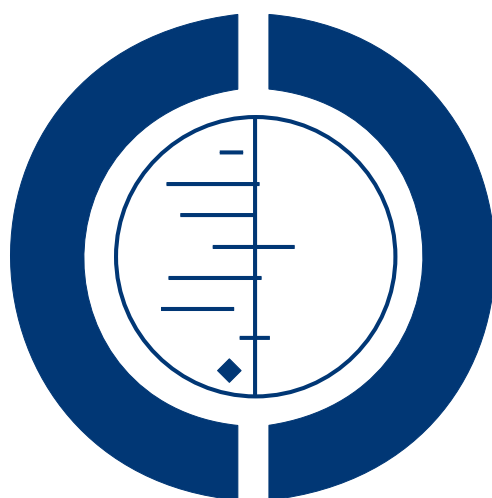


Granulocyte transfusions for preventing infections in people with neutropenia or neutrophil dysfunction (Review)

Estcourt LJ, Stanworth S, Doree C, Blanco P, Hopewell S, Trivella M, Massey E



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[Intervention Review]

Granulocyte transfusions for preventing infections in people with neutropenia or neutrophil dysfunction

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ABSTRACT

Background

Despite modern antimicrobials and supportive therapy, bacterial and fungal infections are still major complications in people with prolonged disease-related or therapy-related neutropenia. Since the late 1990s there has been increasing demand for donated granulocyte transfusions to treat or prevent severe infections in people who lack their own functional granulocytes. This is an update of a Cochrane review first published in 2009.

Objectives

To determine the effectiveness and safety of prophylactic granulocyte transfusions compared with a control population not receiving this intervention for preventing all-cause mortality, mortality due to infection, and evidence of infection due to infection or due to any other cause in people with neutropenia or disorders of neutrophil function.

Search methods

We searched for randomised controlled trials (RCTs) and quasi-RCTs in the Cochrane Central Register of Controlled Trials (*Cochrane Library* 2015, Issue 3), MEDLINE (from 1946), EMBASE (from 1974), CINAHL (from 1937), the Transfusion Evidence Library (from 1980) and ongoing trial databases to April 20 2015.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs comparing people receiving granulocyte transfusions to prevent the development of infection with a control group receiving no granulocyte transfusions. Neonates are the subject of another Cochrane review and were excluded from this review. There was no restriction by outcomes examined, but this review focuses on mortality, mortality due to infection and adverse events.

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration.

Main results

Twelve trials met the inclusion criteria. One trial is still ongoing, leaving a total of 11 trials eligible involving 653 participants. These trials were conducted between 1978 and 2006 and enrolled participants from fairly comparable patient populations. None of the studies included people with neutrophil dysfunction. Ten studies included only adults, and two studies included children and adults. Ten of these studies contained separate data for each arm and were able to be critically appraised. One study re-randomised people and therefore quantitative analysis was unable to be performed.

Overall, the quality of the evidence was very low to low across different outcomes according to GRADE methodology. This was due to many of the studies being at high risk of bias, and many of the outcome estimates being imprecise.

All-cause mortality was reported for nine studies (609 participants). There was no difference in all-cause mortality over 30 days between people receiving prophylactic granulocyte transfusions and those that did not (seven studies; 437 participants; RR 0.92, 95% CI 0.63 to 1.36, *very low-quality evidence*).

Mortality due to infection was reported for seven studies (398 participants). There was no difference in mortality due to infection over 30 days between people receiving prophylactic granulocyte transfusions and those that did not (six studies; 286 participants; RR 0.69, 95% CI 0.33 to 1.44, *very low-quality evidence*).

The number of people with localised or systemic bacterial or fungal infections was reported for nine studies (609 participants). There were differences between the granulocyte dose subgroups (test for subgroup differences $P = 0.01$). There was no difference in the number of people with infections over 30 days between people receiving prophylactic granulocyte transfusions and those that did not in the low-dose granulocyte group ($< 1.0 \times 10^{10}$ granulocytes per day) (four studies, 204 participants; RR 0.84, 95% CI 0.58 to 1.20; *very low-quality evidence*). There was a decreased number of people with infections over 30 days in the people receiving prophylactic granulocyte transfusions in the intermediate-dose granulocyte group (1.0×10^{10} to 4.0×10^{10} granulocytes per day) (4 studies; 293 participants; RR 0.40, 95% CI 0.26 to 0.63, *low-quality evidence*).

There was a decreased number of participants with bacteraemia and fungaemia in the participants receiving prophylactic granulocyte transfusions (nine studies; 609 participants; RR 0.45, 95% CI 0.30 to 0.65, *low-quality evidence*).

There was no difference in the number of participants with localised bacterial or fungal infection in the participants receiving prophylactic granulocyte transfusions (six studies; 296 participants; RR 0.75, 95% CI 0.50 to 1.14; *very low-quality evidence*).

Serious adverse events were only reported for participants receiving granulocyte transfusions and donors of granulocyte transfusions.

Authors' conclusions

In people who are neutropenic due to myelosuppressive chemotherapy or a haematopoietic stem cell transplant, there is low-grade evidence that prophylactic granulocyte transfusions decrease the risk of bacteraemia or fungaemia. There is low-grade evidence that the effect of prophylactic granulocyte transfusions may be dose-dependent, a dose of at least 10×10^{10} per day being more effective at decreasing the risk of infection. There is insufficient evidence to determine any difference in mortality rates due to infection, all-cause mortality, or serious adverse events.

PLAIN LANGUAGE SUMMARY

Transfusions of white blood cells called granulocytes for preventing infections in people who lack functioning granulocytes

Review question

We evaluated the evidence about whether granulocyte transfusions given to prevent infection are safe and decrease the risk of infection. Our target population was people with neutropenia (a very low count of a type of white blood cell (neutrophil), or white blood cells that did not function properly (neutrophil dysfunction)).

Background

Functioning white blood cells, in particular granulocytes, are important for fighting life-threatening bacterial and fungal infections. For many years, some hospital physicians have been giving granulocyte transfusions to people who lack white cells as a result of disease and/or treatment that has reduced their number or function.

The demand for granulocytes for transfusion has shown a steady increase since the 1990s mainly as a result of the introduction of a drug called granulocyte colony-stimulating factor (G-CSF) which, if given to donors, leads to increased granulocyte numbers in the donor's blood and the collection of a larger dose of granulocytes than was previously possible.

Study characteristics

The evidence is current to April 2015. In this update, 12 trials were identified that compared giving granulocyte transfusions to prevent infections compared to not giving granulocytes to prevent infection. One trial has not yet been completed. Eleven trials containing a total of 653 participants were reviewed. These trials were conducted between 1978 and 2006. Data from one trial were not included in the analyses because patients were included within the trial more than once. Ten studies included only adults, and two studies included children and adults.

Six studies reported their funding sources, and all were funded by charities or governments.

Key results

Giving granulocyte transfusions to prevent infections did not affect the risk of death due to infection, or the risk of death due to any cause.

Giving granulocyte transfusions to prevent infections decreased the number of people who had a bacterial or fungal infection in the blood, but did not decrease the number of people having a localised bacterial or fungal infection.

It is unknown whether granulocyte transfusions increased the risk of having a serious adverse event because adverse events were only reported in people receiving granulocyte transfusions.

Quality of the evidence

The evidence for most of the findings was of very low or low quality. This was because patients and their doctors knew which study arm the patient had been allocated to and two of the studies were not true randomised studies (patients were allocated to the granulocyte transfusion arm if they had a suitable granulocyte donor).

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

Prophylactic granulocytes compared with no prophylactic granulocytes for preventing infection in people with neutropenia or neutrophil dysfunction							
Patient or population: people with neutropenia or neutrophil dysfunction Settings: Hospital Intervention: prophylactic granulocytes Comparison: no prophylactic granulocytes							
Outcomes	Illustrative comparative risks* (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk		Corresponding risk				
	Control	Prophylactic granulocytes					
All-cause mortality up to 30 days Follow-up: median 30 days	145 per 1000	134 per 1000 (91 to 198)		RR 0.92 (0.63 to 1.36)	437 (7 studies)	⊕○○○ very low ^{1,2,3}	
Mortality due to infection up to 30 days Follow-up: median 30 days	98 per 1000	68 per 1000 (32 to 141)		RR 0.69 (0.33 to 1.44)	286 (6 studies)	⊕○○○ very low ^{1,2,3}	
People with localised or systemic bacterial or fungal infections - low-dose granulocyte transfusions Follow-up: median 30 days	374 per 1000	314 per 1000 (217 to 141)		RR 0.84 (0.58 to 1.2)	204 (4 studies)	⊕○○○ very low ^{1,2,3}	

People with localised or systemic bacterial or fungal infections - Intermediate-dose granulocyte transfusions Follow-up: median 30 days	376 per 1000	150 per 1000 (98 to 237)	RR 0.4 (0.26 to 0.63)	293 (4 studies)	⊕⊕○○ low ^{1,2}	
People with bacteraemia or fungaemia Follow-up: median 30 days	249 per 1000	112 per 1000 (75 to 162)	RR 0.45 (0.3 to 0.65)	609 (9 studies)	⊕⊕○○ low ^{1,2}	
People with localised bacterial or fungal infection Follow-up: median 30 days	271 per 1000	204 per 1000 (136 to 309)	RR 0.75 (0.50 to 1.14)	296 (6 studies)	⊕○○○ very low ^{1,2,3}	
People with serious adverse events	See comment	See comment	See comment	See comment	See comment	Adverse events were only reported for the groups receiving granulocyte transfusions See Table 7 & Table 8
<p>*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</p> <p>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.</p>						

¹ Owing to the nature of the intervention (granulocyte transfusion) and difficulty blinding participants, physicians and outcome assessors studies were at high risk of performance and detection bias. We downgraded the evidence by 1 for risk of bias

- ² Two studies were biologically randomised and therefore at high risk of selection bias. Three studies did not include a significant proportion of people who were randomised within the analysis and are at high risk of attrition bias
- ³ The estimate included significant benefit and harm. We therefore downgrade the evidence by 1 for imprecision

BACKGROUND

Description of the condition

Functioning white blood cells are a vital component of the defence system against infection in humans. There are a variety of different white blood cells that work together and perform complementary roles. Granulocytes are white blood cells that contain granules which are directly visible when viewed through a light microscope. Neutrophils are a subtype of granulocytes and are the most numerous circulating white blood cells in healthy adults. Granulocytes in general and neutrophils in particular are crucial in protecting against bacterial and fungal infection. A persisting reduction in neutrophil numbers is called neutropenia, the severity of which has been classified by the World Health Organization (WHO 1992): when the peripheral blood count of neutrophils is below a level of $0.5 \times 10^9/L$ there is an increased risk of severe infection (the normal neutrophil count ranges from 2 to $7.5 \times 10^9/L$ in adults). Idiosyncratic neutropenia occurs in the population with a frequency of 120 per million people per year (van Staa 2003), but neutropenia is also an inevitable complication of chemotherapy for malignant diseases, as well as a presenting feature of many haematological disorders. Infection in people with neutropenia is associated with hospital admission, organ damage, and a significant number of deaths, despite the use of specific and appropriate antibiotic and antifungal drugs (Klastersky 2001). Even with a normal number of neutrophils, other patients may suffer from a similar inability to fight infections adequately if there is an impairment in the function of their neutrophils (Kuijpers 1999).

Description of the intervention

Published reviews have suggested that the efficacy of granulocyte transfusions in neutropenic people is proportional to the dose of granulocytes transfused, with an optimal level being at least 10^{10} granulocytes or at least 10^{10} granulocytes per metre squared of recipient body surface area per transfusion (Engelfriet 2000; Vamvakas 1996). However, there are a number of technical problems that make it difficult to collect adequate granulocyte doses for transfusion. Granulocytes are difficult to separate from other blood cells, and in addition healthy donors do not have very high levels of circulating granulocytes in their peripheral blood. There are a number of different methods for collecting granulocytes for transfusion in humans. Apheresis is a favoured technique utilising equipment incorporating a centrifuge or filter to selectively remove white blood cells from the donor whilst returning other cellular and liquid components to the donor (Freireich 1964). In the early 1990s, growth factors such as granulocyte colony-stimulating factor (G-CSF) that stimulate the bone marrow to produce more white blood cells (particularly granulocytes) were developed for therapeutic use. These drugs allowed high peripheral blood

white cell counts to be achieved in healthy donors. Steroids can also increase the white cell count, but alone they are not as effective as G-CSF. Using this method, adequate doses of granulocytes can be produced for adults. The exposure of a healthy volunteer donor to any form of medication with potential side effects does however present ethical and safety issues (Gutierrez 2001; Strauss 2003).

How the intervention might work

There is limited evidence by laboratory testing that donated granulocytes are functional (Bashir 2003; Dale 1998). The ability to collect greater numbers of granulocytes has however generated renewed interest in the potential role of granulocyte transfusions, either as additional therapy for people with neutropenia and established infections or when given as prophylaxis to prevent severe or life-threatening infections (Dale 2000; Hubel 2001; Illerhaus 2002; Kerr 2003; Peters 1999; Price 2000). These advances have occurred in conjunction with advances in anti-microbial therapy, including antifungal drugs, but the exact relative contributions of these agents in the context of more aggressive chemotherapy regimens and bone marrow transplants remains unclear.

Why it is important to do this review

This systematic review aimed to assess the effectiveness and safety of prophylactic granulocyte transfusions in people with neutropenia or neutrophil dysfunction. Previous Cochrane reviews have been performed with specific reference to neonatal practice and therapeutic granulocyte transfusion in adults (Pammi 2011; Stanworth 2005). Using granulocyte transfusion as part of a strategy for prevention of infection in neutropenic people may be more effective than therapeutic transfusions in response to established infection. This systematic review would therefore complement the previous Cochrane reviews.

This is an update of a previous Cochrane review (Massey 2009).

OBJECTIVES

To determine the effectiveness and safety of prophylactic granulocyte transfusions compared with a control population not receiving this intervention for preventing all-cause mortality, mortality due to infection, and evidence of infection due to infection or due to any other cause in people with neutropenia or disorders of neutrophil function.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs. Quasi-RCTs included those in which allocation to receive granulocyte transfusion was dependent upon the availability of suitably-matched donors; this form of randomisation was referred to as quasi-randomisation in the text.

Types of participants

People with neutropenia (whether due to treatment or disease, or whether reversible or irreversible) were considered. People with inherited disorders of neutrophil dysfunction were also eligible for inclusion. Studies with neonates were excluded as these trials have been appraised in another Cochrane Review (Pammi 2011).

Types of interventions

Intervention

Granulocyte transfusions given as prophylaxis, prior to the development of documented infection. All sources of granulocytes, all doses, and different methods of collection were included.

Control

Prophylactic granulocyte transfusions not administered.

