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GENERAL AND SUPPORTIVE CARE

Prophylactic colony-stimulating factors in children receiving myelosuppressive chemotherapy: A meta-analysis of randomized controlled trials

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KEYWORDS
Colony-stimulating factors;
Febrile neutropenia;
Infection

Summary
Background: The colony-stimulating factors (CSFs) are widely utilized to prevent neutropenic complications in both adults and children, but randomized controlled trials in the pediatric setting have reported varied results. A systematic review of the literature and meta-analysis were conducted to definitively assess the impact of prophylactic CSFs on the risk of febrile neutropenia (FN) in pediatric oncology patients.
Methods: MEDLINE was searched and references hand-searched through July 2004 for randomized controlled trials of prophylactic G-CSF or GM-CSF in pediatric oncology patients. Objectives, outcomes, and quality of the 16 included studies were extracted by two reviewers. Weighted summary estimates of relative risks (RR) were calculated for FN and documented infection (DI). Mean differences in hospitalization, antibiotic use, and duration of neutropenia were calculated.
Results: FN occurred in 68% of 400 controls and 59% of 404 CSF patients. The estimated RR was 0.88 [0.81–0.97; ($P = 0.01$)] favoring the CSFs for leukemia and high grade lymphoma studies and 0.71 [0.51–0.97; ($P = 0.03$)] for solid tumor studies. DI occurred in 25% of controls and 20% of CSF patients for an estimated RR of 0.80 [0.61–1.06; ($P = 0.12$)]. The mean decrease in duration of neutropenia was 3.5 days [2.2–4.7; ($P < 0.0001$)]. Mean decreases favoring CSF use were also observed for

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hospital stay of 1.7 days [0.9—2.5 ($P < 0.01$)] and antibiotic use of 2.0 days [0.4—3.6; $P = 0.02$].
Conclusions: Prophylactic CSFs significantly decrease the incidence of FN and the durations of severe neutropenia, hospitalization, and antibiotic use in pediatric cancer patients, but they do not significantly decrease documented infections.

Introduction

Both intensive chemotherapeutic regimens and improved supportive care have contributed to a dramatic increase in long-term disease-free survival among pediatric cancer patients over the past several decades. However, pediatric oncology patients who receive high-dose chemotherapy are at increased risk for serious infections while neutropenic. The frequency and severity of infections in these patients are directly related to the severity and duration of neutropenia.[1] As with adults, pediatric patients with febrile neutropenia (FN) are generally hospitalized and placed on broad-spectrum antibiotics until resolution of the neutropenia and fever. In addition, chemotherapy treatment may be delayed or reduced because of prolonged neutropenia potentially compromising chemotherapy effectiveness. Recombinant hematopoietic growth factors, particularly granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been used with success when administered prophylactically in both adult and pediatric patients over the past 10—15 years.[2—6]

Much has been written in the adult literature about the benefits of recombinant colony-stimulating factors (CSFs) in reducing the morbidity and mortality of systemic chemotherapy. Multiple randomized controlled trials and several meta-analyses have shown that CSFs reduce the risk of FN, and documented infection.[7—25] Despite the fact that the American Society of Clinical Oncology has developed practice guidelines for the use of CSFs in adults, pediatric chemotherapy protocols do not provide consistent guidance as to when growth factors are needed.[3—5] Pediatric cancer patients differ from adults in that they generally have fewer comorbid illnesses prior to starting therapy, but cancer therapy in pediatric populations is often more intensive and more likely to result in severe myelosuppression.[26—28] For children there remains considerable uncertainty regarding the role of growth factors for prophylaxis.

There have been several randomized controlled trials (RCTs), mostly small, of pediatric oncology patients comparing prophylactic G-CSF or GM-CSF to placebo or no treatment.[29—44] There have also been studies showing that the use of CSFs for the treatment of febrile neutropenia may be beneficial in some patients,[45—51] and many uncontrolled or non-randomized pilot studies have suggested similar results in a variety of clinical settings.[52—69] Studies of prophylactic CSFs have produced variable results with small numbers of patients, so it remains difficult to determine which patients are most likely to derive benefit from therapy.

Although there have been several review articles and general pediatric practice guidelines written,[2,8,29,70—81] there has only been one other effort to conduct a systematic review of the use of CSFs in the pediatric population.[82] Recommendations from a European panel for the use of the CSFs in children with cancer include primary prophylaxis of FN in patients treated with intensive chemotherapy, secondary prophylaxis in those with history of severe neutropenia, intervention for life-threatening infections, preparation for stem cell collection, or enhancement of engraftment following autologous or allogeneic bone marrow transplants.[81]

A systematic review of the literature and formal meta-analysis is reported here of randomized controlled trials of prophylactic G-CSF or GM-CSF versus placebo or no treatment in pediatric cancer patients receiving myelosuppressive chemotherapy.

