Risk factors for adverse outcomes and multidrug-resistant Gram-negative bacteraemia in haematology patients with febrile neutropenia in a Singaporean university hospital

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INTRODUCTION Institutional febrile neutropenia (FN) management protocols were changed following the finding of a high prevalence of ceftazidime-resistant Gram-negative bacteraemia (CR-GNB) among haematology patients with FN. Piperacillin/tazobactam replaced ceftazidime as the initial empirical antibiotic of choice, whereas carbapenems were prescribed empirically for patients with recent extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae colonisation/infection. An audit was conducted to determine the impact of these changes.

METHODS Data from all FN episodes between October 2008 and December 2010 were collected prospectively, with mid-November 2009 demarking the transition between pre-intervention and intervention periods. Outcomes measured included 30-day mortality post-development of FN and the presence of CR-GNB.

RESULTS There were 427 FN episodes (200 in the pre-intervention period) from 225 patients. The prevalence of CR-GNB was 10.3%, while the 30-day mortality was 4.7%, with no difference between pre-intervention and intervention periods. Independent risk factors for 30-day mortality included the presence of active haematological disease, vancomycin prescription and older age. Independent factors associated with initial CR-GNB were profound neutropenia, the presence of severe sepsis and active haematological disease. Recent ESBL-producing Enterobacteriaceae colonisation/infection was not predictive of subsequent CR-GNB (positive predictive value 17.3%), whereas a model based on independent risk factors had better negative predictive value (95.4%) but similarly poor positive predictive value (21.4%), despite higher sensitivity.

CONCLUSION A change in the FN protocol did not result in improved outcomes. Nonetheless, the audit highlighted that empirical carbapenem prescription may be unnecessary in FN episodes without evidence of severe sepsis or septic shock, regardless of previous microbiology results.

Keywords: antimicrobial drug resistance, empirical antibiotics, febrile neutropenia, Gram-negative bacteraemia, mortality
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INTRODUCTION

Febrile neutropenia (FN) remains a common complication for patients with haematological disorders undergoing cytotoxic chemotherapy and/or haematopoietic stem cell transplantation (HSCT). The management of FN is typically algorithm-driven, as these patients often have an impaired response to infection and inflammation.[1] A recent audit of FN at our institution showed that the overall mortality among haematology inpatients hospitalised between October 2008 and June 2009 was 8.0%, comparable to tertiary institutions in developed countries.[2] Almost a third (33.6%) had positive blood cultures, and 10.2% of all FN episodes among haematology inpatients were associated with the isolation of Gram-negative bacteria from the bloodstream that were resistant to the most commonly used first-line antibiotics (intravenous [IV] ceftazidime and cefepime).[2] There were no risk factors found to be independently associated with mortality during that audit, although this was thought to be the result of the small number of deaths.[2]

Recent evidence suggests that a delay in the prescription of appropriate antibiotics beyond 24 hours of index blood cultures is associated with increased mortality in profoundly neutropenic (absolute neutrophil count [ANC] < 100 cells/μL) patients with Gram-negative bacteraemia.[3] This and the results of our previous audit resulted in the revision of our FN protocol in order to minimise the risk of delayed active empirical therapy – and hence potentially the mortality – for FN caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae and other ceftazidime-resistant Gram-negative bacteria. In essence, haematology inpatients with documented ESBL-producing Enterobacteriaceae infection/colonisation up to three months prior to the onset of FN were prescribed carbapenems (mainly imipenem) empirically, and the first-line empirical antibiotic for FN was switched to IV piperacillin/tazobactam from IV ceftazidime (Fig. 1). More than 50% of the ceftazidime-resistant Gram-negative bacteria from our previous audit were sensitive

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Table I. Demographic and clinical characteristics of audited febrile neutropenia (FN) episodes in haematology patients managed at the National University Cancer Institute, Singapore, and pre- and post-changes in the FN protocol.

Characteristic	No. (%)	
	Pre-intervention (n = 200)	Intervention (n = 227)
Median age; IQR (yrs)	45; 33-61	49; 36-56
Male gender	117 (58.5)	136 (59.9)
Ethnicity*		
Chinese	123 (61.5)	145 (63.9)
Malay	12 (6.0)	37 (16.3)
Indian	26 (13.0)	12 (5.3)
Others	39 (19.5)	33 (14.5)
Subsidised hospital class[a]	136 (68.0)	158 (69.6)
Underlying diagnosis*		
Acute myeloid leukaemia	66 (33.0)	80 (35.2)
Diffuse large B-cell lymphoma	15 (7.5)	14 (6.2)
Myelodysplastic syndrome	23 (11.5)	14 (6.2)
Myeloma	11 (5.5)	17 (7.5)
Acute lymphoblastic leukaemia	19 (9.5)	33 (14.5)
Aplastic anaemia	8 (7.1)	2 (1.8)
NK T-cell lymphoma	18 (9.0)	4 (1.8)
Hodgkin's lymphoma	3 (1.5)	7 (3.1)
Others[b]	37 (18.5)	56 (24.7)
Disease status at febrile neutropenia period		
Partial/complete remission	72 (36.0)	97 (42.7)
Active disease[c]	112 (56.0)	123 (54.2)
Not applicable	16 (8.0)	7 (3.1)
Chemotherapy		
First-line	105 (52.5)	136 (59.9)
Second-line	34 (17.0)	48 (21.1)
Third-line and above	16 (8.0)	10 (4.4)
Palliative	22 (11.0)	18 (7.9)
No chemotherapy	23 (11.5)	15 (6.6)
Haematopoietic stem cell transplantation*	55 (27.5)	47 (20.7)
Autologous	27 (49.1)	20 (42.6)
Allogeneic	26 (47.3)	18 (38.3)
Cord Blood	2 (3.6)	9 (19.1)
Febrile neutropenia within 30 days of transplantation*	34 (17.0)	32 (14.1)
Autologous	21 (61.8)	12 (37.5)
Allogeneic	12 (35.3)	14 (43.8)
Cord Blood	1 (2.9)	6 (17.8)
Fluoroquinolone prophylaxis*	98 (49.0)	86 (37.9)
Low-risk febrile neutropenia[d]	151 (75.5)	182 (80.2)
Antifungal prophylaxis*		
Fluconazole	94 (47.0)	89 (39.2)
Itraconazole	11 (5.5)	11 (4.9)
Posaconazole	0 (0)	21 (9.3)
Voriconazole	2 (1.0)	1 (0.4)
Caspofungin	0 (0)	1 (0.4)
No prophylaxis	93 (46.5)	104 (45.8)
Prior extended-spectrum β-lactamase-producing bacterial infection	25 (12.5)	27 (11.9)
Severe sepsis	17 (9.0)	18 (7.9)
Profound neutropenia	132 (66.0)	148 (65.2)
Median ANC; IQR (x 10^4 cells/mm^3)		
At presentation	0.09; 0.03–0.39	0.12; 0.03–0.43
Nadir	0.01; 0.03–0.15	0.03; 0.01–0.16
Central line	135 (67.5)	165 (73.3)
Bacterial cultures		
Positive initial blood culture	71 (35.5)	71 (31.3)
Gram-negative bacteraemia	43 (21.5)	39 (17.2)
Subsequent positive cultures[e]	36 (18.0)	45 (19.8)
Fungal infection		
Invasive fungal infection	10 (5.0)	10 (4.4)
Receipt of antifungal therapy	33 (16.5)	46 (20.3)
Days to ANC recovery; IQR*	6; 3–10	9; 5–14
Days to fever resolution; IQR	3; 1–8	3; 1–7
Antibiotic therapy		
Empirical ceftazidime prescription*	101 (50.5)	7 (3.1)
Empirical piperacillin/tazobactam prescription*	5 (2.5) 133 (66.5)	97(42.7) 153 (67.4)
Carbapenem prescription		
Empirical carbapenem prescription[f]	88 (44.0)	110 (48.5)
Vancomycin prescription	92 (46.0)	120 (52.9)
Antibiotic modification	99 (49.5)	119 (52.4)
Outcomes		
30-day mortality	9 (4.5)	11 (4.9)
Length of stay; IQR (days)	12 (7 – 22)	12.5 (6 – 24)
Ceftazidime-resistant Gram-negative bacteraemia	21 (10.5)	23 (10.1)

[a]Subsidised hospital class refers to B2 or C class patients. [b]Other diagnoses include anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, aplastic anaemia, amyloidosis, Burkitt's lymphoma, chronic leukaemias, drug-induced agranulocytosis, follicular lymphoma, intermediate diffuse large B-cell lymphoma/Burkitt's lymphoma, mast cell leukaemia, myelofibrosis, peripheral T-cell lymphoma, splenic lymphoma with villous lymphocytes, T-cell rich B-cell lymphoma and thalassaemia major. [c]Defined as untreated, relapsed or refractory disease. [d]Defined by Multinational Association for Supportive Care in Cancer risk index score ≥ 21. [e]Positive bacterial cultures > 72 hours after the start of an FN episode. [f]Receipt of a carbapenem as empirical antibiotic therapy.
*$p < 0.05$. IQR: interquartile range; ANC: absolute neutrophil count

to piperacillin/tazobactam (data not shown). The revised protocol was implemented in mid-November 2009.

The objectives of this second audit were to evaluate the impact of the revised protocol in terms of mortality and prevalence of ceftazidime-resistant Gram-negative bacteraemia, as well as to determine the risk factors for mortality and ceftazidime-resistant Gram-negative bacteraemia with a much larger dataset.

METHODS

The single-centre audit was conducted as an ongoing prospective observational cohort study. All adult haematology inpatients with FN who were hospitalised at the National University Hospital (NUH) between October 2008 and December 2010 were reviewed, and the unit of study was an episode of FN. If a patient met previously defined criteria for FN after at least seven intervening days where he/she had been afebrile,[2] it was counted as a new episode of FN. Patient data from October 2008 to June 2009 had previously been published in a separate audit that included FN inpatients with solid cancers.[2] FN episodes occurring between October 14, 2008 to November 15, 2009 were considered the pre-intervention group, whereas those occurring between November 16, 2009 to December 30, 2010 were the intervention group.

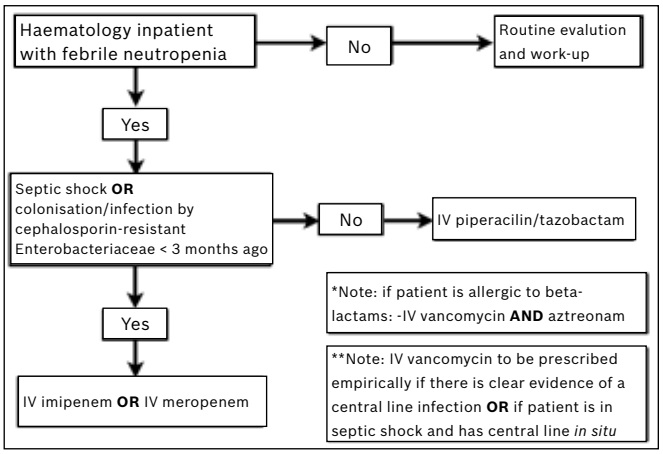

Fig. 1 Empirical antibiotic prescription protocol for haematology patients with febrile neutropenia.

Trained research staff collated demographic, clinical and microbiologic data into a central database. Each FN episode was classified as either high- or low-risk according to the Multinational Association for Supportive Care in Cancer (MASCC) Risk Index.[4] Other covariates included age, gender, ethnicity, status of haematological disease (active, partial or complete remission, or not applicable – active disease defined as untreated, relapsed or refractory disease), type of chemotherapy, presence of profound neutropenia (ANC < 100 cells/μL), HSCT, fluoroquinolone and/or antifungal prophylaxis, presence of severe sepsis or septic shock,[5] bacterial infection (initial bacteraemia and subsequent positive cultures, the latter defined as positive bacterial cultures > 72 hours after the onset of FN), probable/definitive fungal infection (if present),[6] and antimicrobial therapy. The primary outcome was 30-day mortality, while the secondary outcome was the presence of cefazidime-resistant Gram-negative bacteraemia in initial blood cultures.

Intercooled Stata 11.1 (StataCorp, College Station, TX, USA) was used for all statistical calculations. As there was serial autocorrelation due to the repeated measurements of both outcome and covariates for subjects with repeated FN, generalised estimating equation models were used to analyse the association between each outcome and variable.[7] Based on the covariates identified in the univariate analysis with p-value ≤ 0.2, the multivariate model was sequentially built up. Comparative analyses of dichotomous variables between the pre-intervention and intervention groups were appropriately performed with χ^2 test or Fisher's exact test, and continuous variables were analysed with the Mann-Whitney U test.

RESULTS

During the audit period, there were 427 FN episodes in 225 haematology patients. The median number of FN episodes per patient was one for each group – two patients in the pre-intervention group had the maximum of seven FN episodes, whereas two patients in the intervention group had the maximum of six FN episodes. The demographics, clinical variables and outcomes are shown in Table I. Of note, the most common haematological diagnosis was acute myeloid leukaemia.

Table II. Types of microorganisms isolated from initial blood cultures in subjects with febrile neutropenia pre- and post-changes in the FN protocol.

Bacteria[a]	Pre-intervention (n = 77)	Intervention (n = 82)
Gram-positive bacteria (%)		
Bacillus spp.*	11	26
Coagulase-negative staphylococci	14	9
Staphylococcus aureus (MRSA)	0 (0)	2 (1)
Viridans streptococci	3	2
Enterococcus spp.	2	2
Others	3	1
Gram-negative bacteria (%)		
Acinetobacter baumannii†	0	1 (1)
Escherichia coli†	20 (9)	17 (8)
Klebsiella pneumoniae†	14 (11)	13 (11)
Pseudomonas aeruginosa†	6 (0)	5 (1)
Others†	3 (1)	3 (2)
Fungi (%)		
Candida krusei	1	0
Candida tropicalis	0	1

[a]Note that 6 and 11 FN episodes in the pre-intervention and intervention groups were associated with polymicrobial bacteraemia.
*p < 0.05. †ceftazidime-resistant

Carbapenems had been prescribed as an initial empirical therapy in almost half of all FN episodes and in up to two-thirds during the course of all FN episodes. The initial empirical antibiotic therapy had subsequently been modified in almost half of the FN episodes.

There were some differences between the two groups. More patients of Malay ethnicity and fewer of Indian ethnicity were treated for FN during the intervention period. There were significantly more FN episodes associated with acute lymphoblastic leukaemia during the intervention period, but fewer episodes associated with aplastic anaemia. Fewer FN episodes in the intervention period occurred in patients who had ever received HSCT, but this was no longer statistically significant if only the FN episodes that had occurred directly after HSCT were included. However, there were more FN episodes occurring in cord blood stem cell transplant recipients in the intervention period. Fewer patients with FN had received fluoroquinolone prophylaxis, but more had received posaconazole prophylaxis in the intervention period.

Approximately 30% of all FN episodes were associated with bacteraemia. The breakdown of bacteria isolated from initial blood cultures is shown in Table II. There was no difference in the types of bacteria isolated between the two periods except for *Bacillus* spp., owing to a hospital-wide outbreak in early 2010. 51 (62.2%) and 26 (59.1%) FN episodes associated with Gram-negative and ceftazidime-resistant Gram-negative bacteraemia, respectively, were treated with initial empirical carbapenems.

The 30-day mortality was 4.7% (n = 20), whereas the median length of stay was 12 days (interquartile range 6–24 days). 44 (10.3%) FN episodes were associated with initial ceftazidime-resistant Gram-negative bacteraemia. The results of the univariate analysis of the association of subject characteristics with outcomes are shown in Table III. Notably, there were no deaths within 30 days of FN onset for patients who had received allogeneic or cord blood HSCT. On multivariate analysis, the factors independently

Table III. Generalised estimating equation univariate analysis of the impact of cohort characteristics on 30-day mortality and initial ceftazidime-resistant Gram-negative bacteraemia.

Characteristic	30-day mortality			Ceftazidime-resistant Gram-negative bacteraemia		
	OR	95% CI	p-value	OR	95% CI	p-value
Higher age	**1.04**	**1.01–1.07**	**0.012**	0.99	0.97–1.01	0.206
Male gender	**2.15**	**0.76–6.07**	**0.148**	0.81	0.43–1.51	0.503
Ethnicity (%)						
Chinese	1.00	--		1.00	--	
Malay	0.71	0.16–3.25	0.661	0.63	0.18–2.19	0.471
Indian	0.95	0.21–4.36	0.578	2.59	1.07–6.26	0.034
Others	0.23	0.03–1.83	0.167	1.22	0.52–2.82	0.650
Subsidised hospital class[a]	0.78	0.28–2.21	0.634	**0.88**	**0.75–1.03**	**0.106**
Disease status at FN onset						
Partial/Complete remission	**1.00**	**--**	**--**	**1.00**	**--**	**--**
Active disease	**6.81**	**1.58–29.36**	**0.010**	**0.31**	**0.16–0.60**	**0.001**
Chemotherapy						
First-line	**1.00**	**--**	**--**	1.00	--	--
Second-line	**2.18**	**0.68–7.02**	**0.191**	0.61	0.26–1.44	0.259
Third-line and above	**2.73**	**0.53–13.98**	**0.229**	--	--	--
Palliative	**3.67**	**1.02–13.18**	**0.047**	0.53	0.15–1.82	0.410
No chemotherapy	**NA**	**NA**	**NA**	NA	NA	NA
Haematopoietic stem cell transplantation						
Ever received transplant	0.79	0.26–2.41	0.681	0.68	0.31–1.52	0.351
Within 30 days of transplant	0.28	0.04–2.08	0.214	1.04	0.44–2.44	0.930
Fluoroquinolone prophylaxis	1.09	0.45–2.68	0.845	**1.85**	**0.99–3.48**	**0.055**
Antifungal prophylaxis	0.69	0.28–1.70	0.421	1.41	0.74–2.67	0.294
Low-risk FN[b]	0.65	0.24–1.72	0.383	**0.51**	**0.26–1.00**	**0.049**
Severe sepsis	**2.91**	**0.92–9.20**	**0.068**	**2.31**	**0.95–5.64**	**0.066**
Higher ANC* at presentation	2.12	0.49–9.20	0.315	**0.00**	**0.00–0.02**	**< 0.001**
Higher ANC* nadir	0.93	0.11–8.02	0.948	**0.00**	**0.00–0.02**	**0.003**
Profound neutropenia	1.62	0.58–4.53	0.361	**12.79**	**3.05–53.65**	**< 0.001**
Prior extended-spectrum β-lactamase-producing bacterial infection (%)	0.36	0.47–2.80	0.330	**2.03**	**0.92–4.52**	**0.08**
Presence of central line	0.98	0.37–2.60	0.966	**2.88**	**1.18–6.99**	**0.020**
Bacterial cultures				NA	NA	NA
Positive initial blood culture	1.36	0.54–3.39	0.511			
Gram-negative bacteraemia	1.86	0.70–4.98	0.216			
Ceftazidime-resistant Gram-negative bacteraemia	1.57	0.44–5.56	0.303			
Subsequent positive cultures	**1.91**	**0.71–5.09**	**0.198**			
Fungal infection				NA	NA	NA
Invasive fungal infection	1.09	0.14–8.37	0.936			
Receipt of antifungal therapy	**3.18**	**1.26–8.01**	**0.014**			
Antibiotic therapy				NA	NA	NA
Carbapenem usage	**2.93**	**0.85–10.10**	**0.089**			
Empirical carbapenem prescription	0.61	0.24–1.56	0.302			
Vancomycin usage	**3.21**	**1.15–8.92**	**0.025**			
Antibiotic modification	**2.33**	**0.89–6.14**	**0.087**			
Longer hospitalisation prior to FN onset	NA	NA	NA	1.01	0.99–1.03	0.357
Previous hospitalisation within 90 days of FN episode	NA	NA	NA	**1.63**	**0.85–3.13**	**0.145**
Intervention group	1.07	0.44–2.65	0.877	0.78	0.42–1.47	0.446

[a]Subsidised hospital class refers to B2 or C class patients. [b]Defined by Multinational Association for Supportive Care in Cancer Risk Index score ≥ 21. Variables highlighted in bold were included in the respective multivariate analyses. Gram-negative bacteraemia and ceftazidime-resistant Gram-negative bacteraemia were forced into the multivariate model for 30-day mortality.
NA: not applicable; ANC: absolute neutrophil count; FN: febrile neutropenia; OR: odds ratio; CI: confidence interval

associated with 30-day mortality were active haematological disease (odds ratio [OR] 6.28; 95% confidence interval [CI] 1.41–27.92; p = 0.016), vancomycin prescription (OR 4.79; 95% CI 1.60–14.35; p = 0.005) and older age (OR 1.04; 95% CI 1.01–1.08; p = 0.009). These did not change even upon the introduction of Gram-negative and ceftazidime-resistant Gram-negative bacteraemia into the model. With regard to initial ceftazidime-resistant Gram-negative bacteraemia, the independent risk factors were profound neutropenia (OR 9.91; 95% CI 2.34–41.98; p = 0.002) and the presence of severe sepsis (OR 3.04; 95% CI 1.14–8.12; p < 0.027). Patients with active haematological disease at the time of FN were unlikely to have ceftazidime-resistant

Table IV. Prior extended-spectrum beta-lactamase-producing (ESBL) bacterial carriage/infection as a marker for current febrile neutropenia associated with ceftazidime-resistant Gram-negative bacteraemia.

Prior ESBL colonisation/ infection	Current ceftazidime-resistant Gram-negative bacteraemia		Total
	No	Yes	
No	340 (88.8)	35 (79.6)	375 (87.8)
Yes	43 (11.2)	9 (20.5)	52 (12.8)
Total	383 (100)	44 (100)	427 (100)

Note: Data is presented as number (%). Sensitivity = 20.5% (95% CI 10.3% –35.8%); Specificity = 88.8% (95% CI 85.1%–91.7%)

Gram-negative bacteraemia (OR 0.33; 95% CI 0.16–0.67; p = 0.002). Neither high-risk FN according to the MASCC Risk Index nor change in FN protocol had any independent impact on both outcomes. Bacteraemia, Gram-negative bacteraemia and ceftazidime-resistant Gram-negative bacteraemia had no impact on 30-day mortality.

Attempting to predict potential ceftazidime-resistant Gram-negative bacteraemia using the criteria of ESBL-producing Enterobacteriaeceae infection/colonisation up to three months prior to the onset of FN yielded poor results (Table IV). The positive predictive value using the current dataset was 17.3% (95% CI 8.7%–30.8%), whereas the negative predictive value was 90.7% (95% CI 87.1%–93.3%). We attempted to derive a new prediction algorithm for ceftazidime-resistant Gram-negative bacteraemia in FN using the results of the multivariate analysis. As the haematological disease status cannot generally be determined at the time of FN, the two factors used were profound neutropenia and severe sepsis. The presence of both factors as a test for ceftazidime-resistant Gram-negative bacteraemia showed a sensitivity of 70.5% (95% CI 54.6%–82.8%) and specificity of 70.2% (95% CI 65.3%–74.7%). The positive and negative predictive values using the current dataset were 21.4% (95% CI 15.2%–29.1%) and 95.4% (95% CI 92.1%–97.4%), respectively.

DISCUSSION

The alarmingly high rate of Gram-negative bacteraemia, particularly ESBL-producing Enterobacteriaceae bacteraemia, among local haematology patients with FN had resulted in changes to our FN protocol.[2] These were implemented in mid-November 2009. This results of this second audit showed that the objectives of those changes had not been met. Switching the initial empirical therapy from IV ceftazidime to IV piperacillin/tazobactam had no impact on 30-day mortality among haematology patients with FN. Using a previous history of ESBL-producing Enterobacteriaceae infection/colonisation as a guide toward empirical carbapenem prescription probably resulted in excessive prescription of empirical carbapenem, although this was not significantly different between the pre-intervention and intervention periods. The positive predictive value of previous ESBL-positive infection/colonisation was remarkably low at 17.3%. On another note, the dramatic shift from ceftazidime to piperacillin/tazobactam prescription did not result in significant changes in the rates of ceftazidime-resistant Gram-negative bacteria, as had previously been reported, but the time interval of observation had perhaps been too short.[8]

The reason for the lack of impact on mortality was likely because neither Gram-negative bacteraemia nor the specific subset of ceftazidime-resistant Gram-negative bacteraemia was found to be independent risk factors for mortality, although the small sample size, especially with respect to ceftazidime-resistant Gram-negative bacteraemia, suggests that further validation is required. Lin et al had found that a delay in the prescription of appropriate antibiotics beyond 24 hours of index blood cultures was associated with increased mortality in profoundly neutropenic patients with Gram-negative bacteraemia,[3] but it is likely that our practice of switching to carbapenem upon identification of Gram-negative rods on blood cultures (the Gram stain results are usually reported by our microbiology laboratory within 24 hours post-blood cultures) had sufficiently shortened the period of inappropriate antibiotic prescription for such cases.[2]

A recent large meta-analysis has found that almost all anti-pseudomonal beta-lactams resulted in equivalent outcomes when used as an initial empirical therapy for FN. The only differences were that cefepime was associated with higher all-cause mortality, while piperacillin/tazobactam was associated with lower mortality.[9] Our results do not support the finding of lower mortality with regard to piperacillin/tazobactam, but add to this analysis by demonstrating that even in a setting where ESBL-producing Enterobacteriaceae and ceftazidime-resistant *Pseudomonas aeruginosa* cause > 10% of all FN, initial empirical carbapenem prescription may not be mandatory.

Unfortunately, none of the three factors found to be independently associated with 30-day mortality in our cohort of patients with FN is subject to intervention at present. Novel targeted anti-cancer agents without the myelosuppressive toxicity of traditional chemotherapy are needed, especially for older patients, but progress remains slow. Vancomycin prescription was higher in patients who subsequently died, but was probably added as a last-ditch effort in the face of persisting or worsening FN. As before, we found that the MASCC Risk Index was a poor predictor of mortality, and conversely, survival (data not shown) in patients with haematological diseases and FN.[2] This is unsurprising, as the original intent of the Risk Index was to identify FN patients at low risk for complications, of which mortality was not among the list (being a potential endpoint of any of the complications).[5] Independent risk factors were found for ceftazidime-resistant Gram-negative bacteraemia. Although the positive predictive value of any individual factor or combination of these factors is low, the negative predictive value is high, given the current prevalence of antibiotic-resistant Gram-negative bacteria. These findings should result in the discontinuation of the practice of prescribing empirical carbapenems initially for any FN episode when the patient is not in severe sepsis or septic shock.

There are several limitations to our audit. No other common classifications of disease severity (such as the Acute Physiology and Chronic Health Evaluation II score) or burden of chronic conditions (Charlson Comorbidity Index) were used. The impact of a switch to IV piperacillin/tazobactam was not assessed in a randomised controlled trial but rather as two time periods within a cohort study, thus limiting the conclusions that can be drawn from the results. Furthermore, carbapenems were prescribed as an initial empirical therapy as frequently as ceftazidime (in the pre-intervention period) and piperacillin/tazobactam (in the intervention period), rendering any actual comparison between ceftazidime and piperacillin/tazobactam problematic. Lastly, the heterogeneous mix of haematological conditions precluded the elucidation of independent risk factors for specific common individual conditions such as FN post-induction chemotherapy for acute myeloid leukaemia.

In conclusion, we were not able to demonstrate improved outcomes due to a change in our FN protocol. Nonetheless, it would probably be premature to consider switching back to empirical IV ceftazidime given that current evidence suggests the potential benefit of piperacillin/tazobactam prescription on meta-analysis.[9] The audit has also highlighted an area of improvement, i.e. that empirical carbapenem prescription may be unnecessary in FN episodes where there is no evidence of severe sepsis or septic shock, regardless of previous microbiology results. The practice of auditing FN cases in our institution has helped in the implementation of more appropriate and updated antibiotic regimens over time, and should be continued.

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