Types of outcome measures

Primary outcomes

- Death (from all causes)

Secondary outcomes

- Death due to infection
- Number of infections (whether systemic or at specific loci or microbiologically proven, with details of pathogens isolated)
- Numbers of days with fever
- Number of days on treatment with antimicrobials (or courses of treatment with antibiotics/antifungals)
 - Increment of neutrophil count ($\times 10^9/L$)
 - Duration of neutropenia reversal after transfusion (neutropenia defined as count below $0.5 \times 10^9/L$).
- Serious adverse events: resulting in death, requiring or prolonging hospitalisation, resulting in persistent or significant disability/incapacity, or life-threatening
- Adverse events requiring discontinuation of intervention

Other factors which may influence the outcome of neutropenia were extracted and reported in [Characteristics of included studies](#) and discussed in [Overall completeness and applicability of evidence](#). These included the following.

- Use of therapeutic granulocyte transfusion
- Use of colony-stimulating factors in recipients, particularly G-CSF
- Policies and use of prophylactic antibiotics and antifungals
- Method of preparation and source of granulocytes for transfusion

Search methods for identification of studies

Electronic searches

Bibliographic databases

We searched for randomised controlled trials (RCTs) in the following databases.

- CENTRAL (*Cochrane Library* 2014, Issue 3) (Appendix 1)
- MEDLINE (Ovid, 1946 to April 20 2015) (Appendix 2)
- EMBASE (Ovid, 1974 to April 20 2015) (Appendix 3)
- CINAHL (EBSCOhost, 1937 to April 20 2015) (Appendix 4)
- Lilacs (BIREME/PAHO/WHO, 1982 to April 20 2015) (Appendix 5)
- KoreaMed (KAMJE, 1997 to April 20 2015) (Appendix 6)
- PakMediNet (2001 to April 20 2015) (Appendix 6)
- IndMed (ICMR-NIC, 1986 to April 20 2015) (Appendix 7)
- Transfusion Evidence Library (www.transfusionevidencelibrary.com) (1980 to April 20 2015) (Appendix 8)

We updated searches from the original search in October 2008 (Massey 2009). Searches in MEDLINE, EMBASE and CINAHL were combined with adaptations of the Cochrane RCT search filters, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011).

Databases of ongoing trials

We also searched ClinicalTrials.gov (<http://clinicaltrials.gov/ct2/search>) (Appendix 9), the WHO International Clinical Trials Registry (ICTRP) (<http://apps.who.int/trialsearch/>) (Appendix 9), and the ISRCTN Register (<http://www.controlled-trials.com/isrctn/>) (Appendix 10), in order to identify ongoing trials.

All new search strategies are presented as indicated in Appendices 1-10. Search strategies for the original (2008) searches are presented in Appendix 11.

Searching other resources

We augmented database searching with the following methods.

Handsearching of reference lists

We checked references of all included trials, relevant review articles and current treatment guidelines for further literature. These searches were limited to the 'first generation' reference lists.

Personal contacts

We contacted authors of relevant studies, study groups and experts worldwide known to be active in the field for unpublished material or further information on ongoing studies.

Data collection and analysis

Selection of studies

We updated the selection of studies from the selection of studies performed for the previous version of this review (Massey 2009). One review author (CD) excluded all duplicates and studies that were clearly irrelevant (e.g. non-human) that had been identified by the review search strategy. Two review authors (LE, PB) independently screened all remaining electronically-derived citations and abstracts of papers identified by the review search strategy for relevance. We excluded studies that were clearly irrelevant at this stage based on a review of the abstract. Two review authors (LE, PB) independently formally assessed the full texts of all potentially-relevant trials for eligibility against the criteria outlined above. All disagreements were resolved by discussion without the need for a third review author (SS). We sought further information from study authors if the article contained insufficient data to make a decision about eligibility. A study eligibility form was designed for trials of granulocyte transfusion to help in the assessment of relevance, which included ascertaining whether the participants were neonates, and whether the two groups could be defined in the trial on the basis of a therapeutic-only versus prophylactic granulocyte transfusion strategy. We recorded the reasons why potentially-relevant studies failed to meet the eligibility criteria.

Data extraction and management

We updated the data extraction from the one used to extract data for the previous version of this review (Massey 2009). This included data extraction for all new studies that have been included since the previous review and an updated 'Risk of bias' assessment for all included studies.

Two review authors (LE, PB) conducted the data extraction according to the guidelines proposed by The Cochrane Collaboration (Higgins 2011a). We resolved potential disagreements between the review authors by consensus. The review authors were

not blinded to names of authors, institutions, journals, or the outcomes of the trials. Due to minor changes in the format, the data extraction forms were piloted on a further study, thereafter the two authors (LE, PB) extracted data independently for all the studies. The following data were extracted.

General information

Review author's name, date of data extraction, study ID, first author of study, author's contact address (if available), citation of paper, objectives of the trial.

Trial details

Trial design, location, setting, sample size, power calculation, treatment allocation, inclusion and exclusion criteria, reasons for exclusion, comparability of groups, length of follow-up, stratification, stopping rules described, statistical analysis, results, conclusion, and funding.

Characteristics of participants

Age, gender, ethnicity, total number recruited, total number randomised, total number analysed, types of underlying disease, lost to follow-up numbers, drop outs (percentage in each arm) with reasons, protocol violations, previous treatments, current treatment, prognostic factors.

Interventions

Experimental and control interventions, method of preparation and source of granulocytes for transfusion, timing of intervention, dosage of granulocyte given, compliance to interventions, any differences between interventions, and any additional interventions given, especially in relation to the use of therapeutic granulocyte transfusions, the use of colony-stimulating factors in recipients, particularly G-CSF and the use of prophylactic and therapeutic antibiotics and antifungals.

Assessment of bias

Sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.

Outcomes measured

Death (from all causes). Death due to infection. Number of infections (whether systemic or at specific loci or microbiologically proven, with details of pathogens isolated). Numbers of days with fever. Number of days on treatment with antimicrobials (or courses of treatment with antibiotics/antifungals). Increment of neutrophil count ($\times 10^9/L$). Duration of neutropenia reversal after transfusion (neutropenia defined as count below $0.5 \times 10^9/L$).

Serious adverse events: resulting in death, requiring or prolonging hospitalisation, resulting in persistent or significant disability/incapacity, or life-threatening. Adverse events requiring discontinuation of intervention.

We used both full-text versions and abstracts to retrieve the data. For publications reporting on more than one trial, we used one data extraction form for each trial. For trials reported in more than one publication, we extracted data using one form only. Where these sources did not provide sufficient information, we contacted authors and study groups for additional details.

One review author entered data into the software and a second review author checked for accuracy.

Assessment of risk of bias in included studies

We updated the 'Risk of bias' assessment from the 'Risk of bias' assessment performed for the previous version of this review (Massey 2009).

Two review authors (LE, PB) assessed all included studies for possible risk of bias (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). The assessment included information about the design, conduct and analysis of the trial. Each criterion was evaluated on a three-point scale: low risk of bias, high risk of bias, or unclear. To assess risk of bias, the following questions were included in the 'Risk of bias' table for each included study.

- Was the allocation sequence adequately generated?
- Was allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study (including an assessment of blinding of participants, personnel, and outcome assessors)?
- Were incomplete outcome data adequately addressed (for every outcome separately)?
- Are reports of the study free of selective outcome reporting?
- Was the study apparently free of other problems that could put it at risk of bias?

Measures of treatment effect

For dichotomous outcomes, we recorded the number of outcomes in the treatment and control groups and we estimated the treatment effect measures across individual studies as the relative effect measures (risk ratio (RR) with 95% confidence intervals (CIs)). For continuous outcomes, we recorded the mean and standard deviations (SDs). For continuous outcomes measured using the same scale, the effect measure was the mean difference (MD) with 95% CIs, or the standardised mean difference (SMD) for outcomes measured using different scales.

For time-to-event outcomes, we planned to extract the hazard ratio (HR) from published data according to Parmar 1998 and Tierney 2007. However, no time to event data were reported.

If the data available could not be reported in any of the formats described above, we reported the results narratively.

Unit of analysis issues

We did not pre-specify in the protocol how we would deal with any unit of analysis issues. There were unit of analyses issues. In Mannoni 1979 participants were randomised more than once, 44 participants were included within the study but six participants were re-randomised. Data for the first randomisation could not be extracted from the report, and further information from the authors was not available. Data from this study were therefore not incorporated into any meta-analysis.

Dealing with missing data

We dealt with missing data according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We contacted authors in order to obtain information that was missing or unclear in the published report. We contacted the authors of the Vij 2003 study, but no further analyses had been performed apart from the analyses in the primary paper.

Within an outcome, the preferred analysis was an intention-to-treat analysis (ITT). Where data were missing, we recorded the number of participants lost to follow-up for each trial.

Assessment of heterogeneity

If studies were considered sufficiently homogenous in their study design, we conducted a meta-analysis and assessed the statistical heterogeneity (Deeks 2011). We assessed statistical heterogeneity of treatment effects between trials using a Chi² test with a significance level at $P < 0.1$. We used the I² statistic to quantify possible heterogeneity (I² > 50% moderate heterogeneity, I² > 80% considerable heterogeneity). We explored potential causes of heterogeneity by sensitivity and subgroup analyses if possible.

Assessment of reporting biases

We did not perform a formal assessment of potential publication bias (small trial bias) by generating a funnel plot and statistically test using a linear regression test (Sterne 2011) as no meta-analysis contained 10 or more studies.

Data synthesis

We performed analyses according to the recommendations of The Cochrane Collaboration (Deeks 2011). We used aggregated data for analysis. For statistical analysis, we entered data into Review Manager 5.3.

Where meta-analysis was feasible, we used the fixed-effect model for pooling the data. We used the Mantel-Haenszel method for dichotomous outcomes or Peto method as necessary, and the inverse variance method for continuous outcomes. Even in the absence of statistical heterogeneity, we explored the robustness of any summary measures, particularly with respect to study methodological quality.

We planned to use the random-effects model for sensitivity analyses as part of the exploration of heterogeneity. However, none of the analyses performed reported heterogeneity, as expressed by the I^2 above 50%, therefore only the fixed-effect model was reported. If heterogeneity was found to be above 80%, we did not perform a meta-analysis and results were commented on as a narrative.

'Summary of findings' table

We used GRADE to build a 'Summary of findings' table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). This included the following.

- Death from all causes
- Death due to infection
- Number of infections (localised or systemic)
- Number of infections (bacteraemia or fungaemia)
- Number of infections (localised)
- Number of serious adverse events

A GRADE assessment had not been pre-specified in the protocol.

Subgroup analysis and investigation of heterogeneity

The only subgroup analysis pre-specified in the previous version of this review (Massey 2009), was granulocyte dose.

We performed a subgroup analysis on granulocyte dose, classifying studies in to low dose (mean granulocyte dose less than 1×10^{10} per day for an adult patient), intermediate dose (mean granulocyte dose 1×10^{10} to 4×10^{10} per day for an adult patient), and high dose (mean granulocyte dose greater than 4×10^{10} per day for an adult patient).

We commented on differences between subgroups as a narrative. Investigation of heterogeneity between studies also included, if appropriate, age of the study (as the treatment of neutropenic people has changed over the last 40 years).

Sensitivity analysis

We intend to assess the robustness of our findings by the following two sensitivity analyses.

- Including only those trials at low risk of bias
- Including only those trials in which 20% participants or less were lost to follow-up.

A sensitivity analysis including only those studies at low risk of bias was not performed because none of the studies were at low risk of bias.

RESULTS

Description of studies

See [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

See PRISMA Flow Diagram [Figure 1](#).

Figure 1. Study flow diagram.

The original search (conducted 1st January 2009) identified a total of 1253 potentially relevant citations. There were 701 citations after duplicates were removed, 676 records were excluded on the basis of the abstract. The original systematic review identified 25 studies which appeared relevant on the basis of the their full text or abstract.

This updated search (conducted 20th April 2015) identified a total of 2188 potentially relevant citations. There were 1910 citations after duplicates were removed. We were able to exclude 1893 citations on the basis of the abstract by two out of three review authors (LE, CD, and PB). Two review authors (LE, PB) retrieved and assessed 10 full-text articles for relevance.

The previous systematic review (Massey 2009), identified 12 trials that compared prophylactic granulocyte transfusions versus no prophylactic platelet transfusions; 10 completed trials (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980), and two ongoing studies (Price 2014; Seidel 2008), which are now excluded. This updated search identified two additional studies (Vij 2003; NCT01204788). The study by Vij 2003 was not identified in the previous systematic review (Massey 2009). This was because the search strategy we used for this update of the review was much more extensive than the previous search strategy (see [Search methods for identification of studies](#)).

In total, we assessed 12 studies and deemed them eligible for inclusion (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; NCT01204788; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Vij 2003; Winston 1980), however the NCT01204788 study is still ongoing.

Included studies

See [Characteristics of included studies](#) for full details of each study. Twelve studies were eligible for inclusion in this review. Eleven studies have been completed (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Vij 2003; Winston 1980), and one study has been stopped early due to poor recruitment (NCT01204788) but results have not been published.

Of the 11 completed studies, nine studies were randomly controlled studies (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980), and two studies allocated participants to the intervention arm on the basis of a suitable available granulocyte donor (Oza 2006; Vij 2003).

Ongoing Studies

This updated review identified one ongoing study that was eligible for inclusion (NCT01204788). This study has been completed but has not been published. The previous systematic review

(Massey 2009) identified two potentially relevant studies that have since been excluded because they were studying the wrong intervention (Price 2014; Seidel 2008).

See [Characteristics of ongoing studies](#) for further details.

Studies contributing to this review

See [Characteristics of included studies](#) for full details of each study.

Study Design

There were five single-centre parallel randomised controlled trials (RCTs) (Clift 1978; Ford 1982; Gomez-Villagran 1984; Schiffer 1979; Winston 1980); two single centre quasi-randomised studies (Oza 2006; Vij 2003); three multicentre parallel RCTs (Petersen 1987; Strauss 1981; Sutton 1982) and one parallel RCT where the number of centres was unclear (Mannoni 1979).

Study Size

The number of participants enrolled in all studies was small, ranging between 18 (Schiffer 1979) and 225 (Vij 2003) participants analysed. Most of the studies presented no or little information on sample sizes required to power the trial around a main outcome, and only one study made any attempt to justify the statistical analysis of the required size (Oza 2006). All other trials should probably be considered more as hypothesis generating in respect of design.

Setting

The nine RCTs were published between 1978 and 1987 (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980), the two quasi-randomised studies were published between 2003 and 2006 (Oza 2006; Vij 2003). Seven studies were based in the United States (Clift 1978; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Vij 2003; Winston 1980); one study was based in Canada (Sutton 1982); one study was based in France (Mannoni 1979); one study was based in Spain (Gomez-Villagran 1984); and one study was based in the United Kingdom (Ford 1982).

Participants

The majority of participants were people with haematological malignancies receiving intensive chemotherapy or a haematopoietic stem cell transplant (HMST). Most studies included only adults. Two studies included children and adults (Clift 1978; Gomez-Villagran 1984).

