ORIGINAL ARTICLE

Mortality in a heterogeneous population of low-risk febrile neutropenic patients treated initially with cefazolin and tobramycin

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BACKGROUND: At Sunnybrook Health Sciences Centre in Toronto, Ontario, the recommended empiric regimen for febrile neutropenia has been cefazolin and tobramycin for at least 25 years. However, we had no objective data to reassure us that patient mortality had not increased over the past five years.

METHODS: A retrospective chart review of 48 episodes occurring in 44 patients admitted for the treatment of febrile neutropenia secondary to chemotherapy in 2002, and initially managed with cefazolin and tobramycin was conducted. Prospective data from 48 episodes in 2007 had previously been collected. Patients who developed febrile neutropenia while in hospital were excluded. The primary objective of the present study was to compare the all-cause mortality in 2007 with that from 2002.

RESULTS: There were no statistically significant differences between the groups (P>0.05). All-cause mortality in 2007 was 8.3% (four of 48) compared with 10.4% (five of 48) in 2002 (P=1). All deaths occurred in patients considered to be at high risk according to the Talcott score.

CONCLUSION: Mortality has not increased in the past five years with the use of empiric cefazolin and tobramycin for the treatment of patients admitted with febrile neutropenia at Sunnybrook Health Sciences Centre. Rates are comparable with those reported in the literature for similar patients. The results of the present study provide reassurance that the regimen continues to be effective for lower-risk febrile neutropenic patients.

Key Words: *Cefazolin; Fever; Mortality; Neutropenia; Tobramycin*

Mortalité chez une population hétérogène de patients neutropéniques fébriles de faible risque initialement traités par céfazoline et tobramycine

HISTORIQUE : Depuis au moins 25 ans, le schéma empirique recommandé pour la neutropénie fébrile, au Sunnybrook Health Sciences Centre de Toronto, en Ontario, se compose de céfazoline et de tobramycine. On ne disposait toutefois d'aucune donnée objective indiquant que la mortalité des patients n'avait pas augmenté depuis cinq ans.

MÉTHODE : Les auteurs ont procédé à un examen rétrospectif des dossiers portant sur 48 épisodes enregistrés chez 44 patients admis pour neutropénie fébrile secondaire à une chimiothérapie en 2002 et traités initialement par céfazoline et tobramycine. Les données prospectives sur 48 épisodes en 2007 avaient déjà été recueillies. Les patients ayant présenté une neutropénie fébrile durant leur hospitalisation ont été exclus. Le principal objectif de la présente étude était de comparer la mortalité de toutes causes de 2007 à celle de 2002.

RÉSULTATS : On n'a noté aucune différence statistiquement significative entre les groupes (p > 0,05). En 2007, la mortalité de toutes causes était de 8,3 % (4 sur 48), contre 10,4 % (5 sur 48) en 2002 (p = 1). Tous les décès sont survenus chez des patients considérés à risque élevé selon l'indice de Talcott.

CONCLUSION : La mortalité n'a pas augmenté depuis cinq ans avec l'emploi empirique de la céfazoline et de la tobramycine dans le traitement des patients admis pour neutropénie fébrile au Sunnybrook Health Sciences Centre. Les taux sont comparables à ceux publiés dans la littérature pour des patients similaires. Les résultats de la présente étude confirment que ce schéma thérapeutique continue d'être efficace chez les patients neutropéniques fébriles de moindre risque.

Febrile neutropenia is a common complication of chemotherapy, occurring in 10% to 50% of patients with solid tumours and greater than 80% of those with blood malignancies (1). It is defined as a single oral temperature of 38.3°C or greater or an oral temperature of 38.0°C or greater for 1 h or more, in a patient with a neutrophil count less than 0.5×10^9/L, or less than 1.0×10^9/L with a predicted decrease to below 0.5×10^9/L (2). Infection is the most common complication of chemotherapy-induced neutropenia (2-4). Among nonintensive care unit patients with an absolute neutrophil count of less than 0.1×10^9/L and monomicrobial bacterial bloodstream infection, a greater than 24 h delay in active antimicrobial therapy is associated with a significant increase in mortality (5). Accordingly, prompt treatment with empiric antimicrobials having a spectrum of coverage against aerobic Gram-positive and Gram-negative bacteria is required (2).

Several regimens are considered to be effective for the empiric management of febrile neutropenia. Current Infectious Diseases Society of America (IDSA) guidelines recommend assessment of a patient's risk for developing complications and suggest that when selecting an initial regimen, one should consider the type, frequency and susceptibility of bacterial isolates recovered from patients of the same hospital (2). Monitoring emerging resistance patterns within cancer centres is paramount in guiding therapy (6).

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Mortality due to infection in neutropenic patients has decreased significantly in recent years. Recent all-cause mortality rates range from 7% to 10% depending on patient characteristics (7-10).

PURPOSE AND OBJECTIVES

At Sunnybrook Health Sciences Centre in Toronto, Ontario, cefazolin plus tobramycin has been the recommended empiric regimen for at least 25 years. Although this is not a regimen currently recommended by the IDSA guidelines, it has many advantages and may still be the best option for the febrile neutropenic patients seen at this hospital. The objective of the present study was to determine and compare the all-cause mortality in 2007 with that in 2002 in patients admitted for the treatment of febrile neutropenia and managed initially with empiric cefazolin and tobramycin.

