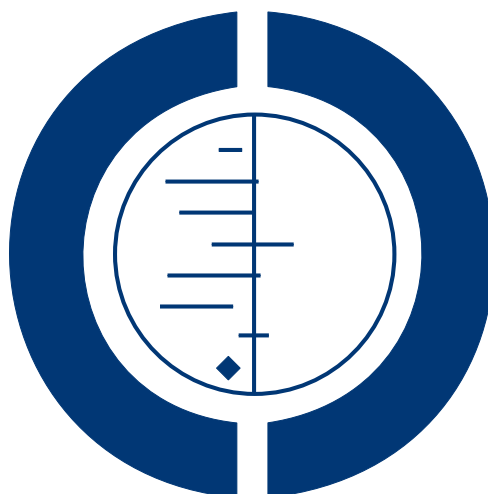


Granulocyte-Colony Stimulating Factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults (Review)

Cheng AC, Stephens DP, Currie BJ



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[Intervention Review]

Granulocyte-Colony Stimulating Factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults

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ABSTRACT

Background

Granulocyte colony stimulating factor (G-CSF) is a naturally-occurring cytokine that has been shown to increase neutrophil function and number. Exogenous administration of recombinant G-CSF (filgrastim, pegfilgrastim or lenograstim) has found extensive use in the treatment of febrile neutropenia, but its role in the treatment of infection in non-neutropenic hosts is less well defined.

Objectives

We explored the role of G-CSF as an adjunct to antibiotics in the treatment of pneumonia in non-neutropenic adults.

Search methods

For this updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2006, issue 4); MEDLINE (1950 to January 2007); EMBASE (1988 to January 2007); and online databases of clinical trials (www.controlled-trials.com, updated 10 November, 2006).

Selection criteria

We considered randomized controlled trials (RCTs) which included hospitalized adult patients with either community-acquired pneumonia or hospital-acquired pneumonia.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality. The primary outcome measure was 28-day mortality. Secondary outcome measures included other markers of mortality as well as markers of adverse events, including organ dysfunction. An assessment of methodological quality was made for each study.

Main results

Six studies with a total of 2018 people were identified. G-CSF use appeared to be safe with no increase in the incidence of total serious adverse events (pooled odds ratio (OR) 0.91; 95% confidence interval (CI): 0.73 to 1.14) or organ dysfunction. However, the use of G-CSF was not associated with improved 28-day mortality (pooled OR 0.81; 95% CI: 0.52 to 1.27).

Authors' conclusions

There is no current evidence supporting the routine use of G-CSF in the treatment of pneumonia. Studies in which G-CSF is administered prophylactically or earlier in therapy may be of interest.

PLAIN LANGUAGE SUMMARY

Granulocyte colony stimulating factor (G-CSF), when given with antibiotics, does not appear to reduce mortality in adults with pneumonia

Pneumonia, or infection involving the lungs, is responsible for a significant number of deaths worldwide. Pneumonia is especially life-threatening in older people and people with other illnesses that may affect the immune system (such as diabetes). In addition to antibiotics, granulocyte colony stimulating factor (G-CSF) has been suggested as a possible option for treatment. G-CSF stimulates the production of white blood cells that fight infection, and is used for people with cancer after chemotherapy, and in febrile neutropenia (infection associated with very low levels of white cells). The review of trials found that, when combined with antibiotics, G-CSF appears to be a safe treatment for people with pneumonia, but it does not appear to reduce mortality. More research is needed to define the optimal timing of dosing (earlier, or prophylactically before the onset of infection) and possible problems when given to patients with severe infection.

BACKGROUND

Description of the condition

This review explores the use of granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of bacterial pneumonia in non-neutropenic adults. Much of the mortality associated with pneumonia is related to sepsis, thought to represent a state of uncontrolled inflammation. Immunomodulation of this response, using physiological doses of corticosteroids (Annane 2002) and recombinant activated protein C (Bernard 2001) have been associated with improved outcomes. G-CSF, a naturally occurring cytokine, may augment the neutrophil response to bacterial infections.

Description of the intervention

Recombinant G-CSF (filgrastim, lenograstim) has been shown to increase proliferation and differentiation of neutrophil precursors. It has found widespread use in reducing the duration of febrile neutropenia following cytotoxic chemotherapy (Welte 1996), although its effect on mortality is questionable (Berghmans 2002). Other accepted indications include neutropenia following bone marrow transplantation, the mobilization of peripheral blood progenitor cells in healthy donors and in the treatment of severe congenital neutropenia.

How the intervention might work

Its use in non-neutropenic bacterial infection is based on three possible mechanisms of action: (1) enhanced chemotaxis, superoxide production and bacterial killing activity (Hartung 1999); (2) immunomodulation of the cytokine response in sepsis (Weiss 1999); and (3) a possible increase in intracellular uptake of antibiotics (McKenna 1996).

