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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

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[Intervention Review]

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

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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 We included full-text, abstracts, and unpublished data if sufficient information on study design, participant characteristics, interventions and outcomes was available.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.

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 found 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

Summary of findings for the main comparison.

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)

Summary of findings 2.

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.

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

BACKGROUND

Description of the condition

Cancer patients receiving myelosuppressive therapy or haematopoetic 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 FNin 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 G-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 G-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 (Gafter-Gvili 2005; Gafter-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; Gafter-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 flouroquinolones, 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; Gafter-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.

Moreoever, 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 ≥ 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 heterogenous 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.

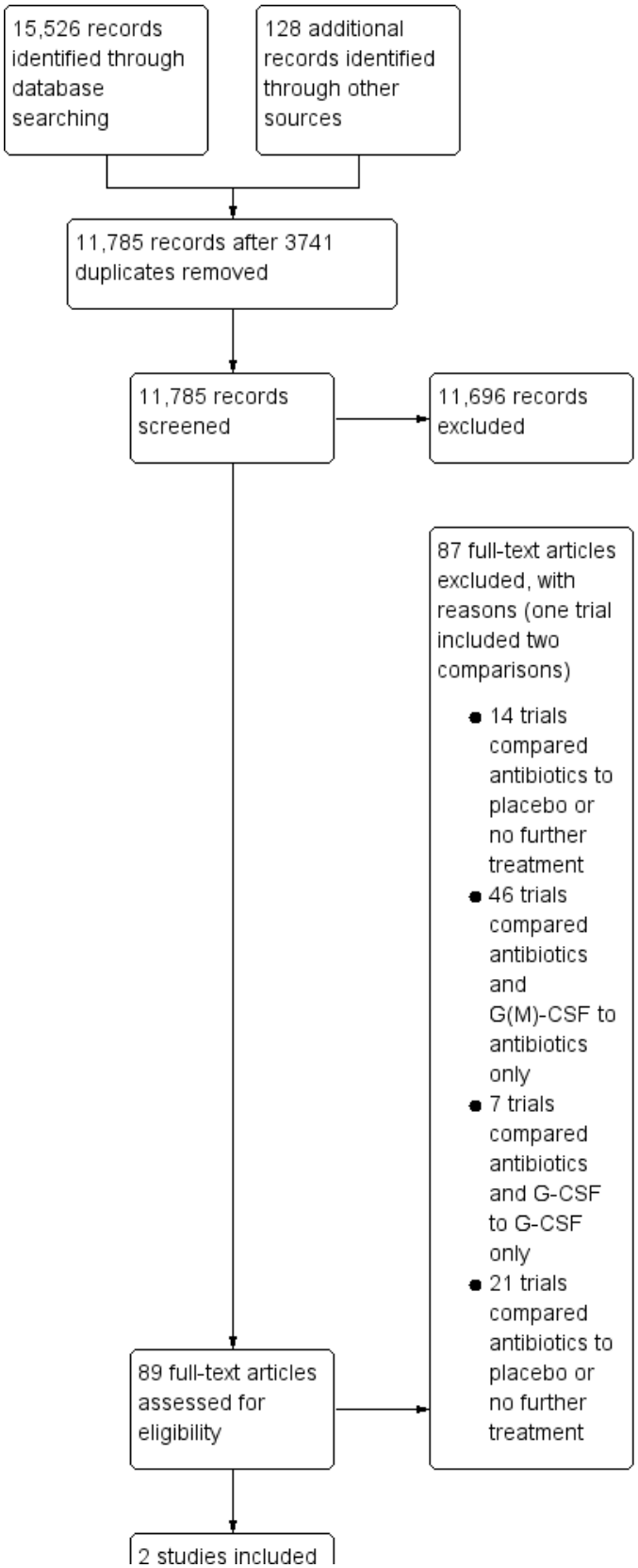
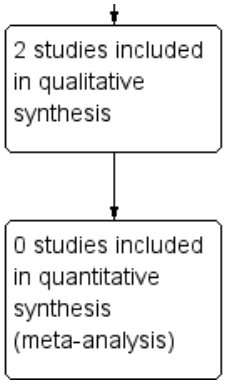