METHODS

Location

The present study was conducted at Sunnybrook Health Sciences Centre in Toronto, Ontario. Sunnybrook Health Sciences Centre is a 1275-bed teaching hospital with approximately 44 medical and 32 surgical inpatient oncology beds and an outpatient cancer care facility.

Patient eligibility

All patients 18 years of age and older admitted to the hospital with a chart-documented diagnosis of febrile neutropenia attributable to chemotherapy and treated initially with cefazolin and tobramycin were eligible for inclusion. Because duration of initial fever was not routinely reported in patient charts, fever was defined as a documented temperature of 38.0°C or greater . If a patient was afebrile on the day of admission, but reported having had a fever at home and was subsequently admitted and treated for febrile neutropenia, then the patient was included. Neutropenia was defined as an admission absolute neutrophil count of 1.0×10^9/L or less and patients were eligible for inclusion if their neutrophil count decreased to less than 1.0×10^9/L during the admission. If an admission neutrophil count was not available, the count on day 2 was recorded. If no neutrophil counts were documented, patients having a white blood cell count of less than 1.5×10^9/L were considered to be eligible for inclusion in the study. Neutropenia was considered attributable to chemotherapy if the calculated time to nadir was consistent with the expected time to nadir indicated in the Cancer Care Ontario drug monographs (11). Patients receiving daily chemotherapy were included if the episode occurred while on therapy or within two to three weeks of discontinuing the agent, provided that neutropenia is a documented side effect of the agent being used. Patients could be enrolled for multiple separate episodes of febrile neutropenia provided that the previous episode had resolved.

Patients were excluded if their neutrophil count did not decrease to less than 1.0×10^9/L during the admission (for those patients with documented neutrophil counts), if the occurrence of neutropenia did not correspond with the expected time to nadir for individual chemotherapy agents as indicated in the Cancer Care Ontario drug monographs (11), if they developed febrile neutropenia as inpatients or if they were treated initially with antibiotics other than cefazolin and tobramycin. Those who received a single dose of an alternative antibiotic upon presentation to the emergency department but whose therapy was subsequently modified to cefazolin and tobramycin were included.

Study design

The study protocol was approved by the Research Ethics Board at Sunnybrook Health Sciences Centre on January 17, 2008. Data regarding consecutive admissions for febrile neutropenia in 2007 had been prospectively collected as part of a pharmacoeconomic study previously completed at our institution. From these data, 48 episodes of febrile neutropenia meeting the study inclusion criteria in 2007 were identified and included in the analysis. A retrospective chart review of all consecutive admissions for febrile neutropenia beginning in January 2002 was then conducted. For admissions occurring between January and March 2002, charts were identified using International Classification of Diseases Revision 9 (ICD-9) codes for neutropenia as most responsible diagnosis (288) or cancer as most responsible diagnosis (140-2089 for malignant and 230-234 for in situ) with neutropenia as 'other' diagnosis. For admissions occurring between April and December 2002, charts were identified using ICD-10 codes for neutropenia as most responsible diagnosis (D700) or cancer as the most responsible diagnosis (C00-C97 for malignant and D00-D09 for in situ) with neutropenia listed as 'other' diagnosis. Charts were reviewed in chronological order until 48 consecutive admissions meeting the inclusion criteria were identified. Information was verified by outpatient chemotherapy computer records when possible.

End points

The primary end point was the rate of all-cause in-hospital mortality. Cause of death was recorded as documented on the death certificate. For patients with pneumonia having respiratory failure as the cause of death, death was considered attributable to infection.

Additionally, data regarding patient antibiotic use, infection, episode resolution and other parameters (Appendix A) were collected and compared. The risk of developing a serious medical complication was also determined and compared, using two validated risk prediction models, the Talcott (12) and The Multinational Association for Supportive Care in Cancer (MASCC) (13) (Appendix B and C).

Statistical analysis

An unpaired *t* test or Fisher's exact test was used to compare interval or nominal data, respectively. $P<0.05$ was considered statistically significant. Data sets from the 2002 and 2007 cohorts were combined and binary logistic forward conditional regression was conducted to determine if any of the following factors were covariates of mortality: MASCC score, Talcott score, age, sex, length of stay, initial neutrophil count, maximum temperature on admission, total number of febrile days, total number of afebrile days before discharge, neutrophil count at nadir, number of days to neutrophil nadir, number of days from nadir to neutrophil recovery and neutrophil count at recovery. To give an indication of the likelihood that the conclusions could be erroneous, Monte Carlo simulation with 100,000,000 iterations was used to determine the probability that three additional deaths could have occurred in 2007 as compared with 2002, given the mortality rates observed in the present study.

TABLE 1
Baseline patient characteristics

Characteristic	2007 (n=43)	2002 (n=44)	P
Female sex, n (%)	22 (51)	26 (59)	0.52
Mean age, years*	59.7±13.5 (31–87)	54±15.3 (22–82)	0.06
Cancer type, n (%)			
Hematological	26 (60)	22 (50)	0.39
Solid tumour	17 (40)	22 (50)	
Patients with previous FN episode(s), n (%)	10 (23)	17 (37)	0.16
Mean time in days from last to current FN episode*	159.4±254.9 (12–951)	95.1± 82.7 (12–301)	0.31
Mean number of previous episodes†	1.8±1.3 (1–5)	1.6±0.9 (1–4)	0.63

**Mean ± SD (range); †Per current episode, in patients with previous episodes (2007 n=13; 2002 n=19). FN Febrile neutropenia*

TABLE 2
Risk of serious medical complication*

Risk score	2007 (n=48)	2002 (n=48)	P
MASSC†, n (%)			
High risk	11 (23)	16 (33)	0.36
Low risk	37 (77)	32 (67)	
Talcott‡, n (%)			
High risk	30 (63)	28 (58)	0.83
Low risk	18 (37)	20 (42)	

**Complications that require therapeutic consequences other than changes in antimicrobial drug regimen. †The Multinational Association for Supportive Care in Cancer (MASCC) risk score assigns integer values to factors associated with a low risk for medical complication. Factors include: absent or mild symptoms, moderate symptoms, absence of hypotension, absence of chronic obstructive pulmonary disease, presence of solid tumour or absence of previous fungal infection in patients with hematological malignancies, outpatient status, absence of dehydration and age younger than 60 years. A score of ≥21 identifies patients at low risk for medical complication (defined as <10%) (13); ‡The Talcott risk score places patients into one of four groups, based on status at time of diagnosis of febrile neutropenia. Groups I, II and III are considered high risk. They consist of patients already hospitalized, outpatients with demonstrated serious concurrent comorbidity within 24 h of presentation and outpatients without serious concurrent comorbidity but with uncontrolled cancer, respectively. Patients who have none of these features comprise group IV and are considered low risk, with an expected rate of serious complications of less than 5% (12)*

TABLE 3
Febrile neutropenia episode characteristics

Characteristic	2007 (n=48)	2002 (n=48)	P
Length of stay, days	7.6±4.5 (2–26)	9.8±10.4 (2–54)	0.19
Time from cancer diagnosis to current episode, years	2.4±4.4 (13 d – 25.6)	3.3±6.3 (46 d – 24.8)	0.42
Intent of chemotherapy, n (%)*			
Adjuvant	9 (19)	10 (24)	0.61
Curative	15 (31)	14 (34)	0.82
Palliative	24 (50)	17 (41)	0.52
G-CSF prophylaxis, n (%)	11 (23)	12 (25)	1
Antibiotic prophylaxis, n (%)	2 (4)	7 (15)	0.16
White blood cell count on admission ($\times10^9$/L)	4.4±12.4 (0–59.5)	3.4±12.9 (0–87.3)	0.69
Neutrophil count on admission ($\times10^9$/L)†	0.3±0.35 (0–1.5)	0.26±0.29 (0–1.6)	0.55
<0.5, n (%)	34 (71)	35 (88)	0.07
≥0.5, n (%)	14 (29)	5 (12)	
<0.1, n (%)	12 (25)	6 (15)	0.30
≥0.1, n (%)	36 (75)	34 (85)	
Neutrophil count at nadir ($\times10^9$/L)†	0.24±0.27 (0–0.9)	0.19±0.16 (0–0.7)	0.29
<0.5, n (%)	36 (75)	38 (95)	0.017
≥0.5, n (%)	12 (25)	2 (5)	
<0.1, n (%)	15 (31)	6 (15)	0.09
≥0.1, n (%)	33 (69)	34 (85)	
Days from last chemotherapy to nadir, n	14.6±7.5 (6–40)	15.7±6.5 (6–48)	0.47
Days from nadir to recovery ≥0.5 or discharge§, n	4.2±5.1 (0–28)	3.7±2.6 (0–14)	0.57
Neutrophil count ($\times10^9$/L) at recovery ≥0.5 or discharge§	1.1±1.1 (0–5.2)	1.0±0.8 (0–3.6)	0.68
Maximum temperature (ºC) on day of admission	38.6±0.7 (36.8¶–40.3)	38.7±0.6 (36.9¶–40.2)	0.35
Febrile days before consistently afebrile** until discharge§, n	3.5±2.8 (0–11)	5.1±6.1 (1–25)	0.12
Afebrile days before discharge§, n	3.6±4.6 (0–27)	4.7±7.8 (0–48)	0.41

*Data are presented as mean ± SD (range), unless otherwise indicated. *Unknown for seven episodes in 2002 (n=41); †Unknown for eight episodes in 2002 (n=40); §Includes episodes ending in death; ¶Patient reported 'fever' at home but febrile temperature not recorded in chart; **Temperature 37.5ºC or less. G-CSF Granulocyte colony-stimulating factor*

RESULTS

Data from 51 admissions occurring from January through September 2007 were available. Three admissions were excluded because they were not initially managed with cefazolin and tobramycin. The remaining 48 episodes, occurring in 43 patients, met the inclusion criteria.

With the use of ICD codes, 162 admissions in 2002 were identified. In reviewing these charts, five additional episodes were identified by the reviewer, resulting in a total of 167 potential admissions. A review of consecutive charts from January 2002 to September 13, 2002, identified 109 admissions. Of these, 61 were excluded due to the following reasons: 19 cases represented episodes of in-hospital febrile neutropenia; 19 cases were treated with alternative antibiotics; 17 cases were not neutropenic or not suffering from febrile neutropenia; and six had not recently received chemotherapy. The remaining 48 admissions were included.

