Original Article

Prospective Audit of Febrile Neutropenia Management at a Tertiary University Hospital in Singapore

Jing Jin,[1] *BM*, Yee Mei Lee,[2] *RN, MsN*, Ying Ding,[3] *MD*, Liang Piu Koh,[2] *MBBS, MRCP*, Siew Eng Lim,[2] *MD, ABIM*, Robert Lim,[2] *MBChB, ABIM*, Paul Ananth Tambyah,[3] *MBBS, ABIM*, Li Yang Hsu,[3] *MBBS, MRCP, MPH*

Abstract

Introduction: Febrile neutropenia (FN) remains a major cause of morbidity and mortality in Oncology/Haematology units. We launched a new protocol for FN management that incorporates risk stratification at our institute from October 2008. An audit was performed concurrently to evaluate the protocol and to define the epidemiology of FN locally. Materials and Methods: Case records of all inpatients with FN between October 2008 and June 2009 were reviewed prospectively. Clinical and microbiological characteristics were collated along with outcomes and programme adherence. Statistical testing was performed using Stata 10.1. Results: There were 178 FN episodes (50 in patients with solid cancers) from 131 patients. Forty-two (23.6%) episodes were classified as high-risk according to MASCC criteria. Initial blood cultures were positive in 49 (27.5%) episodes, of which gram-negative bacilli (GNB) predominated. Overall compliance to the protocol was 56.7%, with the main issue being disinclination to use oral antibiotics as first-line empirical therapy for low-risk episodes. Overall mortality was 7.3% and infection-related mortality was 4.5%. High-risk FN and the presence of central venous catheters were independently associated with bacteraemia on multivariate analysis, but there were no independent predictors of infection-related mortality. Conclusions: GNB accounted for the majority of bloodstream infections at our institute, unlike data from developed countries. Uptake of the new FN protocol was satisfactory, although the use of oral antibiotics as first-line empirical therapy can be improved. A better method for predicting infections caused by antibiotic-resistant GNB is urgently required, and antibiotic resistance trends should be monitored to enable the implementation of more appropriate antibiotic regimens over time.

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Key words: Antimicrobial resistance, Gram-negative bacilli, MASCC score

Introduction

Febrile neutropenia (FN) is considered a medical emergency and remains a major cause of morbidity and mortality in Oncology and Haematology units worldwide. A study analysing pooled FN data from 115 US academic medical centres between 1995 and 2000 showed that the overall in-hospital mortality was 9.5%,[1] whereas pooled data from 5 large clinical FN trials organised between 1985 and 2000 by the European Organization for Research and Treatment of Cancer (EORTC)- International Antimicrobial Therapy Group (IATG) showed similar overall mortality at 8.5% with 3.0% infection-related mortality.[2] Smaller studies in Singapore had demonstrated comparable overall mortality rates of between 3.0% and 8.8%.[3,4]

The current standard of care for FN involves the following principles:[5]

- Rapid and early clinical assessment to identify possible clinical foci of infection.
- Early empirical institution of broad-spectrum antibiotic therapy.
- Monitoring for clinical complications.

It has long been recognised that any delay in treatment may result in a higher risk of mortality in FN patients whose fever and symptoms are caused by invasive gram-negative bacilli (GNB), especially *Pseudomonas aeruginosa*.[6] More recently, it is understood that adult FN patients comprise a heterogeneous population, and the ability to stratify these patients according to their risk of developing

[1] Office of Biomedical Research, National University Hospital, Singapore
[2] National University Cancer Institute, Singapore, National University Health System, Singapore
[3] Department of Medicine, National University Health System, Singapore
Address for Correspondence: Dr Hsu Li Yang, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.
Email: li_yang_hsu@nuhs.edu.sg

complications has allowed for the identification of patient groups for which oral antibiotic therapy and/or outpatient management are effective and safe.[7] The Multinational Association for Supportive Care in Cancer risk-index score for chemotherapy-induced FN (MASCC score) remains the most accurate predictor of clinical outcome and complications internationally,[8] with a positive predictive value for low-risk FN (defined as having a <5% risk of complications and mortality) in excess of 90%.[7,8]

Several algorithms for the management of FN have been published in recent years, and all acknowledge the importance of tailoring the guidelines in accordance with the local epidemiology and conditions.[4,9-11] Previously, all adult FN patients hospitalised at our institute – the National University Hospital (NUH) – received empirical intravenous (IV) antibiotic therapy in accordance with the 2002 Infectious Diseases Society of America (IDSA) guidelines,[9] with the most common choice being ceftazidime plus an aminoglycoside (gentamicin or amikacin). If the FN persisted, subsequent management was driven by clinical assessment and consultant-based practice. There was no definite system for risk assessment and aggregation/analysis of outcomes.

