Management of Febrile Neutropenia in a Private Hospital Oncology Unit

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Abstract: 221

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Abstract

Aim: Febrile neutropenia is a medical emergency, which poses a significant morbidity and mortality risk to cancer patients receiving chemotherapy. National guidelines recommend that patients presenting with suspected febrile neutropenia receive appropriate intravenous antibiotics within 60 minutes of admission. We aimed to investigate the management of febrile neutropenia in a large private oncology centre.

Method: A retrospective audit of all patients who presented to St John of God Hospital, Subiaco in the 2017 calendar year, with a known solid organ malignancy and a recorded diagnosis of febrile neutropenia. Patients were identified through the hospitals Patient Administration System and ICD-10 codes. Information was collected from the hospital medical records using a standardised data collection tool.

Results: There were 98 admissions relating to 88 patients with febrile neutropenia during the study period. The median age was 64 years (range: 23 - 85 years) with 57 (65%) females. Antibiotic selections consistent with the Australian guidelines were made in 88 admissions (89%). The mean time to antibiotic administration was 279 minutes, with a median of 135 minutes (range: 15 - 5160 minutes). Antibiotics were administered within the recommended time frame in only eight (11%) admissions.

Conclusion:

Clinicians prescribed antibiotics in accordance with national guidelines, however there were systemic inefficiencies which resulting in delayed antibiotic initiation. This has resulted in implementation of strategies to minimise delay.

Key words: Febrile Neutropenia, Neutropenic sepsis, Malignancy, empirical antibiotic therapy

Introduction:

Febrile neutropenia is a medical emergency. It is a known complication of cytotoxic chemotherapy which causes significant morbidity and mortality. Patients frequently require hospitalisation for antimicrobial treatment and supportive management.^{1, 2} In addition to the morbidity and mortality directly attributable to febrile neutropenia, these episodes may lead to delays or reductions in chemotherapy doses with the potential to compromise oncological outcomes.^{1, 2}

A 2006 longitudinal database study identified a 9.5% in hospital mortality rate for patients with febrile neutropenia³. Timely administration of intravenous (IV) antibiotics and the use of prophylactic granulocyte-colony stimulating factor (GCSF) has been shown to reduce mortality in patients with Febrile Neutropenia^{1,4}. The Australian guidelines for the immediate management of neutropenic fever state that “All patients presenting with fever following chemotherapy should be managed as if they have neutropenic fever and receive empiric antibiotics without waiting for laboratory confirmation of neutrophil count”.^{5 6} These guidelines are consistent with the National Institute for Health and Clinical Excellence (UK) and the National Comprehensive Cancer Network (USA) guidelines.^{7 8}

As per the guidelines the time to first dose of empiric antibiotics is 30 minutes if the patients presents with features of systemic compromise or one hour if the patient is clinically stable.⁶ The antibiotic regimens recommended by Australian Consensus guidelines are based on meta-analyses of sepsis related randomised control trials.⁶ These meta-analyses conclude that an anti-pseudomonas beta-lactam (e.g.: piperacillin-tazobactam, cefepime) is as efficacious as combination therapy whilst minimising the risk of toxicity.⁶

The study hospital is a large metropolitan private hospital servicing a broad catchment area. There is a dedicated 30 bed oncology ward and a 16 bed day case chemotherapy unit. During 2017 there were 11540 oncology admissions, including day procedure chemotherapy. The hospital accepts admissions directly to the ward, but it did not have an emergency department or a dedicated admissions unit during the period of this study.

We sought to review our institutions performance in regards to compliance with National Guidelines, specifically with regard to timeliness of antibiotic administration and selection of the appropriate antibiotic in patients presenting with fever and/or systemic symptoms receiving chemotherapy.

