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Original Paper

The Economics of Febrile Neutropenia: Implications for the Use of Colony-stimulating Factors*

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The occurrence of fever and neutropenia following cancer chemotherapy generally prompts hospitalisation for evaluation and treatment. Colony-stimulating factors (CSFs) have been shown to reduce the risk of febrile neutropenia (FN) and the need for hospitalisation in such patients. This study was undertaken to obtain estimates of the actual institutional costs associated with FN and the impact of these costs on threshold estimates for the appropriate use of CSFs. Total hospital expenditures for patients admitted with FN over a 2 year period were studied. A cost allocation function was utilised to allocate all direct costs for non-revenue-generating support centres to revenue-generating service centres as indirect costs. A cost accounting function was then utilised to allocate direct and indirect costs for each service centre to the charge code level. Two groups of patients were defined based on diagnostic codes to represent the spectrum of patients with FN. Total hospital costs were estimated and incorporated into a cost model for the use of CSFs. Variation in the total cost of hospitalisation for FN relates primarily to differences in the average length of stay. The daily cost of hospitalisation was comparable in the groups studied, averaging between US$1675 and US$1892. Incorporation of these cost estimates into the cost model yielded FN risk threshold projections for CSF use in the range of 20–25%. Preliminary studies suggest that incorporation of non-medical, indirect and intangible costs into the CSF decision models will further decrease FN risk threshold projections. Total hospitalisation cost estimates for managing patients with FN are greater than those previously reported, reducing projected FN risk thresholds for CSF use. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: febrile neutropenia, economics, granulocyte colony-stimulating factor (G-CSF), costs
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INTRODUCTION

MYELOSUPPRESSION REPRESENTS the major dose-limiting toxicity of systemic cancer chemotherapy. The risk of infection and mortality increases in direct proportion to the degree and duration of neutropenia experienced [1]. Fever in the setting of neutropenia generally prompts immediate hospitalisation for evaluation and the administration of empiric broad spectrum antibiotics [2]. The risk of hospitalisation for febrile neutropenia (FN) varies with the nature and intensity of the treatment regimen, as well as host-related factors related to age, the type of cancer and various co-morbid conditions. Recombinant granulopoiesis-stimulating agents, such as granulocyte colony-stimulating factor (G-CSF, filgrastim) and granulocyte-macrophage colony-stimulating factor (GM-CSF, sargramostim) are capable of reducing the severity and duration of neutropenia associated with systemic cancer chemotherapy [3–5].

The clinical and economic value of these agents administered therapeutically after the onset of FN or afebrile neutropenia has not been clearly defined [6–8]. CSFs have, however, demonstrated considerable efficacy when administered prophylactically prior to the onset of neutropenia or FN. In a pivotal double-blind, placebo-controlled, randomised trial by Crawford and colleagues G-CSF administration was associated with a 50% reduction in the incidence of hospitalisation for FN [9]. Similar reductions were observed in the mean number of days of hospitalisation and antibiotic use and in the number of culturally confirmed infections. These results were subsequently confirmed in a virtually

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identical European trial by Trillet-Lenoir and associates who also observed a significant difference in dose reductions and treatment delays between the two groups [10]. More recently, CSFs have demonstrated efficacy in sustaining dose intensity in patients with responsive and potentially curable malignancies receiving high dose regimens with or without peripheral blood or bone marrow stem cell support [11–13]. Although episodes of FN clearly add substantial costs to the care of cancer patients receiving systemic chemotherapy, until recently there had been little systematic study of the actual costs involved [14, 15].

Approximately 10% of healthcare expenditures are associated with cancer care, which totals nearly US$100 billion annually in the U.S.A. alone [16, 17]. The direct medical costs of cancer care are greatest during the period of initial diagnosis and treatment, with hospital care accounting for approximately 50% of all cancer-related expenditures [18]. Other illness-related costs in cancer patients include direct non-medical costs, such as transportation and childcare, as well as indirect costs associated with illness-related morbidity and lost earnings due to premature death from disease [19]. There are also certain intangible costs of illness to the patient and family that relate to the impact on quality of life. Methods of economic analysis are available for evaluating studies where either improved outcomes are associated with the same or greater cost or where reduced cost is associated with the same or worse outcome [20–22].