Methods

Selection of studies

MEDLINE, the Cochrane Library, and Best Evidence (ACP Journal Club and Evidence-Based Medicine), were searched through July 2004 for RCTs of prophylactic G-CSF or GM-CSF in pediatric cancer patients. Subject headings and key words included: ''colony-stimulating factor,'' ''granulocyte colony-stimulating factor,'' ''granulocyte-macrophage colony-stimulating factor,'' and ''neutropenia.'' We used an Ovid saved expert search for ''therapy'' to identify clinical trials and meta-analyses (Table 1). We limited the search to pediatric patients by using truncated forms of ''pediatric,'' ''child,'' ''infant,''

Table 1 Ovid expert therapy search strategy

EB filter − therapy, treatment	
1	exp research design/
2	exp clinical trials/
3	comparative study/or placebos/
4	exp treatment outcome/
5	double-blind method/or single-blind method/
6	((single or double or triple) adj blind$3).ti,ab.
7	random$.ti,ab.
8	controlled clinical trial.pt.
9	randomized controlled trial.pt.
10	practice guideline.pt.
11	clinical trial.pt.
12	(clinical adj trial$1).ti,ab.
13	placebo$1.ti,ab.
14	clinical protocols/or feasibility studies/or pilot projects/
15	exp epidemiologic research design/
16	(control$3 adj trial$1).ti,ab.
17	5 or 7 or 10 or 11 or 13
18	or/1−16

and ''adolescent'' in either the title or abstract in an attempt to exclude those studies consisting of only adult patients.

We included those studies of children ⩽18 years or those ⩽25 years of age and being treated on pediatric oncology cooperative group protocols. We excluded studies of patients receiving treatment with CSFs after established FN and those studies of patients receiving high-dose chemotherapy followed by bone marrow or stem cell transplants. The references of the studies as well as those of major pediatric oncology textbooks were hand-searched for additional studies.

This electronic search yielded 596 studies; 26 additional studies were obtained by hand-searching the references, and another 13 studies were obtained by searching for names of key authors. Of these 635 abstracts, 112 studies were read in full, and 16 RCTs of prophylactic CSFs were included in our final analysis. Of the studies that were excluded, 28 were background information or review articles,[1,2,6,12−16,18,27,28,45,70−73,76,77,79−81,83−89] 14 were studies only containing adults,[7,11,17,18,20,21,25,26,45,49,90−93] and 10 studies included both adults and children but the pediatric data could not be separated out.[8,10,23,94−100] Five studies were cost analyses,[101−106] 4 were in patients who received bone marrow or stem cell transplants,[107−110] and 5 were pharmacokinetic studies.[111−115] Of the excluded studies that contained only children, 2 were retrospective case−control studies,[53,59] 11 had no control groups,[52,54−56,58,66,68,69,75,116,117] 11 the CSF was not randomly assigned,[46,57,60−65,67,112,118] and 6 were of treatment rather than prophylactic uses of CSFs.[47,48,50,51,119,120] (Fig. 1)

Both parallel and crossover studies were included. Ten of the studies were of acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL), while four were of solid tumors and two were mixed. Eleven of the studies were conducted in Europe,[29,31,32,34,36−39,41−43] and 5 in the United States and Canada.[30,33,35,40,44] Three studies used GM-CSF,[29,30,42] and 13 used G-CSF.[31−41,43,44] (Table 2). Although the doses and modalities of delivery of the CSFs varied, all studies employed doses and schedules that appeared reasonable and unlikely to affect the outcomes of interest.[2,116] (Table 3). The studies varied in size from 12 to 287 patients.

Data extraction

Two independent reviewers (BW and JH) extracted data on basic study design, patient characteristics, study outcomes, and measures of study quality. Primary outcomes considered in this analysis included the incidence of FN, incidence of documented infection (DI), duration of neutropenia, length of hospitalization, and length of antibiotic therapy. Other outcomes reported in fewer than half the studies included the number of red blood cell or platelet transfusions, incidence and severity of mucositis, and overall and infection-free survival, so these outcomes were not analyzed further. In the event that more than one chemotherapy cycle was reported, the first cycle for each patient was analyzed.

Evaluation of study adherence to CONSORT guidelines

All studies were evaluated for compliance with the guidelines provided by the CONSORT Statement.[121] All 16 studies randomized patients to CSF treatment versus control or not treatment, but only two studies[36,39] described the randomization process in detail. Six of the studies were crossover designs with patients serving as their own controls in different cycles of chemotherapy. Only the first cycle of treatment were included in the analysis in such studies. Only two of the studies had placebo controls and were double blinded,[30,40] and the rest used no treatment as a control. All studies clearly stated their inclusion and exclusion criteria, described patients' baseline characteristics, accounted for withdrawals and missing data, and obtained approval from the local institutional review boards. Six of the 16 studies provided sample