Figure 1. (Continued)



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-naive patients with breast cancer who received three, three-week courses of intravenous cyclophosphamide (1500 mg/m^2), epirubicin (80 mg/m^2), and 5-fluouracil (1500 or 1000 mg/m^2) given on day one; followed by three cycles of intravenous cyclophosphamide (1500 mg/m^2), 5-fluouracil (600 mg/m^2) on day one and intravenous methotrexate (1500 mg/m^2) on day two. Sculier 2001 included patients with small-cell lung cancer receiving six courses of EVI (epirubicin 90 mg/m^2, vindesine 3 mg/m^2 and ifosfamide 5 g/m^2) 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 mm^3 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; Ardizzoni 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-Papaiakovou 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.

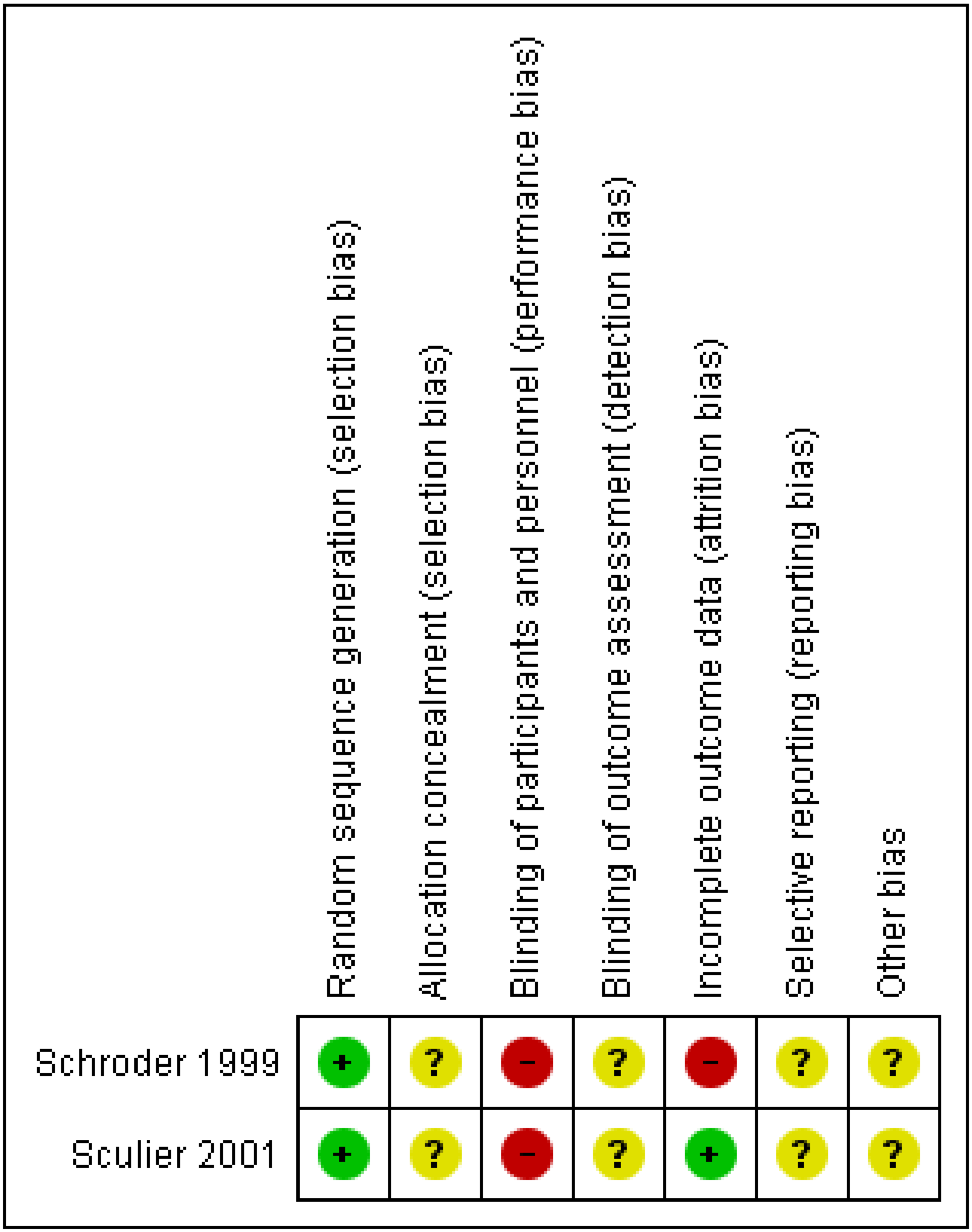
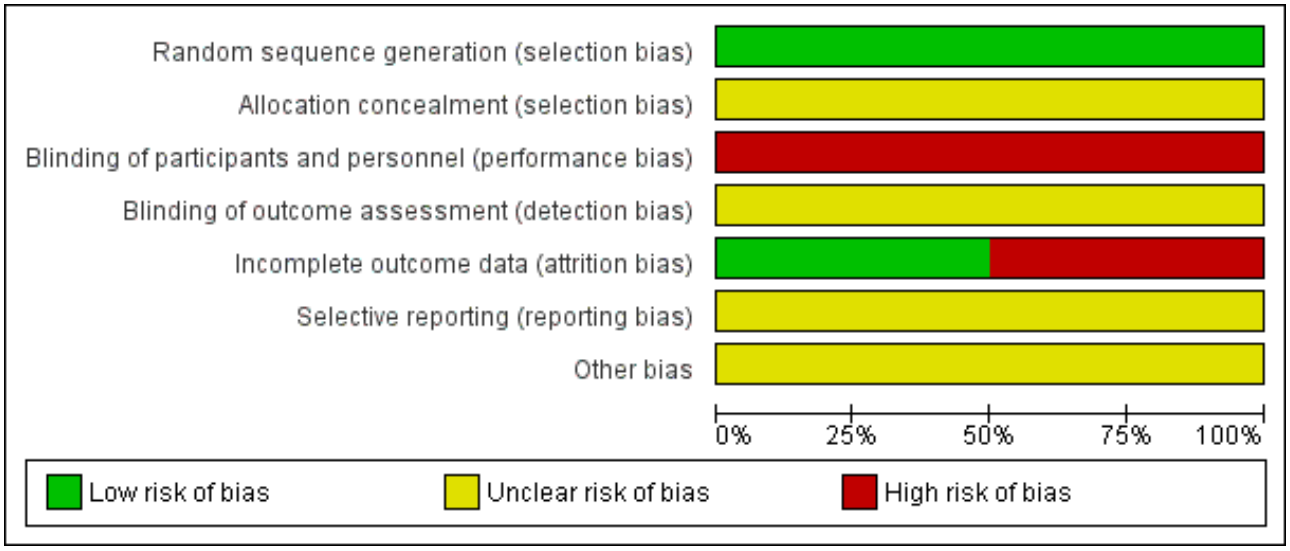


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



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.

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; Gafter-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 infection 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.

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CHARACTERISTICS OF STUDIES

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

Schroder 1999

Methods	Randomisation • 1:1 ratio • Intervention arm: G-CSF for prevention of infection • Control arm: ciprofloxacin and amphotericin Recruitment Period • Not reported Median follow-up time • Not reported

Schroder 1999 *(Continued)*

Participants	40 patients randomised
	• 18 patients G-CSF
	• 22 patients antibiotics
	Inclusion criteria
	• Patients with metastatic breast cancer
	• Age ≤ 65 years
	• Chemotherapy-naive
	Mean age in years
	• G-CSF arm: 39 years (range: 28 to 50)
	• Antibiotics arm: 42 years (range: 29 to 51)
	Metastases
	• G-CSF arm:
	  ○ 8 single metastases
	  ○ 10 multiple metastases
	• Antibiotics arm
	  ○ 14 single metastases
	  ○ 8 multiple metastases
	Country
	• Not reported

Interventions	All patients • 3 courses of IV cyclophosphamide (1500 mg/m^2), epirubicin (80 mg/m^2) and 5-fluorouracil (5-FU; 1500 or 1000 mg/m^2) on day 1 • 3 courses of IV cyclophosphamide (1500 mg/m^2) and 5-FU (600mg/m^2) on day 1 and IV methotrexate (1500 mg/m^2) on day 2 G-CSF arm • 263 µg subcutaneously on days 3 to 12 Antibiotics arm • 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	• Episodes of hospitalisation for febrile neutropenia • Duration of hospitalisation for febrile neutropenia • Grade IV leucopenia • Cost analyses
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Before chemotherapy, patients were randomized to group I or II."

Schroder 1999 *(Continued)*

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

Sculier 2001

Methods	Randomisation • 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 Recruitment Period • April 1993 to April 2000 Median follow-up time • Not reported
Participants	243 patients randomised, 233 eligible • 78 standard arm (not evaluated in this review) • 78 patients GM-CSF • 77 patients antibiotics Inclusion criteria • 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) Mean age in years

Sculier 2001 *(Continued)*

- GM-CSF arm: 64 years (range: 35 to 74)
- Antibiotics arm: 61 years (range: 37 to 74)

Stage

- GM-CSF arm:
  - Stage III: 7 patients
  - Stage IV: 71 patients
- Antibiotics arm
  - Stage III: 7 patients
  - Stage IV: 70 patients

Brain metastases

- GM-CSF arm:
  - 14 patients
- Antibiotics arm
  - 17 patients

Countries

- Several countries in Europe

Interventions	All patients • 6 courses of EVI (epirubicin 90 mg/m^2 , vindesine 3 mg/m^2 and ifosfamide 5 g/m^2 ; all drugs given IV on day 1, in the accelerated arms every 14 days GM-CSF arm • 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 mm^3 after nadir. Antibiotics arm • 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	• 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)

Sculier 2001 *(Continued)*

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

Study	Reason for exclusion
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
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

Study	Reason for exclusion
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
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

Study	Reason for exclusion
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

APPENDICES

Appendix 1. 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 (antimyocobacterial*) 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 Enoxa*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 ratiograstim*

#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 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 beta-lactam$.tw,kf,ot.

40 PENICILLINS/

41 peni#illin$.tw,kf,ot.

42 AMOXICILLIN/

43 amoxi#illin$.tw,kf,ot.

44 CEPHALOTHIN/

45 (cephalot?in$ or cefalot?in$).tw,kf,ot.

46 CEFTRIAXONE/

47 ceftriaxone$.tw,kf,ot.

48 TICARCILLIN/

49 ticar#illin$.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 nivestim$.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 antimyocobacterial?).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-STIMULATINGING 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

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

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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 Chi^2 test with a significance level at $P < 0.1$. We will use the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ 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]; Breast Neoplasms [drug therapy]; Febrile Neutropenia [prevention & control]; Fever [prevention & control]; Granulocyte Colony-Stimulating Factor [*therapeutic use]; Granulocyte-Macrophage Colony-Stimulating Factor [*therapeutic use]; Infection Control [methods]; Lung Neoplasms [drug therapy]; Neoplasms [drug therapy] [mortality]; Randomized Controlled Trials as Topic; Small Cell Lung Carcinoma [drug therapy]

MeSH check words

Female; Humans