However, a possible concern with its use in sepsis is the role of neutrophils in the development of organ dysfunction, and in particular acute respiratory distress syndrome (ARDS). Increasing neutrophil number and function may increase the risk of these adverse sequelae. A review of 84 cases of probable G-CSF related pulmonary toxicity, mostly administered following chemotherapy, found that G-CSF might increase the toxicity associated with cytotoxic agents and infectious insults in neutropenic patients (Azoulay 2001).

G-CSF has shown promise in the treatment of infection in non-neutropenic hosts in many animal models (Hebert 1990; Smith 1995) and in at least one case series with a historical control group (Stephens 2002). It should be distinguished from GM-CSF (sargramostim), which is used occasionally in stem cell mobilization and to promote engraftment following bone marrow transplantation.

Why it is important to do this review

Community-acquired pneumonia is the leading cause of death

from infectious disease and results in approximately 600,000 admissions per year in the United States (Bartlett 1995). Both community-acquired pneumonia and hospital-acquired pneumonia are associated with a significant mortality (Fagon 1993a; Niederman 1993). A number of trials of G-CSF in the treatment of pneumonia have been performed. A review of these trials may clarify the role of this immunomodulatory therapy and aid design of future trials.

OBJECTIVES

To assess the efficacy and safety of G-CSF as an adjunct to antibiotics for the treatment of pneumonia in non-neutropenic adults.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomized controlled trials were included in this review.

Types of participants

The population studied included hospitalized adult patients (older than 18 years) with:

1. community-acquired pneumonia;
2. hospital-acquired pneumonia, including ventilator-associated pneumonia.

“Community-acquired pneumonia” was defined as follows (BTS 2001):

1. clinical features suggestive of lower respiratory tract infection (such as fever, cough, pleuritic chest pain, examination suggestive of consolidation);
2. chest X-ray demonstrating new infiltrate suggesting pneumonia;
3. onset in community setting (outpatient or less than 48 hours following admission to hospital);
4. no alternative diagnosis at admission or during follow up.

There has been controversy regarding the optimal definition of hospital-acquired pneumonia (Fagon 1993b) and a paucity of studies of mortality. In general, hospital-acquired pneumonia is associated with a high mortality (Fagon 1993a). In this review, we regard “hospital-acquired pneumonia” as a clinical definition (ATS 2005; Garner 1988):

1. onset of illness more than 72 hours following admission;
2. new infiltrate on chest X-ray;
3. signs of sepsis (leucocytosis, fever, tachypnoea, tachycardia);

4. increasing sputum production;
5. no alternative diagnosis (such as Acute Respiratory Distress Syndrome (ARDS)) at time of evaluation or follow up.

“Suspected ventilator associated pneumonia”, a sub-set of patients with hospital-acquired pneumonia, was defined as:

1. hospital-acquired pneumonia (defined above);
2. patients intubated for more than 72 hours.

“Confirmed ventilator associated pneumonia” was defined as 1 and 2 above, supported by quantitative microbiological techniques (Sanchez-Nieto 1998), including:

1. protected specimen brush sampling with quantitative culture techniques;
2. quantitative cultures of bronchoalveolar lavage;
3. quantitative cultures of endotracheal aspirates.

We had originally intended to only include patients with severe community-acquired pneumonia, but subsequently found that the studies we identified were performed prior to the development of standard definitions of severity (Ewig 1998; Fine 1997; Niederman 1993). We thus incorporated a group with “severe sepsis”, defined by standard criteria (Bone 1993) which detail definitions of sepsis (fever, tachycardia, tachypnoea and leucocytosis) and end-organ perfusion abnormalities (hypotension, oliguria, gas exchange abnormalities).

A sensitivity analysis would have been performed excluding studies in which there was uncertainty if the specific inclusion criteria were met.

We excluded studies specifically involving neutropenic patients or patients following chemotherapy.

Types of interventions

We assessed the use of G-CSF as an adjunct to antibiotics. We included studies involving all doses of G-CSF administered intravenously or subcutaneously. Trials that allowed concurrent use of other therapies, including mechanical ventilation, immunomodulatory agents including steroids, bronchodilators and so on were included if they allowed equal access to such medications for patients in both arms of the trial.

Types of outcome measures

Primary outcomes

The primary outcome was 28-day mortality.

Secondary outcomes

1. In-hospital mortality.
2. Rate of mechanical ventilation.
3. Duration of intensive care unit (ICU) admission following randomization.
4. Duration of hospital admission following randomization.

5. Adverse events, including the incidence of organ failure (ARDS, disseminated intravascular coagulation, acute renal failure, development of shock).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases for the first publication of this review in mid-2003. Searches were updated in 2004 and 2007.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2006, issue 4); MEDLINE (1950 to January 2007); EMBASE (1988 to January 2007); and online databases of clinical trials (www.controlled-trials.com, updated 10 November, 2006).

We searched MEDLINE and CENTRAL using the following search strategy combined with the highly sensitive search strategy suggested in the Cochrane Reviewers Handbook 5.2 (Higgins 2005) for identification of randomized clinical trials (see below). For the EMBASE search strategy see Appendix 1. We included studies in all languages. Studies identified as randomized controlled trials in non-neutropenic adults were examined further for eligibility.