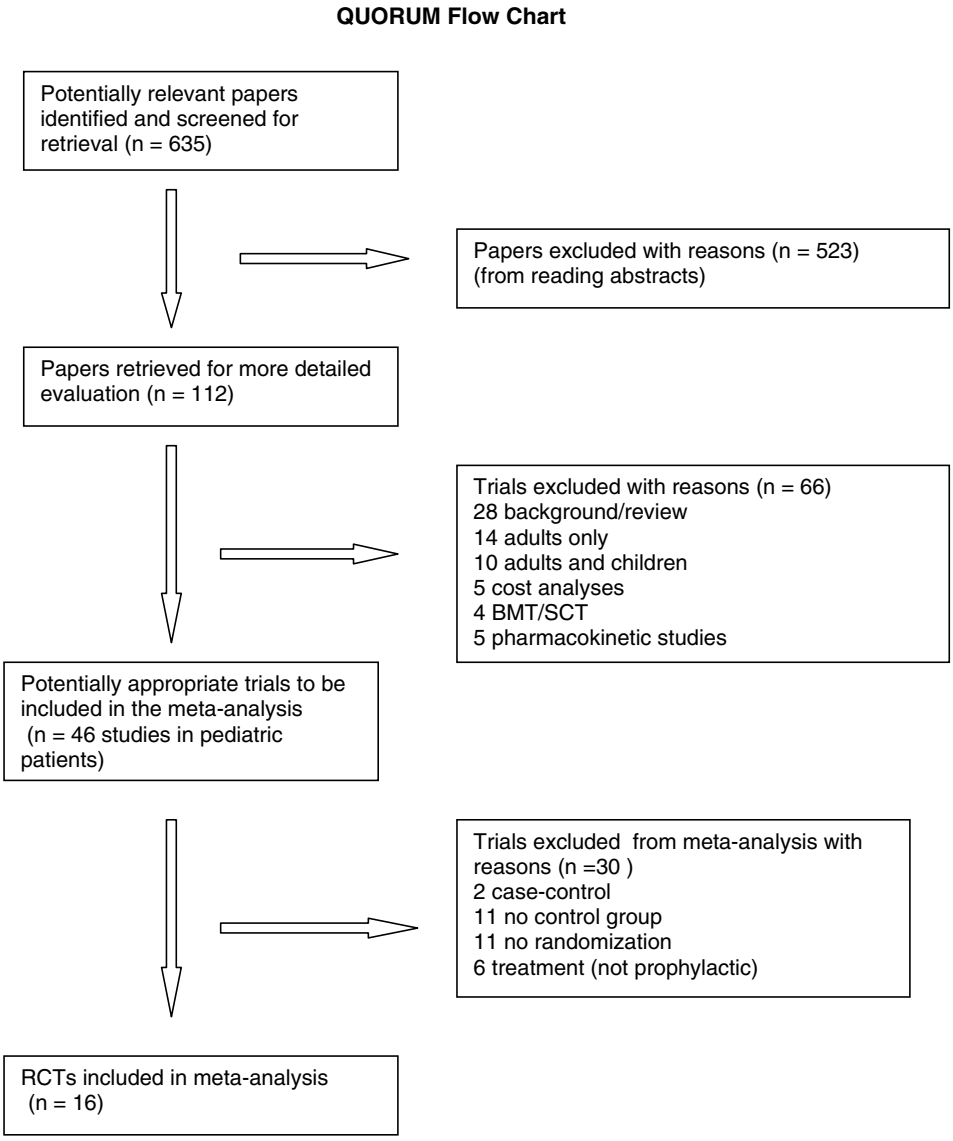

Figure 1 The QUOROM statement flow diagram.

size calculations based on detecting clinically important differences between the two treatment groups with a reasonable degree of confidence.[35,38–40,43,44] All studies used an intention-to-treat analysis, and one study[36] allowed for patients to receive CSFs if they were admitted with FN. This would most likely decrease the detectable differences between the two groups. Since all selected studies were randomized trials and generally followed the requirements of the CONSORT guidelines in reporting data, study quality appeared consistent across the trials included.

Statistical methods

Testing for statistical heterogeneity was conducted for each of the outcomes. The hypothesis that the studies are all drawn from a population of studies with the same effect size is rejected if Q exceeds the upper 100 (1-a) percentile of the χ^2 distribution.[122] Weighted summary odds ratios (OR) were estimated for FN and DI by the method of Peto based on a fixed effects model.[123] Mean differences in durations (days) were estimated by the method of Cohen using a random effects model due to significant heterogeneity.[124] An inconsistency index (I^2) was calculated as an estimate of the proportion of variation in estimates due to heterogeneity rather than between study variation. The I^2 was estimated by the method of Higgins as $(H^2 - 1)/H^2$, where $H^2 = Q/(k - 1)$ and K is the degrees of freedom.[125] The combined estimates were then calculated as the weighted sum of the individual estimates where the weights are the reciprocal of the variance or the interstudy-adjusted variance of the estimates depending upon the model applied.[126]

Table 2 Characteristics of included studies

First author	Year of publication	Years of study	Number of patients	Placebo controlled	Crossover design	Chemotherapy regimen	Type of cancer	Study attrition
Burdach	1995	1988–1990	12	No	Yes	VCR, Actinomycin, DOX Ifosfamide, VP-16, dacarbazine, cisplatin, teniposide	Soft tissue sarcomas	1 early death 2 from side effects only cycle 1 analyzed
Calderwood	1994	1989–1992	40	Yes	No	Cytoxan, Ara-C, 6-MP, MTX	ALL	CSF arm: 4 Control: 1 Noncompliance
Clarke	1999	1995–1996	17	No	Yes	VCR, Prednisolone, L-Asp, 6-MP, MTX	ALL and T-Cell NHL	No drop outs
Dibenedetto	1995	1991–1993	32	No	No	Cytoxan, 6-MP, Ara-C	ALL	No drop outs
Heath	2003	1991–1994	129	No	Yes	VCR, Prednisone, L-Asp, Daunorubicin, Cytoxan, 6-TG, MTX	ALL	10% inevaluable for unclear reasons No difference between arms
Kalmanti	1994	1989–1991	46	No	No	VCR, DOX, Cisplatin, CCNU, Procarbazine, Hydroxyurea, Ara-C, Dacarbazine, methylprednisolone, teniposide, Ifosfamide, MTX, Cytoxan	ALL, NHL, CNS, sarcomas	Not discussed
Laver	1998	1994–1995	88	No	No	VCR, Prednisone, Cytoxan, Doxorubicin, Ara-C, L-Asp, MTX, 6-MP	T-cell ALL or Stage III/IV lymphoblastic lymphoma	No drop outs
Little	2002	1996–1997	48	No	Yes	Daunorubicin, Ara-C, 6-TG, VP-16	ALL, NHL	1 went on to BMT 1 requested withdrawal
Michel	2000	1993–1998	67	No	No	Ara-C, VP-16, Dexamethasone, VCR, MTX, Cytoxan, DOX, Prednisone	ALL	No discussed
Michon	1998	1990–1992	59	No	No	Cytoxan, VCR, DOX, VP-16, cisplatin	Metastatic neuroblastoma	Control arm: 2 (sepsis, disease progression) CSF Arm: death from sepsis
Patte	2002	1994–1996	148	No	No	Cytoxan, VCR, prednisone, DOX, MTX	NHL	Control: 1 for major protocol violation CSF: 0
Pui	1997	1991–1994	148	Yes	No	MTX, Prednisone, VCR, L-Asp, daunorubicin, Vp-16, Ara-C	ALL	16 patients already hospitalized with FN at start of study (9 controls; 7 CSF)
Riikonen	1995	1992–1993	16	No	Yes	''Strong conventional multiagent chemotherapy''	ALL, Wilm's tumor, lymphoma, rhabdomyosarcoma, CNS, neuroblastoma	No drop outs
Van Pelt	1997	1993–1995	13	No	Yes	''Myelosuppressive but not myeloablative''	Sarcomas	No drop outs
Welte	1995	1991–1992	34	No	No	Dexamethasone, 6-MP, VCR, Ara-C, MTX, L-Asp, 6-TG, Daunorubicin, ifosfamide	ALL	No drop outs
Wexler	1996	1990	37	No	No	VCR, Cytoxan, DOX, VP-16, Ifosfamide	Soft tissue sarcomas	1 removed for progressive disease

