Assessment and management of febrile neutropenia in emergency departments within a regional health authority—a benchmark analysis

D. Szwajcer MD,*† P. Czaykowski MD,*† and D. Turner PhD†

ABSTRACT

Objectives

Febrile neutropenia is considered an oncologic emergency, for which prompt initiation of antibiotics is essential.

Methods

We conducted a retrospective cohort study for the 2006 calendar year involving all adult oncology patients presenting with febrile neutropenia to a regional health authority's emergency departments. The objective was to determine the time from triage to antibiotic administration and its impact on patient outcomes.

Results

We identified 68 patients presenting with febrile neutropenia, most of whom (76%) were seen in tertiary care centers. Of those patients, 65% were triaged to be seen within 15 minutes of arrival in the emergency room; however, the median time to reassessment was 57 minutes. The median time from triage to antibiotic administration was 5 hours (range: 1.23–22.8 hours). No increased risk of death or increased length of hospital stay was associated with delayed antibiotic administration. Older patients and patients without caregiver support were more likely to experience delayed antibiotic administration (odds ratio: 3.8 and 12.7 respectively).

Conclusions

We were not able to show a deleterious effect of delay in antibiotic administration, but our analysis identified several points at which patient flow through the emergency room could be improved.

KEY WORDS

Antineoplastic chemotherapy, febrile neutropenia, emergency department

1. INTRODUCTION

Neutropenia is one of the major dose-limiting toxicities of systemic cancer chemotherapy. The depth and duration of neutropenia correlate with the risk of developing infection and death¹.

Episodes of febrile neutropenia (FN) are considered an oncologic emergency. Among cancer patients presenting with an episode of FN, one series found that 30% had microbiologically confirmed bacteraemia². Another group identified a 10% prevalence of gram-negative bacterial infections³. An episode of FN is a potentially life-threatening condition⁴, and therefore prompt evaluation and timely antibiotic administration are considered crucial.

Several studies have described wait times for adult oncology patients presenting to emergency departments (EDs) with episodes of FN. One group identified a 75-minute median wait time from ED admission to examination, with the median time to antibiotic administration being 210 minutes. Patients with advanced cancer and those with more comorbidities waited longer than did those with earlier-stage, less complex disease⁵. Another group identified a 107-minute median wait time from triage to antibiotic administration for adult patients presenting to the ED with an episode of FN⁶. A prospective study examined the time from presentation in the ED to antibiotic administration in patients with a presumptive serious infection in need of immediate empiric antibiotic therapy. The median time to antibiotic administration was 5 hours⁷. In the setting of sepsis and hypotension, a delay in antibiotic administration is associated with a survival decrement of 7.5% per hour of delay⁸.

Currently, a limited number of benchmarks have been established for evaluation of adult patients with FN in Canada, but several Canadian pediatric centres have developed benchmarks for the evaluation and therapy of pediatric patients with FN. The Child Health Program of Manitoba benchmarks for all pediatric patients presenting with the diagnosis of FN to the ED are these:

- To be assessed within 15 minutes by a nurse and a physician [Canadian Triage and Acuity Scale (CTAS) level 2⁹]
- To commence antibiotic administration within 2 hours of initial presentation¹⁰

Similar benchmarks are in use in other centres across Canada (Chagla Y. Canadian Nosocomial Surveillance Program. Personal communication).

In the current study, we retrospectively analyzed the initial management of all adult oncology patients presenting to EDs within a regional health authority over the course of 1 year.

2. METHODS

2.1 Cohort Assembly

A population at risk was assembled by identifying all adult patients (18 years of age and over) within the Manitoba cancer registry who received systemic chemotherapy between November 1, 2005, and December 31, 2006. Each hospital within the Winnipeg Regional Health Authority (WRHA) generated a list of all adult admissions for the management of neutropenia (ICD10 code D70) between January 1 and December 31, 2006. Patients were included if they had an absolute neutrophil count less than $1.5 \times 10^9/\text{L}$ with a temperature of at least 38.0°C at the time of triage or within the 24 hours preceding their presentation to the ED. Cases were excluded if the episode of FN developed in hospital rather than in the ED, if fever was absent, or if the admission for FN occurred directly from clinic to a hospital ward. The final cohort consisted of the adult patients who had received systemic chemotherapy within the 60 days preceding presentation to the ED for an episode of FN. A professional data abstractor then undertook a detailed chart review for those patients. Triage assignment in the ED was determined by the CTAS score (1, immediate assessment; 2, within 15 minutes; 3, within 30 minutes; 4, within 1 hour)⁸. Vital status was ascertained at 5 and 30 days after the ED visit, through linkage with the provincial cancer registry. Ethics approval for the study was granted by the Health Research Ethics Board of the University of Manitoba and by the Research Review Committee of the WRHA.

2.2 Analysis

Two groups were identified: patients receiving timely antibiotics (less than 5 hours from ED triage to antibiotic administration), and those not receiving timely antibiotics. Univariate logistic regression was used to compare the groups. Variables on univariate analysis with a *p* value less than 0.1 were then entered into a multivariate logistic analysis. Multivariate logistic regression was performed to

identify predictors of delayed antibiotic administration. Univariate logistic regression was used to examine whether delayed antibiotic administration affected vital status at 5 and 30 days after ED triage. A Kaplan–Meier survival analysis¹¹ was used to determine whether time to antibiotic administration was different for patients with hematologic and nonhematologic malignancies.

All statistical analyses were performed using the SAS software application (version 9.1: SAS Institute, Cary, NC, U.S.A.). Unless otherwise indicated, data are presented as medians or means with ranges.

3. RESULTS

3.1 Baseline Cohort Description

We identified 68 oncology patients who, between January 1 and December 31, 2006, experienced an episode of FN and underwent assessment through an ED within a WRHA facility. Neutrophil counts for the cohort were distributed as follows:

- 39 patients (57%) presented to the ED with an absolute neutrophil count below $0.5 \times 10^9/\text{L}$.
- 23 patients (34%) had an initial neutrophil count between 0.5 and $1.0 \times 10^9/\text{L}$.
- 6 patients (9%) had only an initial white blood cell count available, which ranged from 1.0 to $1.2 \times 10^9/\text{L}$.

Of the 68 patients, 6 (9%) visited the ED more than once in close proximity to the FN visit for which antibiotics were administered. In the cohort, 27 patients (40%) had a hematologic malignancy [the most common diagnosis being large cell lymphoma (8 patients)] and 41 patients (60%) had a solid malignancy [the most common diagnosis being breast cancer (27 patients, Table 1)]. The median age in the cohort was 59.5 years (range: 20–83 years), and 30 of 67 patients (45%) were men. Most members of the cohort (52 patients, 76%) were seen in a tertiary care facility. Filgrastim was administered in 42 patients (62%) before their ED presentation, and filgrastim was started in 6 patients (9%) after ED presentation. A central venous catheter was present *in situ* in 46 patients (68%). Median duration from last chemotherapy to ED triage was 8.5 days (range: 1–42 days). Almost two thirds of the cohort (44 patients, 65%) were assigned a CTAS score of 2 (see Table 1). After ED triage and assessment, 2 patients (3%) with FN required admission to an intensive care unit. In 15 patients (22%), blood cultures were positive, with 9 patients (13%) having gram-negative bacterial isolates.

3.2 Time to Antibiotic Administration

The median time from ED triage to antibiotic administration was just over 5 hours (range: 1.23–22.8 hours).

TABLE I Baseline characteristics

<i>Variable</i>	<i>Value</i>
Patients (<i>n</i>)	68
Sex (<i>n</i>)	
Men	30
Women	38
Age (years)	
Median	59.5
Range	20–83
Disease (<i>n</i>)	
Hematologic malignancy	27
Multiple myeloma	6
Large cell lymphoma	9
High-grade lymphoma/ALL	3
Other	9
Solid tumors	41
Breast cancer	27
GI malignancy	8
Other	6
CVC <i>in situ</i> [<i>n</i> (%)]	46/68 (68)
Days from last chemotherapy	
Median	8.5
Range	1–42
CTAS score = 2 [<i>n</i> / <i>N</i> (%)]	44/68 (65)
Absolute neutrophil count	
Median	0.23
Range	0–1.5
Triage mean blood pressure	
Median	84
Range	49–118
Maximal ED temperature (°C)	
Median	38.7
Range	38–40
Time (minutes) from ED triage to	
Nurse assessment	
Median	57
Range	2–335
EMO assessment	
Median	60
Range	7–427
Antibiotic administration	
Median	616
Range	74–1369
Hospital stay (days)	
Median	5.1
Range	0.2–55.4

ALL = acute lymphocytic leukemia; GI = gastrointestinal; CVC = central venous catheter; CTAS = Canadian Triage and Acuity Scale; ED = emergency department; EMO = emergency medical officer.

In our cohort, only 4 patients (6%) were administered antibiotics within 2 hours of triage. A log rank test showed that the median times to antibiotic administration of 6 hours for those with hematologic malignancies and 5 hours for those with nonhematologic malignancies (by Kaplan–Meier time-to-event analysis) were not significantly different.

To examine factors predictive for delayed antibiotic administration, we divided the cohort into those receiving antibiotics within 5 hours of triage and those receiving antibiotics more than 5 hours after triage.

3.2.1 Predictors of Delayed Antibiotic Administration

On both univariate and multivariate analysis, age greater than 60 years and lack of a caregiver (either a family member or a friend) were associated with delayed antibiotic administration, with odds ratios of 3.8 (95% confidence interval: 1.3 to 11) and 12.7 (95% confidence interval: 1.4 to 112) respectively (Tables II and III).

TABLE II Univariate logistic regression examining predictors of delayed antibiotic administration^a

<i>Variable</i>	<i>OR</i>	<i>95% CI</i>	<i>p Value</i>
Sex (men vs. women)	0.85	0.3 to 2.2	0.74
Age (<60 vs. ≥60 years)	3.1	1.1 to 8.6	0.03
Diagnosis (hematologic vs. solid)	0.7	0.3 to 1.9	0.51
Caregiver status (family- vs. self-care)	9.6	1.1 to 81	0.04
Prior ED notification (yes vs. no)	2.2	0.6 to 8.2	0.21
Patient history of FN episodes (yes vs. no)	1.0	0.4 to 3.0	0.94
Central venous catheter (present vs. absent)	0.9	0.29 to 2.8	0.86
CTAS score (2 vs. ≥2)	2.2	0.82 to 6.0	0.12
ED maximal temperature (<39°C vs. ≥39°C)	0.5	0.19 to 1.3	0.17
Triage mean BP (<90 vs. ≥90 mmHg)	1.2	0.41 to 3.3	0.76
Triage heart rate	0.99	0.97 to 1.0	0.55
Triage respiratory rate	0.91	0.79 to 1.0	0.17
Absolute neutrophil count	0.67	0.23 to 1.9	0.45

^a More than 5 hours after emergency department triage.

OR = odds ratio; CI = confidence interval; ED = emergency department; FN = febrile neutropenia; CTAS = Canadian Triage and Acuity Scale; BP = blood pressure.

TABLE III Multivariate logistic regression examining predictors of delayed antibiotic administration^a

<i>Variable</i>	<i>OR</i>	<i>95% CI</i>
Age (≥60 vs. <60 years)	3.8	1.3 to 11
Caregiver status (self vs. family)	12.7	1.4 to 112

^a More than 5 hours after emergency department triage.

OR = odds ratio; CI = confidence interval.

3.2.2 Time to Antibiotic Administration and Patient Outcomes

The proportion of patients alive at 5 days and 30 days after ED triage were 0.94 and 0.91 respectively. In univariate logistic regression, we observed no increased risk of death associated with delayed antibiotic administration. The median length of hospital stay for the entire cohort was 5 days (range: 0.2–55 days). Delayed antibiotic administration did not lead to an increased length of hospital stay.

4. DISCUSSION

During the period studied, the median time to antibiotic administration was 5 hours in adult oncology patients with an episode of FN. Only 4 of 68 patients received antibiotics within 2 hours of ED triage. Most patients (44 of 68, 65%) were triaged in the ED with a CTAS score of 2 (suggesting reassessment within 15 minutes). However, for that group, the median wait to be reassessed by a nurse was 57 minutes. The median wait for a laboratory evaluation, including blood draw for culture, was 101 minutes. The primary oncologist or the oncology team notified the ED of the patient's impending arrival in 11 cases (16%).