Intervention

Average dose and range

The dose of granulocytes transfused varied between studies (Table 1). The mean dose varied from 0.6×10^{10} (Strauss 1981) to 5.9×10^{10} (Oza 2006) (Table 1). No dose was reported by two studies (Petersen 1987; Vij 2003).

Schedule for transfusion

Granulocyte transfusions were commenced when the recipient's neutrophil count fell below a pre-defined value in eight of the 11 studies. This "trigger" neutrophil count was 0.2×10^9 /L for two studies (Clift 1978; Petersen 1987), and 0.5×10^9 /L for six studies (Ford 1982; Gomez-Villagran 1984; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980). In the Schiffer study, the granulocyte component contained a significant number of platelets and was therefore commenced if the patient needed platelet transfusion, even if the defined neutrophil count trigger had not been met (Schiffer 1979).

The other three studies started granulocyte transfusions at pre-specified time points after treatment (Mannoni 1979; Oza 2006; Vij 2003).

Once prophylactic granulocyte transfusions had commenced, daily transfusions were given in seven of the 11 studies (Clift 1978; Gomez-Villagran 1984; Mannoni 1979; Petersen 1987; Strauss 1981; Sutton 1982; Winston 1980) (Table 1). Granulocyte transfusions were given on alternate days by one study (Ford 1982), and for four days out of seven by one study (Schiffer 1979). Two studies gave granulocyte transfusions on two occasions at fixed time points after HSCT (Oza 2006; Vij 2003).

Granulocyte transfusions were discontinued when the recipient's neutrophil count rose above a pre-defined value in eight of the 11 studies. This "trigger" neutrophil count was 0.2×10^9 /L for two studies (Clift 1978; Petersen 1987), and 0.5×10^9 /L for six studies (Ford 1982; Gomez-Villagran 1984; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980). Mannoni gave transfusions for a set period of 12 days but continued for 15 days in one case as there was evidence of infection at 12 days (Mannoni 1979). Two studies gave granulocyte transfusions on two occasions at fixed time points after HSCT (Oza 2006; Vij 2003).

Method of collection of granulocytes

The method of collection of granulocytes varied between trials. Nine studies used either intermittent or continuous flow centrifugation (Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982;

Vij 2003). One study used both filtration leucapheresis and continuous flow centrifugation (Clift 1978). One study only used filtration leucapheresis (Winston 1980). Methods of collection have developed considerably since these publications. Filtration leucapheresis is rarely used now, as despite possibly higher yields compared to continuous flow centrifugation, there are concerns about toxicity to the donor and recipient, in addition to evidence of poor increments and functionality of transfused granulocytes.

Premedication of donors

Four studies did not administer any form of medication to the donors to increase the granulocyte yield (Clift 1978; Petersen 1987; Strauss 1981; Winston 1980).

Five studies gave donors steroids, either dexamethasone, hydrocortisone or prednisolone (Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Schiffer 1979; Sutton 1982).

Two studies gave donors G-CSF (Oza 2006; Vij 2003).

Donor selection

Human leucocyte (HLA)-matched and ABO matched the granulocyte donor in two studies (Oza 2006; Vij 2003); one study ensured that donor and recipient were HLA and ABO compatible (Mannoni 1979). One study stated that family members were used as granulocyte donors and the HLA-matched sibling donor was used whenever possible (Petersen 1987).

Two studies used serological compatibility based upon leucocyte crossmatch (rather than HLA matching) (Clift 1978; Gomez-Villagran 1984), in which donor leucocytes were crossmatched against recipient serum/plasma by lymphocytotoxic (LCT) techniques prior to transfusion, and donors were ABO and Rh compatible.

Four studies did not HLA-match the granulocyte donor (Ford 1982; Schiffer 1979; Strauss 1981; Winston 1980). Schiffer 1979 discontinued unmatched transfusions if transfusion reactions or refractoriness to platelet transfusions occurred, at which point HLA-matched donors were used if available. One study did not report whether any assessment of leucocyte compatibility was assessed (Sutton 1982).

Co-interventions and/or alternative interventions

Differences between the studies were also identified in the co-interventions provided to participants. Specifically, this would include the diagnostic and therapeutic options available for anti-microbial practice.

One study (Petersen 1987) had an important difference in that there was an alternative intervention. Petersen 1987 randomised participants between two study arms. One arm received prophylactic granulocyte transfusions, the other arm received prophylac-

tic broad-spectrum antibiotics (vancomycin 2 g/24 hours, ticarcillin 300 mg/kg/24 hours (cefotaxime if allergic) and tobramycin 5 mg/kg/24 hours) (Petersen 1987).

Four studies gave prophylactic antibiotics to all participants (Ford 1982; Gomez-Villagran 1984; Schiffer 1979; Winston 1980). Three studies did not give prophylactic antibiotics (Mannoni 1979; Oza 2006; Strauss 1981). Three studies did not report whether prophylactic antibiotics were given (Clift 1978; Sutton 1982; Vij 2003).

Five studies defined the empirical antibiotic treatment to be given if a patient had a febrile episode (Ford 1982; Gomez-Villagran 1984; Oza 2006; Strauss 1981; Winston 1980). Five studies did not specify the antibiotics to be given (Clift 1978; Mannoni 1979; Schiffer 1979; Sutton 1982; Vij 2003).

Six studies gave therapeutic granulocyte transfusions to control participants (Clift 1978; Mannoni 1979; Petersen 1987; Strauss 1981; Sutton 1982; Winston 1980). Two studies did not give therapeutic granulocyte transfusions to control participants (Ford 1982; Gomez-Villagran 1984). Three studies did not report whether therapeutic granulocyte transfusions were given (Oza 2006; Schiffer 1979).

Specific regimens for antifungal diagnosis and therapy were not stated in any trial except for Oza 2006 who stated that Amphotericin B was used as therapy and Winston 1980 who stated that people remaining febrile for seven days and people with surveillance cultures that were positive for *Candida* or *Aspergillus* were eligible to receive amphotericin. Amphotericin B was the most widely used antifungal agent at the time of the other included studies.

Funding Sources

Six studies reported their funding sources, and all were funded by charities or governments (Clift 1978; Ford 1982; Petersen 1987; Strauss 1981; Sutton 1982; Winston 1980).

Definition of infection (used to recruit uninfected people or identify those who became infected)

Studies also applied different criteria for definition of infection although defined in all studies on the basis of temperature, clinical signs and isolation of organisms.

Seven studies stated that patients with infections were excluded from the studies (Ford 1982; Gomez-Villagran 1984; Mannoni

1979; Petersen 1987; Schiffer 1979; Strauss 1981; Winston 1980); the specific exclusion definitions varied (See [Characteristics of included studies](#)).

Four studies did not specifically state whether infected patients were excluded from the studies (Clift 1978; Oza 2006; Sutton 1982; Vij 2003), and in the Clift 1978 study it is clear in the analysis that some patients were on systemic antibiotics at enrolment.

Outcomes

Although few studies examined exactly the same range of outcomes, most trials reported mortality and survival (at different time points), information on fever (or days with fever), and information on episodes of infection (however defined), together with a measure of antibiotic use. (See [Characteristics of included studies](#)).

Excluded studies

Twenty-three studies within 27 citations did not meet the inclusion criteria for this review (See [Characteristics of excluded studies](#)).

- Twelve studies were excluded because they evaluated the therapeutic use of granulocyte transfusions (Alavi 1977; Bow 1984; DRKS00000218; Herzig 1977; Higby 1975; Klastersky 2001; Price 2014; Scali 1978; Seidel 2008; Vogler 1977; Wheeler 1987; Winston 1982)
- Two studies evaluated the prophylactic use of granulocyte transfusions in neonates (Baley 1987; Christensen 1982)
- Two studies compared two different types of granulocyte transfusions (Ambinder 1981; Freireich 2013)
- Five studies were not randomised (Altrichter 2011; Atay 2011; Ikemoto 2012; NCT01932710; UMIN000014777)
- One study included both randomised and allocated people, and the results of the study did not separate out these categories of enrolled participants. (Buckner 1983)
- One article study was a review (Pammi 2011)

Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#) for visual representations of the assessments of risk of bias across all studies and for each item in the included studies. See the [Characteristics of included studies](#) section 'Risk of bias' table for further information about the bias identified within the individual studies.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

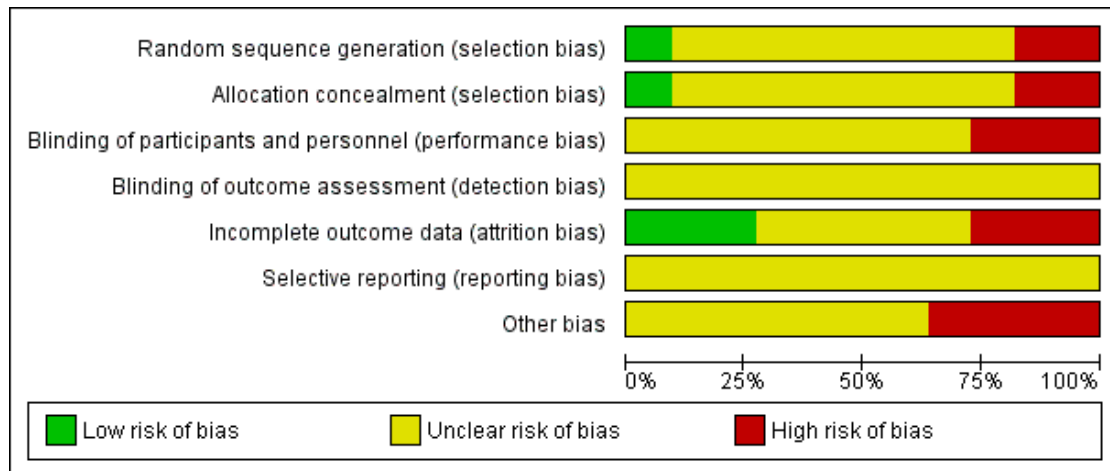


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	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
Clift 1978	?	?	?	?	-	?	?
Ford 1982	?	?	-	?	-	?	?
Gomez-Villagran 1984	?	?	-	?	+	?	?
Mannoni 1979	?	?	-	?	?	?	-
Oza 2006	-	-	?	?	?	?	-
Petersen 1987	?	?	?	?	-	?	-
Schiffer 1979	?	?	?	?	?	?	?
Strauss 1981	+	+	?	?	?	?	?
Sutton 1982	?	?	?	?	+	?	?
Vij 2003	-	-	?	?	?	?	-
Winston 1980	?	?	?	?	+	?	?

Although nine of the 11 included studies were RCTs (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980), many of the studies had some threats to validity. The majority of these potential risks were due to a lack of detail on the specific criteria and were judged as “unclear risk” according to the Cochrane grading system. Two studies were quasi-randomised studies that allocated participants to the intervention arm if they had a suitable donor (Oza 2006; Vij 2003).

Allocation

We considered two studies to be at high risk of selection bias (Oza 2006; Vij 2003). In Oza 2006 and Vij 2003 the recipient was “randomised” to the prophylactic granulocyte group if the donor who donated stem cells for the transplant was ABO-matched and able to donate. Eight studies were at an unclear risk of bias because they did not report the methods of sequence generation or allocation concealment (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Petersen 1987; Schiffer 1979; Sutton 1982; Winston 1980). We considered one study (Strauss 1981) to be at low risk of selection bias because it reported that separate randomisation schedules were prepared for each institute and stratum. An algorithm that ensured an approximate balance between treatment groups was used to generate each schedule. Participants were randomly assigned to receive daily granulocyte transfusions or not to receive them by a telephone call to the co-ordinating centre.

Blinding

None of the studies provided any details on whether participants, investigators or outcome assessors were blinded to the intervention. For all subjective outcomes (all secondary outcomes of this review), we considered three studies to be at high risk of bias because they noted that the participants receiving prophylactic granulocyte transfusions did not require prophylactic platelet transfusions because of the number of platelets contained within the granulocyte transfusion (Ford 1982; Gomez-Villagran 1984; Mannoni 1979). Investigators would have been able to identify which participants were receiving prophylactic granulocyte transfusion even if they had been blinded to the intervention. We considered the other eight studies to be at an unclear risk of bias (Clift 1978; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Vij 2003; Winston 1980).

Incomplete outcome data

We considered three studies to be at high risk of attrition bias due to the large number of participants who were randomised but not included in the final analysis (Clift 1978; Ford 1982; Petersen

1987). Between 16% (Petersen 1987) and 50% (Ford 1982) of participants were randomised but not included within the analysis. In Clift 1978 and Petersen 1987 there was also a significant imbalance between the number of participants randomised and included within the study between those participants in the prophylactic granulocyte transfusion group and those in the control group.

Selective reporting

We could not assess this for any of the studies because protocols were not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified. We therefore classified all studies as at unclear risk of bias.

Other potential sources of bias

One study publication (Vij 2003) was classified as an “advertisement” in accordance with 18 USC section 1734 because the publication costs of the article were defrayed in part by part charge payment, this study was classified as high risk because of this.

We classified the Mannoni 1979 study at high risk of bias because six participants had been re-randomised within the study. We classified the Oza 2006 study at high risk of bias because people who were cytomegalovirus (CMV) mis-matched with their donor were excluded from being in the prophylactic granulocyte transfusion group. This mis-match may have increased the risk of CMV viraemia within the control group. We classified the Petersen 1987 study at high risk of bias because of the number of deviations from the original study design in the prophylactic granulocyte arm of the study.

The small numbers of participants in all the studies compromised the likelihood that there was equivalence in baseline and prognostic parameters. We therefore classified the seven other studies at unclear risk of bias (Clift 1978; Ford 1982; Gomez-Villagran 1984; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980).

Effects of interventions

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

See [Summary of findings for the main comparison](#).

The Vij 2003 study reported none of the outcomes pre-specified in our review. We contacted the study authors who were unable to provide any additional data not reported in the original paper. Therefore, data were available for only 10 of the 11 included studies (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980).

All-cause mortality (10 studies)

All-cause mortality was reported by 10 studies (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980) (Table 2). The time points for assessment of mortality varied between studies. Eight studies reported mortality up to 30 days (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Oza 2006; Schiffer 1979; Strauss 1981; Winston 1980); one study reported mortality up to 100 days (Petersen 1987); and one study reported mortality over 100 days (Sutton 1982).

The Mannoni 1979 study re-randomised six participants and the information was therefore not included within the meta-analysis. Information on overall mortality was available and extracted from nine studies (Clift 1978; Ford 1982; Gomez-Villagran 1984; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980).

Seven studies (437 participants) reported mortality up to 30 days (Clift 1978; Ford 1982; Gomez-Villagran 1984; Oza 2006; Schiffer 1979; Strauss 1981; Winston 1980). A meta-analysis showed no difference between participants receiving prophylactic granulocyte transfusions and those that did not (risk ratio (RR) 0.92; 95% confidence interval (CI) 0.63 to 1.36) (Analysis 1.1), nor was any difference seen if only studies that gave a median granulocyte dose of over $1 \times 10^{10}/L$ per day were included (four studies (Clift 1978; Gomez-Villagran 1984; Oza 2006; Winston 1980); 293 participants; RR 0.74; 95% CI 0.47 to 1.16) (Analysis 1.1).