Clinical decision models represent a useful type of economic analysis, incorporating data from the published literature and professional experience, permitting the definition, measurement and comparison of the relevant positive and negative economic consequences of health care technologies [23, 24]. Such models allow the simultaneous consideration of both clinical and economic outcomes in the form of cost-effectiveness and cost-utility analyses [25, 26]. When therapeutic outcomes such as survival appear to be equal between groups, the comparison of treatment options may be based on differences in resource utilisation or cost in the form of a cost minimisation study. When therapeutic benefit is evident in terms of reduced morbidity or mortality, a cost-effectiveness analysis can be used to define the cost per year of life gained. When the additional benefit is measured in terms of patient preferences, a cost-utility analysis can provide a measure of the cost per quality-adjusted life year gained. Clinical decision models have been very useful in studying the trade-off between the added cost of growth factor use and any reduction in cost related to decreased incidence or duration of FN [27, 28]. These models have been utilised to support the development of clinical practice guidelines for the use of CSFs in cancer therapy [29]. Clearly, however, such models are very sensitive to the hospitalisation cost assumptions utilised.

The study presented here was undertaken in order to define more precisely the economic impact of FN in patients receiving cancer chemotherapy. An improved understanding of the actual costs associated with the management of FN should provide a more rational basis for evaluating CSFs and further refinement of clinical practice guidelines.

PATIENTS AND METHODS

Economic analysis

Economic measures on patients admitted to the H. Lee Moffitt Cancer Center and Research Institute with FN during fiscal years 1994 and 1995 were evaluated. Data were retrieved from an institutional Decision Support System utilised as a management tool for administrative problem solving and planning. This system includes information on patient demographics, diagnostic and procedure coding, outpatient and in-patient costs and payor reimbursement. The Decision Support System includes functions for cost allocation and cost accounting. The cost allocation function is utilised to allocate all fixed and variable direct costs for non-revenue-generating (support) centres to the revenue-generating (service) centres as indirect costs. In the allocation process, each support centre is assigned an allocation statistic based on an appropriate measure of activity, such as utilised space, supplies and man-hours of activity. Each service centre then receives a portion of the overhead centre's cost based on their share of the allocation statistic. The cost accounting function is utilised to assign direct and indirect costs for each revenue-generating centre to the level of a charge code. This involves defining estimates of labour and non-labour costs for each charge code. Salary, non-salary and capital relative value units are calculated for each charge code and utilised to allocate the corresponding expense to the charge code level. The total operating expenses for each department represent the sum of direct and indirect costs across all diagnostic and procedure codes assigned to the department.

The definition and coding of FN for charge and cost analysis have been inconsistent. The criteria for admission and discharge for FN varies between institutions and physicians. In addition, no unique International Classification of Diseases-Oncology (ICD-O) code for FN has been established or applied. In an effort to encompass the range of patients admitted with fever and neutropenia in different settings across institutions, two groups were defined. Group 1 represents patients admitted with neutropenia as the primary reason for admission. Group 2 consists of patients with neutropenia as either the primary or a secondary reason for admission. A retrospective chart audit demonstrated that group 1 represents patients with few other major complications at the time of admission. Group 2 contains the patients of group 1, but also includes patients with a variety of other primary reasons for admission, including various co-morbid conditions. Thus, the two groups appear to represent the range of possible costs. In chart review, it was not possible to attribute the proportion of an admission that was due to FN, due to the frequent strong interaction between FN and the other medical conditions. Results were analysed for all patients in both groups, as well as for patients with solid tumours, excluding those with haematological malignancies.

Economic measures collected in this study include charges, direct and indirect institutional costs and revenues actually collected. However, only estimated costs are utilised in the decision analysis for CSF use described below. Study results are presented for each episode of hospitalisation and on a per day basis. Economic measures were evaluated separately by department, including the room, pharmacy, laboratory, blood bank, radiology, respiratory care, supply and other units. The distribution of economic measures and length of stay were evaluated and summary measures calculated. Measures of central tendency and variation were based on the mean and the standard error of the mean. Of the economic measures, only costs were utilised in the cost minimisation decision model discussed below. Costs are expressed in monetary units as US dollars ($). The purchasing power parity (PPP)

represents the rate of exchange eliminating the differences in price levels between countries, such that a given sum will permit purchase of the same amount of goods and services in each country. Average PPPs for 1994–1995 represent annual benchmark results calculated by Eurostat and expressed in national currency units per US dollar (Main Economic Indicators, OECD, Paris, March 1997).

