The addition of Colony Stimulating Factors to Antibiotic Therapy in Febrile Neutropenia

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Three Part Question
In patients with [chemotherapy induced febrile neutropenia] does the [addition of colony stimulating factors to antibiotic therapy] reduce [mortality and hospitalisation time]?

Clinical Scenario
You are the Oncology registrar on call. A 38 year-old man with relapsed Acute Myelogenous Leukemia (AML) who is receiving induction chemotherapy presents to hospital with fever. On clinical assessment he has a temperature of 101°F (38.3°C) and a neutropenia (absolute neutrophil count(ANC) is 150 cells/mm³). He also has a mucositis, hypotension and pallor. He is classed as a high risk febrile neutropenic patient and admitted in isolation on the wards. He is commneced on Timantin and Amikin antibiotic therapy. Your inquisitive medical student asks you about the role of colony stimulating factors in febrile neutropenia and you send her off to search for the evidence...

Search Strategy
MEDLINE search using PubMed:

colony-stimulating factors/therapeutic use[mh] AND antibiotics[mh] NOT prevention AND (fever/chemically induced[mh] OR fever/prevention & control[mh] OR neutropenia/chemically induced[mh] AND neoplasms/drug therapy) LIMIT to English

Search Outcome
16 papers found of which 6 were relevant to the 3 part question. Of these, 3 were randomised control trials included in another paper which was a large Cochrane systematic review. Another was a systematic review which included the same trials as the cochrane review, however it included 2 less trials, used a more restricted search strategy and looked at less end-points. The results of the two reviews were quite similar. So this BET will used the Cochrane review.

Relevant Paper(s)

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study Weaknesses
Clark et al 2003 Brazil	1518 patients undergoing chemotherapy for cancer (adults and children) who experience neutropenia (ANC less than 1*10^9/l) and fever (body temperature higher than 38.5°C on one occasion or higher than 38°C on two or more occasions). 779 were randomised to CSF and 739 to the control group (antibiotics plus no treatment or placebo).	Systematic Review of 13 RCTs with parallel design. Level 1a.	Overall Mortality (From 12 trials – 1303 patients)	No benefit of adding CSF [OR= 0.87; 95% CI 0.51 to 1.49; p=0.6]	It was impossible to pool data for all endpoints e.g. time to resolution of fever and time to antibiotic withdrawal, which have the potential to influence decision about the use of CSF.
			Infection related mortality (From 9 trials – 872 patients)	No benefit of adding CSF [OR- 0.85; 95% CI= 0.33 to 2.20; p= 0.7]	
			Length of hospitalisation	Significant benefit in favour of CSF use [HR= 0.63; 95% CI= 0.49 to 0.82; p= 0.0006] Effect remains significant in subgroup analyses restricted to trials with adequate allocation concealment and double blind trials	

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			A subgroup analysis into the effect of criteria for hospital release on the effect of CSF on duration of hospitalisation	No detectable difference of hospital discharge criteria on the effect of CSF to reduce hospitalisation times	
			Time to neutrophil recovery (From 5 trials – 794 patients)	CSF has a significant effect in reducing recovery time [HR= 0.32; 95% CI= 0.23 to 0.46; p= 0.062]	
			Time to antibiotic withdrawal (5 trials - data not pooled)	Medians were one day shorter in all 5 trials	
Ozkaynak et al. 2005 United States	66 patients 21 years or younger with ALL (59) or solid malignancy (7), fever of at least 38.3°C and ANC less than 500/µl - 34 assigned to antibiotics, 32 to G-CSF plus antibiotics.	Paediatric randomised control trial. Level 1b.	Time to recovery of febrile neutropenia	Significant reduction with addition of CSF - median days to resolution 9 earlier with G-CSF (4 compared with 13 days) (p<0.0001) - primarily due to reduction in time of neutropenia. Time to resolution of fever was similar.	Small trial population (due to early cancellation of enrolment because of emerging differences in primary endpoints) which may have precluded the detection of small true differences in some of the endpoints e.g. days of antibiotics
			Time to recovery of febrile neutropenia results based on ANC at admission (ANC > 200 compared with ANC < 200)	Significantly shorter time to recovery for patients with ANC >200 (p=0.009)	
			Median days of hospitalisation	Shorter by 1 day on the G-CSF arm (4 compared with 5 days) (p=0.04)	
			Number of days of IV or oral antibiotics	No statistically significant difference – median days on IV antibiotics 5.9 for G-CSF arm, 7.2 for control arm (p=0.19)	

Comment(s)

The use of colony stimulating factors in febrile neutropenia have produced consistent results throughout several randomised control trials for both adult and paediatric patients. The addition of CSF to antibiotics appears not to affect mortality however reduces the length of hospitalisation. This effect is causally linked to a faster recovery of neutropenia, not surprisingly considering the mechanism of action of CSF. Shortening the length of hospitalisation has the potential to change clinical practice. An economic analysis should be performed to assess the benefit of this against the cost of CSF. A shorter median number of days on antibiotics could also have benefits in terms of cost. The effect of reducing hospital stay on the quality of life for the patients is also important to consider. The only significant side effects of CSF reported in the studies were increased incidence of bone pain and flu like symptoms, which were more common with GM CSF compared with G CSF These results should also be considered in terms of patient risk. The effects of speedier recovery from neutropenia could be more beneficial for high risk patients at admission (e.g. low ANC counts), who take significantly longer to recover than low risk patients. Those at high risk include patients with uncontrolled cancer, inpatients, and patients with serious independent co-morbidities (e.g. hypotension (systolic blood pressure < 90 mmHg), altered mental status, respiratory failure, uncontrolled bleeding with severe thrombocytopenia, inadequate outpatient fluid intake or pain control, suspected spinal cord compression, symptomatic hypercalcemia). Studies have shown that outpatient management of low-risk febrile neutropenic patients is quite successful (Mustafa, 1996). One trial in the Cochrane review was a trial of high risk patients based on criteria from talcott et al (Talcott, 1992). In this trial significant reductions in recovery time lead to an overall median cost reduction of 11% per patient.

Clinical Bottom Line

Colony Stimulating Factors do not reduce mortality in febrile neutropenia however they reduce the length of hospitalisation due to faster recovery from neutropenia. CSF should not be used routinely in uncomplicated febrile neutropenia however its benefits should be considered in the management of high risk febrile neutropenics.

References

1. Clark OAC et al. Colony stimulating factors for chemotherapy induced febrile neutropenia (Review) *Wiley* July 2003, 1-40
2. Ozkaynak et al. Randomized Comparison of Antibiotics With and Without Granulocyte Colony-Stimulating Factor in Children With Chemotherapy-Induced Febrile Neutropenia: A Report From the Children's Oncology Group *Wiley-Liss, Inc.* 2005; 274-280

3. JA Talcott, RD Siegel, R Finberg and L Goldman. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *Journal of Clinical Oncology* 1992; 10: 316-322.
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5. Mustafa, Mahmoud M. MD; Aquino, Victor M. MD; Pappo, Alberto MD et al. A pilot study of outpatient management of febrile neutropenic children with cancer at low risk of bacteremia. *Journal of Pediatrics,* 1996; Jun;128(6):847-9.