One study reported all-cause mortality up to 100 days (Petersen 1987). There was no difference in all-cause mortality between participants receiving prophylactic granulocyte transfusions and those that did not (112 participants; RR 1.28; 95% CI 0.69 to 2.39) (Analysis 1.2).

One study reported all-cause mortality over 100 days (Sutton 1982). There was no difference in all-cause mortality between participants receiving prophylactic granulocyte transfusions and those that did not (65 participants; RR 0.94; 95% CI 0.67 to 1.33) (Analysis 1.3).

Mortality due to infection (eight studies)

Mortality due to infection was reported by eight studies (Clift 1978; Gomez-Villagran 1984; Mannoni 1979; Oza 2006; Petersen 1987; Strauss 1981; Sutton 1982; Winston 1980) (Table 3). The Mannoni 1979 study re-randomised six participants and the information was therefore not included within the meta-analysis.

Six studies (286 participants) reported mortality due to infection up to 30 days (Clift 1978; Gomez-Villagran 1984; Oza 2006; Schiffer 1979; Strauss 1981; Winston 1980). A meta-analysis showed no difference between participants receiving prophylactic granulocyte transfusions and those that did not (RR 0.69; 95% CI 0.33 to 1.44) (Analysis 1.4), nor was any difference seen if only studies that gave a median granulocyte dose of over $1 \times 10^{10}/L$ per day were included (three studies (Clift 1978; Gomez-Villagran

1984; Winston 1980); 142 participants; RR 0.25; 95% CI 0.06 to 1.10) (Analysis 1.4).

One study reported mortality due to infection up to 100 days (Petersen 1987). There was no difference in mortality due to infection between participants receiving prophylactic granulocyte transfusions and those that did not (112 participants; RR 1.01; 95% CI 0.18 to 5.79) (Analysis 1.5).

Number of infection episodes (10 studies)

The numbers of localised or systemic bacterial or fungal infections were reported by 10 studies. (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980) (Table 4). The Mannoni 1979 study re-randomised six participants and the information was therefore not included within the meta-analysis.

Nine studies (609 participants) reported localised or systemic infections up to 30 days (Clift 1978; Gomez-Villagran 1984; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980). A meta-analysis showed that there were significant differences between the granulocyte dose subgroups (test for subgroup differences: $\chi^2 = 8.54$, $df = 2$ ($P = 0.01$), $I^2 = 76.6\%$) (Analysis 1.6). We therefore did not perform an overall analysis.

In the intermediate granulocyte dose group, participants receiving prophylactic granulocyte transfusions had fewer infections (four studies (Clift 1978; Gomez-Villagran 1984; Oza 2006; Winston 1980); 293 participants; RR 0.40; 95% CI 0.26 to 0.63) (Analysis 1.6). In the low-dose subgroup no difference was seen between those participants who received prophylactic granulocytes and those that did not (four studies (Ford 1982; Schiffer 1979; Strauss 1981; Sutton 1982); 204 participants; RR 0.84; 95% CI 0.58 to 1.20) (Analysis 1.6).

As there was clinical heterogeneity between studies in the types of infections reported, we performed separate meta-analyses for systemic infections (bacteraemia and fungaemia) and localised infections (bacterial or fungal infections excluding oral candidaemia). Nine studies (609 participants) reported systemic infections (Clift 1978; Ford 1982; Gomez-Villagran 1984; Oza 2006; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980). A meta-analysis showed that overall, there was a reduction in the number of bacteraemias and fungaemias in the participants receiving granulocyte transfusions (RR 0.45; 95% CI 0.30 to 0.65) (Analysis 1.7); this effect was most marked in those studies giving an intermediate dose of granulocytes (four studies (Clift 1978; Gomez-Villagran 1984; Oza 2006; Winston 1980); 293 participants; RR 0.28; 95% CI 0.14 to 0.55) (Analysis 1.7).

Excluding the data for the study that compared prophylactic granulocyte transfusions versus prophylactic antibiotics from the analysis had no effect on the overall result (Petersen 1987), (RR 0.37; 95% CI 0.23 to 0.59) (Analysis 1.8).

Six studies (296 participants) reported localised infections (Clift

1978; Ford 1982; Gomez-Villagran 1984; Petersen 1987; Schiffer 1979; Winston 1980). A meta-analysis showed that overall, there was no difference in the number of localised infections between participants receiving prophylactic granulocyte transfusions and those that did not (RR 0.75; 95% CI 0.50 to 1.14) (Analysis 1.9). There was also no difference seen when only those studies giving an intermediate dose of granulocytes were included in the analysis (three studies (Clift 1978; Gomez-Villagran 1984; Winston 1980); 142 participants; RR 0.71; 95% CI 0.38 to 1.31) (Analysis 1.9).

Excluding the data for the study that compared prophylactic granulocyte transfusions versus prophylactic antibiotics from the analysis had no effect on the overall result (Petersen 1987), (RR 0.62; 95% CI 0.37 to 1.02) (Analysis 1.10).

Number of days with fever (five studies)

Five studies reported the number of days with fever (Ford 1982; Gomez-Villagran 1984; Oza 2006; Schiffer 1979; Winston 1980). These data were reported in different ways and could not be incorporated in to a meta-analysis (Table 5). There was no obvious trend in the number of days with fever between studies.

Number of days on treatment with antimicrobials (courses of treatment with antibiotics/antifungals) (five studies)

Five studies reported the number of days on treatment with antibiotics (Ford 1982; Gomez-Villagran 1984; Oza 2006; Schiffer 1979; Winston 1980). these data were reported in different ways and could not be incorporated in to a meta-analysis (Table 5). Three of the five studies showed a slightly lower number of days on antibiotics in the prophylactic granulocyte arm of the study (Ford 1982; Gomez-Villagran 1984; Oza 2006); one study showed no difference (Schiffer 1979); and one study showed an increased number of days on antibiotics (Winston 1980).

Increment of neutrophil count ($\times 10^9/L$) (six studies)

Neutrophil increments were reported as an absolute rise in the peripheral blood neutrophil count, known as the count increment, or as a corrected count increment see Table 6. The data could not be incorporated in to a meta-analysis because of the different ways the data had been reported.

Six studies report the count increment or corrected count increment (Clift 1978; Ford 1982; Gomez-Villagran 1984; Mannoni 1979; Schiffer 1979; Winston 1980). Two studies reported the count increment, and it varied from a median of $< 0.15 \times 10^9/L$ to $0.32 \times 10^9/L$ (Ford 1982; Schiffer 1979). Four studies reported the corrected count increment (Clift 1978; Gomez-Villagran 1984; Mannoni 1979; Winston 1980), and it varied from a median of $0.06 \times 10^9/L$ (Clift 1978) to a mean of $0.5 \times 10^9/L$ (Gomez-Villagran 1984).

Duration of neutropenia reversal after transfusion (neutropenia defined as count below $0.5 \times 10^9/L$)

None of the studies reported the duration of neutropenia reversal after transfusion.

Serious adverse events: resulting in death, requiring or prolonging hospitalisation, resulting in persistent or significant disability/incapacity, or life-threatening (four studies)

Serious adverse events were reported by four studies (Table 7). One study reported a donor event (Clift 1978), and three studies reported recipient events (Ford 1982; Gomez-Villagran 1984; Sutton 1982).

Clift 1978 described an episode of haemodynamic compromise due to loss of blood after a section of tubing was accidentally disconnected.

Ford 1982 described one death due to transfusion-associated graft versus host disease in a participant who had received 10 granulocyte transfusions that had not been irradiated from related donors. Gomez-Villagran 1984 described one case of haemolysis due to passive transfer of anti-A, and six pulmonary reactions (dyspnoea, cyanosis, but no pulmonary infiltrates on chest X-ray).

Sutton 1982 described severe dyspnoea and wheezing in three participants.

Adverse events requiring discontinuation of intervention (six studies)

Adverse events requiring discontinuation of the granulocyte transfusions were reported for six studies (Clift 1978; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980) (See Table 8). Two studies reported donor events (Clift 1978; Petersen 1987) and six studies reported recipient events (Clift 1978; Petersen 1987; Schiffer 1979; Strauss 1981; Sutton 1982; Winston 1980).

DISCUSSION

Summary of main results

This Cochrane review aimed to evaluate the literature on the effectiveness and safety of prophylactic granulocyte transfusions. This review should be read in conjunction with another review undertaken to evaluate the randomised trial evidence base for the use of therapeutic granulocyte transfusions (Stanworth 2005).

We identified 12 randomised and quasi-randomised trials that met our inclusion criteria; one of which is still ongoing (

[NCT01204788](#)). Eleven trials were included in this review containing a total of 653 participants. These trials were conducted between 1978 and 2006 and enrolled participants from fairly comparable patient populations. None of the studies included people with neutrophil dysfunction. Ten of these studies contained separate data for each arm and were able to be critically appraised. One study re-randomised participants and therefore quantitative analysis was unable to be performed.

The findings of the review led to the following main conclusions.

- There was insufficient evidence to detect a difference in all-cause mortality between people receiving prophylactic granulocyte transfusions and those that did not. This was measured over 30 days in seven studies (437 participants; RR 0.92, 95% CI 0.63 to 1.36).
- There was insufficient evidence to detect a difference in mortality due to infection between people receiving prophylactic granulocyte transfusions and those that did not. This was measured over 30 days in six studies (286 participants; RR 0.69, 95% CI 0.33 to 1.44).
- There were differences between the granulocyte dose subgroups (test for subgroup differences $P = 0.01$) in the number of people with localised or systemic bacterial or fungal infections. There was no difference in the number of people with infections in the low-dose granulocyte group ($< 1.0 \times 10^{10}$ granulocytes per day) between people receiving prophylactic granulocyte transfusions and those that did not (four studies, 204 participants; RR 0.84, 95% CI 0.58 to 1.20). There was a decreased number of people with infections over 30 days in the people receiving prophylactic granulocyte transfusions in the intermediate-dose granulocyte group (1.0×10^{10} to 4.0×10^{10} granulocytes per day) (4 studies; 293 participants; RR 0.4, 95% CI 0.26 to 0.63). There was a decreased number of people with bacteraemia and fungaemia in the people receiving prophylactic granulocyte transfusions (nine studies; 609 participants; RR 0.45, 95% CI 0.30 to 0.65). There was no difference in the number of people with localised bacterial or fungal infection in the people receiving prophylactic granulocyte transfusions (six studies; 296 participants; RR 0.75, 95% CI 0.50 to 1.14).
- There was insufficient evidence to detect a difference in the number of serious adverse events between people receiving prophylactic granulocyte transfusions and those that did not. This was because serious adverse events were only reported for people receiving granulocyte transfusions and donors of granulocyte transfusions.
- There was no obvious trend in the number of days with fever, or number of days with antibiotics between people receiving prophylactic granulocyte transfusions and those that did not.
- None of the studies reported the duration of neutropenia reversal.

Overall completeness and applicability of evidence

This review provides the most up-to-date assessment of the effectiveness and safety of a prophylactic granulocyte transfusion policy compared with not administering prophylactic granulocyte transfusions. This updated review identified one additional quasi-randomised trial ([Vij 2003](#)). This review provides some low-quality evidence that prophylactic granulocytes decrease the risk of developing a bacterial or fungal infection.

However, the results of this review should not be interpreted without considering the impact of the following factors.

- The studies included in this review range over a 28-year period (1978 to 2006) during which chemotherapy protocols, predicted survival rates, supportive care, including antibiotics and antifungal medication, have changed substantially. Newer less toxic antifungal drug options are now available.
- None of the studies reported on quality control measures operating for blood components, including granulocytes, and current blood components may be manufactured to a higher specification than in the time period of these studies.
- Only two of the studies gave granulocyte colony-stimulating factor (G-CSF) to the granulocyte donors ([Oza 2006](#); [Vij 2003](#)).
- None of the studies assessed the use of granulocytes derived from whole blood donations ([Bashir 2008](#)). This component has been assessed in a small safety study ([Massey 2012](#)). The process of obtaining granulocyte collections from directed G-CSF and/or steroid-stimulated donors who are 'family and friends' of patients or unrelated donors involves multiple steps. It is important that family and 'friends' of patients are given time and adequate explanation of the small risks to which they are exposed by both taking specific drugs (steroids or G-CSF, or both) to mobilise granulocytes into the peripheral blood and by undergoing an apheresis procedure. To date, most of these risks have been theoretical or weak associations only but posterior capsular cataracts, splenic rupture and venous thrombosis have been described ([Bennett 2006](#); [Ghodsi 2001](#); [Goldman 2006](#); [Gutierrez 2001](#)). There are also a number of potentially important constraints that can limit provision of apheresis products on a regular and timely basis; e.g. hospitals in Europe managing granulocyte collections by apheresis now have a requirement for meeting 'blood establishment status' according to EU legislation.
- One study ([Petersen 1987](#)), compared prophylactic granulocyte transfusions with prophylactic broad-spectrum antibiotics. Data from this study were only incorporated into meta-analyses for two outcomes, people with bacteraemia or fungaemia and people with localised bacterial or fungal infection. There was no significant difference to the overall analysis when results from this study were excluded.
- Not all end points from the studies could be analysed due to varying methods of reporting the outcomes. This was true for: numbers of days with fever; number of days on treatment with

antimicrobials (or courses of treatment with antibiotics/ antifungals); and increment of neutrophil count ($\times 10^9/L$).

- In three of the studies many of the participants enrolled were not included in the final analysis (Clift 1978; Ford 1982; Petersen 1987). Between 16% (Petersen 1987) and 50% (Ford 1982) of participants were randomised but not included within the analysis.

Quality of the evidence

Overall, the quality of the evidence was rated as very low to low across different outcomes according to GRADE methodology (Summary of findings for the main comparison). This was due to many of the studies being at high risk of bias, and many of the outcome estimates being imprecise.

Two outcomes were considered low-grade quality evidence according to GRADE methodology due to the very serious risk of bias of the included studies.

- People with localised or systemic bacterial or fungal infections - Intermediate-dose granulocyte transfusions.
- People with bacteraemia or fungaemia.

This was because of: a high risk of selection bias because two studies were quasi-randomised; a high risk of attrition bias because three studies did not include a significant proportion of randomised people in the analysis; and a high risk of performance bias and detection bias due to the nature of the intervention (granulocyte transfusion) and difficulty blinding participants, physicians and outcome assessors.

Four outcomes were considered very low-grade quality evidence according to GRADE methodology due to the very serious risk of bias of the included studies (see above) and the serious imprecision of the estimates.

- All-cause mortality.
- Mortality due to infection.
- People with localised or systemic bacterial or fungal infections - low-dose granulocyte transfusions.
- People with localised bacterial or fungal infection.

