Original Article

Improved Clinical Outcomes with Appropriate Meropenem De-escalation in Patients with Febrile Neutropenia

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Abstract

Introduction: Antibiotic stewardship is a critical aspect of managing cancer patients with febrile neutropenia (FN) to limit the development of drug-resistant organisms and minimize adverse drug effects. Thus, it has been recommended that patients with FN receiving empiric antibiotics should be re-evaluated for safe antibiotic de-escalation. **Methods:** Subjects treated with meropenem for febrile neutropenia who met Loyola University Medical Center's (LUMC) criteria for de-escalation were stratified based on whether meropenem was de-escalated, and 30-day all-cause mortality for both groups was assessed. **Results:** 181 patients met criteria for meropenem de-escalation. Sixty patients (31.3%) were ade-escalated (MDE), and 121 subjects were not (NDE). The 30-day all-cause mortality was 8.3% (n = 5/60 subjects) in the MDE group and 2.4% (n = 3/121) in the NDE group but was not statistically significant (P=0.1). Median hospital length of stay was 13 days in the MDE group versus 20 days in the NDE group (P = 0.049). CDI rate was also lower in the de-escalated group. In addition, consultations by infectious diseases physicians were more common in the de-escalation group. Logistic regression model demonstrated positive culture (OR 4.78, P = 0.03), including positive blood culture (OR 8.05, P = 0.003), and GVHD (OR 19.44, P = 0.029), and were associated with high rates of appropriate de-escalation. Immunosuppression (OR 0.22, P = 0.004) was associated with lower rates of appropriate de-escalation. **Conclusion:** Appropriate meropenem de-escalation in FN patients is safe and can result in improved clinical outcomes.

Keywords: *Clostridioides difficile* infection, empiric antibiotic therapy, febrile neutropenia, hematological disorders, meropenem

Introduction

Cancer patients, especially those with hematologic malignancies, have an increased risk of infection, particularly when neutropenic.[1] The lack of granulocyte number and/or function, need for vascular access, injury to skin and mucosal integrity, and alterations of host flora from illness and antibiotic exposure all contribute to this risk.[2] Febrile neutropenia (FN) is defined as a single oral temperature ≥101°F (38.3°C) or a temperature ≥100.4°F (38°C) for at least an hour, with an absolute neutrophil count (ANC) of <1500 cells/μl.[3]

For high-risk patients presenting with neutropenic fever, prompt intravenous antibiotic therapy should be given within 1 h of presentation, after blood cultures are obtained.[4] The Infectious Diseases Society of America recommends monotherapy with antipseudomonal beta-lactam agents such as cefepime, carbapenems, or piperacillin/tazobactam.[5] Specific empiric agent of choice is institution dependent and often based on local and/or regional antibiograms.[6] At Loyola University Medical Center (LUMC), meropenem is used empirically for FN. Antibacterial therapy is typically continued until the ANC is ≥500 cells/μl. The National Comprehensive Cancer Network Guidelines for the Prevention and Treatment of Cancer-Related Infections suggest

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de-escalating antibiotic therapy in those who are clinically stable and have resolved fever, despite an ANC <500 cells/μL, and in those with a documented or identified infection amenable to pathogen-directed therapy.[2]

Prior studies have shown several clinical benefits of antibiotic de escalation to narrower spectrum in FN such as decreased rates of *Clostridioides difficile* infection (CDI). Aguilar-Guisado *et al*. reported on withdrawing empiric antibiotic therapy after 72 h or more of apyrexia plus clinical recovery and showed that empiric antibiotics can be discontinued in these settings, irrespective of neutrophil count, without worse outcomes, allowing reduction in excessive exposure to broad-spectrum antimicrobials.[7] Furthermore, in patients with acute myeloid leukemia (AML) undergoing chemotherapy induction, antibiotic de-escalation for FN with negative infectious workup before ANC recovery was associated with a lower risk of recurrent fever and had no impact on adverse drug events, intensive care unit transfer, and in-hospital mortality.[8] Not all medical centers have comprehensive clinical guidelines on antimicrobial management in patients with FN, and even when they exist, adherence to such guidelines may be suboptimal due to practitioner concerns about the vulnerable nature of the patient population. The purpose of this retrospective cohort study was to assess the compliance within our inpatient hematology and hematopoietic stem cell transplantation (HSCT) units with our antimicrobial de-escalation protocol and to evaluate outcomes after meropenem de-escalation (MDE) in patients with FN.

Methods

This was a retrospective, observational, single-center, cohort study of hospitalized patients at LUMC between January 2019 and January 2021. Patients were included in the study if they were 18 years of age or older, on the hematology or HSCT unit with FN, and had underlying acute lymphoblastic leukemia, acute myeloblastic leukemia (AML), aplastic anemia, multiple myeloma, myelodysplastic syndrome, lymphoma, or had undergone allogeneic/autologous HSCT and received meropenem for at least 48 h [Figure 1]. The study was approved by the LUMC Institutional Review Board.

Potential study subjects were then assessed to observe if they met criteria for MDE using the LUMC's FN antimicrobial de-escalation protocol [Figure 2]. This protocol was developed by the facility's Antimicrobial Stewardship Program with input from the hematology–oncology department and was introduced in 2018. In brief, FN patients will meet criteria for MDE if they have either low clinical suspicion for bacterial infection particularly having alternative noninfectious explanations of fever, clinically stable, and afebrile for 48 h, or documented bacterial infection. Subjects were then stratified into two groups: MDE group and non-de-escalation (NDE) group, based on the decision to continue meropenem after an initial monitoring period. Baseline characteristics collected included age, sex, type of hematologic malignancy, history and type of bone marrow transplantation (BMT), immunosuppressive therapy, usage of antineoplastic agents, and quick Sepsis-related Organ Failure Assessment (qSOFA) score in the first 72 h of meropenem initiation. Antimicrobial data collected included prior antibiotic prophylaxis, duration of meropenem, concomitant antibiotics, clinical infectious diagnosis, infection source, presence of bacteremia, and pathogen(s) isolated. The primary outcome was 30-day all-cause mortality from the onset of FN. The secondary outcomes included hospital length of stay, rate of CDI, presence of infectious diseases (IDs) consultation, and cause of death. Data elements were identified using electronic medical record chart review.

Data collection points were analyzed using descriptive statistics including mean, standard deviation, median, interquartile range, and percentages. Continuous variables were tested for normality by the Shapiro–Wilk test. Continuous data that were normally distributed were analyzed using the independent *t*-test. Continuous data that were nonnormally distributed

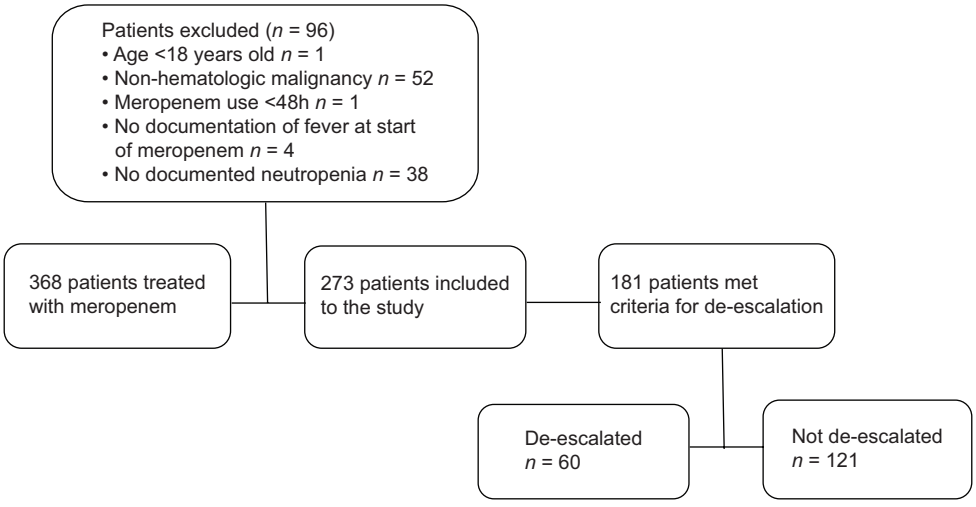

Figure 1: Study design

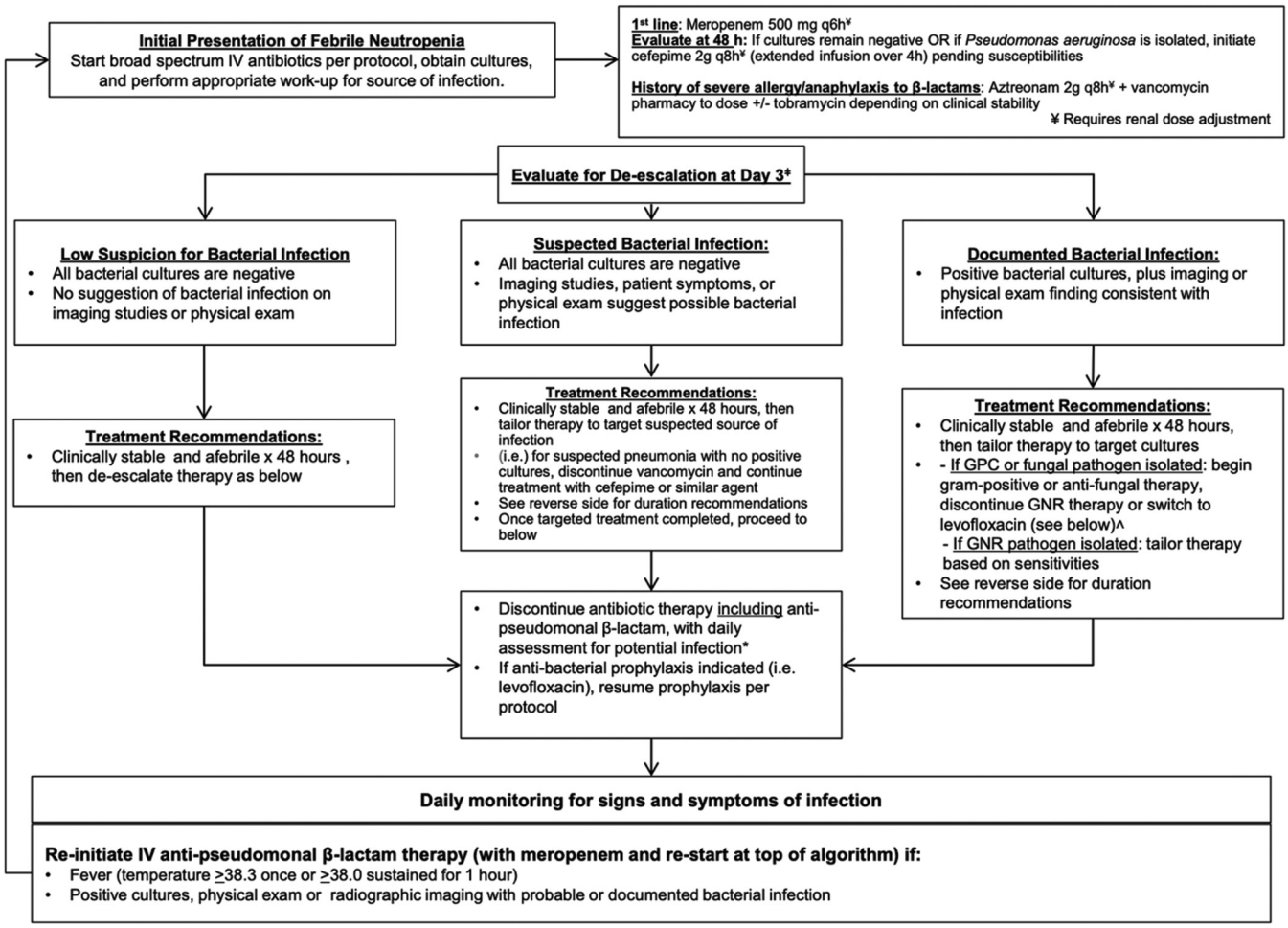

Figure 2: Antimicrobial de-escalation guidelines in febrile neutropenia for adult patients

were analyzed using the Mann–Whitney *U*-test. Chi-square and Fisher's exact tests were used to analyze categorical data. A multivariable logistic regression model was fit to the data with appropriate de-escalation as the dependent variable. Independent variables included age, sex, BMT, malignancy, graft versus host disease (GVHD), immunosuppression, recent antineoplastic, pressors, antibiotic prophylaxis, qSOFA score, positive culture, including blood culture, and imaging, and blood culture positivity. *P* values were computed with 2000 replicates of a Monte Carlo simulation (Hope. A.C.A., *Journal of the Royal Statistical Society Series*, 1968). $P < 0.05$ was considered statistically significant. All data were analyzed using R statistical programming language, Microsoft Excel, and SPSS (R Core Team. R Foundation for Statistical Computing, 2019).

Results

Out of 368 subjects who received meropenem in the LUMC inpatient hematology and HSCT units, 273 patients met the study's inclusion criteria, and 181 patients met the criteria for MDE. Sixty (31.3%) patients were appropriately de-escalated, and 121 subjects were not [Figure 1]. Overall, the MDE cohort was older compared to the NDE one (median age of 62.7 and 57.7 years old, respectively, $P = 0.004$ [Table 1]). Prior BMTs, type of BMT, and type of hematologic malignancy were not statistically different between the two cohorts. There was no difference in the highest qSOFA score in the first 72 h of meropenem between the two groups. There were two patients who required vasopressors in each group and three patients were intubated when on meropenem in the MDE versus none in the NDE group. The majority of the subjects received antineoplastic agents within 30 days prior to their FN (88.3% and 93.4% in de-escalated and non-de-escalated group, respectively, $P = 0.26$). 80% of patients in both the groups were on neutropenic prophylactic antibiotic therapy prior to the episode of their FN ($P = 1$). Fluoroquinolone antibiotics were used for prophylaxis in 71.7% and 71.1% of the de-escalated and non-de-escalated groups, respectively. Other prophylactic antibiotics included penicillins, cephalosporins, sulfonamides, and macrolides. Vancomycin was the most common concomitant antibiotic used with meropenem in both the groups, and there was no statistical difference in the use of concomitant antibiotics between the groups [Table 2]. The average meropenem therapy duration was 3 days in the MDE group and 7 days in the

Table 1: Baseline characteristics

Parameter	MDE (*n*=60), *n* (%)	NDE (*n*=121), *n* (%)	*P*
Age (years), median (IQR)	62.7 (55.0–70.0)	57.7 (46.3–67.3)	0.005
Sex			
Male	35 (58.3)	60 (49.6)	0.268
Female	25 (41.7)	61 (50.4)	
Hx of BMT			
Yes	24 (40)	58 (47.9)	0.211
No	36 (60)	63 (52.1)	
Types of BMT			
Autologous	12 (20)	24 (19.8)	0.663
Allogeneic cord	2 (3.3)	7 (5.8)	
Allogeneic MSD or MUD	10 (16.7)	27 (22.3)	
Type of hematologic malignancy			
ALL	4 (6.7)	19 (15.7)	0.268
AML	24 (40)	53 (43.8)	
Aplastic anemia	4 (6.7)	3 (2.5)	
CLL	0	1 (0.8)	
Lymphoma	9 (15)	20 (16.5)	
MDS	7 (11.7)	9 (7.4)	
MM	12 (20)	16 (13.2)	
GVHD being treated 30 days			
Yes	3 (5)	1 (0.8)	0.102
No	57 (95)	120 (99.2)	
Immunosuppressive therapy			
Yes	22 (36.7)	72 (59.5)	0.004
No	38 (63.3)	49 (40.5)	
Usage of antineoplastic agents within the 30 days prior			
Yes	53 (88.3)	113 (93.4)	0.264
No	7 (11.7)	8 (6.6)	
Pressor requirement on meropenem			
Yes	2 (3.3)	2 (1.7)	0.613
No	58 (96.7)	119 (98.3)	
Intubation on meropenem			
Yes	3 (5)	0	0.035
No	57 (95)	121 (100)	
Highest qSOFA score in the first 72 h of meropenem?, median (IQR)	1 (1–1)	1 (1–1)	0.146

BMT: Bone marrow transplantation, MSD: Matched sibling donor, MUD: Matched unrelated donor, ALL: Acute lymphoblastic leukemia, AML: Acute Myeloid Leukemia, CLL: Chronic lymphocytic leukemia, MDS: Myelodysplastic syndrome, MM: Multiple myeloma, GVHD: Graft versus host disease, qSOFA: Quick Sepsis-related Organ Failure Assessment, IQR: Interquartile range, MDE: Meropenem de-escalation, NDE: Non-de-escalation

NDE group ($P < 0.001$). Thirty seven out of sixty subjects (61.7%) in the MDE group had positive cultures , including blood, urine and respiratory, compared to 35/121 subjects (28.9%) in the NDE group ($P < 0.001$) [Table 2].

The primary endpoint of 30-day all-cause mortality was 8.3% in the MDE group and 2.4% in the NDE group ($P = 0.114$). Mortality causes in the MDE group included gastroenterological bleed ($n = 2$), acute hypoxic respiratory failure due to volume overload ($n = 1$), candida septicemia ($n = 1$), and culture negative sepsis ($n = 1$). In the NDE group, causes of death included sepsis with *Enterobacter cloacae* bacteremia ($n = 1$), acute hypoxic respiratory failure ($n = 1$), and malignancy ($n = 1$). The secondary outcome of the median hospital length of stay was 13 days in the MDE group versus 20 days in the NDE group ($P = 0.049$). CDI rate was also lower in the de-escalated group. In the MDE group, 16 *C. difficile* polymerase chain reaction (PCR) tests were collected with 100% negative rate. In comparison, 38 *C. difficile* PCR tests were done in the NDE group, with a positive rate of 32.7% ($P = 0.015$). In addition, ID specialists were consulted in 40% of subjects in the MDE group, compared to only 14.9% of the subjects in the NDE group ($P < 0.001$) [Tables 2 and 3].

Our multivariable logistic regression model demonstrated that positive blood culture (odds ratio [OR]: 8.05, $P = 0.003$), GVHD (OR: 19.44, $P = 0.029$), and positive infection (OR: 4.78, $P = 0.03$) were associated with high rates of appropriate de-escalation. Immunosuppression (OR: 0.22, $P = 0.004$) was associated with lower rates of appropriate de-escalation [Table 4].

Table 2: Antimicrobial therapy

Parameter	MDE (*n*=60), *n* (%)	NDE (*n*=121), *n* (%)	*P*
Antibiotic prophylaxis at time of dx			
Yes	48 (80)	97 (80.2)	1
No	12 (20)	24 (19.8)	
Antibiotic choice			
Penicillin	2 (3.3)	6 (5)	0.987
Cephalosporin	1 (1.7)	1 (0.8)	
Quinolone	43 (71.7)	86 (71.1)	
Macrolide	1 (1.7)	1 (0.8)	
Sulfonamide	5 (8.3)	10 (8.3)	
Meropenem duration, median (IQR)	3 (3–4)	7 (5–10)	<0.001
Concomitant antibiotic			
Yes	28 (46.7)	53 (43.8)	0.836
Vancomycin	24 (85.7)	42 (72.4)	
Daptomycin	1 (3.6)	2 (3.8)	
Other	3 (10.7)	9 (17.0)	
No	32 (53.3)	69 (57.0)	
Infection status, *n* (%)			
Positive culture	37 (61.7)	35 (28.9)	<0.001
Negative culture (resumed infection status)	4 (6.7)	17 (14.0)	
Negative culture (unclear infection status)	19 (32.7)	69 (57.0)	
Imaging suggestive of infection			
Yes	7 (11.2)	17 (14.0)	0.445
Skin and soft tissue	2 (28.6)	7 (41.2)	
Bone	0	0	
Intra-abdominal	1 (14.3)	4 (23.5)	
Lung	4 (57.1)	7 (41.2)	
No	51 (85)	104 (86.0)	
Unclear	2 (3.3)	0	
UA with automatic culture performed			
Yes	58 (96.7)	111 (91.7)	0.191
No	2 (3.3)	10 (8.3)	
Blood cultures, *n* (%)			
Positive	31 (51.7)	13 (10.7)	<0.001
MSSA	1 (3.2)	0	
MRSA	0	0	
Coagulase negative *Staphylococcus*	4 (12.9)	0	
Enterococcus species	2 (6.5)	1 (7.7)	
Escherichia coli	7 (22.6)	3 (23.1)	
Enterobacter cloacae	4 (12.9)	0	
Klebsiella pneumoniae	2 (6.5)	0	
Pseudomonas aeruginosa	2 (6.5)	0	
Other	9 (29.0)	8 (61.5)	
Negative	29 (48.3)	108 (89.3)	
Antibiotic escalation followed de-escalation			
Yes	8 (13.3)	6 (5.0)	0.104
No	52 (86.7)	115 (95.0)	

UA: Urinalysis, MSSA: Methicillin-sensitive *Staphylococcus*, MRSA: Methicillin-resistant *Staphylococcus*, IQR: Interquartile range, MDE: Meropenem de-escalation, NDE: Non-de-escalation. + stands for positive (Culture positive) and – stands for negative (Culture negative)

Discussion

FN is a common yet serious complication in patients with hematologic malignancies receiving antineoplastic therapy and is associated with high mortality and morbidity.[9] In FN, most infections are bacterial, but viral and fungal etiologies are also possible. Gram-negative bacteria such as *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*, and *Enterobacterales* are the leading causes of FN. However, emergence of multidrug-resistant organisms has continued to pose a great threat in many institutions.[10] Carbapenem resistance is rapidly developing and has been identified in 57.9% of *Klebsiella pneumoniae* isolates in some European

Table 3: Outcome data

Parameter	MDE (*n*=60), *n* (%)	NDE (*n*=121), *n* (%)	*P*
30-day mortality	5 (8.3)	3 (2.4)	0.114
Length of stay, median (IQR)	13 (5.5–24)	20 (11–26)	0.049
Was *C. difficile* PCR collected			
Yes	16 (26.7)	38 (31.4)	0.015
Positive	0	12 (31.6)	
Negative	16 (100)	26 (68.4)	
No	44 (73.3)	83 (68.6)	
Was ID consulted during the hospital stay?			
Yes	24 (40)	18 (14.9)	<0.001
No	36 (60)	103 (85.1)	

C. difficile: *Clostridioides difficile*, PCR: Polymerase chain reaction, ID: Infectious disease, IQR: Interquartile range, MDE: Meropenem de-escalation, NDE: Non-de-escalation

Table 4: Factors associated with appropriate meropenem de-escalation

Parameter	OR	*P*
Age	1	0.997
Male sex	0.84	0.683
History of BMT	0.4	0.096
ALL	0	0.997
AML	0	0.997
Aplastic anemia	0	0.996
Lymphoma	0	0.997
MDS	0	0.997
MM	0	0.996
Graft versus host disease	19.44	0.029
Immunosuppressive therapy	0.22	0.004
Usage of antineoplastic agents within the 30 days prior	0.17	0.108
Pressor requirement on meropenem	0	0.993
Highest qSOFA score in the first 72 h of meropenem	1	0.99
Antibiotic ppx	2.07	0.3
Positive culture	4.78	0.03
Positive blood culture	8.05	0.003
Imaging suggestive of infection	0.38	0.196

qSOFA: Quick Sepsis-related Organ Failure Assessment, OR: Odds ratio, ppx: Prophylaxis, ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, MM: Multiple myeloma, MDS: Myelodysplastic syndrome, BMT: Bone marrow transplantation

countries, increasing the rates of mortality and morbidity in these patients.[11] Recently, multiple studies have shown that shorter courses of antibiotic therapy for a variety of conditions are just as effective as longer courses and may be associated with fewer adverse effects or the development of antimicrobial resistance.[12] Thus, it has been recommended that patients with FN receiving empiric antibiotics should be re-evaluated frequently for safe antibiotic de-escalation.[4,5] Practices such as empiric antibiotic de-escalation can decrease the duration of broad-spectrum antibiotic exposure and associated complications.[13] Although antimicrobial stewardship activities are now required in hospitals, implementation of specific guidelines for FN antibiotic de-escalation is much needed, along with monitoring for adherence. We assessed the rate of adherence to de-escalation guidelines at our hospital and compared clinical outcomes among patients with FN who underwent appropriate MDE to their counterparts that did not. Overall, we observed no statistical difference in 30-day all-cause mortality between the two groups. This is in accordance with several prior clinical studies which supported the safety of shorter course of empiric antibiotic therapy in clinically stable FN patients or those with positive microbiologic data.[7,8,14]

The rate of CDI was also markedly lower in the MDE group. CDI has been associated with significant morbidity and mortality, with potentially life-threatening complications including pseudomembranous colitis, toxic megacolon, perforations of the colon, and sepsis.[15] Furthermore, hospital-acquired, CDI-associated health-care costs are significant. In a 10-year systematic review (2005–2015), the estimated mean cost for CDI-attributable hospitalized patients per case was US$ 21,448 and the total CDI-attributable cost was US$ 6.3 billion.[16] In our study, the hospital length of stay was also noted to be longer in the NDE group. Prolonged stays in hospitals increase the risk of hospital-acquired infections, poor nutritional status, and health-care costs, and they decrease the access to care due to bed shortages.[17-19] Reducing CDI and hospital length of stay in these patients may not only improve patient outcomes but also decrease health-care costs.

Overall, MDE occurred only in 33.1% of subjects that met criteria for de-escalation. This falls far below the adherence rate targeted. Predictors for sepsis in the first 72 h of meropenem (qSOFA score) were not statistically different between the two groups, suggesting that severity of illness did not play a major role in the decision to de-escalate. The rate of culture positivity in the MDE group was significantly higher than in the NDE group. This was affirmed association between positive blood culture and infection with high rates of de-escalation using a logistic regression model. This may suggest that providers felt more comfortable narrowing antibiotics when therapy could be targeted to an identified pathogen. Other factors that may have influenced the rate of de-escalation include a lack of provider awareness of the de-escalation protocol and of the safety and beneficial effects

of de-escalation. We also found that the involvement of the IDs consultation team was associated with significantly lower rates of prolonged meropenem use in individuals with FN who met criteria for de-escalation. We also found that the involvement of the ID consultation team was associated with significantly lower rates of prolonged meropenem use in individuals with FN who met criteria for de-escalation. This suggests that hands-on instruction by the ID consult team may increase de-escalation adherence. It is worth noting that de-escalation recommendations may have been provided by pharmacists or ID consultants, but decisions were made at the discretion of the treating physician. In the future, implementation of reminders in the electronic medical record and ordering system, adding reminders to nursing/pharmacy shift checklists, department-wide surveys and education workshops regarding the topic may improve protocol adherence. In addition, studies on the efficacy and even economic impact of ID and/or antimicrobial stewardship practitioner involvement in this patient population are encouraged and necessary. This will add to the evidence-based and rational use of antimicrobials, which will hopefully counter the high rate of emerging multidrug-resistant pathogens and nudge slow development of novel anti-infective agents.

The main limitation of this study is the small sample size. Second, due to the nature of the study's retrospective design, we may not be able to account for all possible confounding factors between the study groups. Finally, the findings of this study are limited to a single center and so may not be applicable to other settings and centers.

Conclusions

MDE in clinically stable, afebrile patients with hematologic malignancies did not affect 30-day all-cause mortality. It did, however, positively impact other clinical outcomes including length of hospital stay and CDI rates. Although additional studies are needed, our findings add to the increasing body of literature, suggesting that antibiotic de-escalation in this population is safe and can result in improved clinical outcomes.

Research quality and ethics statement

This study was approved by the Institutional Review Board of Loyola University Chicago (LU# 214540). The authors followed applicable EQUATOR Network guidelines during the conduct of this research project.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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