There were no statistically significant differences between patients from 2002 and 2007 with respect to baseline characteristics (Table 1). There were no differences in the proportion of patients considered to be at high risk according to either the Talcott or MASCC risk prediction models between 2002 and 2007 (Table 2). However, a greater number of patients were considered to be high risk using the Talcott model compared with the MASCC model (63% versus 23% in 2007, P=0.0002; 58% versus 33% in 2002, P=0.024; 30% versus 14% combined 2002 and 2007 data, P<0.0001).

There were no statistically significant differences between groups with respect to the episode characteristics defined in Appendix D and itemized in Table 3. Similar characteristics were analyzed for the subgroup of patients with neutrophil count of less than 0.5×10^9/L on admission (Table 4). Statistically significant differences were detected for neutrophil count on admission (0.11×10^9/L in 2007 versus 0.17×10^9/L

TABLE 4
Characteristics of episodes with admission neutrophil count of less than 0.5×10^9/L only

Characteristic	2007 (n=34)	2002 (n=35)	P
Length of stay in days	7.7±5 (2–6)	8.1±9 (2–54)	0.83
Neutrophil count on admission (x10^9/L)	0.11±0.11 (0–0.4)	0.17±0.12 (0–0.4)	0.03
<0.1, n (%)	12 (35)	6 (17)	0.11
≥0.1, n (%)	22 (65)	29 (83)	
Neutrophil count at nadir (x10^9/L)	0.09±0.11 (0–0.4)	0.15±0.12 (0–0.4)	0.04
<0.1, n (%)	15 (44)	6 (17)	0.02
≥0.1, n (%)	19 (56)	29 (83)	
Days from last chemotherapy to nadir	13.1±6.3 (6–40)	14.5±3.9 (6–22)	0.26
Days from nadir to recovery ≥0.5 or discharge*	5.7±5.3 (2–28)	3.9±2.5 (1–14)	0.08
Neutrophil count (x10^9/L) at recovery ≥0.5 or discharge*	1.2±1.3 (0–5.2)	1 ±0.8 (0–3.6)	0.54
Maximum temperature (ºC) on day of admission	38.7±0.7 (36.8–40.3)	38.8±0.7 (36.9–40.2)	0.7
Febrile days before consistently afebrile† until discharge*	3.2±2.7 (0–11)	4.5±4.8 (1–23)	0.11
Afebrile† days before discharge*	4.1±4.7 (0–27)	5±8.1 (0–48)	0.53
Episodes ending in death, n (%)			
All-cause	1 (3)	2 (6)	1
Infectious cause	1 (3)	1 (3)	

*Data are presented as mean ± SD (range) unless otherwise indicated. *Includes episodes ending in death; †Temperature 37.5ºC*

TABLE 5
Treatment of current episode of febrile neutropenia (FN)

Treatment	2007 (n=48)	2002 (n=48)	P
Length of therapy for FN in hospital in days			
Cefazolin	5.1±2.9 (1–18)	5.4±3.5 (1–19)	0.73
Tobramycin	5.3±3.3 (1–18)	5.6±4.1 (1–21)	0.66
Any antibiotic	6.7±3.6 (2–21)	7.5±6.0 (2–28)	0.44
Episodes requiring addition of broader spectrum antibiotics for the treatment of FN*, n (%)	18 (38)	16 (33)	0.83
Length of therapy with cefazolin and tobramycin alone before broadening of therapy required, days	2.8±1.5 (1–5)	4.6±4.4 (1–15)	0.12
Patients given antibiotics on discharge, n (%)	31 (65)	27 (56)	0.53
Episodes treated with G-CSF, n (%)	14 (29)	15 (31)	1

*Data are presented as mean ± SD (range) unless otherwise indicated. *Includes empiric broadening of spectrum as well as broadening for treatment of identified infection. G-CSF Granulocyte colony-stimulating factor*

in 2002, P=0.03) and neutrophil count at nadir (0.09×10^9/L in 2007 versus 0.15×10^9/L in 2002, P=0.04); however, these were not considered clinically important differences. The proportion of patients with neutrophil counts of less than 0.1×10^9/L at nadir was significantly greater in 2007 (44% versus 17%, P=0.02). However, it is possible that this difference could have been due to the absence of neutrophil count data in eight episodes from 2002.

TABLE 6
Infection identification*

Infection identification	2007 (n=48)	2002 (n=48)	P
Patients with identified source of infection, n (%)	13 (27)	12 (25)	1.0
Type of infection, n (%)†			
Pneumonia/possible pneumonia	7 (50)	8 (53)	1.0
Bacteremia	6 (43)	5 (33)	0.71
Other‡	1 (7)	2 (13)	1.0

**Based on x-ray and microbiology laboratory reports; †The total number of infections exceeds the number of infected patients because some patients had more than one type of documented infection (2007, n=13, number of identified infections = 14; 2002, n=12, number of identified infections = 15); ‡Includes documented urinary tract infection,* Clostridium difficile *infection and cellulitis*

There were no statistically significant differences between 2007 versus 2002, respectively, in terms of episode management (Table 5), including length of therapy with cefazolin (5.1 versus 5.4 days), length of therapy with tobramycin (5.3 versus 5.6 days), length of therapy with any antibiotic for febrile neutropenia (6.7 versus 7.5 days), episodes requiring the addition of broader spectrum antibiotics for the treatment of febrile neutropenia (18 versus 16 episodes), proportion prescribed antibiotics on discharge (65% versus 56%) and proportion treated with granulocyte colony-stimulating factor (29% versus 31%).

There were no statistically significant differences between the groups (2007 versus 2002) regarding the proportion of patients with an identified source of infection (27% versus 25%) or type of infection: pneumonia/possible pneumonia (50% versus 53%), bacteremia (43% versus 33%) or other, including urinary tract and *Clostridium difficile* infections (7% versus 13%) (Table 6). In 2007, there were six bacteremias, two of which were polymicrobial. Gram-positive organisms were isolated in four cases (one beta-hemolytic streptococcus, two *Streptococcus salivarius* and one coagulase-negative staphylococcus). Gram-negative organisms were isolated in five cases (one *Klebsiella pneumoniae*, one *Pseudomonas aeruginosa*, two *Enterobacter* and one *Escherichia coli*). All were sensitive to cefazolin or tobramycin. There were seven cases of pneumonia/possible pneumonia. *P aeruginosa* was isolated in one case and was found to be resistant to tobramycin and sensitive to piperacillin. There was one *C difficile* infection. In 2002, there were five bacteremias, three of which were polymicrobial. Gram-positive organisms were isolated in two cases (one *Staphylococcus aureus* and one beta-hemolytic streptococcus). All were sensitive to cefazolin. Viridans group streptococcus was isolated in one case, but considered a contaminant. Gram-negative organisms were isolated in six cases (one *Klebsiella oxytoca*, one *E coli*, two *K pneumoniae* and two *P aeruginosa*). All were sensitive to tobramycin. There were eight cases of pneumonia/possible pneumonia, one urinary tract infection with *Enterococcus* and one cellulitis with *P aeruginosa* sensitive to tobramycin.

There were four deaths due to any cause in 2007 and five deaths due to any cause in 2002 (P=1). All deaths occurred in patients considered to be at high risk of serious medical complication according to the Talcott risk model (Table 7). Two patients in 2002 who died were considered low risk according to MASCC. Most patients who died suffered from hematological malignancy (three of four in 2007 and four of five in

TABLE 7
Summary of episodes ending in death

Mortality				2007 (n=48)	2002 (n=48)		P
All-cause, n (%)				4 (8)	5 (10)		1
Infectious cause, n (%)				3 (6)	3 (6)		1.3
Patient, sex and age (years)	**Cancer diagnosis**	**Risk**	**Nadir (x10^9/L)**	**Infection and organism**	**Sensitivity**	**Broaden antibiotics**	**Cause of death***
2007							
Male, 69	NHL	High	0.9	None	N/A	No	Liver failure
Male, 84	AML	High	0	Bacteremia – *Streptococcus salivarius*	Penicillin	No	Sepsis
Female, 60	Breast	High	0.7	Pneumonia	N/A	Yes †	Respiratory failure
Female, 66	CLL	High	0.5	Pneumonia – *Pseudomonas aeruginosa*‡	Amikacin, ceftazidime, piperacillin	Yes§	Respiratory failure
2002							
Female, 46	ALL	High	0.1	Pneumonia	N/A	Yes¶	Sepsis
Female, 72	Ovarian	High	0.1	None	N/A	No	Respiratory failure
Male, 49	AML	High	0	Pneumonia, Bacteremia – *Klebsiella oxytoca***, *Escherichia coli*, Viridans group streptococci	Ceftazidime, ciprofloxacin, gentamicin, TMP/SMX	Yes††	Sepsis
Male, 63	AML	T: High M: Low	unknown	Bacteremia – *Klebsiella pneumoniae***	Cefazolin, TMP/SMX, gentamicin, ciprofloxacin	Yes‡‡	Intracranial hemorrhage
Female, 49	AML	T: High M: Low	unknown	Pneumonia, Bacteremia – *K pneumoniae***, *P aeruginosa*	Cefazolin, TMP/SMX, gentamicin, ciprofloxacin Gentamicin, tobramycin, ciprofloxacin, ceftazidime, piperacillin	Yes§§	Pneumonia

**Death certificate documented cause of death; †Levofloxacin 500 mg by mouth every 24 h; ‡Resistant to ciprofloxacin, gentamicin and tobramycin; §Trimethoprim/sulfamethoxazole (TMP/SMX) 2 double strength by mouth every 6 h, levofloxacin 750 mg by mouth daily, caspofungin 70 mg intravenously ×1, piperacillin/tazobactam 4.5 g intravenously every 6 h; ¶Ceftazidime 1 g intravenously every 6 h, cloxacillin 2 g intravenously every 6 h, amphotericin B 45 mg intravenously ×1; **Resistant to ampicillin; ††Vancomycin 1 g intravenously every 48 h, ceftriaxone 1 g intravenously every 12 h, ceftazidime 1 g intravenously every12 h; ‡‡Ceftazidime 1 g intravenously every 12 h; §§Clindamycin 600 mg intravenously every 8 h, ceftriaxone 1 g intravenously every 24 h, ciprofloxacin 400 mg intravenously every 12 h, amphotericin B per protocol. ALL Acute lymphoblastic leukemia; AML Adult acute myeloid leukemia; CLL Chronic lymphocytic leukemia; M The Multinational Association for Supportive Care in Cancer risk prediction model (13); NHL Non-Hodgkin lymphoma; T Talcott risk prediction model (12)*

2002). No source of infection was identified in one case in each group. There was one bacteremia and two pneumonias among patients who died in 2007, compared with three bacteremias and three pneumonias among patients who died in 2002. Death was attributable to infection in three cases in each group.

The sample size of 48 episodes per group had a power of 80% to detect a rise (one-tailed) in mortality of 7.4% (upper one-tailed limit of 95% CI is 17.8% mortality) at an alpha of 0.05 and incidence of mortality in 2002 of 10.4%.

No statistically significant covariates predicting death, including either the MASCC or Talcott score, were identified using binary logistic forward conditional regression. When Monte Carlo simulation was used to produce 100,000,000 iterations of the data set, the probability of three additional deaths occurring in 2007 as compared with 2002, given the mortality rates observed in this study, was less than 7.5%. Therefore, there is less than 7.5% risk that the mortality rate in 2007 is actually higher than that in 2002.

DISCUSSION

The present study found overall all-cause mortality rates to be 8.2% in 2007 and 10.4% in 2002. Mortality rates for febrile neutropenic patients reported in the literature are variable and depend on patient characteristics. A 1999 review of discharge databases from hospitals across seven states in the United States revealed a mortality rate of 6.8% among patients hospitalized for febrile neutropenia (9). The highest projected rates were associated with lung and bronchus carcinomas (10.5%), leukemia (8.2%) and gastric carcinomas (7.8%) (9). A similar study of adult cancer patients hospitalized with febrile neutropenia in 115 medical centres in the United States between 1995 and 2000 found an inpatient mortality of 9.5% (10). The study included patients who developed febrile neutropenia as outpatients or inpatients, but excluded those receiving bone marrow transplant. No change in mortality rate was observed over the five-year period (10). Although it is difficult to objectively compare mortality rates from other studies to our mixed patient population of both hematological and solid organ tumours, it appears as though the mortality rates at our institution are in the same range as those reported by other centres.

This sample size of 48 patients per group is relatively small. Because there is no recent literature regarding the use of cefazolin and tobramycin, even a small statistically nonsignificant increase in mortality would have been considered clinically significant and would serve as a signal that the current regimen may require updating. Because 48 episodes in both

study years represent all admissions for febrile neutropenia treated with cefazolin and tobramycin over a nine-month period, it would be impractical to complete a study of much larger magnitude. Because this sample is not random, but instead represents all consecutive episodes, it is likely a good representation of the patients treated at our institution. Given that there was one less death in 2007 than in 2002, the data do not provide any signal that cefazolin and tobramycin has become less effective in this patient population. The results of the Monte Carlo simulation further provide assurance that despite the small sample size, there is a low probability that mortality actually increased over the five-year period.

It was found that a number of patients were admitted and treated for febrile neutropenia who did not strictly meet the definition of febrile neutropenia. Recording of exact temperature was inconsistent and not all patients had a neutrophil count of less than 0.5×10^9/L. To account for this, we did a subgroup analysis of only those patients with an admission neutrophil count below 0.5×10^9/L. Some statistically significant differences between groups were noted; however, these differences are very small and unlikely to be clinically important. If anything, the differences found would bias for a higher mortality in 2007, and thus would bias against the continued use of cefazolin and tobramycin at Sunnybrook Health Sciences Centre.

It is known that the Talcott risk prediction model over estimates the proportion of patients considered to be at high risk of developing serious medical complications (13). Compared with the Talcott model, the MASCC index has a lower misclassification rate (30% versus 59%), better sensitivity (71% versus 30%) and lower specificity (68% versus 90%) (14). The MASCC index increases the number of patients being classified as low risk (63% versus 26%) (13). This was observed in our study because more patients were considered high risk according to Talcott compared with MASCC. We found that all patients who died were classified as high risk according to Talcott; however, two episodes ending in death in 2002 were classified as low risk according to the MASCC index. While the MASCC index has been validated for the purpose of identifying patients who may be safely managed with less intensive antimicrobial therapy (13), it has not been validated to predict death. The Talcott method has been validated to predict the risk of serious medical complication, which includes the risk of death (12).

Resistance to cefazolin and tobramycin has increased over the last five years at our hospital. In 2007, 84% of all *S aureus* blood isolates were sensitive to cefazolin compared with 95% in 2002 and 88% of *P aeruginosa* blood isolates were sensitive to tobramycin in 2007 compared with 93% in 2002 (15,16). In the present study, the low number of isolates prevents us from making definitive conclusions about the frequency and susceptibility of pathogens isolated from patients admitted with febrile neutropenia at our institution, but it does suggest that resistance to cefazolin and tobramycin has not become overly concerning.

Approximately 25% of patients in each group had a microbiologically or radiographically identified infection. These rates are slightly lower than the overall rates reported in the literature (2) and may in part be due to the definition of documented infection used in the present study (ie, only microbiologically and radiographically confirmed infection and not clinically documented infection). Regardless, the identification of infection source is not a validated marker of increased risk and is not used in either the Talcott or MASCC risk prediction model. Therefore, no inference of lower risk of medical complications in this patient population can be made by the lower rate of documented infection observed in our study. In fact, using the Talcott risk prediction model, 58% of patients in 2002 and 63% of patients in 2007 were considered to be at high risk of developing a serious medical complication in this study. The types of pathogens isolated from patients in this study are consistent with those commonly associated with infection in a neutropenic patient (17). The average length of therapy with tobramycin (five to six days) in our patient population is not long enough to raise concerns regarding the development of nephrotoxicity, becasue this type of toxicity typically occurs with longer duration of therapy (18).

This study is limited by the exclusion of patients who developed febrile neutropenia while in hospital. These patients are considered high risk for developing a serious medical complication according to both risk prediction models (13,19) and require study. Should the mortality rates in these patients be found to be higher than those identified in this study, a stratified approach to the management of febrile neutropenia may be warranted. This approach is advocated in the IDSA guidelines and practiced in some institutions. Another limitation is that the data sets (2007 versus 2002) were collected by different investigators. Thus, the potential exists for variability in the collection of subjective data, such as burden of illness. However, the investigators met to review the risk stratification of sample patients, to identify and correct inconsistencies.

The present study is further limited by its retrospective design. For example, we report low rates of prophylactic antibiotic use in both cohorts (15% in 2002 and 4% in 2007). It is possible that antibiotic use was not completely documented in all cases and therefore these rates may not accurately estimate the use of prophylactic antibiotics. Similarly, because temperatures were inconsistently documented, a modified definition of fever which technically does not meet the IDSA criteria was developed and used in this study. Other missing laboratory values and appropriate assessments may have also biased the results and further highlight the limitations of a retrospective study design. A prospective observational study would be required to capture all necessary information.

CONCLUSION

The mortality rates observed in our mixed hematological and solid tumour patients with febrile neutropenia were comparable to rates reported in the literature for similar patients. Mortality did not increase over the past five years (8.3% in 2007 versus 10.4% in 2002; P=1) with the use of empiric cefazolin and tobramycin for the treatment of patients admitted for febrile neutropenia at our hospital. Our study had a power of 80% to detect a 7.4% rise in mortality from 2002 to 2007. The results of the present study provide reassurance that initial empiric therapy with cefazolin and tobramycin continues to be effective for patients admitted to Sunnybrook Health Sciences Centre for febrile neutropenia. Evaluation of patients who develop febrile neutropenia while in hospital is warranted and plans are underway for this study.

APPENDIX A
Data collected for each episode reviewed

- Age
- Sex
- Dates of admission and discharge
- Cancer-related diagnosis
- Date cancer was diagnosed
- Chemotherapy most recently received
- Febrile neutropenia risk associated with chemotherapy regimen
- First date of most recent cycle of chemotherapy
- Neutrophil count on day of admission
- Maximum oral temperature on day of presentation with febrile illness diagnosed as febrile neutropenia
- Start and stop dates for cefazolin and tobramycin
- Initial cefazolin and tobramycin dosing received by patient
- Number of febrile days before becoming consistently afebrile until discharge
- Number of afebrile days before discharge
- Additional or replacement antimicrobials during febrile neutropenic episode with documentation of start and stop dates
- Neutrophil count at nadir, date that nadir occurred
- Total number of days of antimicrobial therapy overall
- Date that neutrophil count recovered to 0.5×10^9/L
- Neutrophil count at recovery
- Chest x-ray results (ie, pneumonia present or absent)
- Documentation of any culture and sensitivity results (eg, blood cultures)
- Documentation of any identified infection
- Use of antibiotic or granulocyte colony-stimulating factor prophylaxis
- Survival or death during admission for this episode
- Number of previous febrile neutropenia episodes
- Date of last episode of febrile neutropenia
- Chart documented cause of death
- Concurrent comorbidities as defined by the Talcott risk stratification tool
- Presence of uncontrolled cancer as defined by the Talcott risk stratification tool
- Burden of illness (classified as no, mild or moderate symptoms)
- Presence or absence of hypotension
- Presence or absence of dehydration
- Presence or absence of previous fungal infection
- Intent of chemotherapy

APPENDIX B
Talcott risk assessment tool (12) to determine risk of developing a serious medical complication

Group	Risk
I: Patients already hospitalized	
II: Outpatients with demonstrated serious concurrent comorbidity* within 24 h of presentation	High
III: Outpatients without serious concurrent comorbidity but with uncontrolled cancer†	
IV: Patients who have none of the features of groups I to III	Low (<5%)

**Patients with another medical condition that independently requires inpatient observation or therapy (eg, 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 hypocalcemia, etc; †For patients with leukemia: the absence of documented complete remission. For lymphoma or solid tumours: development of new lesions, 25% or more enlargement of a measurable lesion while on chemotherapy or premature termination of chemotherapy due to other evidence of failure by the primary medical oncologist. Patients with disease progression while not receiving active systemic therapy are not rated as having uncontrolled cancer*

APPENDIX C
The Multinational Association for Supportive Care in Cancer risk prediction model scoring system (13)

Characteristic	Weight
Burden of illness*: no or mild symptoms	5
No hypotension†	5
No chronic obstructive pulmonary disease‡	4
Solid tumour or no previous fungal infection	4
No dehydration§	3
Burden of Illness*: moderate symptoms	3
Outpatient status	3
Age <60 years	2
Points attributed to the variable 'burden of illness' are not cumulative. The maximum theoretical score is therefore 26	TOTAL