A more structured FN protocol had been developed and implemented at NUH since October 2008, taking into account the recent developments such as the MASCC score,[7] utilisation of the predominantly monotherapy-based IV antibiotic regimens for high-risk FN patients with a decreased role for empirical glycopeptides[5] and the formalisation of empirical antifungal therapy for prolonged (≥6 days) FN.[9]

The aims of this study were to audit the compliance with the new protocol with regards to the initial management of FN and to describe the epidemiology and clinical outcomes of FN in adult inpatients at our institute.

Materials and Methods

Study Population

All adult FN patients hospitalised at 3 NUH Oncology/Haematology wards between October 2008 and June 2009 were reviewed prospectively. Demographic, clinical and microbiological data were collated along with clinical outcomes and protocol compliance by trained research staff.

FN was defined as a single episode of fever ≥38.3°C (oral/tympanic) or fever ≥38.0°C for at least 1 hour and an absolute neutrophil count (ANC) of <1.0 x 10^9/L with a predicted decrease to <0.5 x 10^9/L. Each patient may have more than one FN episode within a single hospitalisation. If the above criteria were met again after at least 7 intervening days where the patient had been afebrile, it was counted as a new episode of FN.

Protocol

The workflow for the initial management of FN according to the new protocol is shown in Figure 1a while the algorithm for prolonged FN is shown in Figure 1b. The MASCC score is recorded by the managing physicians and is the primary determinant to differentiate high- and low-risk FN (Table 1).[7] Patients with documented severe/anaphylactic penicillin or cephalosporin allergies are prescribed IV vancomycin and IV aztreonam empirically, while patients with penicillin or fluoroquinolone allergies are not eligible for oral antibiotic therapy. Patients with overt evidence of central line infections are managed as high-risk FN and additionally prescribed IV vancomycin until culture results are available.

Because the median time to defervescence for high-risk FN patients is between 3 and 5 days,[9] changes in antibiotic therapy for persistent fever without clinical deterioration for the 2nd to 6th day of therapy are strongly discouraged. Use of granulocyte-colony stimulating factors (G-CSF) is in accordance with the American Society of Clinical Oncology guidelines and routine usage in FN is discouraged.[12]

Outcomes

The primary study outcomes were infection-related mortality and compliance to protocol (the first 6 days of management of FN only). Mortality was attributed to infection by a single reviewer if no other clear cause of death was present and signs of infection persisted. The secondary outcome analysed was bacteraemia.

Statistics

Statistical testing was performed using Intercooled Stata

Table 1. Multinational Association for Supportive Care in Cancer Risk-index Score for Chemotherapy-induced Febrile Neutropenia

Characteristic	Score*
Extent of illness (choose one)	
No symptoms/mild symptoms	5
Moderate symptoms·	3
Severe symptoms	0
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour or haematological malignancy with no previous fungal infection	4
No dehydration	3
Outpatient at onset of fever	3
Age <60 years†	2

* A score of 0 is given if the criteria for each row are not matched. A score of ≥21 indicates that the patient is likely to be at low (<5%) risk for complications and mortality.

† Not applicable for patients <16 years of age

10.1 (StataCorp, Texas, USA). For intergroup comparison of independent data, the non-parametric Mann-Whitney test was used for continuous variables while the χ^2 test or Fisher's exact test was used for dichotomous variables. Univariate analyses of the association between individual variables and outcomes were performed using logistic regression. Variables with a *P* value of <0.3 on univariate analysis were included in the corresponding step-wise multivariate analyses. $P \leq 0.05$ was considered statistically significant. We included all FN episodes when comparing the treatment or clinical outcomes. If 1 patient had more than one FN episodes, only the first episode was included for describing demographic results.

Ethics

The institutional ethics review board approved this audit.

Results

There were 178 FN episodes from 131 patients during the 8-month study period. The demographic and clinical characteristics of the cases are shown in Table 2. The median age of the patients was 53 years (range, 19 to 80) and 67 (51.1%) were male. The majority of the patients were of Chinese ethnicity (67.9%) and were subsidised at either B2 or C class rates (73.0%). Forty-two FN episodes (23.6%) were classified as high risk according to their MASCC score. In comparison with Oncology patients, Haematology patients were younger and more likely to be male, have a central venous catheter (CVC) in place and to develop bacteraemia. They were also more likely to be placed on fluoroquinolone prophylaxis, and took a longer time to recover from neutropenia and fever (Table 2).

Initial blood cultures were positive for 49 FN (27.5%) episodes. The distribution of microorganisms cultured is shown in Table 3. Gram-negative bacilli (GNB) predominated, of which 13 (26.5%) were resistant to third- and fourth-generation cephalosporins, including 2 carbapenem-resistant *P. aeruginosa*, while 21 (84.0%) were resistant to the ciprofloxacin. Gram-positive bacteria were mainly coagulase-negative *Staphylococci* and *Bacillus* spp. These were presumed to be pathogenic because they were cultured from patients with CVCs.

The antibiotic most commonly used for empirical therapy was ceftazidime. It was used as monotherapy in 91 (51.1%) episodes and in combination with an aminoglycoside or vancomycin in 21 (11.8%) and 5 (2.8%) episodes, respectively. Other empirical antibiotics included carbapenem monotherapy (24 episodes, 13.5%), piperacillin/tazobactam (7 episodes, 3.9%), and the combination of a carbapenem with vancomycin (6 episodes, 3.4%). Oral antibiotics were used empirically in only 10 episodes (5.6%). The initial empirical regimen was changed (upgraded or addition of antibiotic) in 68 (38.2%) FN episodes, although auditing these systematically showed that only 35 (51.5%) changes were clinically indicated. Evaluation of empiric antibiotic coverage of the blood culture-positive FN episodes is shown in Table 3. Overall coverage was poor (21 of 49 FN episodes, 42.9%), albeit better for the subgroup with gram-negative bacteraemia (64.0%). For 3 FN episodes with associated ceftriaxone-resistant *Enterobacteriaceae* bacteraemia, a carbapenem was prescribed in accordance with the protocol (Fig. 1).

Overall compliance to the protocol was 56.7% (101 FN episodes). In addition to non-essential changes of antibiotics in 33 FN episodes, combination IV antibiotics (aminoglycosides and vancomycin) was prescribed outside the protocol in 29 FN episodes and oral antibiotics were not prescribed for 74 low-risk FN episodes despite meeting criteria for their use. Some protocol breaches overlapped, that is prescription of combination IV antibiotics in FN episodes fulfilling criteria for the use of oral antibiotics.

The median time to defervescence was 3 days, although 1 patient with aplastic anaemia and intracerebral haemorrhage had fever for 45 days. It took a median period of 6 days for the absolute neutrophil count to rise above 1 x 10^9/L. The median length of stay for each episode of FN was 15 days (range, 1 to 92). Thirteen (7.3%) patients died, of which 8 (4.5%) were deemed infection related. Three of 8 deaths were associated with carbapenem-resistant *P. aeruginosa* bacteraemia, one of which was cultured out only after a prolonged FN duration complicated by the invasive fungal disease. Four were culture-negative, while 1 was associated with cephalosporin-sensitive *Escherichia coli* bacteraemia.

Results of the univariate analysis for association of demographic/clinical characteristics with outcomes are shown in Table 4. Significant characteristics associated with positive blood cultures included haematological diagnosis, high-risk FN, fluoroquinolone prophylaxis and presence of a CVC. Significant univariate predictors of infection-related mortality included positive blood cultures, gram-negative bacteraemia, and possible/probable invasive fungal disease.

On multivariate analysis, high-risk FN [Odds ratio (OR), 2.78; 95% confidence interval (CI), 1.24-6.23; $P = 0.01$] and presence of a central line (OR, 3.36; 95% CI, 1.46-7.72; $P < 0.01$) were independently associated with bacteraemia, but there were no independent predictors of infection-related mortality found.

Discussion

This prospective audit of FN management at our institution revealed that the microbiological epidemiology differed significantly from other developed countries in that GNB formed the majority of blood culture-positive episodes.[14] This is despite the significant use of CVCs and fluoroquinolone prophylaxis, both of which have contributed

Table 2. Demographic Characteristics of Patients with Febrile Neutropenia (FN) and Clinical Characteristics of FN Episodes Segregated by Division

FN patients	**Oncology (n = 49)**	**Haematology (n = 82)**	***P***
Male gender (%)	15 (30.6)	52 (63.4)	<0.01
Median age (range), y	55 (26-80)	50.5 (19-80)	0.02
Ethnicity (%)·			
Chinese	37 (75.5)	52 (63.4)	NS*
Malay	9 (18.4)	7 (8.5)	NS*
Indian·	3 (6.1)	9 (11.0)	NS*
Others	0 (0.0)	14 (15.9)	< 0.01
FN episodes	**Oncology (n = 50)**	**Haematology (n = 128)**	***P***
Underlying disease (%)			
Acute lymphoblastic leukaemia	-	14 (10.9)	Not applicable
Acute myeloid leukaemia	-	42 (32.8)	
Aplastic anaemia	-	9 (7.0)	
B-cell lymphoma	5 (10.0)	18 (14.1)	
Breast cancer	26 (52.0)	-	
Gastrointestinal cancers	4 (8.0)	-	
Gynaecologic cancers	4 (8.0)	-	
Myelodysplasia	-	10 (7.8)	
Myeloma	-	11 (8.6)	
Nasopharyngeal cancer	4 (8.0)	-	
Other lymphomas	-	10 (7.8)	
T-cell lymphoma	-	12 (9.4)	
Others	9 (18.0)	2 (1.6)	
Hospital class, subsidised (%)†	38 (76.0)	91 (71.1)	NS*
Stem cell transplantation			
Allogenic (Cord blood)	-	13 (2)	Not applicable
Autologous	-	23	
Central venous catheter (%)	15 (30.0)	84 (65.6)	<0.01
Positive initial blood culture (%)	6 (12.0)	43 (33.6)	<0.01
Positive non-blood cultures (%)	8 (16.0)	27 (21.1)	NS*
Invasive fungal disease (%)			
Candidemia	0 (0.0)	0 (0.0)	NS*
Probable invasive pulmonary aspergillosis	0 (0.0)	8 (6.3)	NS*
Possible invasive pulmonary aspergillosis	0 (0.0)	7 (5.5%)	NS*
Pneumocystis pneumonitis	1 (2.0)	0 (0.0)	NS*
Quinolone prophylaxis (%)	4 (8.0)	65 (50.8)	<0.01
Median time to defervescence (range), days	2 (1-11)	3 (0-45)	0.01
Median time to neutrophil recovery (range), days	3 (1-14)	7 (1-31)	<0.01
Low-risk FN (%)	41 (82.0)	95 (74.2)	NS*
Overall mortality (%)	4 (8.0)	9 (7.0)	NS*
Infection-related mortality (%), N	1 (2.0)	7 (5.5)	NS*

* NS: not statistically significant
† B2 or C class

towards gram-positive infections being more common in developed countries.[14]

The majority of GNB isolated on initial blood cultures from patients with haematological diagnoses (but not solid tumours) were resistant to the non-carbapenem first-line antibiotics recommended in our protocol (13 of 22 isolates, 59.1%) – this is unsurprising given high rates of cephalosporin resistance among *Enterobacteriaceae* locally.[15] Although these composed but a small percentage (7.3%) of all FN episodes and there was no significant impact on infection-related mortality, it nonetheless represents a worrying phenomenon.

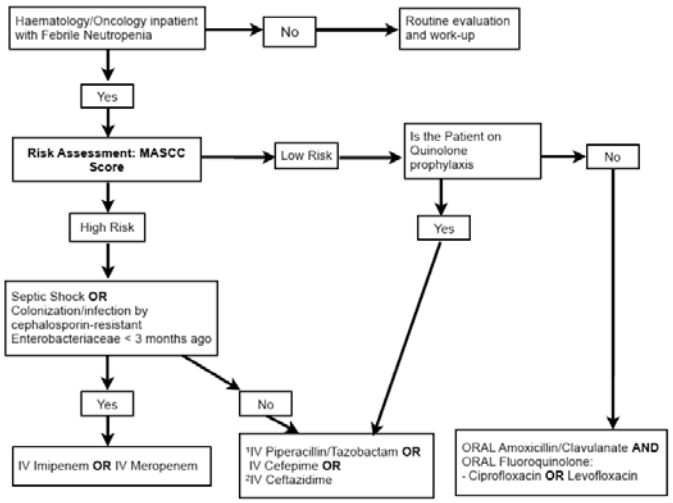

Fig. 1a. Algorithm for the initial management of febrile neutropenia.
Footnotes:
[1] Piperacillin/tazobactam administration may result in a false-positive serum galactomannan result.
[2] Ceftazidime monotherapy is not recommended in patients with severe mucositis or suspected bacterial pneumonia. Increased usage drives extended-spectrum beta-lactam rates in the hospital.

Table 3. Distribution of Positive Initial Blood Cultures for FN Episodes and Percentage Adequate Coverage of These Organisms by Initial Antibiotic Prescription

Initial blood cultures	No. (%)	Coverage by empirical antibiotic choice (%)
Gram-negative bacteria·	25 (51.0)	16 (64.0)
Ceftriaxone-sensitive *E. coli*	7 (14.3)	7 (100.0)
Ceftriaxone-resistant *E. coli*	4 (8.2)	1 (25.0)
Ceftriaxone-resistant *Klebsiella* spp.	7 (14.3)	2 (28.6)
Ceftriaxone-sensitive *Klebsiella* spp.	3 (6.1)	3 (100.0)
Pseudomonas aeruginosa	3 (6.1)	1 (33.3)
Salmonella typhimurium	1 (2.0)	1 (100.0)
Gram-positive bacteria	24 (49.0)	5 (20.8)
Coagulase-negative Staphylococci	8 (16.3)	0 (0.0)
Bacillus spp.	8 (16.3)	0 (0.0)
Viridans streptococci	3 (6.1)	2 (66.7)
Corynebacterium spp.	3 (6.1)	2 (66.7)
Methicillin-resistant *S. aureus*	1 (2.0)	0 (0.0)
Methicillin-sensitive *S. aureus*	1 (2.0)	1 (100.0)

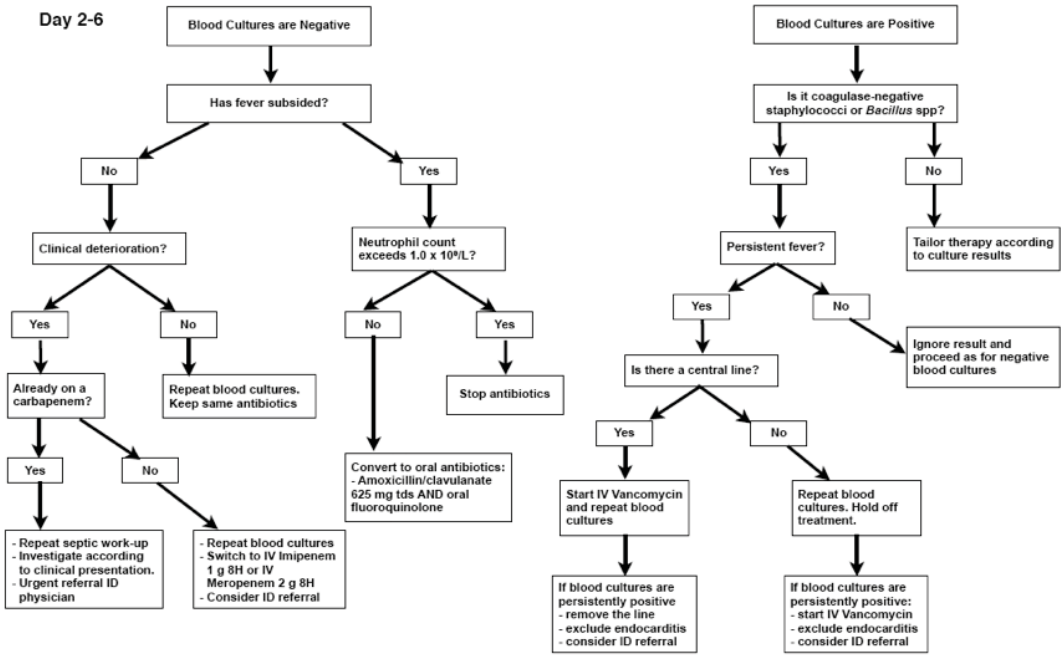

Fig. 1b. Algorithm for the subsequent management of febrile neutropenia – stratified by blood culture results.

Table 4. Univariate Analysis of the Impact of Demographic and Clinical Characteristics on Bacteraemia and Infection-related Mortality

Characteristic	Bacteraemia		Infection-related mortality	
	Odds ratio [CI]	*P*	Odds ratio [CI]	*P*
Demographics				
Male gender	1.34 [0.69-2.61]	0.39	1.45 [0.34-6.25]	0.62
Age >60 years	1.71 [0.86-3.40]	0.12	2.21 [0.53-9.16]	0.28
Subsidised hospital class	1.07 [0.51-2.25]	0.85	2.75 [0.33-22.98]	0.35
Oncology unit	0.27 [0.11-0.68]	<0.01	0.35 [0.04-2.94]	0.34
Clinical				
High-risk febrile neutropenia (FN)	3.35 [1.61-6.97]	<0.01	3.47 [0.83-14.54]	0.09
Quinolone prophylaxis	2.24 [1.14-4.38]	0.02	1.02 [0.24-4.41]	0.98
Central venous catheter	4.49 [2.06-9.75]	<0.01	1.35 [0.31-5.82]	0.40
Stem cell transplant	1.50 [0.70-3.24]	0.30	1.24 [0.24-6.41]	0.80
Microbiological				
Positive blood culture	Not applicable	-	8.86 [1.72-45.55]	<0.01
Gram-negative bacteraemia	Not applicable	-	13.25 [2.93-59.89]	<0.01
Possible/probable IFD	Not applicable	-	3.36 [1.39-8.11]	<0.01
Therapy				
Inadequate empirical coverage*	Not applicable	-	1.58 [0.26-9.59]	0.62
Inadequate gram-negative coverage†	Not applicable	-	3.50 [0.46-26.62]	0.23

CI: 95% confidence interval; IFD: invasive fungal disease. Criteria for possible and probable IFD are based on international guidelines.[13]

* Inadequate empirical antibiotic coverage for blood culture positive FN episodes.

† Inadequate empirical antibiotic coverage for gram-negative bacteraemia.

In practice, all FN patients with haematologic diagnoses with a preliminary blood culture report of GNB are switched to a carbapenem pending antibiotic susceptibility results – which may take a further 24 hours to process – and de-escalated to a narrower-spectrum antibiotic if the organism proves susceptible. This cumbersome process may have ameliorated the morbidity and mortality from antibiotic-resistant gram-negative bacteraemia somewhat. However, a better method to accurately identify high-risk patients for cephalosporin- or carbapenem-resistant GNB infection is necessary, as the widespread use of carbapenems as first-line antibiotics for FN remains unjustified at our institution.

Fluoroquinolone prophylaxis did not appear to protect our patients against either bacteraemia or infection-related mortality even upon confining the analysis to FN post-chemotherapy for haematological malignancies (data not shown), although its effectiveness in the prevention of fever cannot be derived from our data. This is consistent with meta-analyses[16] albeit not with the results of the largest recent trial on this issue.[17] Of note, the majority of GNB isolated in our patients were resistant to quinolones and the prevalence of quinolone resistance among GNB in Singapore hospitals exceeds 30%.[15] It would be prudent to evaluate the cost-benefits of continued fluoroquinolone prophylaxis for post-chemotherapy neutropenia under such circumstances.

High-risk FN according to the MASCC score was not associated with infection-related mortality (although there was a trend towards it on univariate analysis). It should be noted that the MASCC score was originally developed to define a subset of FN patients with low risk (<5%) of complications.[7] Hence, in conjunction with clinical discretion, it may remain a useful tool to stratify our patients with regards to oral antibiotics and possibly earlier discharge/outpatient management.

Mortality as a consequence of FN is low at our institute and is comparable with other local and international results.[1-4] The small number of infection-related deaths may have precluded the identification of a statistically significant risk factor/association at this point. However, of related concern is the fact that the empirical antibiotics in our protocol failed to cover a significant proportion of the bacteria isolated from initial blood cultures. While the majority of these were low-virulence gram-positive bacteria where treatment delay is of negligible impact,[18] a better predictive model as mentioned above is necessary

to minimise the risks of failure of antibiotic coverage for gram-negative bacteraemia. On a minor note, the class status of the patients had no impact on either bacteraemia or mortality.

Overall compliance to the protocol was reasonable at 56.7%.[4] The largest issue in compliance was the failure to prescribe oral antibiotics to eligible patients with FN. This is probably because of the prevailing culture and cautiousness on the part of the physicians – although multiple studies have validated the use of oral antibiotics for low-risk FN,[19] it has not been the routine practice in our institute and the rest of Singapore.[4] With increasing familiarity and confidence, supported by continuous educational efforts, we anticipate that this will improve over time.

Conclusion

In summary, our audit revealed that GNB accounted for the majority of bloodstream infections among FN patients at our institute. Uptake of and compliance to the new FN management protocol was satisfactory, although this can and will be improved over time. A better method for predicting infections caused by antibiotic-resistant GNB in our FN patients is a matter of high priority and continued audit of FN cases and antibiotic resistance trends should be conducted to enable the implementation of more appropriate antibiotic regimens and updated guidelines over time.

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