Methods:

The study was approved by the St John of God Human Research Ethics Committee. The study population comprised of a cohort of consecutive adult cancer patients with a recorded diagnosis of febrile neutropenia who were hospitalized at a tertiary care hospital between January 2017 and December 2017. Eligible patients were identified by searching the admissions database for cases coded with the International Classification of Disease – Clinical Modification (ICD-CM) code D70.1 (Agranulocytosis secondary to cancer chemotherapy). All identified cases were individually screened by two researchers to limit any coding errors. Cases were excluded if the admission was primarily related to reasons other than febrile neutropenia or if the management of the patient during that admission may have been impacted by an alternate diagnosis (Figure 1). -Data was collected from the hospital medical records retrospectively using a standardised data collection tool. The inclusion criteria were: patients with a diagnosis of solid organ malignancy treated by chemotherapy that was causative of or contributed to neutropenia (granulocyte count $< 0.5 \times 10^9$ cells/L or is expected to decrease to $< 0.5 \times 10^9$ cells/L over the next 48 hours), temperature greater than 38°C (documented by the patient or the medical/nursing staff), and age greater ≥ 18 years. Descriptive statistics was used to analyse the data in Microsoft Excel® 2016. Mean, Median and Ranges were calculated and results were summarised.

Results:

During the study period, there were 98 admissions in 88 patients meeting the inclusion criteria (figure 1). The median age was 64 years (range: 23 - 85 years) with 57 (65%) females. Table 1 shows the baseline characteristics of the sample.

The median peak temperature recorded was 38.3 degrees Celsius (36.5 - 40.1). The median admission neutrophil count was 0.6×10^9 cells /L (0.0 - 11.6×10^9 cells /L) with a median neutrophil nadir of 0.4×10^9 cells /L (0.0 - 4.7×10^9 cells /L) (Table 1).

Antibiotic selections consistent with the Australian guidelines were made in 88 admissions (89%) (Table 3). Two patients received directed antibiotic therapy with intravenous flucloxacillin for clinically diagnosed Staphylococcal infection. The median duration of intravenous antibiotics was 5 days (range: 1 - 16 days).

A septic screen, including blood cultures and urine cultures was conducted on 66 admissions (67%) with an incomplete septic screen performed in a further 29 patients (29%) and four patients (4%) not having any microbiological cultures performed. Positive microbiological cultures were obtained on 18 occasions. A further three patients had a specific infectious source identified in the absence of a positive microbiological culture. In total 77 admissions (79%) were ultimately diagnosed as having febrile neutropenia of an unknown source, with no organism identified.

Eighteen (18%) admissions involved significant medical morbidity. Six of these patients developed fluid overload, five developed acute kidney injury, three developed delirium and three developed

atrial fibrillation. Other single episodes of morbidity included: urinary retention, deep vein thrombosis, paralytic ileus, seizure, aspiration pneumonitis and infusaport related cellulitis.

Of 72 admissions directly to our hospital, the mean time to antibiotic administration was 279 minutes, with a median of 135 minutes (range: 15 - 5160 minutes). Two patients did not receive any antibiotics and in three patients we were unable to calculate the time that they received their antibiotics. - Only 8 (11%) admissions in our cohort of patients received antibiotics within the guideline recommended 60 minutes.

The median time from last chemotherapy administered to presentation with febrile neutropenia was 7.5 days (range: 2-18 days). Nine patients received prophylactic granulocyte colony stimulating factor (G-CSF) alongside their chemotherapy and 57 received rescue G-CSF during their febrile neutropenia admission.

Eight deaths occurred which resulted in an inpatient mortality rate of 8.2%. Two patients died directly from sepsis, four from sepsis related complications (three due to renal failure and one from multi-organ failure) and two from their underlying malignancy. Three of these patients were given antibiotics prior to being transferred to the study hospital. In the remaining patients who were directly admitted to the hospital, the commencement of antibiotics was delayed. They received antibiotics at 90, 180, 275, 390 and 5160 minutes.

The mean length of stay was 7.7 days with a median of 5 days (1-41 days). Following discharge there have been 22 known deaths which occurred at a median of 138 days (27 - 320 days), with an average

known follow up time of 189 days (27 - 516 days). 17 patients did not have follow up data available as they were followed up at facilities outside of our institution.

Discussion:

Suspected febrile neutropenia is a medical emergency which requires urgent admission, assessment and administration of broad spectrum antibiotics. Cytotoxic chemotherapy leads to myelosuppression with the potential for marked neutropenia, together with compromise of mucosal surfaces of the GI tract. In this situation, patients are vulnerable to bacterial infection due to a reduction in innate immunity, with an increased risk of sepsis related morbidity and mortality. This risk has been widely recognised with guidelines recommending that all patients presenting with febrile neutropenia receive broad spectrum antibiotics within an hour of presentation or 30 minutes if features of systemic compromise are present.⁵

Within our cohort 79% of patients were diagnosed with febrile neutropenia in the absence of an organism being identified on microbiological culture. This is similar to previously published data highlighting that an infectious source is only identified in approximately one third of patients presenting with febrile neutropenia.^{9 10} Our higher number of cases without an identified source may reflect the fact that 27% of our admissions had an incomplete septic screen. This highlights the importance of thorough microbiological work up in this patient cohort which provides an opportunity to identify resistant organisms and escalate antibiotic therapy in a timely manner.

Our mortality rate of 8.2% is consistent with papers by Kuderer et al and Lingaratnam et al.^{3, 11}

Kuderer et al published results from a longitudinal database study of more than 40,000 adult cancer patients who were hospitalised in the United States with febrile neutropenia identifying an in-hospital mortality of 9.5%.^{3, 11} In 2008, an epidemiological study by Lingarathan et al identified a mortality of 7.6% in Australian patients with a solid organ malignancy with febrile neutropenia.¹¹ In our cohort two patients died directly from sepsis and a further four from sepsis related complications (three died of renal failure and one from multi-organ failure). It is known from the sepsis literature that earlier administration of antibiotics (i.e: within 60 minutes of presentation) improves outcomes.²

Nine admissions (9%) received prophylactic G-CSF for neutropenic prevention at the time of chemotherapy administration, with 57 (58%) receiving rescue G-CSF once neutropenia confirmed during their febrile neutropenia admission. The use of rescue G-CSF was at the discretion of the treating clinician – the reasons for use were not captured in the medical record. A meta-analysis has shown that the use of G-CSF for primary febrile neutropenic prophylaxis is associated with a significant risk reduction for the development of febrile neutropenia (RR: 0.51).⁴ Routine use of prophylactic G-CSF in all patients is highly costly. Its use requires careful selection of at risk patients based on patient related factors, tumour type and chemotherapy regimen.¹³ A Cochrane systematic review states that the use of rescue G-CSF, although having no effect on mortality, does hasten neutrophil recovery and reduce duration of hospitalisation.¹⁴

A large prospective US database study identified that 80.3% of patients presenting with febrile neutropenia received guideline based antibiotics.¹ Within this study they were able to demonstrate

that compliance with guideline based antibiotics conferred an in-hospital mortality risk reduction of 37% (OR=0.65; 95% CI, 0.42–0.95).¹ Our study showed comparable results with 89% of patients receiving either piperacillin-tazobactam or cefepime as their first line empiric antibiotic. Further to this, two patients (2%) appropriately received intravenous flucloxacillin for clinically diagnosed Staphylococcal infections.

At our centre the timeliness of antibiotic delivery was poor with only 11% of our cohort receiving antibiotics within 60 minutes of presentation. This finding was similar to that reported by Perron et al¹⁵. Potential reasons for delay as reported in previous studies include: delayed assessment by nursing and junior medical staff, lack of awareness regarding the seriousness of febrile neutropenia and failure to have appropriate antibiotic therapy readily available. In comparison to many hospitals of a similar size, in our hospital, patients are admitted directly to an inpatient ward after liaising directly with their treating oncologist. Our hospital does not contain an emergency department nor did it have an acute admissions unit at the time of this study. This impacted the specific strategies that have been put in place to improve timeliness of antibiotic administration (discussed below).

Early recognition of the possibility of febrile neutropenia in any patient presenting with fever following myelosuppressive chemotherapy is critical thus ensuring the need for rapid assessment and management. This requires a system wide approach to facilitate appropriate triage of presenting patients, a streamlined admissions process and rapid nursing/medical assessment with implementation of management, including prompt administration of broad spectrum intravenous antibiotics according to the appropriate local guidelines. Improvements in the timeliness of antibiotic administration and subsequently the quality of care delivered to febrile neutropenic

patient can be achieved with identification of local barriers to appropriate care and individual solutions to the issues uncovered. Education and engagement of staff is paramount in the management of this oncologic emergency.

