAMICINS/
- 27 Gentami#in\$.tw,kf,ot.
- 28 exp NEBRAMYCIN/
- 29 Tobramy#in\$.tw,kf,ot.
- 30 NEOMYCIN/
- 31 Neomy#in\$.tw,kf,ot.
- 32 VANCOMYCIN/
- 33 Vancomy#in\$.tw,kf,ot.
- 34 ROXITHROMYCIN/
- 35 Roxithromy#in\$.tw,kf,ot.
- 36 RIFAMPIN/
- 37 (rifampin\$ or rifampicin\$).tw,kf,ot.
- 38 BETA-LACTAMS/
- 39 PENICILLINS/
- 40 AMOXICILLIN/
- 41 CEPHALOTHIN/
- 42 CEFTRIAXONE/
- 43 TICARCILLIN/
- 44 (beta-lactam\$ or beta\$ lactam\$).tw,kf,ot.
- 45 Peni#illin\$.tw,kf,ot.
- 46 Amoxi#illin\$.tw,kf,ot.
- 47 (Cephalot?in\$ or cefalot?in\$).tw,kf,ot.
- 48 Ceftriaxone\$.tw,kf,ot.
- 49 Ticar#illin\$.tw,kf,ot.
- 50 framycetin\$.tw,kf,ot.
- 51 or/1-50
- 52 COLONY-STIMULATING FACTORS/

53 exp GRANULOCYTE COLONY-STIMULATING FACTOR/
 54 exp GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR/
 55 MACROPHAGE COLONY-STIMULATING FACTOR/
 56 (RHG?CSF\$ or RH-G?CSF\$ or RHGM?CSF\$ or RH-GM?CSF\$).tw.
 57 (RMETHUG\$ or RHMETHUG\$ or R-METHUG\$ or RH-METHUG\$).tw.
 58 (RHUG\$ or RHUGM\$).tw.
 59 (GCSF\$ or G-CSF\$).tw.
 60 (GM-CSF\$ or GMCSF\$).tw.
 61 (GRANULO?YT\$ adj3 FA#TOR\$).tw.
 62 (MA#ROPHAG\$ adj5 FA#TOR\$).tw.
 63 CSF.ti.
 64 FILGRASTIM\$.tw,hw,nm,kf.
 65 neupogen\$.tw,hw,nm,kf.
 66 LENOGRASTIM\$.tw,hw,nm,kf.
 67 Granocyte.tw,hw,nm,kf.
 68 Euprotin.tw,hw,nm,kf.
 69 PEG?FILGRASTIM\$.tw,hw,nm,kf.
 70 Neulasta.tw,hw,nm,kf.
 71 LEUKINE.tw,hw,nm,kf.
 72 sagramostim\$.tw,kf,nm,ot.
 73 MOLGRAMOSTIN\$.tw,hw,nm,kf.
 74 Mielogen\$.tw,kf,nm,ot.
 75 Leucomax\$.tw,hw,nm,kf.
 76 nartograstim\$.tw,kf,nm,ot.
 77 pegnartograstim\$.tw,kf,nm,ot.
 78 ecogramostim\$.tw,kf,nm,ot.
 79 regramostim\$.tw,kf,nm,ot.
 80 leridistim\$.tw,kf,ot.
 81 or/52-80
 82 biograstim\$.mp.
 83 ratiograstim\$.mp.
 84 XM02\$.mp.
 85 immunex\$.mp.
 86 granulokin\$.mp.
 87 nivistim\$.mp.
 88 tevagrastim\$.mp.
 89 zarzio\$.mp.
 90 or/82-89
 91 81 or 90
 92 51 or 91
 93 exp NEOPLASMS BY HISTOLOGIC TYPE/
 94 exp NEOPLASMS BY SITE/
 95 neoplas\$.tw,kf,ot.
 96 tumo?r\$.tw,kf,ot.
 97 (Krebs\$ or cancer\$).tw,kf,ot.
 98 malignan\$.tw,kf,ot.
 99 (carcino\$ or karzino\$).tw,kf,ot.
 100 karzinom\$.tw,kf,ot.
 101 sarcom\$.tw,kf,ot.
 102 leuk#?m\$.tw,kf,ot.
 103 lymphom\$.tw,kf,ot.
 104 melano\$.tw,kf,ot.
 105 metastas\$.tw,kf,ot.