MEDLINE (OVID)

#1 exp pneumonia/
#2 exp respiratory tract infection/
#3 or/1-2
#4 exp Community-Acquired Infections/
#5 3 and 4
#6 exp cross infection/
#7 exp ventilators, mechanical/
#8 or/6-7
#9 3 and 8
#10 (community-acquired pneumonia or CAP).mp.
#11 (hospital acquired pneumonia or HAP).mp.
#12 nosocomial pneumonia.mp.
#13 (ventilator associated pneumonia or VAP).mp.
#14 exp Sepsis/
#15 or/1,5,9-14
#16 exp granulocyte colony stimulating factor/
#17 g-csf.mp.
#18 lenograstim.mp.
#19 exp Filgrastim/
#20 filgrastim.mp.
#21 pegfilgrastim.mp.
#22 or/16-21
#23 15 and 22

Searching other resources

We also contacted corresponding authors, contacted the manufacturers and distributors of filgrastim (Amgen) and lenograstim (Chugai, Japan and Merck, Australia); and reviewed citations in publications identified by the above strategies.

Data collection and analysis

Data extraction and management

Two review authors independently extracted data. Disagreements were resolved by discussion.

Data that were extracted included, where possible:

1. description of participants and recruitment;
2. description of pathogens and antimicrobial resistance;
3. description of intervention and co-interventions;
4. description of control therapy;
5. description of antibiotics used;
6. methodological details, including criteria for quality assessment (below);
7. total number of participants in each arm of the trial;
8. study setting, in particular intensive care unit (ICU) versus non-ICU;
9. markers of duration of morbidity, including intubation, time to discharge from ICU and hospital;
10. mortality; in-hospital and 28 day;
11. adverse events, including organ dysfunction;
12. source of funding.

Two review authors assessed study quality based on standard Cochrane criteria for the assessment of the following components of study design (Alderson 2004):

1. generation of allocation sequence;
2. allocation concealment;
3. blinding;
4. loss to follow up.

We did not exclude studies of poor methodology from the primary analysis.

We assessed population, intervention and outcome measures of each study to see if the pooling of results was feasible. Heterogeneity was tested using the chi squared test. However, given the intrinsic heterogeneity of the study populations, random-effects analysis was to be employed if pooling was still felt to be appropriate. It was intended that where appropriate, we would calculate relative risk/odds ratios, event rates, time-to-event and risk difference and corresponding 95% CIs. We analyzed the data using Review Manager (version 4.2).

Publication bias was to be assessed by the use of a "funnel plot".

Subgroup analysis and investigation of heterogeneity

Intended *a priori* subgroup analyses, where possible, were to be performed for:

1. age category (older than 65 years);
2. patients with specific chronic diseases (diabetes, renal failure, hazardous alcohol use, chronic obstructive airways disease) separately;
3. bacterial aetiology;
4. community-acquired pneumonia, hospital-acquired pneumonia and suspected and confirmed ventilator-associated pneumonia separately;
5. patients with and without severe sepsis.

Sensitivity analysis

It was intended that a sensitivity analysis would be performed excluding studies of low methodological quality, unpublished studies and studies where some ambiguity exists about whether they met inclusion criteria.

RESULTS

Description of studies

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

Results of the search

Following a MEDLINE (OVID) search, we identified 93 studies for screening. Of these, 87 studies were excluded (duplicate studies, animal studies, studies of neonatal or pediatric patients, studies of neutropenic patients or patients following chemotherapy or transplantation, studies that did not assess G-CSF as therapy (mainly basic science articles), review articles, non-randomized controlled studies, studies that did not involve patients with pneumonia and studies of G-CSF prophylaxis rather than therapy). One additional study was identified using EMBASE (n = 81), online searches of clinical trials registers (n = eight) or CENTRAL (*The Cochrane Library*, 2004, issue 1) (n = 11). The authors of this review conducted one as-yet unpublished study in 2003 to 2005 ([Cheng 2006](#)). A repeat search in 2006 did not identify any further studies, although one trial previously cited as unpublished had since been published ([Hartmann 2005](#)).

Included studies

Five of the six remaining studies were sponsored by Amgen, the manufacturers of filgrastim. All studies met the definitions

of community-acquired pneumonia and confirmed hospital-acquired pneumonia where indicated. Patients in the later two studies ([Root 2003](#); [Wunderink 2001](#)) included patients that met our definition for severe sepsis.

Following the initial clinical trial, a subsequent trial ([Nelson 2000](#)) included patients with community-acquired multilobar pneumonia, as the previous trial had suggested that this group, recognized as a group at higher risk for mortality, might have benefited from G-CSF. In this study (n = 480), there were fewer diabetics in the intervention group, but they were otherwise well balanced. The primary endpoint was a composite endpoint of organ dysfunction, empyema or death. Mortality and markers of adverse events, including organ dysfunction was reported.

A small trial ([Wunderink 2001](#); n = 18) was conducted specifically in patients with pneumonia and septic shock primarily to evaluate safety. Patients were randomized 2:1 to filgrastim (300 mcg / day for five days) or placebo and included patients with both community-acquired and hospital-acquired pneumonia. Mortality at seven and 28 days as well as markers of adverse events including organ dysfunction was reported.