The reason for the imprecision is because of the small number of participants within the trials and the low number of events. For example, if we assume an all-cause mortality rate of 14.5% (overall rate within the included studies within this review up to 30 days), we need a sample size of approximately 15,000 participants to be able to detect with 90% power the ability to save two extra lives per 100 people within a 30-day period.

See Figure 2 and Figure 3 for visual representations of the assessments of risk of bias across all studies and for each item in the individual studies.

Potential biases in the review process

To our knowledge, our review process is free from bias. We conducted a comprehensive search; searching data sources (including multiple databases, and clinical trial registries) to ensure that all relevant trials would be captured. There were no restrictions for the language in which the paper was originally published. The relevance of each paper was carefully assessed and all screening and data extractions were performed in duplicate. We pre-specified all outcomes and subgroups prior to analysis. There were insufficient numbers of included studies within the meta-analyses for us to use a funnel plot to examine the risk of publication bias.

Agreements and disagreements with other studies or reviews

We know of no other recent systematic reviews on the use of prophylactic granulocyte transfusions in people with neutropenia or neutrophil dysfunction. The last review on this subject was the previous version of this review (Massey 2009). Although the methodology of the review has changed in this update of the review to conform to current Cochrane Collaboration recommendations, the overall message of the review is unaltered.

AUTHORS' CONCLUSIONS

Implications for practice

The review has identified low-quality evidence that prophylactic granulocyte transfusion lead to a reduction in the number of people developing a bacterial or fungal infection, especially if the dose is at least 1.0×10^{10} per day. It would however, be premature to conclude that the use of granulocytes as prophylaxis in people with neutropenia would improve outcomes and prove cost-effective as the potential harms of the intervention could not be fully assessed. Supportive therapy in this setting has changed since most of the reviewed studies were performed. None of the studies in this review specifically evaluated people with congenital disorders of neutrophil function or production. None of the studies in this review assessed the use of blood product-derived granulocytes. In keeping with the conclusions from the systematic review of the use of granulocyte transfusions for therapeutic indications, the use of granulocyte transfusions should still be regarded as investigational and should ideally be conducted in the context of ongoing prospective trials designed to answer the question of effectiveness.

Implications for research

Contemporary well-designed prospective trials of sufficient power are required to evaluate the effectiveness of granulocyte transfusions as prophylaxis. The design of trials needs to consider multiple factors. Most importantly, the power calculations should be based upon the outcome measures currently encountered with standard

therapy in the population selected. If mortality rate is to be used as an outcome measure that may be improved by granulocyte transfusion then populations with a higher mortality rate may be more amenable to show evidence of benefit.

All systematic reviews performed to date have suggested that the dose transfused is important although the exact minimal effective dose remains uncertain. Such a dose could be consistently obtained by secondary processing of “buffy coat” granulocytes or by administering G-CSF and steroids to ABO-compatible apheresis donors. The schedule for administration of granulocyte transfusions in the identified studies varied considerably, and would need to be standardised. However, the frequency of transfusion is to a major part also governed by logistical issues and therefore it is likely that the schedule will continue to be dictated by availability of donors and facilities.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Clift 1978

Methods	Parallel RCT (conducted from February 1974 to September 1977). Single centre. Country: USA
Participants	<p>Inclusion criteria: Adults and children with acute leukaemia and aplastic anaemia undergoing related HLA-matched allogeneic haematopoietic stem cell transplantation</p> <p>Exclusion criteria: Infection criteria for excluding people from the study was not reported</p> <p>Total randomised N = 86</p> <p>Total analysed N = 69</p> <p>Arm 1 (Granulocyte transfusions): randomised = 41, analysed = 29 ; Acute leukaemia = 17, Aplastic anaemia = 12</p> <p>Arm 2 (Control): randomised = 45, analysed = 40: Acute leukaemia = 27 , Aplastic anaemia = 13</p>
Interventions	<p>Comparison between standard treatment and prophylactic granulocyte transfusions</p> <p>Granulocyte dose: mean 2.22×10^{10} (leucofiltration) 1.57×10^{10} (centrifugation)</p> <p>Granulocyte method of collection: by either continuous flow centrifugation or reversible leukoadhesion to nylon columns</p> <p>Donor premedication: None</p> <p>Initiation of granulocyte transfusions: 1st post-transplant day neutrophil count $\leq 0.2 \times 10^9/L$</p> <p>Frequency of granulocyte transfusions: Daily</p> <p>Termination of granulocyte transfusions: Neutrophil count $> 0.2 \times 10^9/L$ [not clearly stated]</p>
Outcomes	<p>Primary Outcome: The effectiveness of granulocytes in reducing the acquisition of bacterial or fungal infection during the first 21 post-transplant days</p> <p>Secondary Outcomes:</p> <p>Mortality/survival, fever (days or episodes), infection (days or episodes), antibiotic use, adverse events</p>
Definition of infection	<p>Febrile day - two temperatures greater than $38.3^\circ C$ in 24 hours.</p> <p>Febrile episode - not defined</p> <p>Proven infection: subdivided in to:-</p> <p>Septicaemia - at least one positive blood culture with appropriate symptoms, or two consecutive blood cultures growing the same organism (daily surveillance blood cultures were performed)</p> <p>Local infection - lesions with symptoms or signs of infection and isolation of causative bacterial or fungal organisms</p>
Definition of neutropenia	Not reported but the 'trigger' neutrophil count was $0.2 \times 10^9/L$

Co-interventions	Prophylactic antibiotics: not reported Therapeutic antibiotics: no restrictions on type of systemic antibiotic treatment given Therapeutic granulocyte transfusions: participants in the control group were eligible for granulocyte transfusions as clinically indicated for the treatment of established infection	
Notes	Funding Sources: Grants CA18579, CA18029, CA17117 and CA15704 from the National Cancer Institute. Dr Thomas is the recipient of a research career award (AI 02425) from the National Institute for Allergy and Infectious Diseases Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether participants were blinded to the intervention. It was not reported whether clinicians or investigators were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 40 of the 45 participants randomised to the control group were included in the analysis. Only 29 of the 41 participants randomised to the intervention group were included in the analysis Five randomised participants were not included in the control group: <ul style="list-style-type: none">• One patient was not eligible for treatment with the marrow transplantation protocol• Three participants could not be evaluated because the decision was made to transplant them elsewhere• One patient died of cardiac failure on the 11th day after transplantation. This patient was not receiving antibiotics before the first day but antibiotics were initiated on the second day because of

Clift 1978 (Continued)

		<p>fever without documented infection. There was no autopsy evidence of an infective process</p> <p>Twelve randomised participants were not included in the intervention group:</p> <ul style="list-style-type: none"> • Three participants were withdrawn because the potential granulocyte donors were unacceptable for medical reasons • Three participants the granulocyte transfusions were abandoned because of donor complications • Three participants the granulocyte transfusions were abandoned because their HLA-matched granulocyte donors were the only source of effective platelets and granulocyte collections were jeopardising the recipients' platelet support • One participant did not receive a transplant in accordance with the protocol • One participant died on the 10th post-transplant day after receiving nine daily granulocyte transfusions • One participant reason not given
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	Unclear risk	Although none identified, it is difficult to rule out any significant bias due to insufficient reporting of the study. More control participants had relapsed disease (16/40 compared to 8/29)

Ford 1982

Methods	Parallel RCT (recruitment period not reported). Single centre. Country: England
Participants	<p>Inclusion criteria: People over 15 years old with acute myeloid leukaemia undergoing induction chemotherapy</p> <p>Exclusion criteria: "afebrile, free of infection and not receiving antibiotics". Microbiological proof of absence of infection was required prior to commencing granulocyte transfusion therapy</p> <p>Total randomised: N = 49</p> <p>Total analysed: N = 24</p> <p>Arm 1 (Granulocyte transfusions): randomised = 26, analysed = 13 with acute myeloid leukaemia</p>

	Arm 2 (Control): randomised = 23 , analysed = 11 with acute myeloid leukaemia	
Interventions	Comparison between standard treatment and prophylactic granulocyte transfusions Granulocyte dose: 1.45 x 10 ¹⁰ (0.28 to 3.45) Granulocyte method of collection: intermittent flow centrifugation Donor premedication: dexamethasone Initiation of granulocyte transfusions: Day after the neutrophil count < 0.5 x 10 ⁹ /L Frequency of granulocyte transfusions: Alternate days Termination of granulocyte transfusions: Neutrophil count > 0.5 x 10 ⁹ /L	
Outcomes	Primary Outcome: Not reported Other Outcomes: Mortality/survival, fever (days or episodes), infection (days or episodes), antibiotic use, adverse events	
Definition of infection	Febrile day - two temperatures greater than 38.0°C in 24 hours. Febrile episode - a temperature greater than or equal to 38°C for greater than or equal to 4 hours in the absence of blood transfusion Proven infection - a causative organism was cultured either from blood or infected site or there were clinical signs strongly suggestive of infection or pneumonia was identified by chest X-ray changes and clinical signs or symptoms	
Definition of neutropenia	Not reported but the 'trigger' neutrophil count was 0.5 x 10 ⁹ /L	
Co-interventions	Prophylactic antibiotics: all participants received oral, non-absorbable antibiotics (Storring 1977). Therapeutic antibiotics: if a fever occurred lasting more than 4 hours intravenous tobramycin and carbenicillin (or flucloxacillin for identified skin sepsis) were administered Therapeutic granulocyte transfusions: not given to control participants	
Notes	Funding Sources: Imperial Cancer Research Fund, Department of Medical Oncology and Department of Haematology, St Bertholomew Hospital, London Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not reported whether participants were blinded to the intervention If participants received granulocyte transfusions, "patients needed no platelet sup-

Ford 1982 (Continued)

		port because of the coincidentally transfused platelets". Clinicians and investigators would therefore be able to tell whether patients were receiving granulocyte transfusions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	49 participants were randomised, of whom 26 received granulocyte transfusions 25 of the 49 participants were excluded from the analysis because they did not meet the criteria for study entry <ul style="list-style-type: none"> • 12 participants were randomised but excluded from the study because fever or infection developed either before their neutrophil count fell below 0.5 (eight participants) or before the first granulocyte transfusion (4 participants) • 13 participants were randomised but excluded, the specific reason for not meeting the study criteria was not reported
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	Unclear risk	Although none identified, it is difficult to rule out any significant bias due to insufficient reporting of the study

Gomez-Villagran 1984

Methods	Parallel RCT (conducted from January 1981 to June 1982). Single centre. Country Spain
Participants	<p>Inclusion criteria: Adults and children with acute myeloid leukaemia (AML) undergoing induction chemotherapy</p> <p>Exclusion criteria: had to have no evidence of infection or fever</p> <p>Total randomised: N = 35</p> <p>Total analysed: N = 35</p> <p>Arm 1 (Granulocyte transfusions): N = 19; Acute myeloid leukaemia = 19</p> <p>Arm 2 (Control): N = 16, Acute myeloid leukaemia = 16</p>

Interventions	Comparison between standard treatment and prophylactic granulocyte transfusions Granulocyte dose: 1.24 x 10 ¹⁰ (0.55 to 4.2) Granulocyte method of collection: intermittent flow centrifugation Donor premedication: dexamethasone Initiation of granulocyte transfusions: Neutrophil count < 0.5 x 10 ⁹ /L Frequency of granulocyte transfusions: Daily Termination of granulocyte transfusions: Until <ul style="list-style-type: none">○ The neutrophil count was greater than 0.5 x 10⁹/L, or○ 21 days of granulocyte transfusion had been given.○ There were no donors available or○ There were “other signs of bone marrow recovery”	
Outcomes	Primary Outcome: Not reported Other Outcomes: Mortality/survival, fever (days or episodes), infection (days or episodes), antibiotic use, adverse events	
Definition of infection	Febrile day: Not reported Febrile episode: Temperature ≥ 38°C in the absence of a recent blood product transfusion Proven infection: Not reported	
Definition of neutropenia	Not reported but the 'trigger' neutrophil count was 0.5 x 10 ⁹ /L	
Co-interventions	Prophylactic antibiotics: oral non-absorbable drugs neomycin, colimycin and nystatin Therapeutic antibiotics: cephalosporin, tobramycin and carbenicillin as empirical treatment of infection Therapeutic granulocyte transfusions: participants in the control group were not eligible for granulocyte transfusions during the on-study period (21 days), even if a documented infection developed	
Notes	Funding Sources: Not reported Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not reported whether participants were blinded to the intervention “The patients under prophylactic transfusions did not require isolated platelet trans-

		fusions during pancytopenic episodes because of the high contaminating level of platelets in the granulocyte concentrate” Therefore medical staff would have been aware of whether patients were in the intervention arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants either died or remission status was assessed after the chemotherapy
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	Unclear risk	The median age of participants was higher in the control group 35 years versus 27.5 years. Three of the participants in the control group had AML M3, and none of the participants in the intervention group had AML M3. Participants were receiving induction chemotherapy and therefore participants with AML M3 would have had a higher risk or early death due to bleeding or disseminated intravascular coagulation There were also more AML M1 cases in the transfused arm (14/19) when compared with controls (6/16)

Mannoni 1979

Methods	Parallel RCT (recruitment period not reported). Number of centres unclear. Country: France
Participants	<p>Inclusion criteria: Adults (>16 years old) with acute myeloid leukaemia receiving standardised chemotherapy inducing profound bone marrow depression</p> <p>Exclusion criteria: “not severely infected”, severe infection being defined as pulmonary or perineal localisation or diarrhoea with abdominal distension</p> <p>Total randomised: N = 44 participants and 50 episodes of aplasia</p> <p>Arm 1 (Granulocyte transfusions): randomised = 20, Acute myeloid leukaemia = 20 (22 separate episodes of aplasia)</p> <p>Arm 2 (Control): randomised = 26*, Acute myeloid leukaemia = 26 (28 separate episodes of aplasia)</p> <p>Acute leukaemia (myeloid)</p> <p>* Six participants may have been re-randomised but this is not clear in the text. Ran-</p>

	domisation occurred at the onset of 50 episodes of aplasia	
Interventions	Comparison between standard treatment and prophylactic granulocyte transfusions Granulocyte dose: 2.1 x 10 ¹⁰ (1.3 to 3.7) Granulocyte method of collection: intermittent flow centrifugation Donor premedication: dexamethasone or hydrocortisone Initiation of granulocyte transfusions: Fourth day of chemotherapy Frequency of granulocyte transfusions: Daily Termination of granulocyte transfusions: After approximately 12 days in the absence of fever or infection	
Outcomes	Primary Outcome: Not reported Other Outcomes: Mortality/survival, infection (days or episodes), adverse events	
Definition of infection	Febrile day - Not reported Febrile episode - temperature elevation alone of 38°C for at least 24 hours excluding febrile reactions to blood products or administration of chemotherapy Minor infection: Bacteraemia alone, with at least 2 positive blood cultures, or local skin or mucocutaneous infection, or in case of diarrhoea without abdominal distension Major infection: Any life-threatening infection or the associations of septicaemia and local infections were considered as major infections	
Definition of neutropenia	Neutrophils < 0.5 x 10 ⁹ /L	
Co-interventions	Prophylactic antibiotics: non absorbable antibiotics Therapeutic antibiotics: combination of two systemic antibiotics if the patient was febrile for 24 hours Therapeutic granulocyte transfusions: given to the control group if participants had a severe infection or in the case of refractoriness to antibiotics in minor infections	
Notes	Funding Sources: Not reported Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	It was not reported whether participants were blinded to the intervention In the intervention group “the number of platelets contaminating the leucocyte transfusions was usually enough to main-

		tain the platelet count" above 20. Therefore clinicians would be able to tell whether patient was receiving prophylactic granulocyte transfusions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Clinical data were collected and re-examined by two different persons who had not been in charge of the participants, in order to determine the diagnosis and severity of infection. However it was not reported whether these outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear whether any participants were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	High risk	Study funding and any conflicts of interest were not reported. Baseline characteristics of the participants were not reported It appeared that at least six participants had been re-randomised, 44 participants and 50 episodes of aplasia