106 (mesothelio\$ or mesotelio\$).tw,kf,ot.
 107 carcinomatos\$.tw,kf,ot.
 108 (gliom\$ or glioblastom\$).tw,kf,ot.
 109 osteo?sarcom\$.tw,kf,ot.
 110 (blastom\$ or neuroblastom\$).tw,kf,ot.
 111 or/93-110
 112 92 and 111
 113 randomized controlled trial.pt.
 114 controlled clinical trial.pt.
 115 randomi?ed.ab.
 116 placebo.ab.
 117 clinical trials as topic.sh.
 118 randomly.ab.
 119 trial.ti.
 120 or/113-119
 121 humans.sh.
 122 120 and 121
 123 112 and 122

Appendix 3. EMBASE search strategy

From 1980 to 20 January 2008

1 exp ANTI-BACTERIAL AGENTS/
 2 (antibacterial? OR anti-bacterial?).tw.
 3 antibio?.tw.
 4 (antimicrobial? OR anti-microbial?).tw.
 5 (anti-mycobacterial? OR antimycobacterial?).tw.
 6 bacteriocid?.tw.
 7 (selective ADJ3 decontaminat?).tw.
 8 ANTIBIOTIC PROPHYLAXIS/
 9 exp QUINOLONE/
 10 fluoroquinilones?.tw.
 11 ciprofloxa#in?.tw.
 12 ofloxa#in?.tw.
 13 norfloxa#in?.tw.
 14 enoxa#in?.tw.
 15 pefloxa#in?.tw.
 16 exp TRIMETHOPRIM/
 17 trimethoprim?.tw.
 18 sulfamethoxazol?.tw.
 19 (trimethoprim-sulfamethoxazol? OR (trimethoprim ADJ3 sulfamethoxazol?)).tw.
 20 tmp-smz?.tw.
 21 exp POLYMYXIN/
 22 colistin?.tw.
 23 (nalidixic? ADJ3 acid?).tw.
 24 polymyxin?.tw.
 25 AMINOGLYCOSIDE/
 26 GENTAMICIN/
 27 gentami#in?.tw.
 28 exp NEBRAMYCIN/
 29 tobramy#in?.tw.
 30 NEOMYCIN/

31 neomy#in?.tw.
 32 VANCOMYCIN/
 33 vancomy#in?.tw.
 34 ROXITHROMYCIN/
 35 roxithromy#in?.tw.
 36 RIFAMPIN/
 37 (rifampin? OR rifampicin?).tw.
 38 BETA-LACTAMS/
 39 PENICILLINS/
 40 AMOXICILLIN/
 41 CEPHALOTHIN/
 42 CEFTRIAXONE/
 43 TICARCILLIN/
 44 (beta-lactam? OR beta\$ lactam\$).tw.
 45 peni#illin?.tw.
 46 amoxi#illin?.tw.
 47 (cephalot#in? OR cefalot#in?).tw.
 48 ceftriaxone?.tw.
 49 ticar#illin?.tw.
 50 framycetin?.tw.
 51 OR/ 1-50
 52 COLONY-STIMULATING FACTORS/
 53 exp COLONY-STIMULATING FACTORS, RECOMBINANT/
 54 exp GRANULOCYTE COLONY STIMULATING FACTOR, RECOMBINANT/
 55 exp GRANULOCYTE COLONY-STIMULATING FACTOR/
 56 GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR/
 57 MACROPHAGE COLONY-STIMULATING FACTOR/
 58 (rhg#csf? OR rhgm#csf?).tw.
 59 (rmethug? OR rhmethug?).tw.
 60 (rhug? OR rhugm?).tw.
 61 (gcsf? OR g-csf?).tw.
 62 (gm-csf? OR gmcsf?).tw.
 63 (granulo#yt? ADJ3 fa#tor?).tw.
 64 (ma#rophag? ADJ5 fa#tor?).tw.
 65 csf.ti
 66 filgrastim?.tw.
 67 neupogen?.tw.
 68 lenograstim?.tw.
 69 euprotin?.tw.
 70 granocyte?.tw.
 71 peg#filgrastim?.tw.
 72 neulasta?.tw.
 73 leukine?.tw.
 74 molgramostine?.tw.
 75 mielogen?.tw.
 76 leucomax?.tw.
 77 OR/ 52-76
 78 * LEUKOPENIA/
 79 exp AGRANULOCYTOSIS/
 80 granulocytopen?.tw.
 81 agranulocyto?.tw.
 82 neutropen?.tw.
 83 leu#open?.tw.