Following the safety analysis of the previous study, a large study ([Root 2003](#); n = 701) evaluated filgrastim (300 mcg / day for five days) in patients with severe sepsis and community-acquired or hospital-acquired pneumonia requiring admission to intensive care. Neutropenic patients and those who had received chemotherapy were not excluded. Intervention and control groups were well balanced at baseline. Mortality at 28 days and total adverse events were reported. Unpublished data regarding specific rates of organ dysfunction was provided by the study sponsors ([Foote 2003](#)).

A fifth trial was initially identified as an abstract in German (with data obtained from correspondence with the authors ([Kober 2004](#))) and subsequently published ([Hartmann 2005](#); n = 29). This study enrolled patients with hospital-acquired pneumonia but was terminated early due to poor enrolment. G-CSF was administered according to a weight-based protocol (300 mcg / day for patients less than 75 kg, 480 mcg / day for patients more than 75 kg; for up to seven days). Mortality at 15 days was the primary endpoint but 30-day mortality was also reported. Rates of serious adverse events were sought, as were rates of ARDS.

A small sixth trial was conducted in Thailand in patients with severe sepsis due to suspected melioidosis (a tropical infection due to *Burkholderia pseudomallei* (*B. pseudomallei*)) ([Cheng 2006](#)). Study subjects were allocated to receive lenograstim (263 mcg intravenously daily for three days). Although treatment allocation was by computer generated list and pre-prepared boxes, only treating clinicians and investigators were blinded to the treatment. Of the 60 patients enrolled, 36 had pneumonia and this data was included in this review; G-CSF was not associated with a mortality benefit in all patients, those with melioidosis or those with pneumonia. The primary outcome measure was 28-day mortality. Due to the short survival of patients in this study, adverse events were not able

to be attributed to treatment.

The bacterial aetiology was similar in all studies, with *Streptococcus pneumoniae* (*S. pneumoniae*) the most common organism found. In the studies of patients with septic shock, there was a greater proportion of *Staphylococcus aureus* (*S. aureus*) compared to *Haemophilus influenzae* (*H. influenzae*) reflecting the more severe illness that accompanies infection with *S. aureus*. Gram negative organisms predominated in the study of patients with hospital-acquired pneumonia (Hartmann 2005) and the Thai study which enrolled patients with suspected melioidosis (due to *B. pseudomallei*) (Cheng 2006).

Excluded studies

Ten studies were identified for detailed evaluation. Correspondence with the study sponsors confirms that a then-unpublished study of G-CSF in pneumococcal pneumonia referred to in Nelson (Nelson 2000) refers to a subgroup of Root (Root 2003). Of the remaining studies, one was not a randomized controlled trial (Hustinx 1998). One study (Meyanci 2001) did not report clinical endpoints such as mortality and the rate of organ dysfunction and thus was excluded from further analysis. Another study reported primarily immunological endpoints following a single dose of filgrastim (Droemann 2006). A small pilot study was excluded as study subjects were administered a range of doses of G-CSF but no placebo group was included (deBoisblanc 1997).

An initial clinical trial (Nelson 1998) excluded patients with septic shock, regarded as high risk for developing ARDS, and was conducted in multiple sites in North America and Australia. It included only patients with community-acquired pneumonia requiring hospital admission. Although patients were required to have two risk factors that had been demonstrated to be associated with increased mortality, patients with septic shock were specifically excluded. In this large study (n = 756), filgrastim (300 mcg / day for 10 days) and control groups were balanced with regard to risk factors. The primary end point was a composite measure of clinical findings ("time to resolution of morbidity"), but other endpoints were reported.

Risk of bias in included studies

There was general agreement between the study review authors; a number of minor issues regarding outcome measures were resolved by discussion.

Follow up was generally good but incomplete in between 3% to 7.9% of participants.

Allocation

The method of randomization and generation of allocation sequence was only reported in one paper (Root 2003), but contact

with the study authors and sponsors confirms that computer-generated randomization lists and *a priori* numbered boxes were used in each centre in all studies (Foote 2003).

Blinding

It is likely that blinding after allocation of healthcare providers and observers may have been incomplete as median white cell counts were much higher in the G-CSF treated groups (Nelson 1998; Nelson 2000) but the degree of blinding was not formally assessed.

Effects of interventions

Six studies with a total of 2018 patients were identified.

Mortality and other efficacy endpoints

None of the studies demonstrated a statistically significant mortality benefit; a pooled estimate of efficacy similarly did not demonstrate a significant benefit associated with G-CSF. There was some heterogeneity amongst studies with regard to 28-day mortality (P = 0.13, I-squared (I²) = 41%) but this was not statistically significant. Pooling results across all five studies, the pooled odds ratio for 28-day mortality was 0.81 (random-effects model), 95% confidence interval (CI) 0.52 to 1.27).