Oza 2006

Methods	Biologically randomised study (recruitment period not reported). Single centre. Country: USA
Participants	<p>Inclusion criteria: People aged at least 15 years of age undergoing related HLA-matched allogeneic haematopoietic stem cell transplantation</p> <p>Exclusion criteria: infection criteria for excluding people from the study was not reported</p> <p>Total cohort N = 151</p> <p>Arm 1 (Granulocyte transfusions): Allocated and analysed N = 53 Leukemia = 38; Lymphoroliferative disorders = 15</p> <p>Arm 2 (Control): Allocated and analysed = 98; Leukaemia = 59, Lymphoroliferative disorders = 39</p> <p>Allograft BMT, acute leukaemia</p>
Interventions	<p>Comparison between standard treatment and prophylactic granulocyte transfusions</p> <p>Granulocyte dose: participants received two granulocyte transfusions. The mean dose and range were given separately for the first dose, 5.9×10^{10} (0.02 to 15.5) and the second dose 5.2×10^{10} (0.02 to 21.0)</p> <p>Granulocyte method of collection: intermittent flow centrifugation</p>

	Donor premedication: G-CSF Initiation of granulocyte transfusions: Day plus 3 or 5 (depending on protocol) Frequency of granulocyte transfusions: Twice during neutropenic interval Termination of granulocyte transfusions: Day plus 6 or 7 (depending on protocol)	
Outcomes	Primary Outcomes: The number of febrile days and days of intravenous antibiotic use during the initial transplant hospitalisation period Secondary Outcomes: Mortality/survival, fever (episodes), antibiotic use, adverse events	
Definition of infection	Febrile day - Any day during the initial hospitalisation that the recipient’s temperature was 38.3°C Febrile episode - Temperature of at least 38.3°C Proven infection: Documented bacteraemia included only culture-proven systemic blood infections for either gram-positive or gram-negative bacteria	
Definition of neutropenia	Neutrophil count < 0.5 x 10 ⁹ /L	
Co-interventions	Prophylactic antibiotics: not given Therapeutic antibiotics: IV vancomycin and imipenem as empirical treatment for infection Therapeutic granulocyte transfusions: not reported.	
Notes	Funding Sources: Not reported Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were allocated to the intervention arm dependent on ABO-matching and donor’s ability to donate granulocytes. “Donor-recipient pairs that were ABO-matched were assigned as potential candidates for Cohort G (Granulocyte transfusions), whereas those that were not ABO-matched were assigned to Cohort C (control). Donor-recipient pairs assigned as potential candidates for Cohort G remained in Cohort G if the donors also satisfied the criteria to donate granulocytes. Otherwise, these donors were reassigned to Cohort C. ABO mismatch included major (donor-recipient ABO typing of A-O, B-O, AB-O, AB-B, and AB-A, respectively) and bidirectional (donor-recipient ABO typing of A-B and B-A, respectively) mismatches.”

Allocation concealment (selection bias)	High risk	Treatment allocation was dependent on availability of an appropriate granulocyte donor
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether participants were blinded to the intervention. It was not reported whether clinicians or investigators were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear whether any participants were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	High risk	In the control group 26 participants were ABO mis-matched, 14 participants had CMV mis-match with their donors. CMV mis-match could have increased the risk of CMV infection in the recipient. 17 donors underwent more than 1 PBSC collection and were therefore not eligible as granulocyte donors

Petersen 1987

Methods	Parallel RCT (2:1 ratio) (conducted from February 1981 to March 1984). Multicentre (2 sites). Country USA
Participants	<p>Inclusion criteria: people with a haematological malignancy admitted to the Fred Hutchinson Cancer Research Center or the Swedish Hospital Medical Center for marrow transplantation from HLA-matched sibling donors</p> <p>Exclusion criteria: people on broad-spectrum antibiotics and those with a “documented major infection”</p> <p>Total randomised: N = 134</p> <p>Total analysed: N = 112</p> <p>Arm 1 (Granulocyte transfusions): randomised = 87, analysed = 67. Acute myeloid leukaemia = 32, Acute lymphocytic leukaemia = 14, Chronic myeloid leukaemia = 19, Myelodysplasia = 2</p> <p>Arm 2 (Control): randomised = 47, analysed = 45, Acute myeloid leukaemia = 15, Acute lymphocytic leukaemia = 12, Chronic myeloid leukaemia = 17, Myelodysplasia = 1</p>

Interventions	Comparison between prophylactic broad-spectrum antibiotics and prophylactic granulocyte transfusions Granulocyte dose: Not reported Granulocyte method of collection: continuous flow centrifugation Donor premedication: not reported Initiation of granulocyte transfusions: Neutrophil count < 0.2 x 10 ⁹ /L Frequency of granulocyte transfusions: Daily Termination of granulocyte transfusions: Neutrophil count “self-sustaining” > 0.2 x 10 ⁹ /L	
Outcomes	Primary Outcome: Major infectious complications occurring in patients treated in conventional rooms Other Outcomes: Mortality/survival, infection (days or episodes)	
Definition of infection	Febrile day - Not reported Febrile episode - Fever was defined as an oral temperature >38.3°C. Proven infection: Septicaemia: single positive blood culture associated with signs and symptoms of infection (documented local site and/or fever) or two consecutive positive blood cultures of the same organism Major localised infection: potentially life-threatening infection requiring systemic antibiotic therapy and/or surgical intervention	
Definition of neutropenia	Not reported but the ‘trigger’ neutrophil count was 0.2 x 10 ⁹ /L	
Co-interventions	Prophylactic antibiotics: broad-spectrum antibiotics given to the study arm not receiving prophylactic granulocyte transfusions Therapeutic antibiotics: no restrictions were imposed on the attending physician. Therapeutic granulocyte transfusions: were given if a patient in the prophylactic broad-spectrum antibiotic arm had a major infectious episode with deterioration of the clinical condition despite appropriate antibiotics and a granulocyte donor was available	
Notes	Funding Sources: PHS Grant Numbers CA 15704, CA 18029, CA 18221, and CA 18579, awarded by the National Cancer Institute, DHHS. Dr. Petersen is the recipient of a grant (12-5057) from the Danish Medical Research Council. Dr. Thomas is the recipient of a Research Career Award (AI 02425) from the National Institute of Allergy and Infectious Diseases Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether participants were blinded to the intervention. It was not reported whether clinicians or investigators were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	87 participants were randomised to receive granulocyte transfusions and 47 to receive prophylactic broad-spectrum antibiotics. Twenty participants in the granulocyte transfusions group did not receive granulocyte transfusions and were excluded from the study because of problems related to using the proposed granulocyte donor or because the granulocyte donor was found to have antibodies to cytomegalovirus (CMV) while the recipient was negative Two participants in the prophylactic broad-spectrum antibiotics group were excluded because of delay of the transplant and subsequent placement into laminar air flow isolation
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	High risk	Only 42 (63%) participants received granulocyte transfusions according to the study's protocol (as reported in final report of study, initial protocol not available. Granulocyte transfusions were stopped in 25 (37%) participants, 19 permanently and six temporarily. Ten (40%) of the 25 protocol violations were caused by complications in the donor, and in four of these cases the transfusions were resumed after one to three days. Eight (32%) of the protocol violations were due to complications in the patient, five of which were transfusion reactions involving pulmonary symptoms

		in four. All five transfusion reactions occurred in participants receiving granulocyte transfusions from a parent (three from the mother and two from the father), and none were observed following transfusions from HLA-matched donors. Seven (28%) protocol violations were caused by the donor being needed for platelet transfusion
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Schiffer 1979

Methods	Parallel RCT (recruitment period not reported). Single centre. Country: USA
Participants	<p>Inclusion criteria: Previously untreated adults (> 18 years) with acute myeloid leukaemia</p> <p>Exclusion criteria: excluded infected patients and patients on systemic antibiotics</p> <p>Total randomised: N = 22</p> <p>Total analysed: N = 18</p> <p>Arm 1 (Granulocyte transfusions): randomised = 12, analysed = 9 , Acute myeloid leukaemia = 12</p> <p>Arm 2 (Control): randomised = 10, analysed = 9 , Acute myeloid leukaemia = 10</p>
Interventions	<p>Comparison between prophylactic platelet transfusions on alternate days (3 to 4 out of 7 days) versus prophylactic granulocyte and platelet transfusions on alternate days (4 out of 7 days)</p> <p>Granulocyte dose: 1.15×10^{10} (0.34 to 2.4)</p> <p>Granulocyte method of collection: intermittent flow centrifugation</p> <p>Donor premedication: dexamethasone</p> <p>Initiation of granulocyte transfusions: Neutrophil count < $0.5 \times 10^9/L$ or platelet count < $20 \times 10^9/L$</p> <p>Frequency of granulocyte transfusions: Four days out of seven each week</p> <p>Termination of granulocyte transfusions: Until recovery (or rising neutrophil count > $0.5 \times 10^9/L$ with no dependence on platelet transfusions)</p>
Outcomes	<p>Primary Outcomes: Microbiologically or clinically documented severe infection and detected alloimmunisation</p> <p>Other Outcomes:</p> <p>Mortality/survival, fever (days or episodes), infection (days or episodes), antibiotic use, adverse events</p>
Definition of infection	<p>Febrile day - not reported</p> <p>Febrile episode - temperature > $38.3^\circ C$</p> <p>Proven infection: - not reported</p>
Definition of neutropenia	Not reported but the 'trigger' neutrophil count was $0.5 \times 10^9/L$
Co-interventions	<p>Prophylactic antibiotics: all participants received oral non-absorbable antibiotics</p> <p>Therapeutic antibiotics: empirical systemic antibiotics were started if the temperature was > $38.3^\circ C$ and / or there was clinical evidence of infection but the nature of these</p>

	antibiotics were not stated Therapeutic granulocyte transfusions: not reported	
Notes	Funding Sources: Not reported Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether participants were blinded to the intervention. It was not reported whether clinicians or investigators were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Ten participants were randomised to the control. One participant developed alloimmunisation after her first platelet transfusion and was not continued in the study. 12 participants were randomised to receive granulocyte transfusions. Two participants developed infections prior to receiving their first granulocyte transfusion and were excluded from the study. A third participant refused further granulocyte transfusions after two severe transfusion reactions
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	Unclear risk	Two participants in the control group had acute promyelocytic leukaemia and developed disseminated intravascular coagulation. This could have increased the risk of mortality in the control arm

Strauss 1981

Methods	Parallel RCT (recruitment period not reported). Multicentre, four clinical centres. Country: USA
Participants	<p>Inclusion criteria: people with untreated acute leukaemia who were at least 12 years old, and were “found by examination, chest roentgenography, urinalysis and cultures of blood and urine to be free of infection”</p> <p>Exclusion criteria: people with an infection</p> <p>Total randomised: N = 102</p> <p>Total analysed: N = 102</p> <p>Arm 1 (Granulocyte transfusions): randomised and analysed = 54, Acute myeloid leukaemia = 54</p> <p>Arm 2 (Control): randomised and analysed = 48 , Acute myeloid leukaemia = 48</p>
Interventions	<p>Comparison between standard treatment and prophylactic granulocyte transfusions</p> <p>Granulocyte dose: Median dose $0.34 \times 10^{10}/m^2$</p> <p>Granulocyte method of collection: intermittent flow centrifugation</p> <p>Donor premedication: none</p> <p>Initiation of granulocyte transfusions: Neutrophil count $< 0.5 \times 10^9/L$</p> <p>Frequency of granulocyte transfusions: Daily</p> <p>Termination of granulocyte transfusions: For 28 days, or until bone marrow recovery defined as a neutrophil count above $0.5 \times 10^9/L$ for 48 hours. death, a severe transfusion reaction, withdrawal of the patient's consent, or gram negative septicaemia</p>
Outcomes	<p>Primary Outcome: Documented infection</p> <p>Other Outcomes:</p> <p>Mortality/survival, infection (days or episodes), antibiotic use, adverse events</p>
Definition of infection	<p>Febrile day - not reported</p> <p>Febrile episode - fever was defined as an oral temperature above $38^\circ C$, unrelated to transfusions, that was recorded on two separate occasions separated by at least four hours during a 24 hour period</p> <p>Septicaemia: culture of an organism from the blood of patients with fever</p> <p>Pneumonia: fever plus either a localised infiltrate or cavity seen on chest X-ray</p> <p>Urinary tract infection: fever and the isolation of a single pathogenic organism ($\geq 100,000$ colonies per millilitre)</p> <p>Cellulitis: fever plus and inflammatory lesion $\geq 9cm$ in diameter</p> <p>Abscess: $\geq 4cm$ in diameter with either a fluctuant mass or drainage from which a single organism was cultured</p>
Definition of neutropenia	Not reported but the 'trigger' neutrophil count was $0.5 \times 10^9/L$
Co-interventions	<p>Prophylactic antibiotics: not given</p> <p>Therapeutic antibiotics: systemic carbenicillin or ticarcillin plus an aminoglycoside if a participant suffered two temperatures $>38.5^\circ C$ in 24 hours.</p> <p>Therapeutic granulocyte transfusions: if participants in the control group acquired gram-negative septicaemia</p>

Notes	Funding Sources: National Heart, Lung and Blood Institute; the National Cancer Institute; Masonic Hospital Fund Incorporated; the Minessota Medical Foundation Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Separate randomisation schedules were prepared for each institute and stratum. An algorithm that ensured an approximate balance between treatment groups was used to generate each schedule
Allocation concealment (selection bias)	Low risk	By a telephone call to the co-ordinating centre, participants were randomly assigned to receive daily granulocyte transfusions or not to receive them
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether participants were blinded to the intervention. It was not reported whether clinicians or investigators were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participants were monitored and data were collected daily by personnel trained by the co-ordinating centre but it was unclear whether these outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up was not reported
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	Unclear risk	A policy and data-monitoring board, composed of scientists from institutions not participating in the trial was appointed by the NHLBI to review the study results periodically. Randomisation into the study was terminated in the basis of this review by recommendation of the policy board, but the reason for the recommendation was not reported