Decision analysis

The decision analysis presented is based upon a previously reported cost minimisation model for the prophylactic use of CSFs in patients receiving systemic cancer chemotherapy (Figure 1) [26]. The model assumes that patients experiencing FN will be hospitalised for empiric parenteral antibiotic therapy. Baseline probabilities for hospitalisation risk and survival, together with the duration of hospitalisation and CSF use, were based on the initial prospective randomised trial of prophylactic G-CSF in patients with small cell lung cancer [9]. Since there was no reduction in the duration of hospitalisation in patients treated with CSF in the randomised trial, no baseline adjustment in hospitalisation duration was assumed. The risk of FN depends most directly on the intensity of the chemotherapy regimen utilised. In the sensitivity analyses, the risk of FN is varied over the spectrum of possible values, making no assumption about the risk at baseline.

Costs considered in the model consist of the daily cost of hospitalisation for FN and the daily cost of CSF and its administration for each treatment cycle. For the purposes of this analysis, it is assumed that CSFs will have no clinical or economic impact on aspects of the patient's disease or treatment other than that related to FN or its prevention. The expected cost per treatment cycle represents the excess cost associated with hospitalisation for FN and treatment with CSFs. The expected cost for each management strategy was calculated as the sum of the products of the costs and probabilities of each outcome. A series of sensitivity analyses was undertaken estimating the expected cost associated with each strategy while varying the assumptions concerning each variable over the range of reasonable values. Thresholds were generated for each variable at which the expected costs were equal for management with and without CSF. A family of threshold curves was generated on the basis of multivariate sensitivity analyses for a combination of two or more variables.

RESULTS

Economic analysis

All episodes of hospitalisation for the two groups as defined were evaluated. During fiscal years 1994 and 1995, there were 309 patients admitted for FN based on the criteria for group 1, where neutropenia was the primary reason for admission. There were 794 patients admitted for FN based on the criteria for group 2, where neutropenia was either the primary or a secondary reason for admission. The primary reasons for admission in group 2 consisted of neutropenia (39%), malignancy-related (34%), infection-related (11%), vascular complications (4%), and other organ system complications (12%). There was no significant difference in the two groups with regard to age, gender or type of payor.

