

Impact of a qualitative intervention with a unique febrile neutropenia management protocol in haematological patients in a tertiary centre

Abstract

Background: Febrile neutropenia (FN) is a common life threatening complication in haematology patients for which reducing time to antibiotics has been shown to improve outcomes. Previous studies have focused on reducing time to antibiotic administration in the outpatient population, however there is limited research from inpatient populations.

Objective: The aim of this study was to investigate whether the implementation of a FN management pathway could reduce the time to antibiotics administration for inpatients with febrile neutropenia.

Design: Prospective observational study from November 2012-October 2014.

Settings: The Canberra Hospital, a tertiary referral centre.

Participants: Haematology in patients with FN defined as an absolute neutrophil count of $\leq 1.0 \times 10^9/L$ and temperature $\geq 38.0^\circ C$.

Intervention: A FN management pathway which included medical registrar review within 30 minutes and empirical antibiotics administration within 60 minutes of fever detection. Main outcome measures: time from fever detection to antibiotic administration, ICU admission rates, mortality.

Results: 133 patient episodes of FN were included in the analysis, 58 prior to implementation of the management plan and 75 in the year following. Mean time to antibiotics improved from 242.8 minutes to 69.7 minutes ($p=0.005$). There was no significant difference in intensive care unit admission rates. Mortality improved from 8.3% to 1.3% with a trend towards statistical significance ($p=0.11$).

Conclusion: Implementation of a FN management pathway effectively reduced the time to antibiotics in haematology inpatients with FN with a trend towards improved mortality.

Volume 4 Issue 4 - 2017

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Received: April 28, 2017 | **Published:** May 09, 2017

Abbreviations: FN, febrile neutropenia; ICU, intensive care unit; MET, medical emergency team; CI, confidence interval; ESBL, extended spectrum beta-lactamase

Introduction

Neutropenia is a common complication of bone marrow dysfunction following chemotherapy in haematology inpatients.^{1,2} Many factors put these patients at increased risk of life threatening infection including compromised mucosal barriers secondary to chemotherapy or radiotherapy and multiple intravenous access devices, in addition to neutropenia. In such patients fever may be the only indicator of life threatening infection although occasionally it manifests with hypothermia. Mortality rates for febrile neutropenia (FN) are approximately 10% in recent studies.^{3,4} Additionally, there is significant morbidity and health care costs associated with episodes of FN, as many patients require prolonged hospital stays, intensive care unit (ICU) admissions or may undergo delays or reduction in chemotherapy.^{5,6}

Due to the risk of rapid progression of infection and the difficulty in identifying patients with neutropenic sepsis at initial evaluation, early administration of antibiotics is imperative in the management of FN with multiple studies showing that this improves mortality.^{7,8,9}

Accordingly, national guidelines advise that antibiotic administration should occur within 1 hour of presentation.^{2,10} However, many centres struggle to meet this goal. Clarke et al.⁴ reported a median time to antibiotics in FN patients of 30min to 4hours across 61 centres in the United Kingdom.⁴ Interventions have focused on patients presenting to the emergency department with FN and have included education programs, implementation of standardized order forms for investigations and antibiotics and making broad-spectrum antibiotics available in the emergency department.^{8,11-14} These appeared to be beneficial however there is a lack of research into improving the time to antibiotic administration in the inpatient setting.

Clinical pathways provide location specific information, linking evidence to practice within a hospital or region. These have been shown to reduce in-hospital complications in a recent Cochrane review.¹⁵ Specifically in the management of FN, clinical pathways and protocols have been shown to be useful in improving clinical outcomes, even when adherence is sub-optimal.⁸ They are able to provide standardized case definitions, assist in streamlining procedures and guide the initial management of patients. The aim of this study was to investigate whether implementation of a management pathway for FN could shorten time to antibiotics and improve clinical outcomes in haematology inpatients at a single tertiary centre.

Methods

We conducted a prospective study at The Canberra Hospital, a 670 bed tertiary hospital, between November 2012 and October 2014 including all haematology in patients with febrile neutropenia. Neutropenia definition has been simplified for more practical management of patients such as: an absolute neutrophil count (ANC) $<1.0 \times 10^9/L$. Fever was defined as a single temperature $>38^\circ C$. Patients who received chemotherapy in the preceding 4 weeks were considered to be neutropenic if no blood test results were available. In October 2013 a FN management pathway was implemented at the site and thus the audit covered one year period prior to and over same duration following the introduction of this pathway. Ethics approval for the study was obtained from the ACT Health Human Research Ethics Committee. Patients were excluded if 1) they were transferred to the Canberra Hospital while receiving treatment for FN, 2) they were not for active management e.g. palliative patients or 3) there was insufficient documentation. Where a single patient had multiple admissions related to febrile neutropenia, each episode was included

separately in the analysis. In the case of multiple episodes of FN within the same admission, only the first episode was included for the analysis.

The FN management pathway is outlined by the flow chart in Figure 1. After a patient is identified as having FN, the pathway requires a “FN call” - that is a phone call made to the senior medical registrar for clinical review and to organize evaluation such as blood test, cultures and imaging studies with aim for this to happen within the first 30 minutes. At that point the on call hematologist needs to be notified and administration of empirical antibiotics, as dictated by the Therapeutic Guidelines, should undertaken within 60 minutes of the fever detection. This pathway was to be followed regardless of the status of patients’ other vital signs as other parameters may not change. However, in the case of altered vital signs such that the patient qualified for a medical emergency team (MET) review, this was to be followed up as per the institutional standard practice in addition to the FN call.

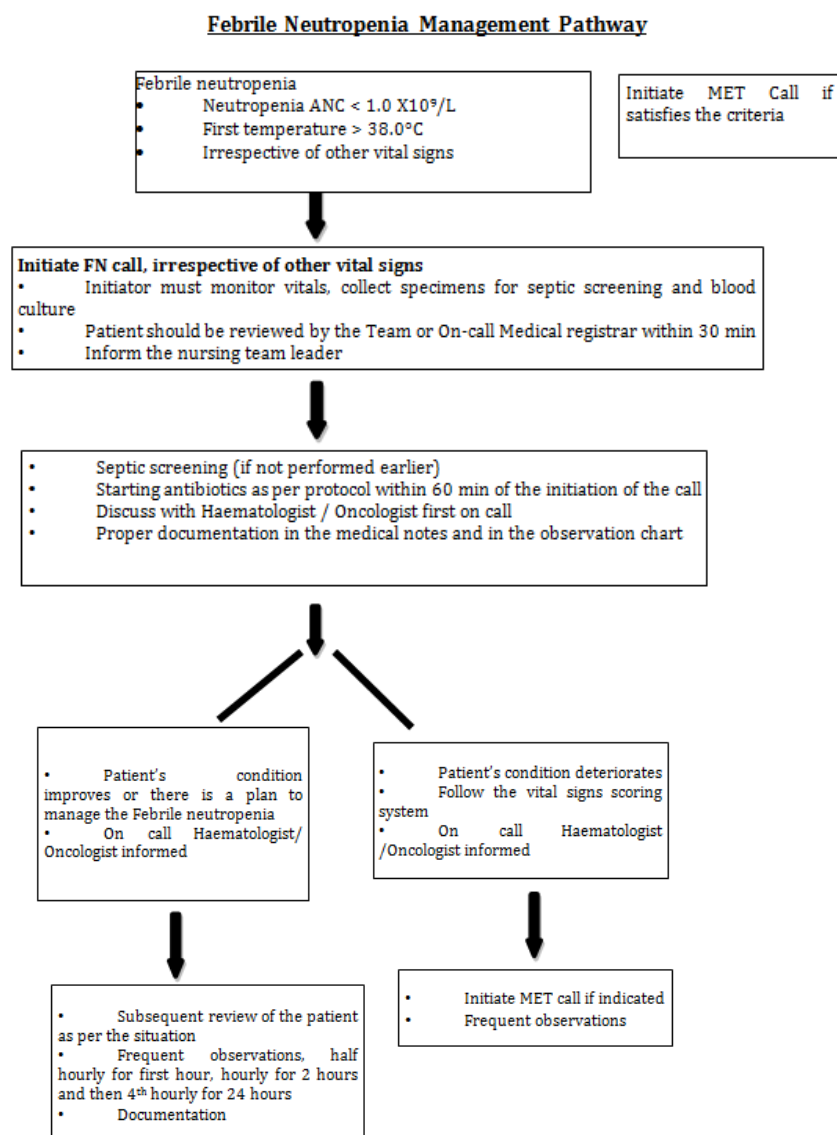


Figure 1 Febrile neutropenia management pathway for the canberra hospital haematology and oncology department.

The primary outcomes assessed were time from recognition of fever to administration of antibiotics, rate of intensive care unit (ICU) admission and death. These outcomes were measured and compared between two groups. Group A consisted of patients between November 2012–October 2013 before implementation of the above management pathway. Group B consisted of patients who developed FN during the period November 2013–October 2014, following the implementation of the FN management pathway. The results of blood cultures taken at the time of review were included in the analysis. A single gram-negative blood culture was considered significant, however two gram-positive cultures were required for the diagnosis of gram positive bacteraemia. Statistical analysis was completed using SPSS (version 22.0.0.0). Quantitative data was reported as mean (95% confidence interval [CI]) and groups were compared using the Student T-test. Categorical variables were recorded as percentages and compared using the Chi-square test. A p value of <0.05 was considered statistically significant.

Results

During the study period 104 inpatients developed FN resulting in a total of 153 episodes. Twenty episodes were excluded: six for incomplete records, seven were transferred to The Canberra Hospital with FN and seven for other reasons (e.g. palliation, treatment antibiotics). A total of 133 episodes of FN were included in the analysis. Group A consisted of 58 episodes and Group B included 75 episodes of FN. None of the patients had multiple episodes of FN within the same admission whereas 23 patients had multiple admissions due to same complication. Patient demographics are detailed in Table 1. The mean ages were 51.8 years and 54.9 years for Group A and Group B, respectively. The proportion of males was similar in both the groups, 65.5% (n=38) in Group A and 64.0% (n=48) in Group B.

Table 1 Patient demographics

	Group A n=58(%)	Group B n=75(%)
Mean age	51.8yrs	54.9 years
Male	38(65.5)	48(64.0)
Haematological Diagnosis		
Acute lymphocytic leukaemia	4(6.9)	2(2.7)
Acute myelocytic leukaemia	26(44.8)	23(30.6)
Non-Hodgkin's lymphoma	18(31)	23(30.7)
Multiple Myeloma	8(13.8)	13(17.3)
Myelodysplastic syndrome	1(1.7)	6(8.0)
Hodgkin's lymphoma	0	3(4.0)
Other	1(1.7)	5(6.7)

*Patients classified as "other" for their haematological diagnosis included post bone marrow transplant for non-haematological conditions, congenital neutropenia and aplastic anaemia.

As part of the FN pathway at least two sets of blood cultures were taken from patients prior to administration of antibiotics. The percentage of patients with positive blood cultures was 34.5% in Group A and 27.6% of patients in Group B (p=0.2). Culture results are detailed in Table 2. Five patients had multiple significant organisms grown from blood culture. Two patients grew multi-resistant organisms. One patient had bacteraemia was due to vancomycin resistant *Enterococcus faecalis* and another due to extended spectrum beta-lactamase (ESBL) *Escherichia coli*. Both of these patients were in Group B. The mean time to initiate antibiotics was 242.8 minutes (95% CI:0-931) in Group A and 69.7 minutes (95% CI:0-219.5) in Group B (p=0.005; Figure 2). The proportion of patients who received empirical antibiotics within 60 minutes improved from 37.9% in Group A to 66.7% in Group B (p=0.001). ICU admission rates were similar between the groups with a rate of 15.5% in Group A and 16.0% in Group B (p=0.87). There was a reduction in the mortality rate in Group B (1.3%; n=1) compared to Group A (8.3%; n=5), however this was not statistically significant (p=0.11; Figure 3).

Table 2 Causative organisms in episodes of FN with bacteraemia

Blood culture result	Group A n=20(%)	Group B n=21(%)
Gram positive	6(30)	7(33.3)
<i>Streptococcus species</i>	5(25)	4(19)
<i>Staphylococcus aureus</i>	1(5)	1(4.8)
<i>Enterococcus species</i>	0	1(4.8)
Gram negative	15(75)	16(76.2)
<i>Escherichia coli</i>	8(40)	14(66.7)
<i>Pseudomonas aeruginosa</i>	3(15)	1(4.8)
<i>Klebsiella pneumoniae</i>	2(10)	2(9.5)

Where a patient grew multiple organisms each has been included separately in the table; both *Staphylococcus aureus* infections were methicillin sensitive *Staphylococcus aureus*.

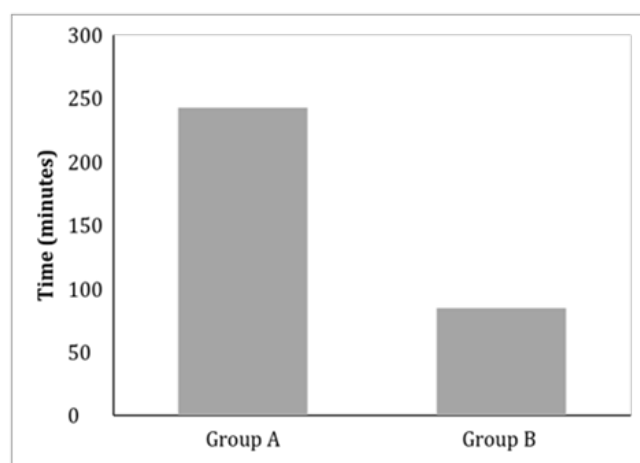


Figure 2 Mean time from fever detection to antibiotic administration.

Group A: 242.8min.

Group B: 69.7minutes (p=0.005).

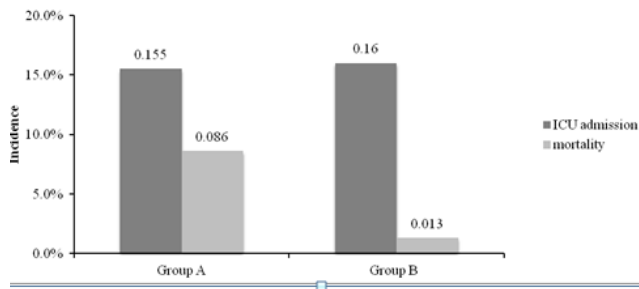


Figure 3 ICU admission rate and mortality rate for group A & group B, $p=0.87$ and $p=0.11$ respectively.

Discussion

We have shown that the implementation of an FN management pathway was associated with a significant reduction in the time to administration of antibiotics, from a mean of 242 minutes to 68 minutes. The proportion of patients who received antibiotics within the desired 60-minute timeframe improved from 37.9% to 66.7%. This supports the use of a strict management pathway in FN and adherence as an effective means of reducing time to antibiotics in the inpatient population. Retrospective studies have supported their use to optimize care in febrile neutropenia however this is the first prospective study in an inpatient population.^{8,12,14}

In the year prior to the implementation of the FN management pathway only 37% of haematology in patients with FN received empiric antibiotics within the 60-minute target as dictated by the Surviving Sepsis and multiple other national guidelines.^{2,10} This is slightly higher than rates seen elsewhere with Clarke et al. reporting a rate of 18-26% of patients presenting to emergency departments in the United Kingdom and Perron et al.¹⁶ finding that only 9% of patients presenting to a tertiary Canadian hospital received antibiotics within this “golden hour.”^{4,16} However, both these papers were focused on patients presenting to emergency departments or review clinics and did not investigate the inpatient population where it may be expected that the time to antibiotics would be reduced. In addition the factors affecting timely administration of antibiotics could be separate, complex and variables different than the emergency department setting. Following implementation of our FN management pathway this figure improved to 67% of patients with FN receiving empiric antibiotics within 60 minutes of fever detection. This may be due to multiple factors including greater awareness among medical staff of the significance of fever in neutropenic patients, explicitly stated requirements for early antibiotic administration, protocolling of procedures such as blood culture collection and the requirement of a senior medical staff such as medical registrar to be the primary medical officer involved in the immediate care of a patient with FN with rapid escalation to consultant if required.

Despite these improvements some patients still waited several hours before receiving antibiotics following implementation of the FN management pathway. The medical notes of the seven patients who had a delay in antibiotic administration of greater than 3 hours were reviewed. Of these patients one died and two were admitted to the ICU. The primary causes of these delays were:

- Not being able to prescribe a “once only” dose of antibiotics at the time of initial review, although patients were prescribed regular treatment antibiotics.
- Non-compliance with the guideline, for example review only by junior medical staff despite the requirement of medical registrar review by the guideline.

This may indicate a lack of awareness by some staff of the importance of time critical medication in FN and highlights the importance of senior medical staff input. Mortality rates improved following implementation of the FN pathway from 8.6% to 1.3% with a trend towards statistical significance ($p=0.11$), however rates of ICU admission were similar between the two groups. The reason for this may be more patients needing review in order to adhere to the protocol and timely intervention with MET call and subsequent ICU admission if deemed essential. ICU admissions were compounded by other comorbidities (e.g. multiorgan failure) of the patient and not solely contributable to FN.

The FN pathway ensures blood cultures are taken prior to administration of antibiotics in all patients with FN. As a standard this remains important for the ongoing management of these patients as it provides information regarding the causative pathogen and susceptibility profiles. Positive blood cultures have been shown to be a risk factor for serious complications in FN.⁷ The percentage of positive blood cultures was similar in the two groups 34.5% and 27.6% for Group A and B respectively. These rates are comparable to those seen in previous studies.¹⁷ A total of five patients grew multiple organisms in their initial blood cultures; four of these patients were in Group B. Gram negative bacteria were more commonly isolated and the predominant species was *Escherichia coli*. This is in keeping with recent trends showing a predominance of gram negative bacteraemia in FN after gram positive organisms predominated in the previous two decades.¹⁷⁻¹⁹ Only two episodes of FN were found to have bacteraemia secondary to multi-resistant organisms, vancomycin resistant *Enterococcus faecalis* and ESBL *Escherichia coli*. There is growing concern regarding multi-resistant organisms in cancer patients and research supports that this is associated with worse outcomes.²⁰

Limitations of this study include its observational nature and relatively small sample size with clinical outcomes approaching significance that may have been reached with a larger sample size. While mean time to antibiotic administration was statistically significant between the two groups, wide 95% confidence intervals were observed. This is likely due to the small sample size as here we report the initial stages of an ongoing intervention. Additionally, the study was performed at a single centre and replication at other health facilities would be beneficial in assessing the utility of a FN pathway in reducing time to antibiotics and most importantly reducing morbidity and mortality in haematology inpatients.

Conclusion

In this simplistic study we have shown implementation of a FN management pathway was an effective measure to reduce the time to antibiotic administration in haematology in patients with FN. Further improvements may be made by simple measures such as mandating a “once only” dose of antibiotics through a pre-approved strategy. Further study is required to validate the effectiveness of this pathway in other hospitals and the benefit of ongoing surveillance of use of this protocol for longer period of time. Further study to obtain information on adherence to FN pathway protocol and measures to improve this is being undertaken.

Acknowledgements

The authors had no competing interests and had full access to all of the data in this study. This study received no specific funding from any agency in the public, commercial or not-for-profit sectors.

Conflict of interest

The author declares no conflict of interest.

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