A number of the endpoints intended for analysis were not reported, including time to hospital discharge (no interquartile range reported in any study), the rate of intubation (only reported in Nelson 1998), in-hospital mortality (only reported in Nelson 1998 and Hartmann 2005). Duration of ICU stay was not reported in one study (Wunderink 2001); in the remaining four studies, no differences were seen in median ICU stay which ranged from four days in both groups (Nelson 1998) to 16 days in both groups (Hartmann 2005), reflecting the severity of illness of each study population

Adverse events

Overall, there was a reduction in adverse events that was not statistically significant (pooled odds ratio was 0.79; 95% CI 0.50 to 1.23). This was largely due to a reduction in rates in organ dysfunction, highest in the study of community-acquired pneumonia (Nelson 1998). In that study, there was a significant decrease in rates of ARDS (OR 0.28; 95% CI 0.09 to 0.28) but this was not seen in subsequent studies; overall use of G-CSF was not associated with a reduction in ARDS (OR 0.92; 95% CI 0.44 to 1.93). When considering rates of individual organ dysfunction, there was a moderate decrease in the rates of disseminated intravascular coagulation (OR 0.74; 95% CI 0.38 to 1.44), acute renal failure (OR 0.79; 95% CI 0.48 to 1.31) and incident septic shock (OR 0.61; 95% CI 0.34 to 1.09), but this was not statistically significant.

community-acquired pneumonia, hospital-acquired pneumonia and ventilator-associated pneumonia

Only two of the three studies that included patients with hospital-acquired pneumonia reported results by category. In the larger study (Root 2003), patients with hospital-acquired pneumonia constituted a minority (20%) of patients and were distributed evenly in intervention and placebo groups.

Presence of severe sepsis

Outcome measures were not reported by the presence or absence of severe sepsis in the earlier trials. (Nelson 1998; Nelson 2000). In these trials, however, septic shock was a specific exclusion; the pooled odds ratio of incident septic shock was 0.60 (95% CI 0.34 to 1.08). There was a moderate decrease in 28-day mortality in these trials (pooled OR 0.80; 95% CI 0.52 to 1.22) that was not statistically significant.

There was a trend to an increasing odds ratio of serious adverse events and organ dysfunction in the studies of patients with severe sepsis in filgrastim-treated patients (Root 2003; Wunderink 2001). For total serious adverse events, the pooled odds ratio (random-effects) in the studies of patients with severe sepsis was 1.10 (95% CI 0.82 to 1.49) compared to the other studies (0.72; 95% CI 0.51 to 1.01). Mortality was higher in the G-CSF groups in the largest trial that included severe sepsis (Root 2003, OR 1.2, 95% CI: 0.86 to 1.67, which did not exclude patients with neutropenia) but lower in the two small trials (OR 0.17, 0.12 respectively, not pooled due to clinical heterogeneity) (Cheng 2006; Hartmann 2005).

Bacterial aetiology

Results were not reported by bacterial etiology; it was not possible to draw conclusions on the efficacy of G-CSF in each of these groups.

Analyses of patients with specific co-morbidities

We were also unable to perform subgroup analyses on patients with specific co-morbid conditions due to a lack of data.

Sensitivity analysis

Given the small number of studies, we did not perform a sensitivity analysis.

Assessment of publication bias

No individual study demonstrated a mortality benefit. The ability to interpret a funnel plot was limited by the small number of trials identified.

DISCUSSION

Efficacy

This analysis suggests that G-CSF may be associated with a small mortality benefit, but there is considerable uncertainty with a plausible range of outcomes ranging from a 48% reduction in mortality odds to a 27% increase in mortality odds. Richard Root (Root 2003) suggests several reasons for the failure of previous animal work to demonstrate a clear benefit in humans; invalid hypothesis, inadequate dosing or activity, improper study design or failed execution. He suggests that, primarily, delays in the administration of G-CSF to satisfy microbiological study criteria may have contributed to its negative result.

Adverse events

Our results suggest that G-CSF does not increase the rates of immunologically mediated organ dysfunction by a clinically significant extent. A theoretical concern has been that the use of G-CSF may increase the rate of immunologically mediated end-organ dysfunction, such as acute respiratory distress syndrome (ARDS), to which patients with severe sepsis are particularly prone.

There was a trend towards an increasing risk of organ dysfunction in patients more severely unwell and treated with G-CSF, suggesting that this may have been due to an exacerbation of immunologically mediated disease in patients more at risk of developing organ dysfunction. However, this was not statistically significant in any study and remains speculative. The trend towards a reduction in incident septic shock in patients without this complication at study enrolment may suggest that G-CSF may be operating to prevent this complication.

Decision to pool data from trials

Despite the clinical heterogeneity present between the study populations, we felt it appropriate to pool the results to obtain an overall estimate of efficacy. It was felt that although the inclusion criteria were different, these patients all had varying severity of the same disease and thus the relative efficacy might be expected to remain the same in each group, although the absolute benefit (or harm) might be expected to vary with the mortality of the population studied. Differences in management, and more particularly antibiotics used, may have contributed to heterogeneity, but an analysis by antibiotic group was not possible. Similarly, it was felt that, although patients with severe sepsis may be a higher risk of developing this complication, the mechanism of end-organ dysfunction was the same.

Possible sources of bias

We felt that given the lack of effect demonstrated by the individual published trials, a significant publication bias is unlikely to be operating. However, it is possible that trials may have been withheld from publication due to harmful effects. We have no specific information suggesting this possibility.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no evidence supporting the routine use of G-CSF in the treatment of pneumonia. There is no data on the use of G-CSF in subgroups such as diabetics that may manifest functional neutrophil deficits. We have not identified any methodological issues or biases that may have influenced our pooled results.

Implications for research

Clinical trials where G-CSF was administered earlier in the course of disease or perhaps even prophylactically to prevent hospital-acquired infection in high risk patients might be of interest. Similarly, studies of G-CSF for organisms where neutrophil function

may be more important, or in hosts with co-morbid illnesses that may manifest acquired neutrophil dysfunction may be of interest.

Researchers are encouraged to report methodological parameters, such as generation of allocation sequence, allocation concealment, blinding and loss to follow up as well as standardized outcome measures. A useful parameter that may have an impact on outcome, the proportion of patients on appropriate antibiotics within the first 24 hours of therapy, should also be reported.

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REFERENCES

References to studies included in this review

Cheng 2006 *{unpublished data only}*

Cheng A. A randomized placebo controlled trial of G-CSF for severe melioidosis. Unpublished data 2006.

Hartmann 2005 *{published and unpublished data}*

Hartmann P, Lammertink J, Mansmann G, Hubel K, Salzburger B, Engert A, et al. A randomized, placebo-controlled study of the use of filgrastim in non-neutropenic patients with nosocomial pneumonia. *European Journal of Medical Research* 2005;**10**(1):29–35. [MEDLINE: 15737951]

Mansmann G, Lammertink J, Hartmann P, Hübel K, Oberhäuser F, Stützer H, et al. A randomized, placebo-controlled trial of Granulocyte Colony-Stimulating Factor (G-CSF, Filgrastim) in nonneutropenic patients with nosocomial pneumonia. Unpublished manuscript 2005.

Mansmann G, Lammertink J, Hartmann P, Salzberger B, Engert A, Fatkenheuer G. Results of a randomised, placebo-controlled study on the use of Granulocyte colony stimulating factor (G-CSF) in nosocomial pneumonia (NP) [Ergebnisse einer randomisierten, plazebokontrollierten Studie zum Einsatz von Granulozyten-Kolonien-stimulierender Faktor (G-CSF) bei nosokomialer Pneumonie (NP)]. *Pneumologie* 2001;**55**(Suppl):60.

Nelson 1998 *{published data only}*

Nelson S, Belknap SM, Carlson RW, Dale D, DeBoisblanc B, Farkas S, et al. A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalized patients with community-acquired pneumonia. CAP Study Group. *Journal of Infectious Diseases* 1998;**178**(4):1075–80.

Nelson 2000 *{published data only}*

Nelson S, Heyder AM, Stone J, Bergeron MG, Daugherty S, Peterson G. A randomized controlled trial of filgrastim for the treatment of hospitalized patients with multilobar pneumonia. *Journal of Infectious Diseases* 2000;**182**(3): 970–3.

Root 2003 *{published data only}*

Root RK, Lodato RF, Patrick W, Cade JF, Fotheringham N, Milwee S, et al. Multicenter, double-blind, placebo-controlled study of the use of filgrastim in patients hospitalized with pneumonia and severe sepsis. *Critical Care Medicine* 2003;**31**(2):367–73.

Wunderink 2001 *{published data only}*

Wunderink R, Leeper K Jr, Schein R, Nelson S, DeBoisblanc B, Fotheringham N, et al. Filgrastim in patients with pneumonia and severe sepsis or septic shock. *Chest* 2001; **119**(2):523–9.

References to studies excluded from this review

deBoisblanc 1997 *{published data only}*

deBoisBlanc BP, Mason CM, Andresen J, Logan E, Bear MB, Johnson S, et al. Phase 1 safety trial of Filgrastim (r-metHuG-CSF) in non-neutropenic patients with severe pneumonia. *Respiratory Medicine* 1997;**91**:387–94.

Droemann 2006 *{published data only}*

Droemann D, Hansen F, Aries SP, Braun J, Zabel P, Dalhoff K, et al. Neutrophil apoptosis, activation and anti-inflammatory cytokine response in granulocyte colony-stimulating factor-treated patients with community-acquired pneumonia. *Respiration* 2006;**73**(3):340–6.

Hustinx 1998 *{published data only}*

Hustinx WN, Van Kessel CP, Heezius E, Burgers S, Lammers JW, Hoepelman IM. Effects of granulocyte colony-stimulating factor (G-CSF) treatment on granulocyte function and receptor expression in patients with ventilator-dependent pneumonia. *Clinical and Experimental Immunology* 1998;**112**(2):334–40.

Meyanci 2001 *{published data only}*

Meyanci G, Oz H. Combination of granulocyte colony-stimulating factor and antibacterial drugs for the treatment of ventilatory associated nosocomial pneumonia. *Middle Eastern Journal of Anaesthesiology* 2001;**16**(1):91–101.

Additional references

Alderson 2004

Alderson P, Green S, Higgins JPT. Assessment of study quality. *Cochrane Reviewers' Handbook 4.2.1. Section 6 [updated December, 2003]*. Vol. **Issue 1**, Chichester, UK: John Wiley & Sons, 2004.

Annane 2002

Annane D, Sibille C, Charpentier C, Bollaert PE, Francois B, Korach JM, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA* 2002;**288**(7):862–71.

ATS 2005

American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine* 2005;**171**:388–416.

Azoulay 2001

Azoulay E, Attalah H, Harf A, Schlemmer B, Delclaux C. Granulocyte colony-stimulating factor or neutrophil-induced pulmonary toxicity: myth or reality? Systematic review of clinical case reports and experimental data. *Chest* 2001;**120**(5):1695–1701.

Bartlett 1995

Bartlett JG, Mundy LM. Community-acquired pneumonia. *New England Journal of Medicine* 1995;**333**(24):1618–24.

Berghmans 2002

Berghmans T, Paesmans M, Lafitte JJ, Mascaux C, Meert AP, Jacqy C, et al. Therapeutic use of granulocyte and granulocyte-macrophage colony-stimulating factors in

febrile neutropenic cancer patients. A systematic review of the literature with meta-analysis. *Supportive Care in Cancer* 2002;**10**(3):181–8.

Bernard 2001

Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *New England Journal of Medicine* 2001;**344**(10):699–709.

Bone 1993

Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. *Chest* 1993;**101**(6):1644–55.

BTS 2001

British Thoracic Society. BTS guidelines for the management of community acquired pneumonia in adults. *Thorax* 2001;**56**(Suppl 4):iv1–iv64.

Ewig 1998

Ewig S, Ruiz M, Mensa J, Marcos MA, Martinez JA, Arancibia F. Severe community-acquired pneumonia. Assessment of severity criteria. *American Journal of Respiratory and Critical Care Medicine* 1998;**158**(4):1102–8. [MEDLINE: 5]

Fagon 1993a

Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *American Journal of Medicine* 1993;**94**(3):281–8. [MEDLINE: 6]

Fagon 1993b

Fagon JY, Chastre J, Hance AJ, Domart Y, Trouillet JL, Gibert C. Evaluation of clinical judgment in the identification and treatment of nosocomial pneumonia in ventilated patients. *Chest* 1993;**103**(2):547–53. [MEDLINE: 9]

Fine 1997

Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *New England Journal of Medicine* 1997;**336**(4):243–50. [MEDLINE: 11]

Foote 2003

Foote M. Personal communication 2003.

Garner 1988

Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections. *American Journal of Infection Control* 1988;**16**(3):128–40. [MEDLINE: 8]

Hartung 1999

Hartung T. Granulocyte colony-stimulating factor: its potential role in infectious disease. *AIDS* 1999;**13**(Suppl 2):3–9. [MEDLINE: 20061789]

Hebert 1990

Hebert JC, O'Reilly M, Gamelli RL. Protective effect of recombinant human granulocyte colony-stimulating factor against pneumococcal infections in splenectomized mice. *Archives of Surgery* 1990;**125**(8):1075–8. [MEDLINE: 2]

Higgins 2005

Higgins JPT, Green S, editors. Developing and documenting a search strategy for studies and organizing search results. *Cochrane Handbook for Systematic Reviews of Interventions 4.2 [updated May 2005]; Section 5. In: The Cochrane Library, Issue 3.* Chichester, UK: John Wiley & Sons, Ltd, 2005.

Kober 2004

Kober T, Engert A. Personal communication 2004.

McKenna 1996

McKenna P, Nelson S, Andresen J. Filgrastim (rHuG-CSF) enhances ciprofloxacin uptake and bactericidal activity of human neutrophils in vitro [abstract 535, American Thoracic Society meeting, May, 1996]. *American Journal of Respiratory and Critical Care Medicine* 1996;**153**:A535.

Niederman 1993

Niederman MS, Bass JB, Jr, Campbell GD, Fein AM, Grossman RF, Mandell LA, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. American Thoracic Society. Medical Section of the American Lung Association. *American Review of Respiratory Disease* 1993;**148**(5):1418–26. [MEDLINE: 4]

Sanchez-Nieto 1998

Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, El Ebiary M, Carrillo A, Ruiz J, et al. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study. *American Journal of Respiratory and Critical Care Medicine* 1998;**157**(2):371–6. [MEDLINE: 7]

Smith 1995

Smith WS, Sumnicht GE, Sharpe RW, Samuelson D, Millard FE. Granulocyte colony-stimulating factor versus placebo in addition to penicillin G in a randomized blinded study of gram-negative pneumonia sepsis: analysis of survival and multisystem organ failure. *Blood* 15–8–1995; **86**(4):1301–9. [MEDLINE: 3]

Stephens 2002

Stephens DP, Fisher DA, Currie BJ. An audit of the use of granulocyte colony-stimulating factor in septic shock. *Internal Medicine Journal* 2002;**32**(4):143–8. [MEDLINE: 1]

Weiss 1999

Weiss M, Moldawer LL, Schneider EM. Granulocyte colony-stimulating factor to prevent the progression of systemic nonresponsiveness in systemic inflammatory response syndrome and sepsis. *Blood* 1999;**93**(2):425–39.

Welte 1996

Welte K, Gabrilove J, Bronchud MH, Platzer E, Morstyn G. Filgrastim (r-metHuG-CSF): the first 10 years. *Blood* 1996;**88**(6):1907–29.

References to other published versions of this review**Cheng 2003**

Granulocyte colony stimulating factor as an adjunct to antibiotics for treating pneumonia in adults. Cheng AC, Stephens DP, Currie BJ. *Cochrane Database of Systematic Reviews* 2003, Issue 4.

Cheng 2004

Cheng AC, Stephens DP, Currie BJ. Granulocyte colony stimulating factor as an adjunct to antibiotics for treating pneumonia in adults. *Cochrane Database of Systematic Reviews* 2004, Issue 3.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Cheng 2006

Methods	Single center, single blinded RCT	
Participants	Community-acquired severe sepsis	
Interventions	Lenograstim 263 mcg iv 3 days	
Outcomes	30 day mortality, duration of survival	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hartmann 2005

Methods	Single center, double blinded RCT	
Participants	Hospital-acquired pneumonia in ICU patients	
Interventions	G-CSF 300 mcg/day or 480 mcg/day for up to 7 days versus placebo	
Outcomes	15 day mortality, safety, duration of antibiotic therapy	
Notes	Study terminated early due to poor enrolment	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nelson 1998

Methods	Multicenter, double blinded RCT	
Participants	Community-acquired pneumonia in hospitalized adults.	
Interventions	G-CSF 300 mcg/day for 10 days versus placebo	

Nelson 1998 (Continued)

Outcomes	Time to resolution of morbidity, 28-day mortality, time to ICU and hospital discharge, adverse events including organ dysfunction	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Nelson 2000

Methods	Multicenter, double blinded RCT	
Participants	Community-acquired multilobar pneumonia in hospitalized adults	
Interventions	G-CSF 300 mcg/day for 10 days versus placebo	
Outcomes	28-day mortality, therapeutic failure, adverse events including organ dysfunction No difference in organ dysfunction	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Root 2003

Methods	Multicenter, double blinded RCT	
Participants	Confirmed hospital-acquired or community-acquired pneumonia with severe sepsis	
Interventions	G-CSF 300 mcg/day for 5 days versus placebo	
Outcomes	28 day mortality, time to ICU discharge, adverse events	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description

Root 2003 (Continued)

Allocation concealment?	Yes	A - Adequate
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Wunderink 2001

Methods	Double blinded RCT in 3 centres in the US	
Participants	Confirmed hospital-acquired or community-acquired pneumonia with severe sepsis	
Interventions	G-CSF 300 mcg/d for 5 days versus placebo	
Outcomes	Safety	
Notes	Small study. Heterogenous population	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

mcg = micrograms

iv = intravenously

ICU = intensive care unit

RCT = randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
deBoisblanc 1997	Dose ranging pilot study; no control group included
Droemann 2006	Controlled trial of single dose of G-CSF, but with immunological endpoints: few clinical endpoints reported
Hustinx 1998	Not a randomized controlled trial
Meyanci 2001	Clinical endpoints, such as mortality or rates of organ dysfunction, were not reported

DATA AND ANALYSES

Comparison 1. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 28 day mortality	6	2018	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.52, 1.27]

Comparison 2. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event (including organ dysfunction)	5	1984	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.50, 1.23]
2 Adult respiratory distress syndrome	5	1984	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.44, 1.93]
3 Disseminated intravascular coagulation	4	1953	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.38, 1.44]
4 Acute renal failure	4	1953	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.48, 1.31]
5 Septic shock	2	1236	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.34, 1.09]

WHAT'S NEW

Last assessed as up-to-date: 28 January 2007.

Date	Event	Description
6 August 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 4, 2003

Date	Event	Description
8 May 2009	Amended	Contact details updated.
21 August 2008	Amended	Converted to new review format.
9 March 2004	New search has been performed	Searches conducted.
24 April 2003	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

AC and BC conceived the idea, AC and DS reviewed the papers and AC drafted the protocol and review. All authors contributed to data analysis and revisions to the draft.

DECLARATIONS OF INTEREST

We conducted a randomized controlled trial of the use of G-CSF in septic shock included in this review ([Cheng 2006](#)) and received a donation of product from Merck, formerly the Australian distributor of lenograstim. We have no other conflict of interest; in particular, we have not received financial support from pharmaceutical companies for this proposed study.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Chemotherapy, Adjuvant; Community-Acquired Infections [drug therapy; mortality]; Granulocyte Colony-Stimulating Factor [*therapeutic use]; Pneumonia [*drug therapy; mortality]; Randomized Controlled Trials as Topic; Recombinant Proteins

MeSH check words

Adult; Humans