Table 3 Specifics of CSF Therapy

Study	Type of CSF	Mode of Delivery	Dosage	Start Time	Criteria for Discontinuation	Length of Therapy
Burdach	GM-CSF	IV continuous infusion	250 mcg/m2/day	48 h after chemo	ANC > 1000 for 5 days or WHO Grade III toxicity	Maximum 14 days
Calderwood	GM-CSF	SQ	5.5 mcg/kg/day	Days 5—11 and 19-25	N/A	14 days
Clarke	G-CSF	SQ	5 mcg/kg/day	4 days after completion of chemo	ANC > 500 on 3 consecutive days	Median 8 days (6—13 days)
Dibenedetto	G-CSF	SQ	10 mcg/kg/day	24 h after last chemo	ANC 200, platelets 50,000	N/A
Heath	G-CSF	SQ	5 mcg/kg/day	24 h after last IV chemo	ANC > 2500 for 2 days	N/A
Kalmanti	G-CSF	SQ	5 mcg/kg/day	Day +1 post chemo	ANC > 8000	Maximum 14 days
Laver	G-CSF	SQ	10 mcg/kg/day	24 h after chemo	ANC > 10,000 after nadir	N/A
Little	G-CSF	SQ	5 mcg/kg/day	24 h after chemo	ANC > 10,000 or 10 days	Max 10 days
Michel	G-CSF	SQ	5 mcg/kg/day	24 h after chemo	ANC > 1000	N/A
Michon	G-CSF	SQ	5 mcg/kg/day	48 h after doxorubicin, 24 h after cisplatin	Before day 14 with ANC > 10,000 for 2 days or after day 14	14 days
Patte	G-CSF	SQ	5 mcg/kg/day	24 h after chemo	ANC > 500 for 48 h or WBC > 20,000	6—15 days
Pui	G-CSF	SQ	10 mcg/kg/day	24 h after chemo	ANC > 1000 for 2 days or 15 days	15 days max
Riikonen	G-CSF	SQ	5 mcg/kg/day	Day +1 after chemo	ANC > 1000	Mean 8.8 days (5—13 days)
Van Pelt	GM-CSF	SQ	5 mcg/kg/day	24 h after chemo	10 days	10 days
Welte	G-CSF	SQ	5 mcg/kg/day	Day 7	Day 20 or ANC > 200 after 28 days max therapy or ANC > 30,000	Max 28 days
Wexler	GM-CSF	SQ	15 mcg/kg/day (19 pts) then 5 mcg/kg/day	24—36 h after chemo	Day 19 of cycle or until ANC > 500 for 2 days	N/A

Fixed effects models were utilized to estimate summary measures of FN and DI as no significant heterogeneity was found across studies. Under the fixed effects model, the true treatment effect is assumed to be the same for all studies. Alternatively, random effects models were utilized to estimate summary measures for the duration outcomes as significant heterogeneity was observed. Under the random effects model, the true treatment effect in each trial is assumed to be randomly distributed. With this conservative approach, the true effect may differ between studies due to differences in patient populations, treatment variation or because outcome measures differ from one study to the next. Therefore, two sources of variation are assumed consisting of random error and variation due to real differences between populations, treatments or measured outcomes.

Measures of treatment effect, standard error and 95% confidence limits (CLs) were estimated for all individual studies as well as an overall summary effect estimate. Results are presented as forest plots with effect estimates and 95% confidence limits presented for each individual study and a summary measure and CLs across all studies. Hypothesis testing on summary effect estimates was based on a *z*-statistic. No adjustment for multiple testing was made in the analysis.