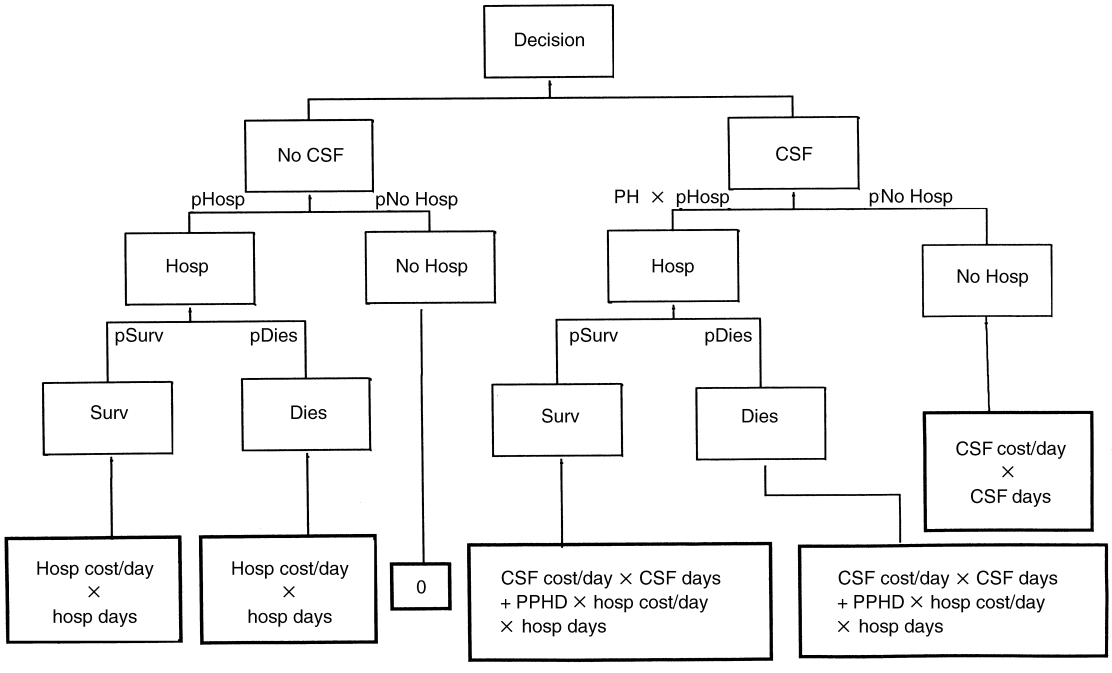

Figure 1. The decision model is based on two therapeutic choices: no colony-stimulating factor (CSF) or prophylactic CSF. Each decision choice is associated with a certain risk of hospitalisation for febrile neutropenia or not. Hospitalised patients are at a certain risk of death or survival. Each set of choice and chance events are associated with specified excess costs based on both hospital cost/day for a specified number of hospital days and CSF cost/day for a specified number of days. Probabilities include the risk of hospitalisation (pHosp), risk of no hospitalisation (pNo Hosp), survival of each episode (pSurv) and death (pDies). Durations include the average hospital length of stay (Hosp Days) and the average duration of CSF administration (CSF Days). Costs include the hospitalisation costs per day (Hosp Cost/Day) and the CSF cost per day (CSF Cost/Day). Proportionality factors include the proportional risk of hospitalisation with CSF compared with no CSF (PH) and the proportional reduction in the duration of hospitalisation with CSF compared with No CSF (PPHD).

Approximately 50% of patients were between 40 and 65 years of age and 25% were 65 years of age or over in both groups.

Patients in group 1 and group 2 spent a total of 2320 and 12 702 days, respectively, in the hospital during this time period. The average length of stay for patients in group 1 was 7.5 ± 0.3 days and for group 2 was 16.0 ± 0.6 days. Economic measures including charges, direct and indirect costs and revenues for the two groups are summarised in Table 1. Data are presented for all patients in both groups for each episode and for each day of hospitalisation. Although the average length of stay, as well as total charges, operating costs and revenues per episode, are greater in group 2, average daily costs are similar between the two groups.

Solid tumour patients in group 1 and group 2 spent a total of 878 and 3279 days in the hospital during the time period under study. The average length of stay for solid tumour patients in group 1 and group 2 was 6.4 ± 0.5 days and 10.4 ± 0.7 days, respectively. Charges, direct and indirect costs and revenues for the two groups are summarised for solid tumour patients in Table 2. While charges, operating costs and revenues for each episode are again greater in group 2, average daily costs in the two groups are virtually identical.

Table 1. *Economic measures associated with febrile neutropenia (all patients)*

	Group 1 (n = 309) (mean ± SEM)	Group 2 (n = 794) (mean ± SEM)
Charge/episode (US$)	22 253 ± 1538	61 936 ± 3049
Cost/episode (US$)	13 181 ± 850	35 814 ± 1686
Direct	7444 ± 935	20 928 ± 1047
Indirect	5738 ± 320	14 887 ± 647
Revenues/episode (US$)	12 851 ± 1075	36 044 ± 2263
Charges/day (US$)	2740 ± 72	3144 ± 56
Cost/day (US$)	1675 ± 37	1892 ± 30
Direct	923 ± 24	1061 ± 20
Indirect	752 ± 14	831 ± 10
Revenues/day (US$)	1712 ± 196	2253 ± 142

The purchasing power parity (PPP) for GDP in the U.K. (Pound/Dollar) for 1994–1995 = 0.672: for Germany (DM/Dollar) = 2.07. SEM, standard error of the mean.

Table 2. *Economic measures associated with febrile neutropenia (solid tumour patients)*

	Group 1 (n = 137) (mean ± SEM)	Group 2 (n = 316) (mean ± SEM)
Charge/episode (US$)	14 416 ± 1464	26 192 ± 2259
Cost/episode (US$)	9345 ± 927	16 500 ± 1382
Direct	5011 ± 540	8850 ± 768
Indirect	4334 ± 392	7650 ± 630
Revenues/episode (US$)	8577 ± 631	14 240 ± 1383
Charges/day (US$)	2 154 ± 67	2257 ± 57
Cost/day (US$)	1435 ± 47	1488 ± 38
Direct	754 ± 28	774 ± 24
Indirect	681 ± 20	714 ± 17
Revenues/day (US$)	1642 ± 93	1478 ± 55

SEM, standard error of the mean.

The departmental allocation of economic measures was analysed for both groups. The distribution of total operating expenses by department is shown in Figure 2. The distribution of net revenues closely followed the distribution of charges, with the pharmacy representing the leading department followed by the bed unit, the laboratory and the blood bank. As shown, however, total operating expenses including both direct and indirect costs were greatest for the room, the pharmacy, the blood bank and the laboratory.

Decision analysis

Baseline probabilities and costs incorporated into the decision model are shown in Table 3. A two-way sensitivity analysis for the threshold risk of hospitalisation for FN while varying the cost associated with hospitalisation is shown in Figure 3. As the daily cost increases, the threshold risk of hospitalisation favouring the use of CSF decreases. Shown are the thresholds generated on the basis of the original cost estimates (+) and those reported in this study (x). FN risk threshold estimates based on total hospital costs for group 1 and group 2 were 24% and 21%, respectively, for all patients. Risk threshold estimates restricted to patients with solid malignancies were 28% and 27% for group 1 and group 2, respectively.

