Original Article

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Quick Response Code:

Website: https://journals.lww.com/ijhm

DOI: 10.4103/ijh.ijh_20_25

The approach of hematologists toward managing neutropenic fever in patients with hematological malignancies: Insights from the Iraqi experience

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Submission: 14-03-2025
Revised: 03-07-2025
Accepted: 21-09-2025
Published: 31-10-2025

Abstract:

BACKGROUND: Febrile neutropenia (FN) is a medical emergency commonly observed in patients undergoing chemotherapy for hematological malignancies, and without timely administration of broad-spectrum antibiotics, infections can quickly worsen within the first few hours of fever onset. Due to the immunosuppressed state of these patients, FN demands immediate evaluation and management to prevent severe complications, including severe illness and death.

OBJECTIVES: The study aimed to evaluate the perspectives and approaches of Iraqi hematologists in treating neutropenic fever in patients with hematological diseases.

MATERIALS AND METHODS: This study is an observational cross-sectional study that included patients with FN while undergoing chemotherapy for various acute and chronic hematological malignancies. The study population was drawn from hematology wards in different centers in Baghdad and Al-Nasiriya, where cases of FN were routinely managed.

RESULTS: The study enrolled 100 patients with FN, with a mean age of 41.53 years (±9.3 years). Among them, 21% had acute lymphoblastic leukemia (ALL), and 26% had acute myeloid leukemia (AML). Regarding empiric antibiotic therapy, 56% of patients were treated with combination antibiotics, while 44% received monotherapy. Infections were most commonly identified in the gastrointestinal tract (34%) and skin (23%), with less frequent involvement of the lungs. In 20% of cases, the infection source remained unidentified despite the presence of bloodstream infections. Cultures of the blood were positive in 25% of patients, while 75% had negative results. No significant association was found between neutrophil count and blood culture positivity or between blood culture results and different underlying hematological diagnoses.

CONCLUSION: Severe neutropenia was closely linked to a higher risk of infection, particularly in patients with AML and ALL. The decision to use mono or combination antibiotic therapy varied based on hematologists' preferences and drug availability. Gastrointestinal and skin infections were the most frequently documented infection sites. These findings underscore the need for improved infection prevention strategies in this vulnerable population.

Keywords:

Attitude and practice, febrile neutropenia, hematological malignancies

Introduction

Febrile neutropenia (FN) is a serious life-threatening complication commonly observed in patients undergoing chemotherapy for hematological malignancies. It is defined as fever, either a single oral temperature of ≥38.3°C or a sustained temperature of ≥38.0°C for more than 1 h, alongside neutropenia, with an absolute neutrophil count below 500 cells/μL or a predicted drop to this

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How to cite this article: Naji AS, Hamodi LE, Alwan AF, Mjali A. The approach of hematologists toward managing neutropenic fever in patients with hematological malignancies: Insights from the Iraqi experience. Iraqi J Hematol 2025;14:243-9.