Interaction between treatment assignment and a priori specified subgroups (study design, cancer type and type of CSF) were evaluated. Statistically significant differences between subgroups were determined on this basis of non-overlapping 95% confidence intervals on subgroup effect estimates and confirmed by comparing the ratio of the difference in the natural logarithm of the relative risks and the standard error of the difference in log relative risks to the standard normal distribution.[127,128]

Results

Overall study results

Outcomes varied across studies with recommending use of CSFs,[29,31,34,37,38,41] and two studies show no benefit in any measured outcomes.[30,32] The remaining eight studies report benefit based on certain outcome measures but not others.[33,35,36,39,40,42–44] Primary outcomes were reported in greater than half of the studies included in the analysis. Among the 16 identified trials, six studies were crossover of which five reported FN outcomes, two reported DI, five reported duration of neutropenia, three reported duration of antibiotics and five reported duration of hospitalization (Table 2). In those studies patients were randomized to receive CSFs after either the first or a subsequent cycle of chemotherapy to avoid a period effect. In crossover studies that reported multiple cycles of chemotherapy, only the first cycle was evaluated. Patients treated with CSF in the first cycle were compared to those not treated during the first cycle.

Two studies[39,42] allowed for non-absorbable oral antibiotics for selective gut decontamination. Heath[33] specifically used oral nystatin while nine studies specifically mentioned TMP-SMX for PCP prophylaxis. None of the studies stated that prophylactic antibiotics were specifically prohibited. All patients were treated with broad-spectrum antibiotics if they became febrile as that is the standard of care.

Incidence of febrile neutropenia

Of the 12 reporting studies, FN occurred in 68% of 400 control patients and 59% of 404 CSF patients. As shown in Fig. 2, all but two RCTs reported a reduction in risk of FN in the CSF arm of the study. The *Q* statistic for FN was 9.66 ($P = 0.5614$) with an I^2 of zero indicating no observed heterogeneity across studies for FN. The summary OR was 0.591 [95% CI: 0.431—0.810, $P = 0.001$] across studies (Fig. 3). The estimated OR was 0.624 [95% CI: 0.431—0.903; $P = 0.012$] favoring the CSFs for leukemia and high grade lymphoma studies and 0.513 [95% CI: 0.281—0.936; $P = 0.029$] in solid tumor studies with no significant difference between cancer types ($z = 0.544$; $P = 0.293$). Study design likewise demonstrated no significant differences in effect estimates with OR for cross over and

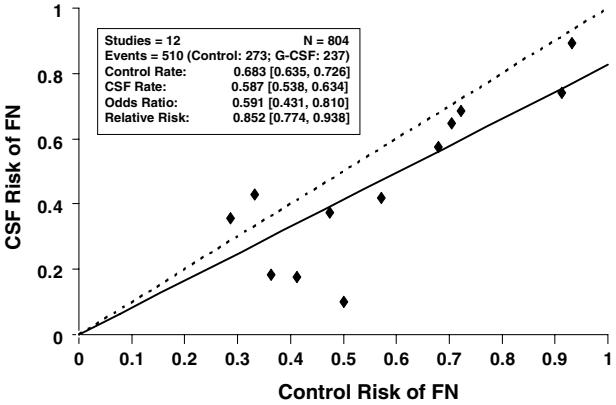

Figure 2 Graph of risk of febrile neutropenia for each study comparing risk in control patients (horizontal axis) to risk in those receiving CSFs (vertical axis). Dashed line represents line of equal risk in both groups under the null hypothesis. The solid line represents a weighted linear regression line through the reported data points.

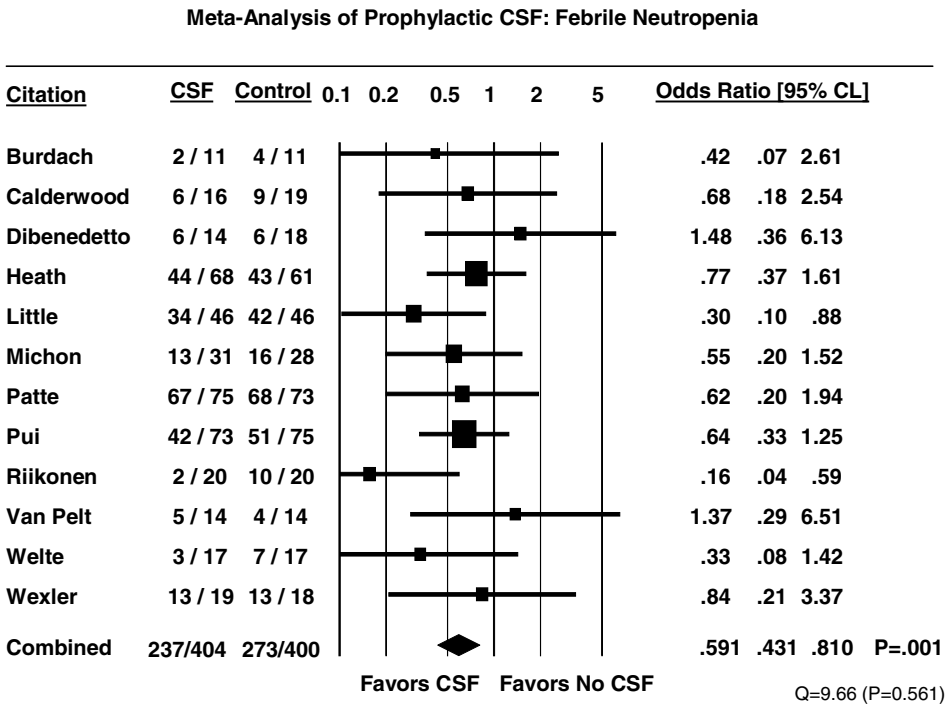

Figure 3 Forest plot of the odds ratio [95% CLs] for febrile neutropenia in CSF compared to control patients.

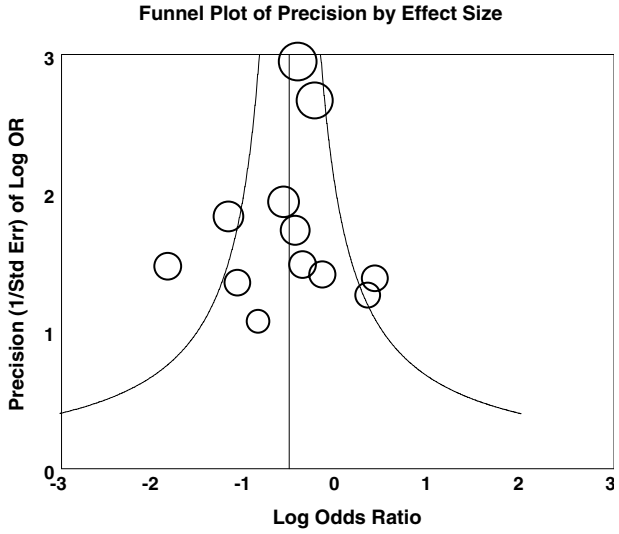

Figure 4 Funnel plot of the treatment effect (logarithm of the estimated odds ratio) and its precision (1/standard error) for each study. The area of each circle is drawn in inverse proportion to the estimate variance. The symmetry observed fails to shown evidence for a publication bias among the studies included in this analysis.

non-cross over studies of 0.509 [95%CI: 0.309—0.839, $P = 0.039$] and 0.652 [95% CI: 0.434, 0.978, $P = 0.008$], respectively ($z = 0.754$; $P = 0.225$). Finally, there was no statistically significant difference between prophylaxis with G-CSF (OR = 0.570 [95% CI: 0.407—0.798; $P < 0.001$]) and GM-CSF (0.759 [95% CI: 0.313—1.837; $P = 0.540$] $z = 0.593$; $P = 0.483$). A funnel plot of the effect size (log OR) versus precision estimated as the reciprocal of the effect size demonstrates a symmetrical pattern with no suggestion of publication bias in this analysis (Fig. 4).

Incidence of documented infection

Nine studies provided information on DI defined in this study as a positive bacterial or fungal culture (blood, urine, skin, CSF) or clinical evidence of infection such as a pneumonia, cellulitis, or overwhelming sepsis. DI occurred in 25% of controls and 20% of CSF patients. The Q-statistic was 13.67 ($P = 0.09$) although the $I^2 = 41\%$ suggesting a moderate degree of heterogeneity for this outcome. The estimated OR was 0.747 [95% CI: 0.518—1.079; $P = 0.12$] demonstrating no significant reduction in documented infection in this subgroup of studies. Of interest, however, the OR = 0.655 [95% CI: 0.427—1.005, $P = 0.053$] among the 7 non-crossover studies (Fig. 5). In addition, the OR for DI among the 8 G-CSF studies was 0.701 [95% CI: 0.479—1.027, $P = 0.068$].

Duration of neutropenia

Thirteen of the 16 studies reported mean or median duration of neutropenia defined as an absolute

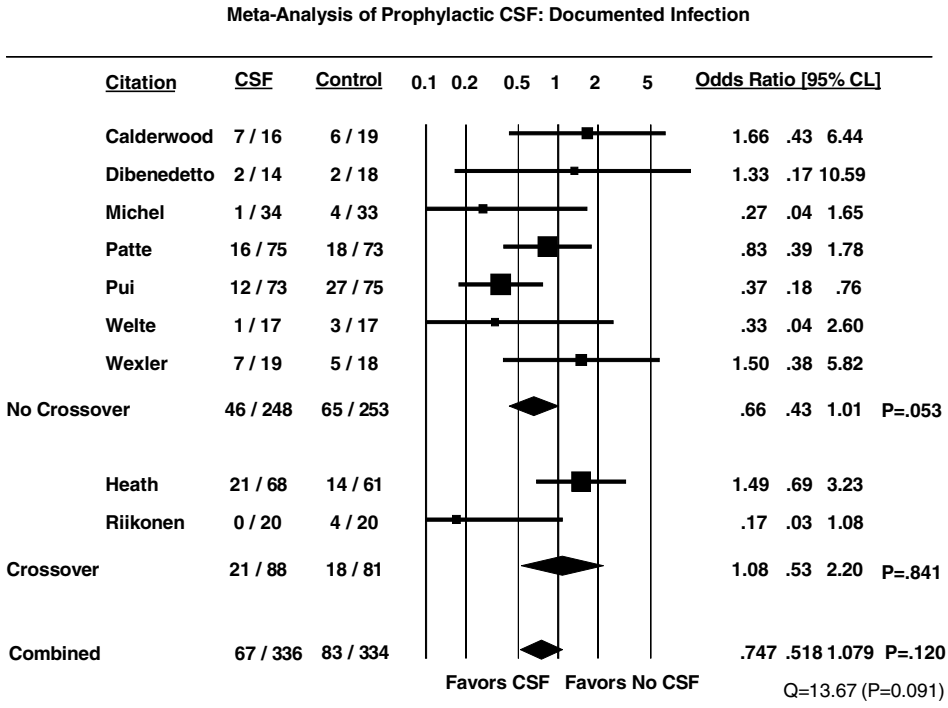

Figure 5 Forest plot of the odds ratio [95% CLs] for documented in patients randomized to receive prophylactic CSF's compared to control patients. Studies are separated based on study design.

neutrophil count (ANC) less than 500/mm^3. As shown in Fig. 6, in all but one study (range: 1—9.8 days), the duration of neutropenia was decreased in patients receiving prophylactic CSF with a mean decrease across studies of 3.40 days [95% CI: 1.85—4.96; $P < 0.0001$].