The Infectious Diseases Society of America guideline on the management of the neutropenic cancer patient¹² and the WRHA *Guidelines for the Management and Monitoring of Low-Risk versus High-Risk Febrile Neutropenic Cancer*¹³ suggest prompt initiation of antibiotics after a timely evaluation. Several pediatric ED programs in Canada have adopted standardized protocols to ensure timely antibiotic administration in pediatric patients with FN. Within the regional health authority institutions in which our study was performed, the pediatric ED and oncology programs introduced a 2-hour benchmark for the time from triage to antibiotic administration. At the same time, a clinical pathway was established, with standard preprinted order sets and an algorithm. Before introduction of the benchmark, median time to antibiotic administration was 5 hours; after adoption of the benchmark, 90% of pediatric patients received antibiotics within 2 hours of ED presentation¹⁰.

The delay in antibiotic administration noted in the present study is likely multifactorial; however, development of a standardized protocol to direct the flow of patients with an episode of FN through the ED would be of significant benefit. The adoption of algorithms, protocols, or standardized order sets within a variety of institutional settings has clearly been shown to lower the time to antibiotic administration in the setting of an episode of FN^{6,10}. Within the broader scope of emergency care, several studies have identified the roles that quality improvement projects, guideline development, and clinical pathway implementation play in improving outcomes in the management of acute myocardial infarction and cerebrovascular disease, among other conditions^{14–16}.

Patients who were older and who did not have caregiver support were more likely to wait longer from triage to antibiotic administration. However, delayed antibiotic administration did not translate into decreased survival or increased length of hospital stay. Oncology patients with FN are on a spectrum of acuity, with some able to manage as outpatients, and others presenting in septic shock. In our study cohort, 13% of patients had cultures positive for gram-negative bacteria. Because patients with FN may worsen acutely, urgent assessment and timely antibiotic administration is justified.

We could identify no patients in the study cohort who were undergoing high-dose cytarabine consolidation in the management of acute myeloid leukemia. Consolidation therapy with high-dose cytarabine is associated with a 60% risk of FN^{17,18}. Patients with acute myeloid leukemia undergoing consolidation receive outpatient treatment in Manitoba, in a process that is highly protocolized and that follows a care map. That patient group is monitored daily from initiation of chemotherapy until count recovery. They are treated prophylactically with antibiotics and growth factors, and with onset of an episode of FN, they are rapidly admitted directly to a specialized ward within the WRHA. Within the context of the WRHA, discussion is ongoing concerning implementation of a care map and preprinted order sets to complement the existing regional clinical practice guideline¹³ so that the management of oncology patients presenting to the ED with FN is optimized.

Our study has several limitations. Because of its retrospective nature, we could not accurately capture patient comorbidity or performance status, both of which affect outcomes in patients with FN¹⁹. We defined timely antibiotic administration as being within 5 hours from triage. The literature holds no definitive guidelines concerning the optimal time to administer antibiotics in the setting of an episode of FN. Various experts have used the 2-hour benchmark from time of triage to antibiotic administration as a treatment target. Within our study cohort, only 6% received antibiotics within 2 hours of ED triage. The 5-hour time point represents the median time to antibiotic administration in this cohort of 68 patients, and it is thus a pragmatic cut-off for our analysis. The small number of patients in the cohort limits the study's power to demonstrate a detrimental effect of delayed antibiotic administration.

We were not able to demonstrate an adverse effect of delayed antibiotic administration in oncology patients with an episode of FN. Nevertheless, patient care could be improved by implementing various strategies to shorten the time from triage to treatment. Protocolizing ED care and producing a care map for these vulnerable patients would streamline their care and provide a framework for the ED staff in managing an uncommon ED event.

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6. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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Correspondence to: David Szwajcer, ON2064 – 675 McDermott Avenue, Winnipeg, Manitoba R3E 0V9.

E-mail: David.szwajcer@cancercare.mb.ca

* Department of Medical Oncology and Haematology, University of Manitoba, Winnipeg, MB.

† CancerCare Manitoba, Winnipeg, MB.