Further sensitivity and threshold analyses were conducted incorporating the direct medical cost estimates obtained in this study. Figure 4 represents a two-way sensitivity analysis displaying the risk threshold for CSF use based on the length of stay in days. The longer the expected length of stay, the lower the threshold, favouring the use of CSF. FN risk threshold estimates for varying lengths of stay are shown for group 1 (7.5 days) and group 2 (16 days). Sensitivity and risk threshold analysis for CSF use are shown in Table 4 for varying length of stay and average daily cost estimates.

Limited information is available pertaining to direct non-medical and indirect costs. Preliminary patient surveys suggest that these costs may range from US$0 to US$1000. The impact of intangible costs based on measures of quality of life in patients with FN is currently under study. Preliminary data assessed as willingness to pay to avoid FN correspond to daily costs of US$0–500. Incorporation of such costs into the decision model yields FN risk threshold estimates for the use of CSFs of 20% or less.

DISCUSSION

FN represents the most important dose-limiting toxicity of systemic cancer chemotherapy. The development of fever in the setting of neutropenia often represents a life-threatening condition prompting hospitalisation for evaluation and administration of broad spectrum antibiotics. The economics of FN has only recently received attention, largely due to the introduction of the haematopoietic growth factors. The high cost of CSFs combined with their current wide scale application has prompted a number of economic analyses, together with the development of clinical practice guidelines.

Several economic analyses of CSFs in patients receiving conventional doses of chemotherapy have attempted to define the threshold of FN risk at which the added cost of the growth factor is offset by the reduction in cost associated with a decrease in the incidence or duration of hospitalisation for FN. In our original cost minimisation study, baseline probabilities derived from the randomised trial of Crawford and associates, together with local direct institutional cost

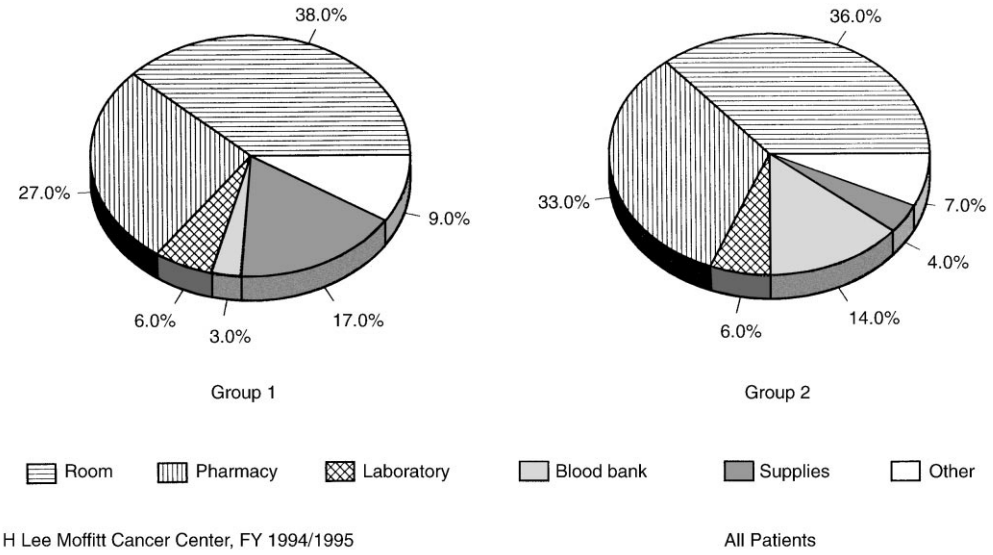

Figure 2. Pie chart illustrating the proportional hospital departmental costs for febrile neutropenia for group 1 and group 2 including room, pharmacy, laboratory, blood bank, supplies and other costs.

information, were incorporated into a decision analytical model [14, 26]. Model thresholds for the use of G-CSF were calculated based on sensitivity analyses for prophylactic use and therapeutic use in FN. A threshold risk of FN of 40% was estimated at which the added cost of the growth factor was offset by the reduction in costs of hospitalisation for FN. Similar conclusions were reached in a study by Glaspy and associates utilising a subgroup of patients from the original randomised trial [27]. FN risk thresholds of 35, 60 and 70% were estimated based on charges, costs and Medicare reimbursement.

The major economic driving factor in these studies has been the cost of hospitalisation, which is the product of the average daily cost and the length of stay. Any combination of factors which increases the cost of treating FN, including hospitalisation costs, will decrease the FN risk threshold and favour the use of these agents.