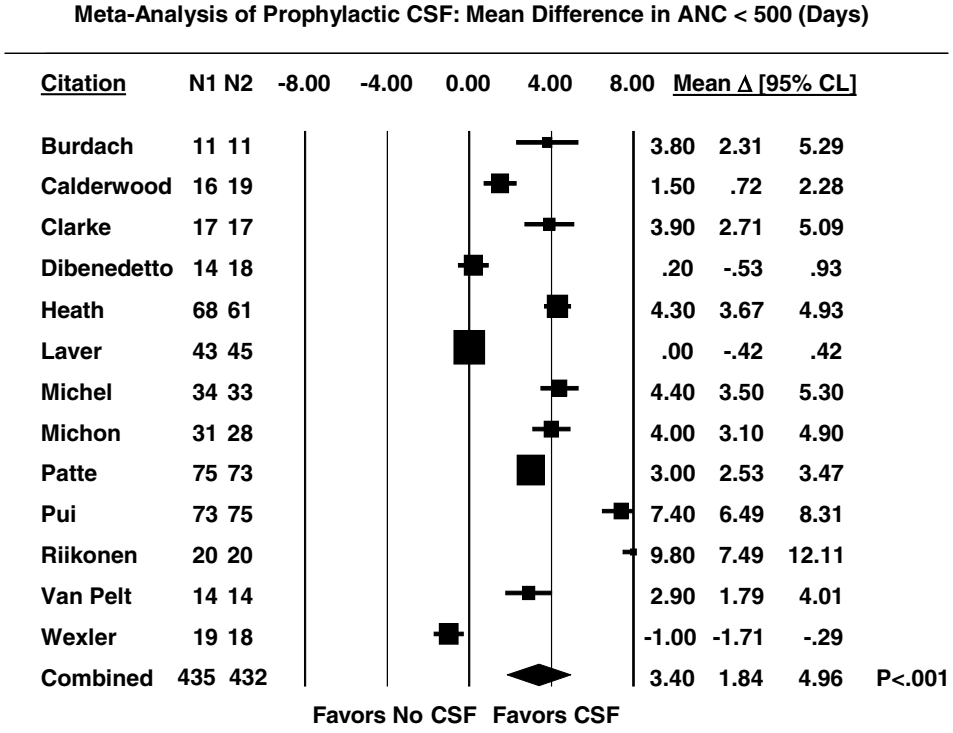

Figure 6 Forest plot of the mean difference in the duration of severe neutropenia (ANC < 500/mm^3) in days ±95% CLs in patients randomized to CSFs compared to control patients.

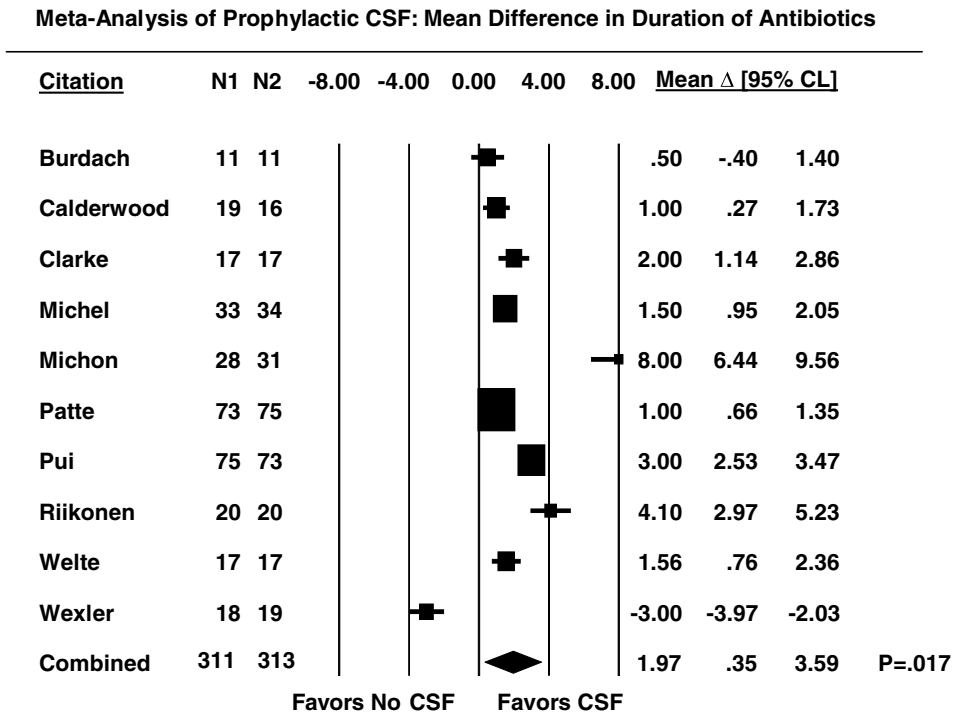

Figure 7 Forest plot of the mean difference in the duration of antibiotic use in days ±95% CLs in patients randomized to CSFs compared to control patients.

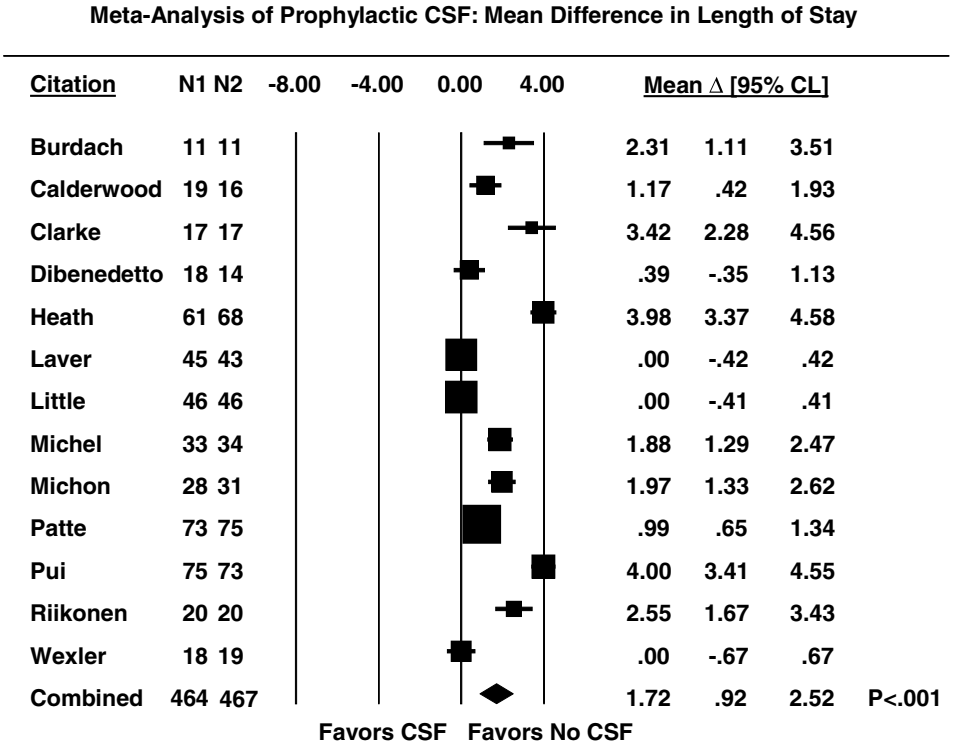

Figure 8 Forest plot of the mean difference in the duration of hospitalization in days ±95% CLs in patients randomized to receive prophylactic CSF compared to control patients.

Length of antibiotic therapy and hospitalization

As shown in Fig. 7, the mean decrease in the duration of reported antibiotic use across the 10 reporting RCTs in patients receiving CSFs ranged from −3 to 8 days with an average decrease of 2.0 days [95% CI: 0.35−3.6; $P = 0.017$]. Overall, the mean decrease in the duration of hospitalization with CSF use across studies ranged from 0 to 4 days across studies, averaging 1.7 days [95% CI: 0.9−2.5; $P < 0.001$] (Fig. 8).

Side effects

Eight of the 16 studies reported side effects including four patients among three studies removed from study for side effects (Table 2). Two studies reported bone pain and vomiting but gave no numbers and reported no withdrawals. Four studies reported no side effects while 8 studies did not report.

Discussion

At this time there have been only small randomized trials of CSFs in pediatric patients, and their mixed results are often difficult to interpret. Since the use of CSFs in children has become quite widespread, it is unlikely that a large randomized trial could be performed to answer questions of efficacy and to guide clinical practice.

The summary estimates reported in this study support the use of growth factors in the pediatric population if the patient has a significant risk of developing FN. The incidence of FN as well as the duration of neutropenia, the duration of hospitalization, and duration of antibiotic therapy all decreased significantly with prophylactic CSFs. The incidence of documented, culture-proven infections was not significantly different in the two groups. This lack of difference may be related to the small sample size of patients or to our strict criteria defining a documented infection. By decreasing the number of episodes of FN, patients benefit from decreased number or duration of hospitalizations and should in turn have quality of life benefits that are important but difficult to quantify since few of the studies reported results from validated measurement instruments.

The heterogeneity of the outcomes seen in the above studies likely reflects the spectrum of patients in the pediatric oncology population as well as the varied treatment protocols. Many of the individual studies included in this analysis had insufficient power to detect small differences in the occurrence of FN or DI. By systematically synthesizing the results of smaller individual studies in this meta-analysis, the impact of CSF prophylaxis on the incidence of FN and DI and the durations of neutropenia, antibiotic use and overall hospitalization has been demonstrated. Such analyses also enable an exploration of a sub-group of pediatric cancer patients who might benefit from the use of CSFs, although such analyses must be considered hypothesis-generating in nature.

A meta-analysis of CSF use in pediatric oncology studies was previously reported.[82] While this review also identified 16 trials, the authors included one study that we chose not to include since there were only a small number of children included without clear separation from the adult data.[100] The study by Kalmanti et al. was not included in their study.[34] They reported a significant reduction in the incidence of FN, a decrease in length of hospitalization, and a decrease in the number of DIs in patients receiving CSFs. They also observed a decrease in the use of amphotericin B to treat fungal infections among CSF treated patients. Our analysis found a significant decrease in the incidence of FN, duration of hospitalization and antibiotic therapy but no difference in the incidence of DI.

Additional differences are seen when comparing the results of the current systematic review with that of the previously reported meta-analysis.[82] The authors of that study did not explicitly define a ''documented infection,'' so it is possible that the subjective definition of an infection could lead to the different conclusions. The definition that we used was a positive blood, urine, skin, or sputum culture or a clinical infection such as pneumonia or cellulitis, and the clinical trials did not report their infection data consistently. Both studies, however, fundamentally arrive at the same overall conclusions.

The prophylactic use of CSFs in pediatric oncology patients receiving systemic chemotherapy for leukemia, lymphoma or solid malignancies provides benefit with a significant reduction in risk of FN and shortened durations of severe neutropenia, antibiotic administration and hospitalization. A formal economic analysis based in part on the results of this meta-analysis with cost information from a large hospitalization database is being conducted.

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