level.[1] Neutropenia caused by cytotoxic chemotherapy is the leading risk factor for severe bloodstream infections.[2] Managing FN is essential due to the increasing risk of infections in immunocompromised individuals, particularly those with hematologic malignancies such as leukemia, lymphoma, and myeloma.[3] The standard management of FN involves initiating empirical antibiotic therapy promptly, typically within the 1 h of detecting a fever, as treatment delays are associated with significantly worse outcomes.[4] This strategy is founded on the principle that infections in neutropenic patients can rapidly escalate and become life-threatening, even when no clear source of infection is identified.[5] Moreover, the prompt initiation of broad-spectrum antibiotics ensures broad coverage against a wide range of potential pathogens, including both Gram-negative and Gram-positive bacteria, which are frequently responsible for infections in cases of FN.[6] Although guidelines are available, managing FN in clinical practice still remains challenging as adherence to these guidelines varies, with studies showing that many patients with FN do not receive timely or adequate antibiotic treatment.[7] Febrile episodes resulting from chemotherapy-induced neutropenia occur in 10%–50% of patients with solid tumors and more than 80% of those with hematologic malignancies.[8] The risk of bloodstream infections in patients with FN has been reported to range from 11% to 38%.[9] Patients with FN are typically treated with empirical antibiotics until their neutrophil count recovers and the fever resolves. If neutropenia persists, treatment may be prolonged for up to 2 weeks or, in some cases, even longer.[10] The use of mono and combined antibiotics varied in different studies. A prospective study involving patients with bloodstream infections caused by Gram-negative bacilli found that neutropenic patients who received empirical combination therapy with a beta-lactam and an aminoglycoside had reduced mortality in comparison to others.[11] However, a meta-analysis found no significant benefit of combination therapy over beta-lactam monotherapy in neutropenic cancer patients.[12] Monotherapy use in patients with FN that caused by high-risk multidrug-resistant Gram-negative strains leads to increased carbapenem usage and a higher risk of carbapenem resistance, including carbapenem-resistant Enterobacteriaceae, which is linked to an elevated mortality rate.[13] The use of a noncarbapenem beta-lactam combined with an aminoglycoside may serve as a potential treatment option for infections caused by high-risk multidrug-resistant strains of Gram-negative bacilli. The rise of multidrug-resistant organisms (MDROs) has added complexity to the management of FN, as standard empirical treatments may be ineffective against these resistant pathogens, often requiring the implementation of more aggressive or innovative antimicrobial strategies.[14] Moreover, the overuse of antibiotics in low-risk patients raises the chances of preventable side effects and contributes to the growing global issue of antibiotic resistance.[15] This study aimed to assess the perspectives and clinical approaches of Iraqi hematologists in the management of neutropenic fever among patients with hematological malignancies.

Materials and Methods

This study is an observational cross-sectional study that included patients diagnosed with various acute and chronic hematological malignancies from different hematological centers in Baghdad and Al-Nasiriya. The total cohort consisted of 100 individuals diagnosed with the following conditions: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and Non-Hodgkin lymphoma (NHL). The study was reviewed and approved by the scientific committee of the Iraqi Society of Hematology under reference no. 17 dated October 11, 2023. All enrolled patients were given their written informed consent.

Data collection

Data were gathered from clinical records, encompassing demographic information, diagnosis, and timing of neutropenia (whether during induction, consolidation, or chemotherapy cycles for chronic leukemias), neutrophil counts, and infection sites. Diagnoses were classified based on clinical assessments and laboratory results, with case counts recorded for each type of malignancy.

Antibiotic treatment protocols

Patients underwent various treatments with different types of antibiotics, including supportive care. Antibiotic types included both monotherapy (meropenem, vancomycin, and tazobactam) and combination therapy (meropenem with amikacin, tazobactam and amikacin, and meropenem plus vancomycin). Patients received neutropenic fever management as monotherapy or combined antibiotic therapy. Prophylactic measures for infection included antifungal agents.

Infection monitoring

Infection sites were identified through clinical assessment and microbiological culture results. Blood cultures were obtained to determine the presence of infections, with results categorized as positive or negative. The sites of infection were documented, including the gastrointestinal tract, skin, urinary tract, and lungs.

Neutrophil count evaluation

Neutrophil counts were assessed at baseline and throughout treatment. Counts were categorized into three groups: <250, between 250 and 500, and more than 500 cells per microliter.

Statistical analysis

Data were analyzed using appropriate statistical methods. *P* values were calculated to assess the significance of differences across the groups using the independent *t*-test and Chi-square test, with $P < 0.05$ considered statistically significant. Comparisons were made between neutrophil counts, infection rates, and treatment outcomes to identify potential correlations. This methodology provides a comprehensive framework for understanding the patient population, treatment approaches, and clinical outcomes associated with different hematological malignancies.

Results

A total of 100 patients are included in this study. Table 1 presents data on the age and distribution of five types of hematological malignancies. The average age of the patients is 41.53 years, with a standard deviation of 9.3 years. The distribution of diagnoses is as follows: commonly in acute leukemia with lymphoblastic (ALL) accounts for 21% and AML for 26%.

The provided data give an overview of disease status and neutrophil counts in acute leukemia's patients. There is a significant proportion of patients who get neutropenic fever during the early and intensive treatment in the induction phase (66%), others during consolidation (28%) and maintenance (8%) phases. A notable 12% only are in relapse. The majority of patients (66%) have a neutrophil count below 250/µl, indicating a high risk of severe neutropenia [Table 2].

Depending on physician preference, availability, a higher proportion of patients receive combination antibiotic therapy (56%), monotherapy (44%) which is likely chosen in less severe or specific infection cases. Proportion of patients do not receive prophylaxis antifungal prophylaxis (26%) with (74%) received. Voriconazole (29%) is the most common prophylactic agent, possibly due to its broad antifungal spectrum. However, still some physician still advocate use fluconazole (20%) as prophylaxis, especially in those with cases of less intensive therapy of CLL and NHL. The gastrointestinal tract is the most common site of infection, accounting for 34% (in form of diarrhea, abdominal pain, and perianal pain or collection). This highlights the increased vulnerability of the gastrointestinal tract to infections in immunosuppressed patients undergoing chemotherapy. A significant proportion of infections occur in the skin (23%) with possibly from cannula site or catheter-related infection and less frequent site of infection occur in the lung. Still 20% of cases there is no identifiable source of infection with bloodstream infection. Blood culture results were positive in 25% with the majority are negative in 75% [Table 3].

Table 1: Age distribution and frequency of different hematological malignancy in this study

Variables	Count (%)
Age	41.53±9.3
Age groups	
20–29	16 (17)
30–39	34 (33)
40–49	32 (31)
50–59	17 (16)
60 or older	1 (1.0)
Diagnosis	
CML/BC	14 (14)
NHL	19 (19)
CLL	20 (20)
ALL	21 (21)
AML	26 (26)

ALL=Acute lymphoblastic leukemia, AML=Acute myeloid leukemia, CLL=Chronic lymphocytic leukemia, CML=Chronic myeloid leukemia, NHL=Non-Hodgkin lymphoma

Table 2: Disease status and neutrophil counts in patients with acute leukemia presented with neutropenic fever

	Count (%)
Acute leukemia	
Induction	66 (66)
Consolidation	28 (28)
Maintenance	8 (8)
Relapse	12 (12)
Neutrophil count/µL	
More than 500	14 (14)
250–500	20 (20)
<250	66 (66)

Table 3: Empiric antibiotic therapy, prophylaxis, infection sites, and blood culture results

	Count (%)
Type of empiric therapy	
Monotherapy	44 (44)
Combination of antibiotics	56 (56)
Prophylaxis received	
No prophylaxis	26 (26)
Itraconazole and shifted to voriconazole	9 (9)
Voriconazole	25 (25)
Fluconazole	25 (25)
Itraconazole	15 (15)
Site of infection	
Gastrointestinal	34 (34)
Skin	23 (23)
Nonidentifible	20 (20)
lung	17 (17)
Urinary tract	6 (6)
Blood culture	
Positive	25 (25)
Negative	75 (75)

Table 4 presents the bacterial culture results, with *Escherichia coli* (9%) being the most commonly

identified bacterial species, followed by *Pseudomonas aeruginosa* (6%) and *Klebsiella* spp. (4%). The remaining species, such as *Burkholderia*, *Acinetobacter baumannii*, and *Staphylococcus pseudintermedius*, are present in much lower percentages (ranging from 1% to 3%).

A statistically significant association was found between the hematological malignancy type and neutrophil count (P = 0.018). Most patients with AML (84%) and ALL (80%) have severe neutropenia (<250/µl), which aligns with the aggressive nature of these diseases and the impact of intensive chemotherapy on bone marrow suppression. Severity of neutropenia does not significantly influence the site of infection. There is insignificant association between culture result and degree of neutropenia [Table 5].

Table 4: The bacterial species identified from blood culture

Type of bacteria	Count (%)
No growth	75 (75)
Escherichia coli	9 (9)
Pseudomonas aeruginosa	6 (6)
Klebsiella spp.	4 (4)
Burkholderia	3 (3)
Acinetobacter baumannii	2 (2)
Staphylococcus pseudintermedius	1 (1)

Table 6 summarizes the data comparing blood culture results and the type of empiric therapy administered across different hematologic malignancies (ALL, AML, CLL, CML/Blastic Crisis [BC], and NHL) along with their respective P values. The P value for this comparison is 0.734, which is not statistically significant. This suggests that the results of positive or negative blood cultures do not significantly differ among the different hematologic malignancies. Combination antibiotic therapy is more commonly used in ALL (85.7%) and AML (76.9%), while monotherapy is dominant in NHL (78.9%) and notably common in CLL (55%) with P < 0.001. This indicates a statistically significant difference in the selection of empiric therapy among these malignancies, and this could reflect differences in treatment protocols, disease severity, or infection risk profiles between the malignancies.

Table 7 presents data on the distribution of antibiotics (mono vs. combination) that used across different sites of infection. P = 0.146 suggests that

Table 5: Association between different variables and degree of neutrophil count

Variables	Neutrophil count			*P*
	<250 per µL, *n* (%)	250–500 per µL, *n* (%)	500 or more per µL, *n* (%)	
Diagnosis				
CLL	9 (45)	5 (25)	6 (30)	0.018
NHL	10 (53)	5 (26)	4 (21)	
CML/BC	8 (57)	5 (36)	1 (7)	
AML	22 (84)	3 (12)	1 (4)	
ALL	17 (80)	2 (10)	2 (10)	
Site of Infection				
GIT	22 (64)	8 (26)	4 (9)	0.773
Lungs	11 (32)	5 (6)	1 (1)	
Nonidentify	18 (53)	8 (7)	2 (2)	
Skin	11 (48)	10 (44)	2 (8)	
Urinary tract	4 (66)	2 (34)	0	
Blood culture				
Positive	16 (64)	7 (28)	2 (8)	0.85
Negative	50 (66)	13 (18)	12 (16)	

ALL=Acute lymphoblastic leukemia, AML=Acute myeloid leukemia, CLL=Chronic lymphocytic leukemia, CML=Chronic myeloid leukemia, NHL=Non-Hodgkin lymphoma, GIT=Gastrointestinal

Table 6: Association between blood culture results, type of therapy, and different hematological disease

Variables	Diagnosis					*P*
	ALL, *n* (%)	AML, *n* (%)	CLL, *n* (%)	CML/BC, *n* (%)	NHL, *n* (%)	
Blood culture						
Positive	5 (21.3)	7 (23.1)	3 (35)	5 (14.3)	2 (26.3)	0.734
Negative	16 (76.2)	21 (76.9)	17 (65)	9 (85.7)	17 (73.7)	
Type of empiric therapy						
Combination	18 (85.7)	20 (76.9)	9 (45)	10 (71.4)	4 (21.1)	0.000
Monotherapy	3 (14.3)	6 (23.1)	11 (55)	4 (28.6)	15 (78.9)	

ALL=Acute lymphoblastic leukemia, AML=Acute myeloid leukemia, CLL=Chronic lymphocytic leukemia, CML=Chronic myeloid leukemia, NHL=Non-Hodgkin lymphoma

the differences in antibiotic usage across different infection sites are not statistically significant. Combination antibiotics are more frequently used than mono-antibiotics among gastrointestinal, lung, and those with nonidentified site than skin and urinary tract.

Discussion

The presented data provide demographic and diagnostic information about a cohort of patients. The average age of the cohort is 41.53 years with a standard deviation of ±9.3, indicating a relatively young to middle-aged population with the majority of patients (33%) fall into the 30–39 years of age group with younger age is the predominant age range and the minimal representation of older adults which reflect that different biological presentation with AML in our population that is consistent with other Iraqi studies.[16]

Acute leukemias and CML with blast crises are the most frequently observed diagnosis, comprising the majority of the cohort, and this reflects that aggressive treatment with potentially higher rates of neutropenic fever. CLL accounts for 20%, despite its known that less frequently associated with neutropenic fever, however, the majority of the patient in this cohort received treatment with chemoimmunotherapy in form of bendamustine and rituximab. Again NHL contributes 19% of cases, and all of them are high-grade lymphoma treated aggressively by chemotherapy. This finding aligns with several other studies, including one conducted by Mucahit *et al*.[17] In that study, AML accounted for 32% of cases, followed by ALL at 20%.

The elevated incidence of neutropenia in AML patients may be attributed to the expansion of a single clone of white blood cells, which inhibits the proliferation of other white cells, ultimately leading to neutropenia in addition to aggressive treatments in AML and ALL, which is myeloablative, targeting the immune system and further depleting neutrophil levels.[18]

The provided data outline the disease status and neutrophil counts of a cohort of patients, likely receiving treatment for hematological malignancies. The majority of patients (66%) have a neutrophil count below 250/microliter, reflecting severe neutropenia that predisposing patients to life-threatening infections and this aligns with the high proportion of patients in aggressive treatment phases like induction and consolidation. This finding consistent with the work of Xu *et al.* (2018),[19] who emphasized that induction chemotherapy represents a critical phase for neutropenia and heightened infection risk. In contrast, the lower prevalence of neutropenia during the consolidation (28%) and maintenance phases (8%) corresponds with the anticipated improvement in neutrophil recovery as treatment intensity decreases.[19]

The presented data describe the administration of empiric therapy in patients with FN. A significant proportion of patients (44%) received single-agent empiric therapy, while more than half of the cohort (56%) received combination therapy, which aligns with guidelines recommending empiric combination therapy to broaden the antimicrobial spectrum and improve outcomes in FN.[20] Combination regimens are typically used like carbapenems with aminoglycosides or vancomycin with or without antifungal agents such as lipid complex amphotericin, voriconazole, and caspofungin for high-risk patients to cover a broader spectrum of pathogens, including MDROs, or to provide synergistic effects. Other combination of antibiotics such as piperacillin–tazobactam with aminoglycosides.

Those patients with suspected infections due to resistant Gram-negative bacteria, a two-drug regimen may be considered by adding a second Gram-negative antibiotic. However, a meta-analysis of 71 trials carried out between 1983 and 2012 revealed that beta-lactam monotherapy had advantages compared to beta-lactam–aminoglycoside combination therapy. These benefits included better survival rates, fewer adverse events, and a lower risk of fungal superinfections.[12]

A Spanish study found that in febrile neutropenic patients with bacteremia, the combination of beta-lactam and aminoglycoside was linked to lower mortality, with no significant difference in renal dysfunction compared to beta-lactam monotherapy.[21]

A quarter of the patients did not receive any prophylactic antifungal therapy, potentially indicating either low perceived risk of fungal infections like in NHL and CLL or because of logistical barriers. Voriconazole in 29%, the most commonly used prophylactic agent as providing

Table 7: Distribution of antibiotic usage as mono or combined with various infectious sites

Type of antibiotic	Site of infection					*P*
	GIT, *n* (%)	Lungs, *n* (%)	Nonidentify, *n* (%)	Skin, *n* (%)	Urinary tract, *n* (%)	
Mono-antibiotic	9 (26.5)	5 (29.4)	9 (45.0)	12 (52.2)	4 (66.7)	0.146
Combination antibiotic	25 (73.5)	12 (70.6)	11 (55.0)	11 (47.8)	2 (33.3)	
Total	34 (100)	17 (100)	20 (100.0)	23 (100.0)	6 (100.0)	

Pearson Chi-square. GIT=Gastrointestinal

broader *Aspergillus* coverage than itraconazole and fluconazole.

Comparison of itraconazole and fluconazole in Allogeneic Hematopoietic Stem Cell Transplantation (Allo-HSCT) prophylaxis. In Nucci *et al.* study, there is a notable decrease in invasive fungal infection (IFI) incidence.[22] Menichetti *et al*. The study found that there were fewer proven IFIs, lower fungal-related mortality, and comparable overall mortality compared to fluconazole, with no variation in fungal-free survival.[23] The use of itraconazole as prophylaxis is still restricted due to the drug's poor absorption when given in capsules, it is also limited by gastrointestinal side effects when administered as an oral suspension.

Study by Vehreschild *et al*. Lung infiltrates incidence: 0% (voriconazole) versus 33% (placebo) with shorter hospital stay[24] and prophylactic oral voriconazole at 200 mg twice daily showed trends toward a reduced incidence of lung infiltrates and hepatosplenic candidiasis. Study by Marks *et al*. with comparison of voriconazole versus itraconazole in recipients of allo-HSCT with voriconazole demonstrated significantly higher efficacy in prophylaxis compared to itraconazole, in addition a greater number of itraconazole patients required additional systemic antifungals and better tolerance for 100-day prophylaxis voriconazole versus itraconazole and there was no difference in proven or probable IFIs or in 180-day survival.[25]

The most frequent site of infection was the gastrointestinal tract and this likely due to the migration of gut flora into the bloodstream, which is a well-known complication of chemotherapy-induced mucositis, and this highlights the importance of maintaining gut integrity and using prophylactic measures to mitigate infection risks in neutropenic patients. Skin infections, the second most common, may result from central line or peripheral cannula sites, especially for those prolonged hospitalization with AML and ALL or breaches in the integumentary barrier of skin which results in cellulitis. In a considerable number of cases, the site of infection remains unidentified, reflecting the challenges of diagnosing FN, where infections may not be clinically apparent despite significant risks or infection due to nonbacterial cause.

In the current study, 25% of patients had blood cultures positive for pathogens, confirming bloodstream infections which provide critical information for tailoring antimicrobial therapy with predominant Gram-negative infection. Despite clinical signs of infection, 75% of patients had negative blood cultures. This may reflect nonbacterial infections such as viral or fungal infection and preculture antibiotic use, leading to reduced culture yield.

Single-center study in hematological ward in Iraq that 30% of patients had cultures that were positive (from blood, urine, sputum, catheter, or stool) with the respiratory tract the most frequent site of infection was, while 16%. had no obvious focus of infection.[26] Similarly, studies by Hughes *et al*., as well as Lyman and Rolston, found that blood cultures were positive in approximately 20% and 30% of cases, respectively.[27,28]

The prevalence of bacterial pathogens had been shifted from Gram-negative in the 1970s–1980s to Gram-positive in the late 1980s–1990s.[29] This change is attributed to factors such as aggressive treatments causing mucositis, increased intravascular catheter use, and widespread fluoroquinolone prophylaxis and use empirical antibiotic therapy that targeted the Gram-negative organisms in cases of FN.[30] The empiric therapy choices should be tailored as guidelines for empiric antibiotic therapy vary globally, as recommendations may not be universally applicable due to differences in microbial spectrum, resistance patterns, antibiotic availability, and economic. In the current study, still Gram-negative bacteria, including *E. coli*, *P. aeruginosa*, and *Klebsiella* spp., were predominant, and this aligns with prospective observational study at the hematology ward of Baghdad Teaching Hospital found that 62.9% of cases involved Gram-negative microorganisms, while Gram-positive accounted for 30%.[26]

In contrary with retrospective study conducted at a tertiary care hospital in Nablus, Palestine, it was found that 68% of cases with culture-positive were Gram-positive, while 44% were Gram-negative. The most common Gram-positive bacterium was *Enterococcus faecalis* (18%), while *Klebsiella pneumoniae* was the most commonly observed Gram-negative organism.[31] Another retrospective study conducted at the King Abdullah University Hospital revealed that Gram-positive bacteria were the most commonly isolated, with coagulase-negative Staphylococcus being the most common pathogen.[32]

Conclusion

The challenges of treating hematologic malignancies, particularly in the induction phase, with high rates of severe neutropenia that emphasizes the importance of implementing aggressive infection control measures and providing supportive care.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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