Sutton 1982

Methods	Parallel RCT (recruitment period not reported). Multicentre (11 hospitals are part of the Toronto Leukemia study group and all sites may have participated) Country: Canada	
Participants	Inclusion criteria: Adults with acute myeloid leukaemia Exclusion criteria: infection criteria for excluding people from the study not reported Total randomised: N = 67 Total analysed: N = 65 Arm 1 (Granulocyte transfusions): randomised and analysed = 29 , Acute myeloid leukaemia = 29 Arm 2 (Control): randomised = 38, analysed = 36, Acute myeloid leukaemia = 36	
Interventions	Comparison between standard treatment and prophylactic granulocyte transfusions Granulocyte dose: 0.9×10^{10} (0.2 to 0.5) Granulocyte method of collection: intermittent flow centrifugation Donor premedication: prednisolone Initiation of granulocyte transfusions: Neutrophil count $< 0.5 \times 10^9/L$ Frequency of granulocyte transfusions: Daily Termination of granulocyte transfusions: until neutrophil count above $0.5 \times 10^9/L$	
Outcomes	Primary Outcome: Not reported Other Outcomes: Mortality/survival, infection (days or episodes), adverse events	
Definition of infection	Febrile day - Not reported Febrile episode - Not reported Proven infection: Not reported	
Definition of neutropenia	Not reported but the 'trigger' neutrophil count was $0.5 \times 10^9/L$	
Co-interventions	Prophylactic antibiotics: not reported Therapeutic antibiotics: participants received broad-spectrum antibiotics as indicated Therapeutic granulocyte transfusions: for documented bacterial septicemia	
Notes	Funding Sources: Grant #384 from the Ontario Cancer Treatment and Research foundation Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported

Sutton 1982 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether participants were blinded to the intervention. It was not reported whether clinicians or investigators were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants both in the control group, were randomised but not included in the analysis, one because the records were lost and the other because the diagnosis was changed to acute lymphoblastic leukaemia. One participant in the control group was discharged with resistant disease and was lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	Unclear risk	Although none were identified, it is difficult to rule out any significant bias due to insufficient reporting of the study

Vij 2003

Methods	Biologically randomised study (recruitment period not reported). Single centre. Country: USA
Participants	<p>Inclusion criteria: people receiving an allogeneic peripheral blood stem cell transplant</p> <p>Exclusion criteria: infection criteria for excluding people from the study not reported</p> <p>Total allocated: N = 225</p> <p>Total analysed: N = 225</p> <p>Arm 1 (Granulocyte transfusions): allocated and analysed = 83, Acute leukaemia = 36, Non Hodgkins lymphoma = 17, Chronic myeloid leukaemia = 17, other = 13</p> <p>Arm 2 (Control): allocated and analysed = 142, , Acute leukaemia = 61, Non Hodgkins lymphoma = 37, Chronic myeloid leukaemia = 18, other = 26</p>
Interventions	<p>Comparison between standard treatment and prophylactic granulocyte transfusions</p> <p>Granulocyte dose: participants received two granulocyte transfusions. The mean dose and range were not reported</p> <p>Granulocyte method of collection: continuous flow apheresis</p> <p>Donor premedication: G-CSF</p> <p>Initiation of granulocyte transfusions: Day plus 3 or 5 (depending on protocol)</p> <p>Frequency of granulocyte transfusions: Twice during neutropenic interval</p>

	Termination of granulocyte transfusions: Day plus 6 or 7 (depending on protocol)	
Outcomes	Primary Outcome: Not reported Other Outcomes: Incidence of CMV viraemia; median time to detection of CMV viraemia	
Definition of infection	Febrile day - Not reported Febrile episode - Not reported Proven infection: Not reported	
Definition of neutropenia	Not reported	
Co-interventions	Prophylactic antibiotics: not reported Therapeutic antibiotics: not reported Therapeutic granulocyte transfusions: not reported	
Notes	Funding Sources: the publication costs of the article were defrayed in part by part charge payment. Therefore and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734 Conflict of Interests: Not reported	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation was biological, determined by the availability of an ABO-compatible allogeneic peripheral blood stem cell donor. The same donor served as both the stem cell and granulocyte donor
Allocation concealment (selection bias)	High risk	Treatment allocation was dependent on availability of an appropriate granulocyte donor
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether participants were blinded to the intervention. It was not reported whether clinicians or investigators were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up was not reported

Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	High risk	The publication costs of the article were defrayed in part by part charge payment, this article was marked as an "advertisement" in accordance with 18 USC section 1734

Winston 1980

Methods	Parallel RCT (recruitment period not reported). Single centre Country: USA
Participants	<p>Inclusion criteria: people received high-dose chemotherapy and/or radiation therapy followed by the intravenous infusion of bone marrow from an HLA identical sibling; neutrophil count $\leq 0.5 \times 10^9/L$; no systemic antibiotic therapy within the preceding 72 hours; no signs or symptoms of infection; and; negative blood cultures before randomisation.</p> <p>Exclusion criteria: excluded people with an infection</p> <p>Total randomised: N = 38</p> <p>Arm 1 (Granulocyte transfusions): randomised and analysed = 19 , Acute leukaemia = 13, Aplastic anaemia = 6</p> <p>Arm 2 (Control): randomised and analysed = 19 , Acute leukaemia = 12, Aplastic anaemia = 7</p> <p>Allograft BMT, aplastic anaemia, acute leukaemia</p>
Interventions	<p>Granulocyte transfusions</p> <p>Granulocyte dose: 1.2×10^{10} (0.3 to 3.5)</p> <p>Granulocyte method of collection: continuous flow centrifugation</p> <p>Donor premedication: none</p> <p>Initiation of granulocyte transfusions: Neutrophil count $< 0.5 \times 10^9/L$</p> <p>Frequency of granulocyte transfusions: Daily</p> <p>Termination of granulocyte transfusions:</p>
Outcomes	<p>Primary Outcome: Not reported</p> <p>Other Outcomes:</p> <p>Mortality/survival, fever (days or episodes), infection (days or episodes), antibiotic use, adverse events</p>
Definition of infection	<p>Febrile day - not reported</p> <p>Febrile episode - temperature $\geq 38.0^\circ C$ on two or more occasions within 24 hours in the absence of blood product transfusions</p> <p>Septicemia: one or more blood cultures were positive for a pathogenic organism in a clinical setting compatible with septicemia</p> <p>Pneumonia: signs and symptoms of pulmonary infection with a lobar or diffuse infiltrate evident on chest film</p>

Definition of neutropenia	Not reported but the 'trigger' neutrophil count was $0.5 \times 10^9/L$
Co-interventions	<p>Prophylactic antibiotics: oral non-absorbable antibiotics to all participants (vancomycin, colistin and nystatin)</p> <p>Therapeutic antibiotics: if a participant suffered two fevers $>38^\circ C$ in 24 hours they were treated systemically with carbenicillin (or cefazolin if allergic) and either amikacin or netilmicin</p> <p>Therapeutic granulocyte transfusions: if a participant remained febrile after 96 hours</p>
Notes	<p>Funding Sources: National Heart, Lung and Blood Institute, the National Cancer Institute and the U.S Public Health Service</p> <p>Conflict of Interests: Not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	It was not reported whether participants were blinded to the intervention. It was not reported whether clinicians or investigators were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not reported whether outcome assessors were blinded to the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomised were included within the analysis
Selective reporting (reporting bias)	Unclear risk	The protocol was not available to assess whether any pre-specified outcomes were not reported or outcomes were reported that were not pre-specified
Other bias	Unclear risk	Although none were identified, it is difficult to rule out any significant bias due to insufficient reporting of the study

AML = acute myeloid leukaemia

BMT = bone marrow therapy

CMV = cytomegalovirus

G-CSF = granulocyte colony-stimulating factor
 HLA = human leucocyte antigen
 IV = intravenous
 PBSC = peripheral blood stem cell
 RCT = randomised controlled trial

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

Study	Reason for exclusion
Alavi 1977	Trial of therapeutic granulocytes
Altrichter 2011	Non-randomised study
Ambinder 1981	Evaluation of different methods
Atay 2011	Non-randomised study
Baley 1987	Trial of neonates
Bow 1984	Trial of therapeutic granulocytes
Buckner 1983	Combined data for randomised and non-randomised participants
Christensen 1982	Trial of neonates
DRKS00000218	Trial of therapeutic granulocytes
Freireich 2013	Comparing irradiated versus non-irradiated granulocytes
Herzig 1977	Trial of therapeutic granulocytes
Higby 1975	Trial of therapeutic granulocytes
Ikemoto 2012	Non-randomised study assessing granulocyte yield in donors
Klastersky 1983	Trial of therapeutic granulocytes
NCT01932710	Non-randomised study
Pammi 2011	Systematic review
Price 2014	Trial of therapeutic granulocytes
Scali 1978	Trial of therapeutic granulocytes
Seidel 2008	Trial of therapeutic granulocytes

(Continued)

UMIN000014777	Non-randomised study
Vogler 1977	Trial of therapeutic granulocytes
Wheeler 1987	Trial of therapeutic granulocytes
Winston 1982	Trial of therapeutic granulocytes

Characteristics of ongoing studies [ordered by study ID]

NCT01204788

Trial name or title	A prospective randomized comparative study of the effect on infections of radiated prophylactic white cell transfusions versus therapeutic radiated white cell transfusions (NCT01204788)
Methods	Allocation: Randomised. First 60 Endpoint Classification: Efficacy study Intervention Model: Parallel assignment Masking: Open label Primary Purpose: Prevention
Participants	Inclusion Criteria: Aged 2 years or older with a diagnosis of acute myelogenous leukaemia (including undifferentiated and bi-phenotypic leukaemia), or high-risk myelodysplastic syndrome, or chronic myelogenous leukaemia in blast crisis who will receive first or second anti-leukaemia therapeutic intent with chemotherapy, targeted therapy or hypomethylating agents Exclusion Criteria: Patients with baseline (at start leukaemia treatment) infection, defined as patients with: 1. fever and known positive cultures at the time of randomisation; or 2. chest or sinus computed tomography with findings suggestive of pneumonia or sinusitis; or 3. one positive galactomannan test ≥ 1 or two positive galactomannan test ≥ 0.5 to 1 Patients with Zubrod performance status ≥ 3
Interventions	Prophylactic Arm - Prophylactic Treatment (standard of care prophylactic antibiotics) + Prophylactic White Cell Transfusion Therapeutic Arm - Prophylactic Treatment (standard of care prophylactic antibiotics) + Therapeutic White Cell Transfusion
Outcomes	Primary Outcome Measures: Number of patients with Infection (yes/no) where patient without infection found by day 42 patient are counted as 'No' to infection Secondary outcomes not reported on clinical trials website
Starting date	September 2010
Contact information	University of Texas MD Anderson Cancer Center Emil J Freireich

NCT01204788 *(Continued)*

Notes	Study completion date January 2013
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DATA AND ANALYSES

Comparison 1. Prophylactic granulocytes versus no prophylactic granulocytes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality up to 30 days	7	437	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.63, 1.36]
1.1 Low-dose granulocytes	3	144	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.64, 2.72]
1.2 Intermediate-dose granulocytes	4	293	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.47, 1.16]
2 All-cause mortality up to 100 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Granulocyte dose unknown	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 All-cause mortality over 100 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Low-dose granulocytes	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mortality due to infection up to 30 days	6	286	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.33, 1.44]
4.1 Low-dose granulocytes	3	144	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.46, 2.86]
4.2 Intermediate-dose granulocytes	3	142	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 1.10]
5 Mortality due to infection up to 100 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Granulocyte dose unknown	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 People with localised or systemic bacterial or fungal infections	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Low-dose granulocyte transfusions	4	204	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.58, 1.20]
6.2 Intermediate-dose granulocyte transfusions	4	293	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.26, 0.63]
6.3 Unknown dose of granulocyte transfusion	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.61, 1.55]
7 People with bacteraemia or fungaemia	9	609	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.30, 0.65]
7.1 Low-dose granulocyte transfusions	4	204	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.27, 0.96]
7.2 Intermediate-dose granulocyte transfusions	4	293	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.55]
7.3 Unknown dose of granulocyte transfusions	1	112	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.39, 1.61]
8 People with bacteraemia or fungaemia (excluding study that compared prophylactic granulocyte transfusions versus prophylactic broad-spectrum antibiotics)	8	497	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.23, 0.59]

8.1 Low-dose granulocyte transfusions	4	204	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.27, 0.96]
8.2 Intermediate-dose granulocyte transfusions	4	293	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.55]
9 People with localised bacterial or fungal infection	6	296	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.50, 1.14]
9.1 Low-dose granulocyte transfusions	2	42	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.19, 1.11]
9.2 Intermediate-dose granulocyte transfusions	3	142	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.38, 1.31]
9.3 Unknown dose of granulocyte transfusions	1	112	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.54, 2.33]
10 People with localised bacterial or fungal infection (excluding study that compared prophylactic granulocyte transfusions versus prophylactic broad-spectrum antibiotics)	5	184	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.37, 1.02]
10.1 Low-dose granulocyte transfusions	2	42	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.19, 1.11]
10.2 Intermediate-dose granulocyte transfusions	3	142	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.38, 1.31]

ADDITIONAL TABLES

Table 1. Dose and frequency of granulocyte transfusions used within the studies ranked from lowest dose to highest dose, and stratified according to the frequency of granulocyte transfusions

Study	Mean dose of granulocyte transfusions	Range of doses of granulocyte transfusions	Frequency of transfusions	Total number of transfusions per patient Mean/median and range
Strauss 1981	$0.6 \times 10^{10*}$	Not reported	Daily	18.5 (mean) (3 to 28)
Sutton 1982	0.9×10^{10}	0.2 to 2.5×10^{10}	Daily	Not reported
Winston 1980	1.2×10^{10}	0.3 to 3.5×10^{10}	Daily	23.4 mean (13 to 34)
Gomez-Villagran 1984	1.24×10^{10}	0.55 to 4.2×10^{10}	Daily	6.16 (mean) (5 to 11)
Clift 1978	2.22×10^{10} (leucofiltration) 1.57×10^{10} (centrifugation)	Not reported	Daily	12.4 (mean) (6 to 25)

Table 1. Dose and frequency of granulocyte transfusions used within the studies ranked from lowest dose to highest dose, and stratified according to the frequency of granulocyte transfusions (*Continued*)

Mannoni 1979	2.1×10^{10}	1.3 to 3.7	Daily	12 (mean) (8 to 15)
Petersen 1987	Not reported	Not reported	Daily	12 (median) (6 to 27)
Schiffer 1979	1.15×10^{10}	0.34 to 2.4×10^{10}	4/7 days per week	11 (mean) (3 to 19)
Ford 1982	1.45×10^{10}	0.28 to 3.45	Alternate days	7 (median) (1 to 12)
Oza 2006	5.9×10^{10} (first dose) 5.2×10^{10} (second dose)	0.02 to 15.5 (first dose) 0.02 to 21.0 (second dose)	Twice	2
Vij 2003	Not reported	Not reported	Twice	2

* Strauss ([Strauss 1981](#)) did not express the dose given in terms of absolute numbers of granulocytes but described the median dose as 0.34×10^{10} per square metre of recipient body surface area. (This would approximate to a dose of 0.6×10^{10} as all participants were over 12 years old).