In the study reported here, total operating expenses, including both direct and indirect institutional costs, were estimated for each episode of FN over a 2 year period. Analysis of total operating expenses by including indirect institutional costs, provides cost estimates for FN which are considerably greater than previously reported. The daily operating expenses reported here of US$1675 and US$1892 for the two groups studied are sufficiently greater than those previously estimated to justify a reconsideration of previous cost analyses. None of these cost estimates, including those reported here, have considered the non-medical direct costs incurred by the patient and family while receiving medical care, such as transportation costs. In addition, these estimates do not consider indirect costs based on the loss of income for days of work lost due to illness or the intangible costs associated with hospitalisation, such as pain and suffering and time spent away from family. We have reported an extension of the original model incorporating quality of life considerations either as patient willingness-to-pay to avoid FN or as utilities in a time trade-off fashion [30]. Incorporation of a utility analysis into the cost minimisation model generates lower FN risk thresholds than those estimated based on cost alone. Further clinical and cost analyses of CSFs incorporating quality of life measures are needed, however.

Table 3. Model baseline assumptions

	Variable	Value
Probabilities	Risk of hospitalisation for febrile neutropenia	0.55
	Risk reduction of CSF	0.50
Durations (days)	Hospitalisation	10
	CSF administration	8
Costs (US$/day)	Febrile neutropenia	
	Direct medical	1000
	Indirect medical	500–1000
	Direct non-medical*	0–500
	Indirect/intangible*	0–1000
	CSF	250

*Estimates.
CSF, colony-stimulating factor.

Episodes of FN vary greatly in severity and complexity, impacting primarily on the duration of hospitalisation. The major cost difference between the two groups of patients with FN studied appears to relate to the longer length of stay observed in group 2. The longer length of stay in group 2 is associated with a greater level of complexity of illness in this group of patients, due to factors related to the malignancy or infection which are specified as the primary reason for admission. This highlights the need for more effective methods for predicting the length of stay in patients as a way of estimating total costs and the potential for benefit from effective but costly technologies. The similarity in average daily costs between the two groups, however, provides a relatively stable estimate for incorporation into clinical decision models. Although the cost associated with FN for solid tumour patients is somewhat lower, the small differences in daily costs again attest to the relative stability of these estimates.

Incorporation of indirect institutional costs associated with support functions provides an improved estimate of the actual costs associated with FN. While the pharmacy

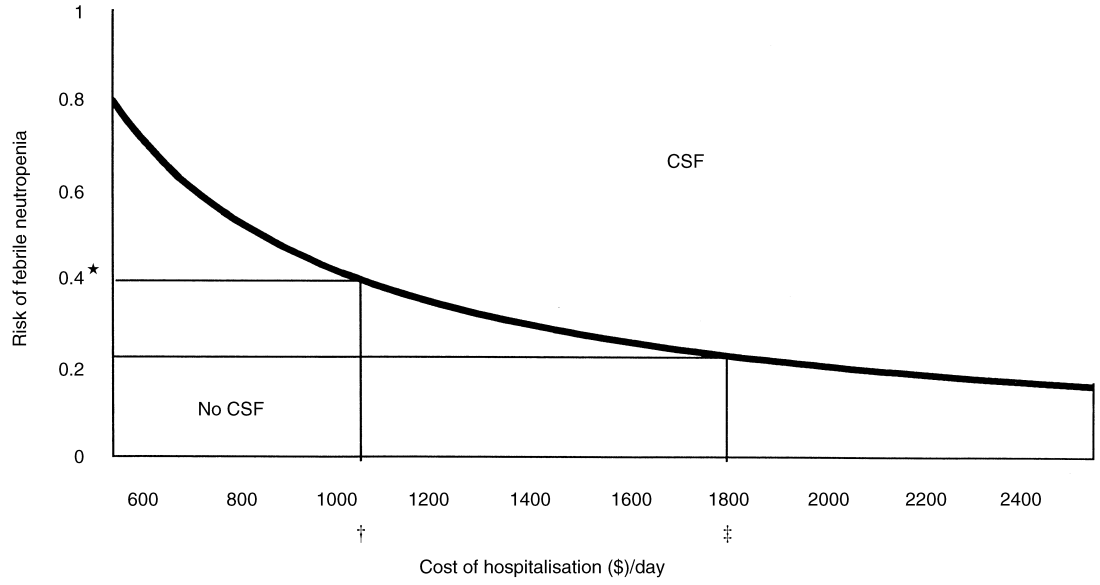

Figure 3. Two-way sensitivity analysis displaying the threshold function (curve) between the cost of hospitalisation/day (US$) shown on the horizontal axis and the risk of hospitalisation for febrile neutropenia shown on the vertical axis. Values of the two variables that lie on the threshold line are associated with equal cost with and without the use of colony-stimulating factors (CSFs). Any combination of values that lie above the threshold curve are associated with a decrease in cost with the use of CSF Any combination of values that lie below the threshold line are associated with an increase in cost with CSF use. Illustrated are the direct medical cost estimates from both the previous and current economic analyses. The associated risk threshold projections are also shown by the horizontal lines. *Current guideline. †Original cost estimate. ‡Current cost estimate.

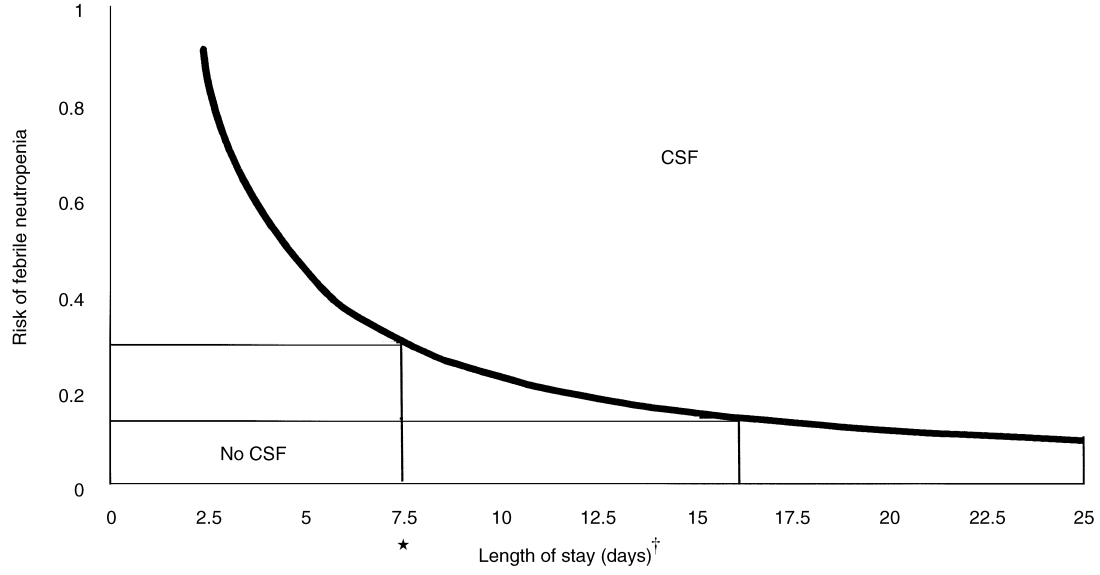

Figure 4. Two-way sensitivity analysis displaying the threshold function (curve) between the duration of hospitalisation (days) shown on the horizontal axis and the risk of hospitalisation for febrile neutropenia shown on the vertical axis. Values of the two variables that lie on the theshold line are associated with equal cost with and without the use of colony-stimulating factors (CSFs). Any combination of values that lie above the threshold curve are associated with a decrease in cost with the use of CSF. Any combination of values that lie below the threshold line are associated with an increase in cost with CSF use. Illustrated are the estimated lengths of stay of patients in group 1 (7.5 days) and group 2 (16.0 days). The associated risk threshold projections are also shown by the horizontal lines. *Group 1. †Group 2.

represents the largest component of charges and net revenues, the nursing unit is the greatest source of the allocated indirect costs. More than one-third of the total hospital expenses for managing patients with FN are concentrated in the room, which together with the pharmacy constitute approximately two-thirds of the total operating expenses. Likewise, while the laboratory represents a greater proportion of generated charges and net revenues, the blood bank incurs a greater proportion of the operating expenses based on the allocation model.

This study is limited by the absence of a specific diagnostic code for episodes of FN. Prospective studies are underway based on individual case analyses involving a time–motion evaluation to further address the costs associated with FN. Nevertheless, the groups defined here based on the available codes represent the range of illness complexity, length of stay

*Table 4. Threshold risk of hospitalisation for febrile neutropenia**

Cost per day (US$)	Length of stay (days)			
	7.5	10	12.5	15
500	–	0.80	0.64	0.53
1000	0.53	0.40	0.32	0.27
1500	0.36	0.27	0.21	0.18
2000	0.27	0.20	0.16	0.13
2500	0.21	0.16	0.13	0.11
3000	0.18	0.13	0.11	0.09
4000	0.13	0.10	0.08	0.07
5000	0.11	0.08	0.06	0.05

*Granulocyte colony-stimulating factor (G-CSF) use is associated with a lower cost whenever the risk of hospitalisation is greater than the calculated threshold.

and cost associated with FN in patients receiving systemic chemotherapy.

Economic analysis of CSFs have more recently been extended to patients with acute leukaemia and those receiving high dose therapy with stem cell support. Bennett and colleagues recently presented an economic model of the use of GM-CSF in patients aged 56–70 years with acute myelogenous leukaemia (AML) based on a previously reported randomised trial from the Eastern Cooperative Oncology Group [31]. Economic data consisting of direct medical costs obtained from one of the study sites were evaluated in a cost minimisation analysis. The investigators concluded that patients receiving GM-CSF have lower costs, largely due to a lower incidence of serious infections. In a study of patients treated by autologous bone marrow transplantation (ABMT), Souêtre and associates found that the subsequent administration of G-CSF was associated with a 3% reduction in mean costs due to a reduced length of stay in the hospital [32]. Additional studies have demonstrated that the use of G-CSF-primed peripheral blood stem cells (PBSC) is associated with a further decrease in length of stay and costs compared with ABMT with or without G-CSF support [33, 34]. Hartmann and colleagues reported a prospective, randomised comparison of PBSC transplantation (PBSCT) and ABMT in 129 adults and children with a variety of solid tumours and lymphomas [35]. The durations of neutropenia, thrombocytopenia and hospitalisation (24 days versus 31 days) were shorter in the subjects receiving G-CSF-mobilised PBSCT ($P < 0.001$). An economic analysis revealed that overall costs with PBSCT were decreased 17% among adult subjects and 29% among children compared with ABMT costs [36]. Smith and associates recently reported the results of an economic evaluation of a previously reported randomised trial comparing G-CSF-mobilised PBSCT and ABMT for malignant lymphoma based on a concurrent resource utilisation study projecting costs to the U.S.A. [37]. The investigators found an overall cost savings of 23% for PBSCT compared with ABMT due to lower autograft collection costs, shorter hospitalisations and less supportive care. McQuaker and colleagues have reported the results of a double-blind, placebo-controlled, randomised trial of low dose (50 $\mu g/m^2$/day) G-CSF in 38 patients following PBSCT for various lymphoproliferative disorders [38]. The post-transplant costs of caring for patients who received G-CSF was less than control patients based on local institutional costs.

Clinical guidelines for the use of CSFs should be re-evaluated in the light of improved economic analyses. The proper decision whether to use CSFs support should consider the total clinical and economic impact of FN on the patient and society, as well as the importance of chemotherapy dose intensity on disease outcomes [29]. We offer the following considerations for possible revision in available CSF clinical practice guidelines based on the results of this study. Routine use of CSFs administered prophylactically should be considered in patients at 20% or greater risk of FN by virtue of either the intensity of chemotherapy or treatment with the same dose and schedule of chemotherapy which previously resulted in hospitalisation for FN. Clinicians should consider use of CSFs prophylactically in chemotherapy patients at risks of FN as low as 10% when an unusually complicated and prolonged course of management is anticipated. Prophylactic use of CSFs should be considered in patients at any risk level when considered necessary to sustain dose intensity in responsive and potentially curable malignancies. Further guideline revisions will be necessary if there are dramatic shifts in the costs associated with the management of FN. Although it is our impression that the majority of patients with FN continue to be managed in the hospital, clearly trends toward shorter hospitalisations and treatment of FN in the ambulatory setting will further impact on the thresholds defined by such an economic analysis.

CSFs have demonstrated both clinical and economic benefit in the support of patients receiving cancer chemotherapy. The relatively high cost and widespread use of these agents has prompted a number of economic analyses. Decision models represent a valuable method of economic analysis, permitting the simultaneous consideration of benefit (decreased risk of hospitalisation for FN) and cost (cost of hospitalisation for FN and cost of CSF). Incorporation of direct medical costs based upon estimated total hospital expenses yields revised FN risk thresholds for CSF use in the range of 20–25%. These risk threshold estimates are considerably less than those reported elsewhere based on previously available cost information. Even below the risk threshold, avoidance of hospitalisation for FN for many patients will partially offset the added cost of CSF use. Models capable of predicting which patients will have prolonged and complicated episodes of FN will further improve estimates of hospitalisation risk thresholds for utilising CSFs. Further studies of the costs associated with FN are needed, including the indirect costs to the patient and family, as well as the non-medical and intangible costs associated in the hospitalisation for FN.

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