**Classification is subjective. To be consistent with definitions used in the pharmacoeconomic study from which prospective data for this study was obtained, the following criteria was used: (N Lathia, personal communication, November 2007) None/mild: Patient is asymptomatic. Severe: Patient is systemically ill with hemodynamic instability (eg, patients with a heart rate >100 beats/min or systolic blood pressure <90 mmHg who require admission to an intensive care unit) Moderate: All other patients. Examples: patients with chills, pain, unable to work for past few days, some signs and symptoms of infection but not sepsis, etc; †Systolic blood pressure <90 mmHg; ‡Active chronic bronchitis, emphysema, decrease in forced expiratory volumes and need for oxygen therapy, corticosteroids and/or bronchodilators; §Requirement for intravenous hydration with other signs of dehydration such as tachycardia or documented poor oral intake*

APPENDIX D
Definitions

- Date of most recent chemotherapy:
  - Recorded as the first day of the cycle for regimens consisting of more than one day of therapy.
  - Recorded as the day therapy was initiated for patients receiving daily chemotherapy
- Time to nadir:
  - Calculated as the number of days from the first day of chemotherapy to the lowest documented neutrophil count, inclusive.
- Number of days before becoming afebrile until discharge:
  - Calculated as the number of days until documentation of consecutive temperatures ≤37.5ºC until discharge.
  - A single recording of a temperature >37.5°C after a patient had become afebrile for more than 2 days was disregarded.
- Additional or replacement antimicrobials:
  - Agents prescribed for the purpose of broadening therapy to cover pathogens not adequately covered by cefazolin and tobramycin alone for the management of febrile neutropenia, including both antibiotic and antifungal agents.
  - Fluconazole 100 mg orally daily and antiviral agents were excluded, because they were presumed to be prescribed for oral thrush or viral infections, respectively, and not specifically associated with continued fever of febrile neutropenia.
  - Modifying therapy to oral antibiotics in a stable patient and narrowing therapy once an infection had been identified were not considered indicators of failure with cefazolin and tobramycin.
- The total number of days of therapy overall:
  - Calculated as the number of days from initiation of cefazolin and tobramycin to the last day of therapy with any antibiotic for the treatment of febrile neutropenia while in hospital, inclusive.
- If the neutrophil count did not decrease to $<0.5\times10^9$/L while in hospital, time to recovery was recorded as 0 days.
- If the patient was discharged or died before recovery, time to discharge or death was used.

REFERENCES

1. Klastersky J. Management of fever in neutropenic patients with different risks of complications. Clin Infect Dis 2004;39(Suppl 1):S32-7.
2. Hughes W, Armstrong D, Bodey G, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 2002;34:730-51.
3. Rolston K. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. Clin Infect Dis 2005;40(Suppl 4):S246-52.
4. Bodey G. Infection in cancer patients. A continuing association. Am J Med 1986;81(Suppl 1A):11-26.
5. Lin M, Weinstein R, Hota B. Delay of active antimicrobial therapy and mortality among patients with bacteremia: Impact of severe neutropenia. Antimicrob Agents Chemother 2008;52:3188-94.
6. Kirby J, Fritsche T, Jones R. Influence of patient age on the frequency of occurrence and antimicrobial resistance patterns of isolates from hematology/oncology patients: Report from the chemotherapy alliance for neutropenics and the control of emerging resistance program (North America). Diagn Microbiol Infect Dis 2006;56:75-82.
7. Viscoli C. Planned progressive antimicrobial therapy in neutropenic patients. Br J Haematol 1998;102:879-88.
8. Viscoli C, Varnier O, Machetti M. Infections in patients with febrile neutropenia: Epidemiology, microbiology, and risk stratification. Clin Infect Dis 2005;40(Suppl 4):S240-5.
9. Caggiano V, Weiss R, Rickert T, Linde-Zwirble W. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer 2005;103:1916-24.
10. Kuderer N, Dale D, Crawford J, Cosler L, Lyman G. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106:2258-66.
11. Cancer Care Ontario. Cancer Drug Information: Drug Monographs for Health Care Professionals. <http://www.cancercare.on.ca/english/home/toolbox/drugs/drugformulary/cancerdrugs> (Version current March to June 2008)
12. Talcott J, Siegel R, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: A prospective, two-center validation of a prediction rule. J Clin Oncol 1992;10:316-22.
13. Klastersky J, Paesmans K, Rubenstein E, et al. The multinational association for supportive care in cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. J Clin Oncol 2000;18:3038-51.
14. Kern W. Risk assessment and treatment of low-risk patients with febrile neutropenia. Clin Infect Dis 2006;42:533-40.
15. The Antimicrobial Subcommittee of the Pharmacy and Therapeutics Committee. Antimicrobial Handbook: Guidelines, Policies and Treatment Recommendations. Toronto: Sunnybrook Health Sciences Centre Medical Advisory Committee, 2002.
16. The Antimicrobial Subcommittee of the Pharmacy and Therapeutics Committee. Antimicrobial Handbook: Guidelines, Policies and Treatment Recommendations. Toronto: Sunnybrook Health Sciences Centre Medical Advisory Committee, 2007.
17. Mutnick A, Kirby J, Jones R. CANCER Resistance Surveillance Program: Initial results from hematology-oncology centres in North America. Ann Pharmacother 2003;37:47-57.
18. Drusano G, Ambrose P, Bhavnani S, Bertino J, Nafziger A, Louie A. Back to the future: Using aminoglycosids again and how to dose them optimally. Clin Infect Dis 2007;45:753-60.
19. Talcott J, Finberg R, Mayer R, Goldman L. The medical course of cancer patients with fever and neutropenia. Arch Intern Med 1988;148:2561-8.