For example a pilot study conducted by Amado et al demonstrated that the immediate availability of guideline recommended broad spectrum antibiotics on an emergency cart was able to significantly reduce time to antibiotics in febrile neutropenia (median 164 minutes to 55 minutes).¹⁶ This study highlights how overcoming simple logistical barriers which have no or limited additional cost can dramatically improve the quality of care delivered.

In our institution, the following strategies have been implemented:

- A redesign of patient education
- Simplification of the febrile neutropenia alert card
- A streamlined admissions pathway with the commencement of an acute admissions unit (Appendix A)
- A “febrile neutropenia box” that contains a flow sheet for immediate patient management and stock of the required antibiotics

The implementation of strategies will be managed by key stakeholders and further studies will be undertaken to assess their effectiveness. These studies may be used to inform similar institutions on specific strategies which can be implemented to facilitate appropriate care for patients with suspected febrile neutropenia.

There are some limitations with our study. As this was a retrospective audit of medical records and a standardised tool was used to extract data, there is a possibility that cases may have been missed due to incorrect ICD-10 - CM coding and information in the medical records may have been documented inaccurately.

We hope that our findings may encourage clinicians managing febrile neutropenia in similar facilities to audit their institutions current practice and outcomes relative to recommended guidelines. Such audits are useful at identifying deficiencies in care when they exist. This may help to identify site specific strategies for improving care of patients with suspected febrile neutropenia.

Conclusion:

Febrile neutropenia is an oncological emergency which requires urgent administration of broad spectrum antibiotics to reduce associated morbidity and mortality. We investigated the medical management of patients presenting to our institution with suspected febrile neutropenia. We found that overall, clinicians prescribed antibiotics in accordance with national guidelines, however there were systemic inefficiencies which resulted in time delays in antibiotic administration. We have sought to address these barriers and will audit the results in a prospective manner.

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Table 1: Baseline characteristics of the study subjects

Characteristics Data	
Age, mean $\pm$ SD	64 $\pm$ 12.25
Female, n (%)	57 (64.8)
Male, n (%)	31 (35.2)
Diagnosis, n (%)	
Breast	16 (18.1)
Pancreatic	12 (13.6)
Bowel/colorectal	10 (11.3)
Lung	8 (9)
Ovarian	8 (9)
Other solid tumors	34 (38.6)
Metastasis, n (%)	57 (64.7)

Table 2: Study Subjects Clinical Data

Table 2:	
G-CSF use n (%)	
Prophylactic G-CSF	5 (5.7)
Rescue G-CSF	53 (60.2)
Both prophylactic and G-CSF	4 (4)
Peak Vital signs - first 24hrs (mean $\pm$ SD)	
Systolic blood pressure (mmHg)	106 $\pm$ 12.3
Diastolic blood pressure (mmHg)	59 $\pm$ 8.31
Body temperature ($^{\circ}$ C)	38.2 $\pm$ 1.5
Pulse rate (per minute)	99 $\pm$ 16.41
Respiratory rate (per minute)	18 $\pm$ 2.73
Last chemotherapy prior to admission (mean $\pm$ SD)	
Days	7.6 $\pm$ 4.3
Admission laboratory values, median (range)	
Neutrophils (Nadir) $\times 10^9$ cells /L (2.0 - 8.0)	0.4 (0-4.7)
Haemoglobin g/L (115 - 165)	102 (62 – 153)
Platelet count (Nadir) $\times 10^9$ /L (150 - 450)	85 (1 – 331)

C-reactive protein mg/L (<3.0)	58.6 (1.6 – 440)
ICU	
ICU Admission, n (%)	4 (4.5)
Length of Stay, mean no.of days	7.69

Table 3: Antibiotics used and time to administration

Antibiotics, n (%)	
Piperacillin/Tazobactam, 4.5g	45 (46)
Cefepime, 2g	42 (43)
Flucoxacillin,	2 (2)
Meropenum	2 (2)
Ciprofloxacin	1 (1)
IV Augmentin, 600mg	1 (1)
Cephazolin	1 (1)
Cephalexin	1 (1)
Cefepime + Vancomycin	1 (1)
Patients receiving no antibiotics	2 (2)
Time to antibiotics, Minutes	
Median	135

Mean	279
Range	15-5160
% compliance with guidelines	11%

Figure 1: Sample Selection

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