84 (aplasia OR aplastic OR aplasion).tw.
 85 leukocyt? ADJ5 nadir).tw.
 86 (neutrophil? ADJ5 nadir).tw.
 87 INFECTION/
 88 infect?.tw.
 89 SEPSIS/
 90 (septicemia? OR septicaemia?).tw.
 91 (bacteraem? OR bacterem?).tw.
 92 FEVER/
 93 pyrexia.tw.
 94 fever?.tw.
 95 FEVER OF UNKNOWN ORIGIN/
 96 (fever ADJ4 (unknown ADJ3 origin)).tw.
 97 PNEUMONIA/
 98 ((lung? OR pulmonary?) AND inflammation?).tw.
 99 pneumonitis?.tw.
 100 engraftment?.tw.
 101 (neutrophil? ADJ3 recover?).tw.
 102 (hematolog? ADJ3 recover?).tw.
 103 (haematology? ADJ3 recover?).tw.
 104 OR/ 78-103
 105 exp NEOPLASMS BY HISTOLOGIC TYPE/
 106 exp NEOPLASMS BY SITE/
 107 neoplas?.tw.
 108 (tumor? OR tumour?).tw.
 109 (krebs? OR cancer?).tw.
 110 malignan?.tw.
 111 (carcino? OR karzino?).tw.
 112 karzinom?.tw.
 113 sarcom?.tw.
 114 (leukaem? OR leukem?).tw.
 115 lymphom?.tw.
 116 melano?.tw.
 117 metastas?.tw.
 118 (mesothelio? OR mesotelio?).tw.
 119 carcinomatos?.tw.
 120 (gliom? OR glioblastom?).tw.
 121 osteo?sarcom?.tw.
 122 OR/ 105-121
 123 CLINICAL TRIAL/
 124 RANDOMIZED CONTROLLED TRIALS/
 125 RANDOM ALLOCATION/
 126 SINGLE-BLIND METHOD/
 127 DOUBLE-BLIND METHOD/
 128 CROSS-OVER STUDIES/
 129 PLACEBOS/
 130 Randomi?ed controlled trial\$.tw.
 131 RCT.tw.
 132 random allocation.tw.
 133 randomly allocated.tw.
 134 Allocated randomly.tw.
 135 (allocated ADJ2 random).tw.
 136 (allocated ADJ2 random).tw.

137 single blind\$.tw.
 138 double blind\$.tw.
 139 ((treble or triple) ADJ blind\$).tw.
 140 placebo\$.tw.
 141 PROSPECTIVE STUDIES/
 142 OR/ 123-141
 143 CASE STUDY/
 144 case report.tw.
 145 ABSTRACT REPORT/ OR LETTER/
 146 OR/ 143-145
 147 142 NOT 146
 148 ANIMAL/
 149 HUMAN/
 150 148 NOT 149
 151 147 NOT 150
 152 51 OR 77
 153 104 AND 122
 154 152 AND 153
 155 154 AND 51

WHAT'S NEW

Last assessed as up-to-date: 3 December 2015.

Date	Event	Description
28 August 2015	New citation required but conclusions have not changed	New search
28 August 2015	New search has been performed	New search, inclusion criteria adapted, RoB adapted

CONTRIBUTIONS OF AUTHORS

Nicole Skoetz: data extraction and analysis, drafting of final review

Julia Bohlius: content input

Ina Monsef: database search

Oliver Blank: data extraction and analysis

Andreas Engert: clinical expertise and content input

Jörg Janne Vehreschild: clinical expertise

DECLARATIONS OF INTEREST

Nicole Skoetz: none known

Julia Bohlius: none known

Ina Monsef: none known

Oliver Blank: none known

Andreas Engert: none known

Jörg Janne Vehreschild: none known

SOURCES OF SUPPORT

Internal sources

- Köln Fortune, Germany.

Funding programme “Köln Fortune” , Medical Faculty University of Cologne

External sources

- BMBF, Germany.

Project grant application NO 01KG1209, Federal Ministry of Education and Research (BMBF)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Outcomes:

We did not evaluate secondary prophylaxis as we identified only two trials, assessing G-CSF or GM-CSF and antibiotics for primary prophylaxis.

Data analysis:

We did not identify time-to-event outcomes and continuous data. For time-to-event outcomes, we would have extracted hazard ratios (HRs) from published data according to Parmar and Tierney (Parmar 1998; Tierney 2007). We would have calculated continuous outcomes as standardised mean differences.

As we included only one trial in each comparison, we could not pool the data. If we identify more trials for future updates, we will check whether the data are sufficiently similar to be combined. Then, we will pool results by applying meta-analyses using the fixed-effect model, and the random-effects model as a sensitivity analysis.

If the trials are too clinically heterogeneous to combine, we will only perform subgroup analyses, without calculating an overall estimate. We will analyse data according to Cochrane recommendations (Deeks 2011), and will use the Cochrane statistical package in Review Manager 5 for analysis (Review Manager (RevMan)).

Assessment of heterogeneity:

As we did not meta-analyse the data, we did not assess heterogeneity. If we perform a meta-analysis in a future update, we will identify heterogeneity by using a Chi² test with a significance level at $P < 0.1$. We will use the I² statistic to quantify possible heterogeneity (I² > 30% moderate heterogeneity, I² > 75% considerable heterogeneity; Deeks 2011). Moreover, we will explore potential causes of heterogeneity by sensitivity and subgroup analyses.

NOTES

Some passages in this review, especially in the methods part, are from the standard template of the Cochrane Haematological Malignancies Review Group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antibiotic Prophylaxis; Antineoplastic Combined Chemotherapy Protocols [adverse effects]; Fever [prevention & control]; Granulocyte Colony-Stimulating Factor [*therapeutic use]; Granulocyte-Macrophage Colony-Stimulating Factor [*therapeutic use]; Infection Control [*methods]; Neoplasms [*drug therapy; mortality]; Neutropenia [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans