Original Article

Evaluation of Direct Medical Costs of Hospitalization for Febrile Neutropenia

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BACKGROUND: Treatment of febrile neutropenia (FN) is costly, because it typically involves hospitalization. As cancer rates continue to increase, the number of patients suffering from FN will also increase, making it important to quantify the costs of treating this condition accurately and comprehensively. **METHODS:** A consecutive sample of patients admitted to an inpatient hematology/oncology ward at a tertiary care hospital for the treatment of chemotherapy-induced FN was enrolled in this study. Patients were followed prospectively during hospitalization, and information on medical resource utilization including length of stay, medications, and laboratory and diagnostic tests was collected. Costs, extracted from hospital and provincial databases, were used to calculate the overall cost per FN episode, from the hospital perspective. **RESULTS:** Fifty-one episodes of FN that occurred in 46 patients were included in the study. Approximately 52% of these episodes occurred in women, and 65% of these episodes occurred in patients with hematologic malignancies. The mean ± standard deviation age of patients was 60.3 ± 13.4 years. The mean length of stay per episode was 6.8 ± 4.9 days. The mean overall cost per episode was 6324 ± 4783 in 2007 Canadian dollars. **CONCLUSIONS:** Hospitalization for the treatment of FN is expensive. The results of this study could be used in future economic evaluations of preventive measures and treatments for FN, including primary prophylactic administration of hematopoietic growth factors and outpatient treatment of this condition. ***Cancer*** **2010;116:742–8.** © *2009 American Cancer Society.*

KEYWORDS: neutropenia, fever, neoplasms, costs and cost analysis, economics.

Febrile neutropenia (FN) is a serious hematologic toxicity of cancer chemotherapy. All patients with FN must be treated aggressively with empiric antibiotics for 2 reasons: it is difficult to distinguish between patients who have an infection and those who do not because fever is often their only sign of infection; and infection can progress rapidly, putting patients at high risk for death.[1,2] In the era before empiric treatment of FN with broad spectrum antibiotics, the mortality rate from infections could be as much as 80% in some patients[3]; however, by 1994 this rate had been reduced to 7%.[4]

It is estimated that the incidence of cancer in Canada from 1987 to 2007 has increased by 66%, and that this increase will continue as the Canadian population continues to grow and to age.[5,6] As cancer rates increase, the number of patients who develop FN will also increase, making it important to quantify the costs of treating this condition accurately and comprehensively. Treatment for FN is costly, as it typically involves hospitalization. Although several studies, including 4 conducted in Canada,[7-10] have evaluated the direct medical costs of hospitalization for this condition, to the best of our knowledge there have been no Canadian studies published on this subject in the last 10 years.

The primary objective of this study was to quantify the direct medical costs of treating FN in the inpatient hospital setting; the secondary objective was to determine the proportion of patients in the study who were considered to be at low risk for FN complications based on the clinical risk prediction model developed by Klastersky et al.[11] This economic information could subsequently be used to evaluate the cost-effectiveness of alternative treatment models for FN, such as outpatient treatment or early hospital discharge programs, and of prophylactic interventions such as the use of hematopoietic growth factors.

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MATERIALS AND METHODS

Study Design and Patient Population

A prospective, incidence-based cost-of-illness study was conducted to determine the direct medical costs, from the hospital perspective, of treating a chemotherapy-induced FN episode in patients admitted to the inpatient hematology/oncology ward at Sunnybrook Health Sciences Centre, Toronto, Canada. Sunnybrook Health Sciences Centre is a tertiary care teaching hospital affiliated with the University of Toronto. It has 671 inpatient acute care beds, 40 of which are oncology beds. The catchment area is a provincially defined urban/suburban region in and around Toronto. Research ethics board approval for this study was granted on December 14, 2006. Informed consent was not required, because the study involved only a chart review and no contact with the study subjects.

Patients admitted to Sunnybrook Health Sciences Centre with FN are initially treated with an antibiotic combination of cefazolin at a dose of 1 g given intravenously 3 times daily and tobramycin at a dose of 7 mg/kg given intravenously once daily. Clinically stable patients who have defervesced by the third day of therapy are usually converted to oral antibiotics (ciprofloxacin and cephalexin), and therapy is continued until the patient remains afebrile for 5 to 7 days. Most patients are discharged while receiving oral antibiotics and complete their therapy as outpatients. Patients who remain febrile on the third day of therapy receive additional antibiotic therapy with piperacillin/tazobactam at a dose of 4.5 g given intravenously 4 times daily. Patients who are persistently febrile with unresolving neutropenia for 4 to 7 days after the addition of piperacillin/tazobactam are initiated on intravenous antifungal therapy.

The inclusion criteria for patients enrolled in the study were a diagnosis of chemotherapy-induced FN on admission to Sunnybrook Health Sciences Centre and age >18 years at the time of admission. Patients who developed FN while already hospitalized and those who developed FN secondary to high-dose chemotherapy administered before bone marrow transplant or peripheral blood stem cell transplant were excluded from the study. Sunnybrook Health Sciences Centre does not currently have a policy for outpatient treatment of patients who present with low-risk FN episodes. Some patients experiencing a low-risk episode of FN may have presented to the emergency department and been discharged home to complete their care in the outpatient setting during the course of this study. These patients were not considered in this analysis.

This study was not designed as a comparison between groups, and therefore no formal sample size calculation was conducted. A convenient sample of patients, based on admission to the inpatient hematology/oncology ward at Sunnybrook Health Sciences Centre, was enrolled in the study. It was estimated that a sample of 50 to 75 episodes of FN would be enrolled in the study during the 9 months of data collection.

Data Collection

Recruitment of study subjects and data collection began on January 3, 2007 and ended on September 30, 2007. Demographic, disease state, and resource utilization information was collected from the inpatient medical chart and the electronic patient record of the study subject during his or her hospital stay. The disease state data included information on underlying malignancy and chemotherapy administered. Klastersky's Multinational Association for Supportive Care in Cancer (MASCC) risk model was used to stratify episodes into either the high- or low-risk group for complications of FN.[11]

In measuring medical resource, the variables considered were length of stay (LOS) in hospital in either the hematology/oncology ward or intensive care unit (ICU), medications, laboratory and diagnostic tests, and blood bank services. Information regarding chemotherapy administration after resolution of the FN episode was also collected; the computer system used for tracking outpatient chemotherapy orders was the source of these data.

Costing

All costs were calculated in 2007 Canadian dollars. Table 1 details the sources of unit costs for each variable considered in estimating the direct medical costs of treating FN from the hospital perspective. Costs for each variable per episode were calculated by multiplying the number of units of each resource used by the cost per unit. To determine the total cost per FN episode, the costs accrued for each variable were summed, and the mean per episode was calculated.

Calculating costs for certain diagnostic procedures, nonoverhead resources, and overhead resources was complicated by the nature of the available information and required additional analysis or interpretation; the methods used for calculation of costs for these variables are detailed below.

Information regarding costs for most diagnostic imaging procedures is listed in the Ontario Health Insurance Plan Schedule of Benefits with 2 separate components: the technical component and the professional

Table 1. Sources of Unit Costs

Variable	Source of Unit Cost
Antibiotics	SHSC 2007 Antimicrobial Handbook[19]
Granulocyte–colony-stimulating factor	SHSC Pharmacy Department (unpublished data)
Other medications	SHSC Pharmacy Department
Laboratory tests	OHIP Schedule of Benefits[20]
Diagnostic tests	OHIP Schedule of Benefits
Blood bank costs	SHSC Blood and Tissue Bank
Other nonoverhead costs (nursing and allied health professional time, food, miscellaneous supplies, etc)	SHSC Decision Support Department (unpublished data)
Overhead costs (ie, administrative costs)	Ontario Case Costing Initiative[13]

SHSC indicates Sunnybrook Health Sciences Centre; OHIP, Ontario Health Insurance Plan.

component. The technical component is the cost of preparing the patient for the procedure, following up, record keeping, and purchasing and maintaining equipment; the professional component is the fee that the physician claims for performing the procedure. Because costs in this study are reported from the hospital perspective, only the technical cost component was included. For computed tomography (CT) scans and magnetic resonance imaging (MRI), no cost is listed for the technical component; therefore, no hospital cost was included for these types of tests that were performed during the FN episodes included in this study.

Information concerning nonoverhead hospital costs (eg, nursing, allied health professionals, medications, laboratory tests) for medical ward beds and ICU beds was obtained in the form of spreadsheets with line items from the Sunnybrook Health Sciences Centre Decision Support Department. The values reported were from 2004, and these were inflated to 2007 dollars using the Bank of Canada Inflation Calculator.[12] The line items specifying costs for medications, laboratory tests, and diagnostics were subtracted to avoid double counting.

Information regarding hospital overhead costs was not available from the Sunnybrook Health Sciences Centre Decision Support Department, so the Cost Analysis Tool of the Ontario Case Costing Initiative was used as the source of these data.[13] These expenses are related to the running of hospitals and include costs of administration, finance, human resources, and plant operations, et cetera. The Ontario Case Costing Initiative does not indicate how overhead expenses are calculated. Sunnybrook Health Sciences Centre does not contribute information to the Ontario Case Costing Initiative, and therefore the mean daily overhead cost for 234 patients admitted with a diagnosis of neutropenia (International Classification of Diseases, 10th revision, Canadian enhancement, code D700) during the 2005-2006 fiscal year to 3 Toronto academic teaching hospitals contributing to the Ontario Case Costing Initiative (University Health Network, Mount Sinai Hospital, and St. Michael's Hospital) was obtained (reported as 2006 cost). The daily hospital per diem cost was calculated by adding the daily nonoverhead cost to the daily overhead cost. This cost was then inflated to the 2007 value using the Bank of Canada Inflation Calculator. A diagnostic code specifically for FN does not exist, which is why the code for neutropenia was used. Although these overhead costs are not specific to Sunnybrook Health Sciences Centre, they were assumed to be representative, because they were provided by academic teaching hospitals located in the same city as Sunnybrook Health Sciences Centre.

Statistical Analyses

Direct medical costs per episode of FN were quantified in the base case analysis. Descriptive statistics (percentages, means, and standard deviations) were used to summarize demographic, resource utilization, and cost data. A 3000-replicate bootstrap was conducted to determine the 95% bootstrap confidence intervals.

A subanalysis was performed on risk categories for FN complications based on the MASCC risk model.

RESULTS

Patient Demographic and Disease State Characteristics

A total of 51 FN episodes that occurred in 46 patients were included in the study. Table 2 provides an outline of demographic and disease state information for these patients. Twenty-nine of the episodes ended when the patient was discharged home independently, 17 of the episodes ended with the patient being discharged home

Table 2. Patient Demographic and Disease State Information

Characteristic	No. of Patients (%)
Sex	
Women	24 (52)
Men	22 (48)
Mean age ± SD, y	60.3 ± 13.4
Cancer type	
Hematologic malignancies	28 (61)
Non-Hodgkin lymphoma	16 (35)
Acute myeloid leukemia	6 (13)
Hairy cell leukemia	1 (2)
Burkitt lymphoma	2 (4)
Chronic lymphocytic leukemia	3 (7)
Solid tumors	18 (39)
Breast cancer	9 (20)
Colon cancer	3 (7)
Nonsmall cell lung cancer	2 (4)
Small cell bladder cancer	1 (2)
Squamous cell carcinoma of skin	1 (2)
Squamous cell carcinoma of tonsil	1 (2)
Neuroendocrine pancreatic tumor	1 (2)

SD indicates standard deviation.

with home care support through community care programs, 1 episode ended with the patient being transferred to a long-term care facility, and 4 of the episodes ended in the death of the patient. Three of the deaths were related to progression of the underlying malignancy, and 1 death resulted from sepsis because of FN.

Direct Medical Costs

Table 3 summarizes LOS and costs for the 51 episodes of FN included in the study as well as their 95% confidence intervals. The mean cost per episode was 6324 ± 4783 Canadian dollars, and the mean LOS was 6.8 days.

Risk Stratification

Each episode was classified as being either low risk or high risk for FN complications according to the MASCC model, by which a score of $\geq$21 is considered low risk and a score of $<$21 is considered high risk. Thirteen (25%) of the episodes were in the high-risk group, and 38 (75%) of the episodes were in the low-risk group. Table 4 presents demographic and disease state information for episodes in the 2 MASCC risk groups. Table 5 summarizes the costs per FN episode for the 2 risk groups.

DISCUSSION

FN is a common, serious adverse effect of cancer chemotherapy. This study, which to our knowledge is the first in 10 years to evaluate the costs of hospitalization for this condition in Canada, found that the mean LOS in hospital for treatment of FN was 6.8 days, with a mean total cost of 6324 ± 4783 Canadian dollars. The main driver of costs was LOS in hospital.

To our knowledge, this is also the first Canadian study to stratify FN episodes into low- and high-risk groups. The majority of patients in this study (75%) were classified as low risk according to the Multinational Association for Supportive Care in Cancer risk score model. The mean cost per episode of FN in the MASCC low- and high-risk groups was 5362 ± 3919 Canadian dollars and 9187 ± 6014 Canadian dollars, respectively; the mean LOS was 6.1 days and 8.8 days, respectively.

The other Canadian studies that have examined the costs of FN found a LOS ranging from 7 days to 21 days, with the majority of episodes involving a LOS of approximately 7 days, and costs per episode ranging from 5007 Canadian dollars to 8378 Canadian dollars, findings that appear to be similar to those of this study. The main cost driver in all of these studies was LOS in hospital, which is consistent with the results of this study.[7-10]

Three important differences must be considered when comparing results of this study to previous Canadian findings. First, 2 of the previous studies did not use actual patient data gathered in the settings in which the investigators applied costs; instead, they abstracted clinical and resource utilization data from the medical literature and applied Canadian cost estimates to derive a total cost per FN episode.[8,9] These costs may not have reflected the true cost of treating FN, because clinical data used in these studies may not have reflected practice in the settings where costs were quantified. In this study, resource utilization and cost data were gathered in the same setting, providing a more accurate estimate of the cost of treating a FN episode.

Second, in 3 of the other studies FN that occurred only in patients with a single type of malignancy was considered. One study examined FN in breast cancer patients, another in patients with non-Hodgkin lymphoma, and the third in patients with ovarian cancer.[7,9,10] The current study included FN episodes in patients with all types of underlying malignancies, including those with leukemia, a malignancy associated with greater LOS in hospital and higher costs when FN occurs.[14]

Third, all previous Canadian studies were done $>$10 years ago. Healthcare costs have risen considerably during that time, and treatment practices may also have changed; for example, days spent in hospital for FN treatment have likely been reduced, as a growing body of literature has

Table 3. Summary of Length of Stay and Direct Medical Costs

Length of Stay/Cost	Mean	SD	Median	Range	95% CI
Length of stay, d	6.8	4.9	5.0	1.0-25.0	5.3-8.3
Hospital per diem cost	$4657	$3411	$3362	$1276-$16,940	3808-5668
Antibiotic cost	$258	$413	$100	$28-$2184	160-377
G-CSF cost	$354	$721	$0	$0-$3358	171-564
Miscellaneous medication cost	$105	$234	$14	$0-$951	49-176
Laboratory and diagnostic test cost	$420	$257	$344	$193-$1538	357-495
Blood bank cost	$530	$1037	$20	$0-$4121	268-829
Total cost per FN episode	$6324	$4783	$4351	$1893-$21,847	5135-7735

SD indicates standard deviation; 95% CI, 95% confidence interval; G-CSF, granulocyte–colony-stimulating factor; FN, febrile neutropenia.

Table 4. Demographic and Disease State Information Based on MASCC Risk Group

Characteristic	MASCC High-Risk Group (n = 13 Episodes)	MASCC Low-Risk Group (n = 38 Episodes)
Women	5 (38%)	21 (55%)
Mean age ± SD, y	67.8 ± 8.6	58.9 ± 13.9
Hematologic malignancies	11 (85%)	22 (58%)
Treatment intent		
Curative	2 (15%)	15 (39%)
Palliative	10 (77%)	15 (39%)
Adjuvant	0 (0%)	8 (21%)
Neoadjuvant	1 (8%)	0 (0%)

MASCC indicates Multinational Association for Supportive Care in Cancer; SD, standard deviation.

demonstrated that early hospital discharge of FN patients is safe and effective.[15-17] Earlier discharge of FN patients that may not have occurred previously may account for similar findings of cost per FN episode between the current study and the 2 previous Canadian ones in which actual patient data were used.

This study provides an accurate and comprehensive estimate of the current costs of treating an episode of FN in hospital in Canada. In contrast to previous studies, costs in this study were based on actual patient data that were collected prospectively, and episodes were risk-stratified using the widely accepted MASCC model. Results from this study could be used in future economic evaluations of interventions to prevent and treat FN, including primary prophylaxis with hematopoietic growth factors and outpatient treatment of FN. Both of these strategies have been discussed in the literature.

There are currently conflicting data regarding the cost-effectiveness of using hematopoietic growth factors as primary prophylactic therapy against FN. Esser and Brunner conducted a review of 14 economic evaluations of granulocyte–colony-stimulating factor used as primary prophylaxis and found that only 6 demonstrated overall cost savings.[18] Data from the current study could be used to inform a cost-effectiveness analysis of hematopoietic growth factors as primary prophylaxis against FN.

Conversely, there have been several promising studies evaluating early hospital discharge for low-risk FN patients in whom a portion of the therapy is administered in the outpatient setting. Klastersky et al used the MASCC model to identify low-risk FN episodes in patients with solid tumors.[15] These patients were admitted to hospital and treated with oral antibiotics if they were considered eligible for oral therapy. Seventy-nine of 178 of these episodes ended in early discharge, with a median time to discharge of 26 hours. The median time to discharge in the other 99 episodes was 137 hours. Three readmissions to hospital occurred in the early discharge group.

Cherif et al used the Multinational Association for Supportive Care in Cancer model to identify low-risk FN episodes in patients with hematologic malignancies.[17] These patients were admitted to hospital and treated with intravenous antibiotics; 24 hours after defervescence, they were discharged on oral antibiotics if they were deemed able to tolerate this therapy. The mean LOS in those eligible for early discharge was 6 days, which is considerably greater than in the other 2 studies. However, it was still a mean of 2.2 days less than those episodes not discharged early. Of

Table 5. Length of Stay and Costs per FN Episode Based on MASCC Risk Group

Cost/Risk Group	Mean ± SD	Range
Length of stay, d		
MASCC high-risk group (n = 13 episodes)	8.8 ± 5.9	1.0-20.2
MASCC low-risk group (n = 38 episodes)	6.1 ± 4.5	1.9-25.0
Total costs		
MASCC high-risk group (n = 13 episodes)	$9187 ± 6014	$3010-$21,847
MASCC low-risk group (n = 38 episodes)	$5362 ± 3919	$1893-$18,424
Antibiotic costs		
MASCC high-risk group (n = 13 episodes)	$520 ± 687	$36-$2184
MASCC low-risk group (n = 38 episodes)	$165 ± 205	$28-$111
G-CSF costs		
MASCC high-risk group (n = 13 episodes)	$529 ± 1138	$0-$3358
MASCC low-risk group (n = 38 episodes)	$293 ± 517	$0-$2149

FN indicates febrile neutropenia; MASCC, Multinational Association for Supportive Care in Cancer; SD, standard deviation; G-CSF, granulocyte–colony-stimulating factor.

the 67 episodes that ended with early discharge, only 1 resulted in the patient requiring readmission to hospital.

The majority of FN episodes (75%) included in this study were classified by the Multinational Association for Supportive Care in Cancer model as being low risk for complications. Given the high success rates and reduced durations of hospital stay that have been demonstrated with early discharge programs in this subset of patients, an economic model of a similar outpatient FN therapy at Sunnybrook Health Sciences Centre could be developed to evaluate potential cost savings that may be realized if such a treatment strategy is implemented.

There were several limitations to this study. First, it was conducted at a single center, which raises questions regarding the generalizability of results. Because referral bias selected for patients with the types of underlying malignancies most commonly treated at Sunnybrook Health Sciences Centre, costs are reflective only of FN treatment practices at this institution. All patients receiving chemotherapy at Sunnybrook Health Sciences Centre are instructed to return to the emergency department at this institution in the event they become febrile; there may be a small proportion of patients who live further from the hospital and present to their local hospital when they become febrile. Second, the sample size was relatively small, with only 51 FN episodes included in the study.

The third limitation stems from some of the sources of cost data used. Data used to calculate nonoverhead costs were composed of only the costs charged to each medical ward for the running of its beds and did not include any costs that were incurred by other centers in the hospital; this figure may have underestimated the actual nonoverhead costs. Data used to calculate overhead costs were those contributed to the Ontario Case Costing Initiative by other university-affiliated teaching hospitals in Toronto, because this information was not available from Sunnybrook Health Sciences Centre; these costs may not have accurately reflected overhead costs for Sunnybrook Health Sciences Centre. Data on costs for the technical component of CT scans and MRI procedures were not included, because they were not listed in the Ontario Health Insurance Plan Schedule of Benefits, and this may have led to an underestimation of the true costs of these diagnostic tests. Finally, the microbiology and biochemistry laboratories at Sunnybrook Health Sciences Centre are financed from a global hospital budget, so the values used for calculating costs of laboratory tests from the OHIP Schedule of Benefits represent only estimates of the real costs. The range of values for cost per FN episode obtained from the bootstrap analysis should account for the uncertainties described above.

In conclusion, hospitalization for the treatment of a FN episode is expensive. A large number of patients treated at Sunnybrook Health Sciences Centre are considered to be at low risk for FN complications. Stratifying care by risk group may be helpful in identifying alternate strategies for FN treatment that could potentially result in cost savings to the healthcare system.

CONFLICT OF INTEREST DISCLOSURES

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