Table 2. All-cause Mortality

Study	Number of participants randomised	Number of participants analysed	Prophylactic Granulocytes	Control
Mortality at up to 21 days				
Clift 1978	86	69	0/29	1/40
Gomez-Villagran 1984	35	35	2/19	6/16
Mortality at up to 30 days				
Ford 1982	49	24	3/13	2/11
Mannoni 1979	44	44 in 50 episodes of aplasia	0/20	4/26
Oza 2006	151	151	2/53	5/98
Schiffer 1979	22	18	0/9	2/9
Strauss 1981	102	102	12/54	6/48
Winston 1980	38	38	13/19	13/19

Table 2. All-cause Mortality (Continued)

Mortality at up to 100 days				
Petersen 1987	134	112	21/67	11/45
Mortality over 100 days				
Sutton 1982	67	64	19/28	25/36

Table 3. Mortality due to bacterial or fungal infection

Study	Number of participants randomised	Number of participants analysed	Prophylactic Granulocytes	Control
Mortality at up to 21 days				
Clift 1978	86	69	0/29	1/40
Gomez-Villagran 1984	35	35	0/19	4/16
Mortality at up to 30 days				
Ford 1982	49	24	1/13	1/11
Mannoni 1979	44	44 in 50 episodes of aplasia	0/20	2/26
Schiffer 1979	22	18	0/9	2/0
Strauss 1981	102	102	8/54	4/48
Winston 1980	38	38	1/19	2/19
Mortality at up to 100 days				
Petersen 1987	134	112	3/67	2/45

Table 4. Number and type of bacterial and fungal infections

Study	Number of participants analysed	Total number of participants with an infection		Localised infections (excluding oral candida)		Systemic infections (Bacteraemia or fungaemia)	
		Prophylactic Granulocytes	Control	Prophylactic Granulocytes	Control	Prophylactic Granulocytes	Control

Table 4. Number and type of bacterial and fungal infections (Continued)

Clift 1978	69	2/29	17/40	2 participants 1 Candidal oesophagitis 1 Rhinitis due to coagulase positive staphylococcus	7 participants	0 participants	10 participants 2 <i>Escherichia coli</i> 2 <i>Pseudomonas aeruginosa</i> 2 <i>Corynebacteria</i> 2 <i>Beta-haemolytic streptococci</i> 1 <i>Serratia</i> 1 <i>Enterobacter</i>
Ford 1982	24	4/13	7/11	3 participants 1 Pneumonia 1 Cellulitis & Abscess 1 Enteritis	5 participants 3 Pneumonia 1 Cellulitis & Abscess 1 Enteritis	1 participant 1 <i>Klebsiella pneumoniae</i>	3 participants 2 <i>Staphylococcus aureus</i> 1 <i>Staphylococcus alba</i>
Gomez-Villagran 1984	35	4/19	10/16	4 participants 1 Pneumonia 0 Cellulitis & Abscess 3 Pharyngitis	6 participants 2 Pneumonia 2 Cellulitis & Abscess 2 Pharyngitis	0 participants	4 participants 2 <i>Escherichia coli</i> 1 <i>Pseudomonas aeruginosa</i> 1 <i>Staphylococcus aureus</i>
Mannoni 1979	44 episodes of aplasia (50)	1/20	11/26	1 episode 0 Pneumonia 1 Cellulitis & Abscess	15 episodes 8 Pneumonia 4 Cellulitis & Abscess 3 Enteritis	0 participants	Not reported
Oza 2006	151	7/53	29/98	Not reported	Not reported	7 participants bacteraemia (not further defined)	29 participants bacteraemia (not further defined)
Petersen 1987*	112	26/67	18/45	15 participants 0 Pneumonia 5 Colitis 1 Sinusitis 1 Mouth/throat 2 Urinary tract infection 4 RAC site 4 Other	9 participants 2 Pneumonia 1 Colitis 2 Sinusitis 2 Mouth/throat 1 Urinary tract infection 1 RAC site 1 Other	13 participants 10 Coagulase -ive Staphylococcus 1 Candida 2 Streptococcus 3 Gram -ive bacilli	11 participants 4 Coagulase -ive <i>Staphylococcus</i> 4 <i>Candida</i> 0 <i>Streptococcus</i> 5 Gram -ive bacilli

Table 4. Number and type of bacterial and fungal infections (Continued)

Schiffer 1979	18	2/9	6/9	2 participants 1 Cellulitis 1 Sinusitis	5 participants 2 Pulmonary aspergillosis 2 Cellulitis 1 Oesophagitis	0 participants	1 participant 1 <i>T. glabrata</i>
Strauss 1981	102	25/54	20/48	12 Pneumonia 5 Cellulitis 3 Abscess 3 Urinary tract infection	6 Pneumonia 3 Cellulitis 3 Abscess 1 Urinary tract infection	8 episodes 2 Gram +ive septicaemia 3 Gram -ive septicaemia 3 fungal isolates	14 episodes 8 Gram +ive septicaemia 8 Gram -ive septicaemia 1 fungal isolate
Sutton 1982	60	3/29	4/31	Not reported	Not reported	3 episodes 1 <i>Escherichia coli</i> 1 <i>Pseudomonas aeruginosa</i> 1 <i>Klebsiella pneumoniae</i>	4 episodes 1 <i>Escherichia coli</i> 1 <i>Pseudomonas aeruginosa</i> 2 <i>Klebsiella pneumoniae</i>
Winston 1980	38	7/19	9/19	7 participants 3 Pneumonia 4 Cellulitis & Abscess 0 Urinary tract infection	6 participants 3 Pneumonia 3 Cellulitis & Abscess 0 Urinary tract infection	0 participants	3 participants 1 <i>Streptococcus viridans</i> 1 <i>Staphylococcus epidermidis</i> 1 <i>Enterococcus</i>

* Data for this trial are for the first 30 days when participants were granulocytopenic prior to engraftment. Data are for a similar time period to the other studies.

RAC = right atrial catheter

Table 5. Number of days with fever and number of days on treatment with antimicrobials

Study	Num-ber of par-ticipants analysed	Number of days with fever		Number of participants receiving antibiotics		Number of days with antibiotics		Number of participants receiving antifungal medication	
		Prophy-lac-tic granu-locytes	Control	Prophy-lac-tic granu-locytes	Control	Prophy-lac-tic granu-locytes	Control	Prophy-lac-tic granu-locytes	Control
Clift 1978	31*	Not reported	Not reported	9/16	13/15	Not reported	Not reported	Not reported	Not reported

Table 5. Number of days with fever and number of days on treatment with antimicrobials (Continued)

Ford 1982	19 [#]	Median 4.5 (range 0 to 18)	Median 9 (range 3 to 12)	9/10	9/9	Median 8 (range 0 to 15)	Median 10.5 (range 6 to 16)	Not reported	Not reported
Gomez-Villagran 1984	35	5.1 ± 3.5	6 ± 5.6	11/19	13/16	6.7 ± 4.4	7.8 ± 6.2	Not reported	Not reported
Oza 2006	151	Median 2 (range 0 to 15)	Median 2 (range 0 to 17)	53/53	97/98	Median 9 (range 1 to 20)	Median 11 (range 0 to 26)	Not reported	Not reported
Petersen 1987	112	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	33	29
Schiffer 1979	18	Mean 9 (range 2 to 16)	Mean 9 (range 2 to 18)	Not reported	Not reported	Mean 13 (range 7 to 25)	Mean 13 (range 9 to 20)	Not reported	Not reported
Winston 1980	38	10.1 (SE 1.3)	7.7 (SE 1.7)	18	15	10.5 (SE 1.6)	8.2 (SE 1.8)	5	5

* Participants who were not on antibiotics at the start of the study

[#] Participants who did not die during the first 26 days of the study

SE = standard error

Table 6. Neutrophil increment after granulocyte transfusion and duration of neutropenia reversal

Study	Total number of granulocyte transfusions	1 hour absolute neutrophil increment	1 hour corrected count increment		Duration of neutropenia reversal
			On antibiotics	Not on antibiotics	
Clift 1978	360	Not reported	CFC Median 0.28 x 10 ⁹ /L (Range 0 to 1.16) LF Median 0.06 x 10 ⁹ /L (Range 0 to 0.49)	CFC Median 0.38 x 10 ⁹ /L (Range 0.1 to 1.32) LF Median 0.06 x 10 ⁹ /L (Range 0 to 0.32)	Not reported
Ford 1982	107	Median 0.32 x 10 ⁹ /L	Not reported		Not reported

Table 6. Neutrophil increment after granulocyte transfusion and duration of neutropenia reversal (Continued)

Gomez-Villagran 1984	254	Not reported	Mean $0.41 \times 10^9/L$ (Range 0.04 to 1.15)	Mean $0.50 \times 10^9/L$ (Range 0.19 to 1.14)	Not reported
Mannoni 1979	Not reported	Not reported	Average $0.30 \times 10^9/L$		Not reported
Schiffer 1979	Not reported	Most $< 0.15 \times 10^9/L$	Not reported		Not reported
Winston 1980	Not reported	Not reported	Mean $0.12 \times 10^9/L$ (range 0 to 0.66)		Not reported

CFC = continuous flow centrifugation

LF = leucofiltration

Table 7. Serious adverse events to donor or recipients

Study	Number of participants receiving granulocyte transfusions	Number of granulocyte transfusions	Donor events	Recipient events
Clift 1978	29 prophylactic 16 therapeutic	360	1 1 - haemodynamic compromise	0
Ford 1982	13 prophylactic	107	0	1 1 - TA GvHD
Gomez-Villagran 1984	19 prophylactic	254	Not reported	7 1 - haemolysis 6 - dyspnoea & cyanosis
Sutton 1982	29 prophylactic 2 therapeutic	Not reported	Not reported	3 3 - dyspnoea and wheeze

TA GvHD = Transfusion-associated Graft versus Host Disease

Table 8. Adverse events requiring permanent discontinuation of the intervention

Study	Number of participants receiving granulocyte transfusions	Total number of granulocyte transfusions	Donor events	Recipient events
Clift 1978	29 prophylactic 16 therapeutic	360	4 1 - haemodynamic compromise	0

Table 8. Adverse events requiring permanent discontinuation of the intervention (Continued)

			1 - abdominal cramps 2 - recurrent blocking of port	
Petersen 1987	67 prophylactic 4 therapeutic	Not reported	6 1 - low platelet count 1 - bleeding from arterio-venous shunt 4 - obstruction of lumen of shunt or catheter	13 5 - transfusion reactions 3 - no increment in granulocyte count 5 - donor required for platelet transfusions
Schiffer 1979	10 prophylactic 0 therapeutic	Not reported	Not reported	1 1 - diffuse pulmonary infiltrate
Strauss 1981	54 prophylactic	987	Not reported	6 (not further defined)
Sutton 1982	29 prophylactic 2 therapeutic	Not reported	Not reported	5 (not further defined)
Winston 1980	19 prophylactic 6 therapeutic	Not reported	Not reported	0

WHAT'S NEW

Last assessed as up-to-date: 20 April 2015.

Date	Event	Description
20 April 2015	New search has been performed	New search, two new citations added, one completed study was identified in the updated search (Vij 2003), and one ongoing study was identified (NCT01204788). 'Risk of bias' assessment of all included studies updated. 'Summary of findings' table added. PRISMA flow diagram added (Stovold 2014).
20 April 2015	New citation required but conclusions have not changed	One new study added but conclusions not changed.
27 March 2014	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 1, 2009

Date	Event	Description
14 May 2008	Amended	Converted to new review format.
29 November 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

- Lise Estcourt: searching, selection of studies, eligibility and methodological quality assessment, data extraction and analysis, and content expert.
- Simon Stanworth: protocol development, data extraction and analysis and content expert.
- Edwin Massey: protocol development and content expert.
- Carolyn Doree: protocol development, searching; selection of studies; final report.
- Patricia Blanco: searching; selection of studies and data extraction.
- Sally Hopwell: methodological expert
- Marialena Trivella: methodological expert

DECLARATIONS OF INTEREST

- Lise Estcourt is partly funded by an NIHR Cochrane Programme Grant.
- Edwin Massey is involved in the design of clinical trials of granulocytes for transfusion.
- Carolyn Doree: none to declare
- Simon Stanworth is involved in the design of clinical trials of granulocytes for transfusion.
- Patricia Blanco is funded by an NIHR Cochrane Programme Grant.
- Sally Hopwell is partly funded by an NIHR Programme Grant
- Marialena Trivella is partly funded by an NIHR Programme Grant

SOURCES OF SUPPORT

Internal sources

- National Blood Service, Research and Development, UK.

External sources

- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not pre-specify in the protocol how we would deal with any unit of analysis issues. There were unit of analyses issues. In [Mannoni 1979](#), participants were randomised more than once, 44 participants were included within the study but six participants were re-randomised. Data for the first randomisation could not be extracted from the report, and further information from the authors was not available. Data from this study were therefore not incorporated into any meta-analyses.

The methodology of the review has changed in this update of the review to conform to current Cochrane Collaboration recommendations.

We used GRADE to build a 'Summary of findings' table as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2011](#)). A GRADE assessment had not been pre-specified in the protocol.

For time-to-event outcomes, we planned to extract the hazard ratio (HR) from published data according to [Parmar 1998](#) and [Tierney 2007](#). However, no time to event data were reported.

We did not perform a formal assessment of potential publication bias (small trial bias) by generating a funnel plot and statistically test using a linear regression test ([Sterne 2011](#)) as no meta-analysis contained 10 or more studies.

We planned to use the random-effects model for sensitivity analyses as part of the exploration of heterogeneity. However, none of the analyses performed reported heterogeneity, as expressed by the I^2 above 50%, therefore only the fixed-effect model was reported.

We did not perform a sensitivity analysis including only those studies at low risk of bias because none of the studies were at low risk of bias.

No study reported the duration of neutropenia reversal.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [therapeutic use]; Antifungal Agents [therapeutic use]; Bacterial Infections [*prevention & control]; Glucocorticoids [therapeutic use]; Granulocyte Colony-Stimulating Factor [therapeutic use]; Granulocytes [*transplantation]; Leukocyte Disorders [complications; therapy]; Leukocyte Transfusion [*methods]; Mycoses [*prevention & control]; Neutropenia [complications; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans