RESEARCH ARTICLE

Incidence, Risk Factors, and Outcomes of Febrile Neutropenia in Thai Hematologic Malignancy Patients Receiving Chemotherapy: A 6-year Retrospective Cohort Study

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Abstract

A 6-year retrospective cohort study was conducted among Thai hematologic malignancy (HM) patients receiving intensive chemotherapy. Of the 145 eligible patients receiving 893 chemotherapy sessions, 46.9% were female, median age was 52 years, and the most common HM diagnosis was diffuse large B-cell lymphoma (46.2%). Febrile neutropenia (FN) occurred in 14.9% of chemotherapy sessions with an incidence of 24.8 per 1,000 chemotherapy cycles per year. Independent factors associated with FN were receiving the first chemotherapy cycle [adjusted hazard ratio (aHR) 4.1], having hemoglobin ≤100 g/L (aHR 3.7) and platelet ≤140,000/μL (aHR 2.7) on chemotherapy day and receiving acute myeloid leukemia regimens (aHR 20.8). Granulocyte colony stimulating factor was significantly associated with reduced rate of FN when given in those receiving CHOP regimen. With the median follow-up time of 16 months, the overall survival time was significantly longer in patients without FN than those with FN (61.7 vs. 20.8 months; p<0.001).

Keywords: Febrile neutropenia - hematologic malignancy - incidence - risk factors - Thailand

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Introduction

Febrile neutropenia (FN) is a common complication of solid and hematologic malignancies (HM) and occurs as a result of bone marrow involvement and/or the treatment of the diseases. Febrile neutropenia poses risk for developing severe infections that sometimes results in mortality. Etiologic organisms may be bacteria, viruses, fungi or other microorganisms depending on the net state of immune suppression. Symptoms and signs of febrile neutropenic patients may be subtle due to the immune effector mechanism suppression. Hence, the infectious foci may not be readily identified and empirical antibiotics need to be promptly administered. Delay in appropriate treatment of FN may results in significant morbidity and mortality of these patients.

Incidence of FN can be as high as 80% in patients with HM (Klastersky, 2004). However, the rate of organism identification in these patients was reported to be 20-30% of the total FN episodes (Freifeld et al., 2011). Mortality from FN was reported to be as high as 24-82% in patients with major comorbidities (Kuderer et al., 2007). A recent systematic review demonstrated that prophylactic granulocyte colony stimulating factor (G-CSF) usage could significantly reduce the rate of FN (46% relative risk reduction) and infection-related mortality (45% relative risk reduction) (Kuderer et al., 2007). Given these benefits, the United States' national comprehensive cancer network guideline recommends the use of prophylactic G-CSF in certain high-risk subgroups (Crawford et al., 2013) such as patients receiving intensive chemotherapy regimen, elderly patients, and those with poor performance status, poor liver and renal function, human immunodeficiency virus (HIV) infection and pre-existing neutropenia.

Asian data regarding febrile neutropenic events is scarce. Studies from Pakistan and Thailand reported mortality of FN in all cancer types of 11.3%, 13.7% and 14.0%, respectively (Lal et al., 2008; Osmani et al., 2012; Chindaprasirt et al., 2013). However, limited data exists regarding the incidence and risk factors of FN in Thai HM patients. Most of the previous published studies reported the overall incidence of FN in populations including both hematologic and non-hematologic cancer patients (Chayakulkeeree and Thamlikitkul, 2003; Leelayuthachai and Kanitsap, 2010; Roongpoovapatr and Suankratay, 2010). Only one study prospectively investigated the incidence and risk factors of FN among patients with aggressive non-Hodgkin's lymphoma (NHL) receiving cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP regimen) without prophylactic G-CSF during their first cycles (Intragumtornchai et al., 2000). There have been no studies that assessed the risk factors of FN and effect of other chemotherapy regimens with and without prophylactic G-CSF on the occurrence of FN among various types of HM in Thailand. The primary objective of this study was to identify risk factors

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associated with the occurrence of FN in Thai HM patients who received chemotherapy. The secondary objectives were to assess the incidence and outcomes of FN in this HM population.

Materials and Methods

This is a retrospective medical record review study performed at Thammasat University Hospital, a 600-bed teaching and referral hospital in Pathumthani province, Thailand. The study was approved by the institutional ethics committee of Faculty of Medicine, Thammasat University, and was conducted in accordance with the declaration of Helsinki and international conference on harmonisation guideline for good clinical practice (ICH-GCP). Patients' informed consents were waived due to retrospective study design.

Patients aged 15 years and older with diagnosis of HM (acute leukemias and lymphomas) who received chemotherapy for definitive treatment of HM during January 2008 to December 2013 were included in the study. Patients were excluded if their medical records

Table 1. Baseline Characteristics and Laboratory Parameters at Diagnosis and at the Beginning of Each Chemotherapy Cycle

Characteristics and parameters	n (%) or median (range)		p-value
	FN (n=133)	No FN (n=760)	
Static data			
Female sex	82 (61.7)	284 (37.4)	<0.001
Median age-years (range)	46 (15-87)	54 (15-87)	0.009
Age more than 60 years	32 (24.1)	306 (40.3)	<0.001
Diagnosis			<0.001
Indolent lymphoma	7 (5.3)	157 (20.7)	
Hodgkin's lymphoma	2 (1.5)	61 (8.0)	
Diffuse large B-cell lymphoma	33 (24.8)	385 (50.7)	
Other aggressive lymphoma	13 (9.8)	80 (10.5)	
Acute lymphoblastic leukemia (ALL)	13 (9.8)	55 (7.2)	
Acute myeloid leukemia (AML)	65 (48.9)	22 (2.9)	
ECOG's performance status 2-4	53 (39.9)	126 (16.6)	<0.001
Bone marrow involvement	100 (75.2)	212 (27.9)	<0.001
Previous chemotherapy or radiation therapy	39 (29.3)	154 (20.3)	0.019
Median hemoglobin g/L (range)	91 (32-146)	119 (31-160)	<0.001
Hemoglobin less than 100 g/L	78 (58.7)	218 (28.7)	<0.001
Median ANC $x10^3$ cell/μL (range)	3.5 (0-21.6)	4.7 (0.5-21.8)	0.005
ANC less than 3000 cells/μL	52 (39.1)	169 (22.2)	<0.001
Median platelet count $x10^3$ /μL (range)	144 (11-624)	251 (4-586)	<0.001
Platelet count less than $140x10^3$ /μL	65 (48.9)	115 (15.1)	<0.001
Median estimated GFR mL/min/1.73 m^2 (range)	84.2 (11.4-174.4)	83.9 (4.1-139.3)	0.545
Median albumin g/L (range)	33 (17-43)	36 (6-47)	<0.001
Albumin less than 30 g/L	44 (33.1)	156 (20.5)	0.001
Median total bilirubin mg/L (range)	6 (1-60)	5 (1-189)	0.37
Median direct bilirubin mg/L (range)	2 (0-18)	1 (0-104)	0.006
Median AST U/L (range)	30 (5-305)	25.5 (7-209)	0.036
Median lactate dehydrogenase U/L (range)	1134 (237-9303)	575 (162-3184)	<0.001
Dynamic data			
First chemotherapy cycle	44 (33.1)	101 (13.3)	<0.001
Infected wound	2 (1.5)	1 (0.1)	0.012
Recent surgery within 30 days	8 (6.0)	20 (2.6)	0.039
Chemotherapy received			<0.001
CHOP regimen	26 (19.6)	436 (57.4)	
CVP regimen	3 (2.3)	125 (16.5)	
ABVD regimen	2 (1.5)	46 (6.1)	
Salvage lymphoma regimen	19 (14.3)	73 (9.6)	
ALL type regimen	16 (12.0)	58 (7.6)	
AML type regimen	67 (50.4)	22 (2.9)	
Median hemoglobin-g/L (range)	92 (32-135)	111 (55-158)	<0.001
Hemoglobin less than 100 g/L	92 (69.2)	192 (25.3)	<0.001
Median ANC-$x10^3$ cells/μL (range)	2.9 (0-23.8)	3.6 (0-22.6)	0.001
ANC less than 3000 cells/μL	71 (53.4)	262 (34.5)	<0.001
Median platelet count $x10^3$ /μL (range)	178 (5-1106)	275 (2-852)	<0.001
Platelet less than 140,000/μL	57 (42.9)	57 (7.5)	<0.001
G-CSF prophylaxis use	77 (57.9)	388 (51.1)	0.145

*Data in table is presented in n (%) unless indicated otherwise; Abbreviation: ANC-absolute neutrophil count, AST-aspartate aminotransferase, FN-febrile neutropenia. G-CSF-granulocyte colony stimulating factor, GFR-glomerular filtration rate by CKD-EPI equation. Regimens: ABVD-adriamycin, bleomycin, vinblastine, dacarbazine, ALL-adult and pediatric protocol for ALL, AML-7+3 induction and cytarabine consolidation, CHOP-cyclophosphamide, doxorubicin, vincristine, prednisolone, CVP-cyclophosphamide, vincristine, prednisolone

could not be retrieved. International classification of disease (ICD)-10 code: C810-C969 and D45-D46 were used for identification of the eligible patients. Patients' information collected was epidemiological data [age, sex, diagnosis, staging, the eastern cooperative oncology group (ECOG) performance status, international prognostic index (IPI) score and other comorbidities], baseline laboratory data [complete blood count (CBC), chemistry, creatinine, liver function test and lactate dehydrogenase (LDH)], treatment received, CBC on the day of chemotherapy, the use of G-CSF prophylaxis and FN occurrence. For each FN episode, additional data collected was date of FN occurrence, parameters in multinational association for supportive care in cancer (MASCC) score (Klastersky et al., 2000), systemic inflammatory response syndrome (SIRS), laboratory results, antibiotics used, time to antibiotic therapy, definite microbiological diagnosis, and outcomes. The primary outcome of this study was the risk factors associated with the occurrence of FN. The secondary outcomes included the incidence of FN, all-cause 30-day mortality, the epidemiology of causative pathogens and the effect of FN occurrence on diseases' overall and event-free survivals. Overall survival in this study was calculated based on time from HM diagnosis to the date of death, while event-free survival was calculated based on time from HM diagnosis to the date of relapse or death.

Statistical analyses were performed using STATA software, version 12.0 (StataCorp, Texas, USA). Categorical variables were compared using the Pearson chi-square or Fisher's exact test, as appropriate. Continuous variables were compared by the Mann-Whitney-U test. Univariable and multivariable regression analyses were performed using mixed effect multi-level model due to the repeated nature of chemotherapy and FN occurrence. Since the effect of G-CSF prophylaxis in FN prevention depends on the chemotherapy regimen, interaction between G-CSF use and chemotherapy regimen was used in regression analysis. Survival analysis between those with and without FN was done using Kaplan-Meier survival analysis. Survivals between groups were compared using the Cox's proportional hazard ratios. All stated p-values were 2-sided and were considered significant if the value is less than 0.05. Given that the incidence of FN in patients receiving prophylactic G-CSF from a recent systematic review was 22.4%, and 39.5% in those without prophylactic G-CSF (Kuderer et al., 2007). The study required FN occurrence of 130 episodes to have 80% power to detect the difference of 17% in rates of FN occurrence between patients receiving and not receiving G-CSF prophylaxis at the 5% significance level.

Results

Patients' Characteristics

A total of 145 patients receiving 893 episodes of chemotherapy were included. Febrile neutropenia occurred in 133 episodes (14.9%). Average incidence of FN was 24.8 per 1,000 chemotherapy cycles per year. Baseline characteristics and laboratory parameters for the study chemotherapy cycles are shown in table 1. Baseline variables that were significantly different

Table 2. Univariable and Multivariable Regression Analysis of Risk Factors Associated with FN

Risk factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Female sex	4.4	1.5-13.5	0.009			NS
Age > 60 years	0.6	0.2-1.8	0.347			NS
ECOG 2-4	4.9	1.7-14.2	0.004	2	0.9-4.3	0.072
BM involvement	24.2	9.0-64.9	<0.001			NS
Previous CMT or RT	2.6	1.1-6.0	0.025			NS
Albumin < 30 g/L	2.3	0.9-6.1	0.09	1.9	0.9-4.2	0.094
LDH > 450 U/L	3.8	1.3-11.0	0.013			NS
First cycle	3.7	2.0-6.8	<0.001	4.1	2.0-8.4	<0.001
On CMT day						
Hb < 100 g/L	11.8	5.9-23.8	<0.001	3.7	1.9-7.2	<0.001
ANC < 3000 cells/μL	2.1	1.2-3.6	0.01			NS
Platelet < 140000/μL	10.6	5.2-21.7	<0.001	2.7	1.3-5.7	0.009
CMT#G-CSF use						
CHOP regimen	Reference			Reference		
CHOP with G-CSF	0.3	0.1-0.9	0.031	0.3	0.1-1.0	0.04
CVP regimen	0.1	0-0.7	0.023	0.1	0-1.2	0.073
CVP with G-CSF	1.5	0.2-10.9	0.694			NS
ABVD regimen	0.3	0-2.7	0.263			NS
ABVD with G-CSF	2	0.1-27.0	0.619			NS
Salvage regimen	3.2	0.5-19.6	0.2			NS
Salvage with G-CSF	3.8	1.3-10.6	0.013			NS
ALL protocol	4	0.9-16.9	0.064			NS
ALL with G-CSF	4	1.0-15.4	0.048			NS
AML regimen	160.6	35.7-721.3	<0.001	20.8	3.4-127.6	0.001
AML with G-CSF	47.8	14.7-155.0	<0.001	34.8	7.6-160.1	<0.001

Abbreviation: ALL-acute lymphoblastic leukemia, AML-acute myeloid leukemia, ANC-absolute neutrophil count, BM-bone marrow, CI-confidence interval, CMT-chemotherapy, ECOG-eastern cooperative oncology group, G-CSF-granulocyte colony stimulating factor, Hb-hemoglobin, HR-hazard ratio, LDH-lactate dehydrogenase, NS-not significant, RT-radiotherapy

between chemotherapy cycles with and without FN were sex, age, HM diagnosis, ECOG performance status, previous chemotherapy or radiation therapy, hemoglobin, absolute neutrophil count, platelet, albumin, direct bilirubin, aspartate aminotransferase and LDH level. Types of medical coverage, the presence of more than 1 extranodal site, having underlying diseases including chronic obstructive pulmonary disease, chronic kidney disease, and cirrhosis, and the level of alanine aminotransferase, and alkaline phosphatase did not differ between chemotherapy cycles with and without FN. Dynamic characteristics for each chemotherapy cycle are also presented in table 1. Receiving first cycle of chemotherapy, infected wound, recent surgery within 30 days, type of chemotherapy received, hemoglobin, absolute neutrophil count and platelet were found to be significantly different between cycles with and without FN occurrence. Prophylactic G-CSF use was not significantly different between cycles with and without FN.

Factors Associated with Febrile Neutropenia Occurrence

Mixed effect, multilevel regression analysis was performed in univariable and multivariable manners. The results are shown in table 2. Independent factors associated with FN occurrence were receiving the first chemotherapy cycle, having hemoglobin less than 100 g/L and platelet less than 140,000/μL on chemotherapy day. Comparing types of chemotherapy with and without use of G-CSF to the CHOP regimen, G-CSF was significantly associated with reduced rate of FN when given in those who received CHOP regimen, while AML type regimens were significantly associated with increased rate of FN regardless of G-CSF use. There were trends of increased risk of FN in the patients with ECOG performance status 2-4, and albumin at diagnosis less than 30 g/L while there was a trend toward association between the CVP regimen and decreased risk of FN.

Febrile Neutropenia Episodes

Of all 133 FN episodes, the common sources of infection were septicemia (35.3%), respiratory tract (30.1%), gastrointestinal tract (26.3%), urinary tract (24.8%), and soft tissue (15.0%) while the infectious foci were unidentifiable in 23.3% of all FN episodes. The most commonly used empirical antibiotics were piperacillin/tazobactam (49.6%), ceftazidime (23.3%), and carbapenems (19.6%). Appropriate antibiotics,

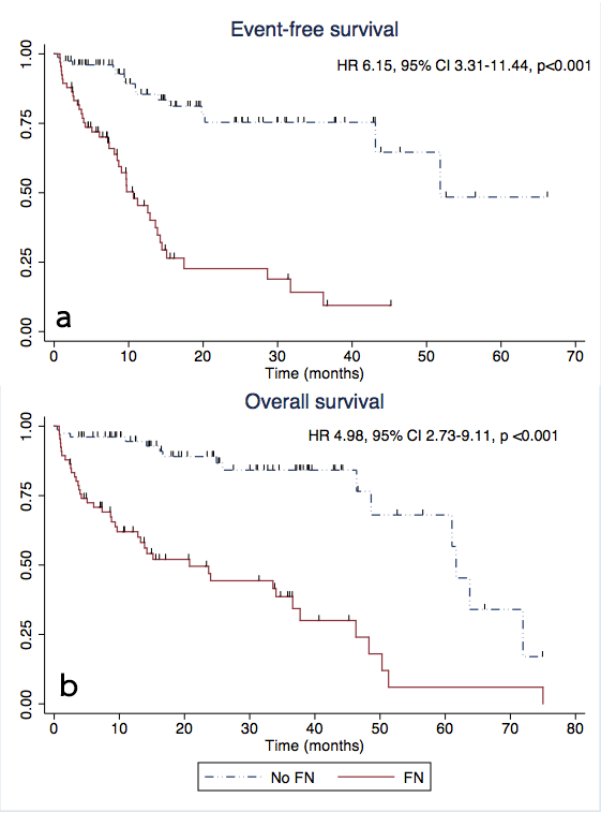

Figure 1. A) Event-free Survival, B) Overall Survival for Patients with and without Febrile Neutropenia Occurrence

Table 3. Comparison of Febrile Neutropenia Incidence and Risk Factors between the Current and Previous Studies

	Hassan et al., 2009.	Chan et al., 2012.	Choi et al., 2014.	This study
Disease	Solid cancers	Breast cancer	Diffuse large B-cell lymphoma	HM
Chemotherapy	Any	Doxorubicin and cyclophosphamide	R-CHOP	Any
Country	Malaysia	Singapore	Korea	Thailand
Study design	Retrospective	Prospective	Prospective	Retrospective
Duration	2003-2006	2007-2010	2004-2013	2008-2013
Febrile neutropenia incidence - %	2.6	13.8	23.8	14.9
Age in year	Median 53 Range 18-93	Median 54 IQR 49-58	Median 57 Range 17-78	Median 54 Range 15-87
Risk factors for neutropenia	No significant risk identified	BMI < 23 kg/m^2	-Female -BM involvement -Comorbid condition”	-First CMT cycle -Hb on CMT day < 100 g/L -Platelet on CMT day < 140,000/uL -AML-type regimen - G-CSF prophylaxis in CHOP (protective)

Abbreviations: AML-acute myeloid leukemia, BM-bone marrow, BMI - body mass index, CHOP-cyclophosphamide-doxorubicin-vincristine-prednisolone, CMT-chemotherapy, G-CSF-granulocyte colony stimulating factor, Hb-hemoglobin, HM-hematologic malignancy, IQR-interquartile range

defined as antibiotics that were active against the causative pathogen and were prescribed at the correct dose and interval, were empirically used in 100 episodes (75.2%). Empirical antibiotics were given later than 120 minutes after diagnosis of FN in 28.6% of the episodes. Etiologic organisms were identifiable in 77 episodes (57.9%). Among the identified organisms, the majority of them were Gram-negative bacteria (52.6%), followed by *Aspergillus* spp. (14.3%), Gram-positive bacteria (9.0%) and *Candida* spp. (8.3%). Therapeutic G-CSF was given in 95 episodes (71.4%). Median neutropenic days and length of stay were 5 days (range 1-63 days) and 12 days (range 1-63 days), respectively. Death occurred in 27 episodes of FN (20.3%).

Febrile Neutropenia and Disease Outcome

The median follow-up time for all HM patients in the study was 16 months (range 0.5-75 months). The median event-free survival time was 51.8 months for patients without FN, and 10.6 months for patients with FN (Cox's proportional hazard ratio 6.2, 95% CI 3.3-11.4, p<0.001). The median overall survival time was 61.7 months for patients without FN occurrence, and 20.8 months for patients with FN (Cox's proportional hazard ratio 5.0, 95% CI 2.7-9.1, p<0.001). The event free survival and overall survival for patients with and without febrile neutropenia are shown in figure 1.

Discussion

The incidence rate of FN in our study was 14.9% in HM patients receiving intensive chemotherapy, which was consistent with the overall rate of FN in HM patients reported in the previous studies (Wolff et al., 2005; Pettengell et al., 2009), while the annual incidence of FN was 24.8 per 1,000 chemotherapy cycles. Independent risk factors associated with FN occurrence in our HM patients included receipt of the first cycle of chemotherapy, having hemoglobin level less than 100 g/L, and platelet less than 140,000/μL on the first day of chemotherapy. Compared to CHOP regimen, AML type regimens significantly increased risk of FN. The use of prophylactic G-CSF was significantly associated with decreased of FN in patients receiving CHOP regimen. The first cycle of chemotherapy posed higher risk for developing FN as reported previously (Crawford et al., 2008). Low hemoglobin status prior to receipt of chemotherapy was previously identified as a risk factor for FN (Salar et al., 2012). Low platelet count on the chemotherapy day has never been reported as a risk factor for FN in HM patients. The low hemoglobin and platelet on chemotherapy day may indicate the inability of patients' marrow to fully recover following chemotherapy, leading to subsequent development of FN. Chemotherapy regimens have different risks for FN depending on the degree of myelosuppression. This study showed that receipt of CVP regimen was associated with lower risk of FN while all AML type regimens (e.g. 7+3 induction, and high dose cytarabine) were associated with higher risk of FN compared to CHOP regimen. The use of salvage lymphoma and ALL treatment regimens were not significantly associated with higher risk of FN. These findings may be due to the small number of patients with ALL or relapsed/refractory lymphoma included in the study. We found that G-CSF use was significantly associated with reduced risk of FN in patients receiving CHOP regimen, but not in those receiving other regimens. These results were consistent with previous reports (Lyman et al., 2011; Salar et al., 2012). We did not identify age more than 60 years as a risk factor for FN as describe in the previous study (Salar et al., 2012). This finding may be explained by the practice of reduction in dose of chemotherapy in elderly HM patients at our institution. In terms of FN incidence and risk factors in Asian population, only few studies were published to date (Hassan et al., 2009; Chan et al., 2012; Choi et al., 2014). Comparison of these studies with the present study is shown in table 3. Overall, risk factors for FN development were related to patients' sex, body mass index, comorbid conditions, baseline bone marrow involvement and function, chemotherapy regimen and co-administration of prophylactic G-CSF.

Our study demonstrated that the patients with FN had a shorter survival time than those without FN, consistent with the results from a large case control study (Lyman et al., 2010). The mortality rate among FN episode was 20.3%, which was similar to previous reports in Thailand (Chayakulkeeree and Thamlikitkul, 2003; Leelayuthachai and Kanitsap, 2010; Roongpoovapatr and Suankratay, 2010). Altogether, these findings suggest the significant impact of FN on the mortality outcomes among HM patients and emphasize early recognition, diagnosis, appropriate treatment and monitoring of FN episodes after intensive chemotherapy.

The strengths of this study include the inclusion of a cohort that all of the patients had received intensive chemotherapy and were at the highest risk of FN. In addition, the study allowed enrollment of patients with multiple episodes of FN and analyzed data using proper statistics. Analysis of risk factors was taking into account both static and dynamic factors throughout every chemotherapy cycle for each patients. Lastly, the median follow-up time was long enough to assess the impact of FN on survival. However, there are notable limitations in this study. First, the study was conducted in a single institutional population, thus results may not be generalizable to other settings with differences in chemotherapy regimens and epidemiology of FN and causative agents. Second, the retrospective design of the study can be associated with information and misclassification biases. Lastly, the enrollment of study population with various HM diagnoses may limit detection of other significant risk factors associated with FN specifically for each HM diagnosis.

In conclusion, this single institution retrospective study demonstrated the incidence of FN and mortality rate among Thai HM patients comparable to previous published studies. Febrile neutropenia remains an important cause of death this population. Patients receiving first cycle of chemotherapy, having hemoglobin less than 100 g/L and platelet less than 140,000/μL on chemotherapy day may require close monitoring for FN occurrence. Prophylactic G-CSF should be used in patients receiving CHOP chemotherapy to prevent FN. Selection

of empirical antibiotic therapy should be based on the local epidemiology of causative pathogens and may need to cover for drug-resistant organisms. Larger prospective studies are needed to assess other risk factors associated with FN and adverse outcomes in HM patients in Thailand and other settings.

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