

Original Articles**Pathogen Distribution, Antimicrobial Resistance, and Mortality in Febrile Neutropenia among Adults with Hematological Malignancies: A Single-Center Cohort Study**

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Abstract. Background: Febrile neutropenia (FN) remains a major infectious complication in patients with hematological malignancies, and local epidemiological data are essential for guiding management.

Objectives: To characterize the pathogen distribution, antimicrobial resistance profile, and antimicrobial exposures in FN and to evaluate factors associated with 28-day infection-related mortality.

Methods: This retrospective single-center cohort included adults with hematological malignancies who developed FN at a tertiary university hospital between April 2022 and September 2024. The primary cohort comprised 156 patients with 226 classical FN episodes. Patient-level analyses were used for clinical outcomes and multivariable analyses, whereas episode-level analyses were used for microbiological and antimicrobial exposure data.

Results: Among 73 clinically significant isolates, Gram-negative bacteria predominated (76.7%), mainly *Escherichia coli* (45.2%) and *Klebsiella* spp. (24.7%). Meropenem resistance was detected in 6.1% of *E. coli* and 77.8% of *Klebsiella* spp. isolates; ceftazidime-avibactam resistance was 3.0% and 33.3%, respectively. Concurrent resistance to both ciprofloxacin and levofloxacin was detected in 75.8% of *E. coli* and 94.4% of *Klebsiella* spp. isolates. No MRSA was recovered, while glycopeptides were administered in 38.9% of classical FN episodes. Infection-related mortality was 10.3% and 28-day all-cause mortality was 12.8%. No variable was significantly associated with infection-related mortality in the exploratory multivariable analysis.

Conclusions: Gram-negative pathogens predominated, with substantial meropenem resistance among *Klebsiella* spp. Continuous local resistance surveillance and antimicrobial stewardship are essential. Larger multicenter studies are needed to better define factors associated with infection-related mortality.

Keywords: Febrile neutropenia; Hematological malignancies; Antimicrobial resistance; Gram-negative bacteria; Infection-related mortality.

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Introduction. Immune deficiency arising from chemotherapy-induced neutropenia or hematopoietic cell transplantation (HCT) renders patients with hematological malignancies highly susceptible to severe and life-threatening infections. Febrile neutropenia (FN) is among the most frequent oncological emergencies in this setting; clinically documented infection develops in 20-25% of episodes and bacteremia in 10-25%, with the great majority of these complications arising in the context of prolonged (>7 days) or deep (absolute neutrophil count <100 cells/mm³) neutropenia. In-hospital mortality may reach 10-30% in high-risk patient groups.^{1,2} Because the inflammatory response is blunted in neutropenic individuals, infections frequently present with subtle or delayed clinical findings, and in some cases fever may be the sole manifestation of underlying infection.¹

According to the framework established by the Infectious Diseases Society of America (IDSA) and the European Organisation for Research and Treatment of Cancer (EORTC), FN episodes are classified into three clinical categories: microbiologically documented infection (MDI; ~20-25%), clinically documented infection (CDI; ~20-25%), and fever of unknown origin (FUO; ~45-50%).^{1,3} The Multinational Association for Supportive Care in Cancer (MASCC) score and the Clinical Index of Stable Febrile Neutropenia (CISNE) are widely used for risk stratification, although patients with hematological malignancies, prolonged neutropenia, or recent hospitalization are generally considered high-risk.^{4,5}

The spectrum of causative pathogens has shifted substantially over the past decades. In the 1980s, Gram-negative bacilli, particularly *Pseudomonas aeruginosa*, predominated; however, the widespread use of central venous catheters, the rising incidence of mucositis, and the routine adoption of antipseudomonal empirical regimens led to the re-emergence of Gram-positive bacteria from the 1990s onward.⁶⁻⁸ Since the 2000s, the global spread of multidrug-resistant (MDR) Gram-negative strains has once again placed Gram-negative bacilli at the forefront of clinical concern in patients with hematological malignancies.⁹⁻¹² Carbapenem-resistant *Enterobacteriales* (CRE), carbapenem-resistant *P. aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) have emerged as pathogens with a particularly adverse impact on clinical outcomes in this population.^{9,10} Among Gram-positive organisms, methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant viridans streptococci, and vancomycin-resistant enterococci continue to complicate antimicrobial selection.^{6,13,14} Invasive fungal disease remains an important cause of mortality in patients with

prolonged neutropenia and is currently evaluated within the framework of the EORTC and Mycoses Study Group Education and Research Consortium (MSGERC) 2020 consensus criteria.¹⁵

In high-risk FN episodes, empirical antibacterial therapy is tailored to the patient's clinical condition, prior colonization patterns, recent antimicrobial exposure, and local resistance profiles.^{13,16} The optimal duration of empirical therapy and the role of de-escalation remain a matter of debate within the framework of antimicrobial stewardship; the "How Long" trial provided evidence that empirical therapy can be safely discontinued after 72 hours in afebrile, clinically stable high-risk patients.¹⁷

Comprehensive and contemporary data simultaneously addressing the microbiological spectrum, antimicrobial resistance patterns, and mortality in FN episodes among adult patients with hematological malignancies in Türkiye remain limited. The primary objective of the present study was to evaluate clinical and laboratory factors associated with 28-day infection-related mortality in the patient-level cohort. The secondary objectives were to characterize episode-level pathogen distribution, antimicrobial resistance patterns, antimicrobial treatment exposure, and the frequency of clinically suspected IPA and other documented fungal infections.

Materials and Methods

Study Design and Setting. This is a single-center, retrospective cohort study evaluating FN episodes that developed in adult patients hospitalized with hematological malignancies at Necmettin Erbakan University Faculty of Medicine Hospital. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.¹⁸ Data were extracted from electronic medical records maintained between April 2022 and September 2024.

Study Population. The cohort was defined by the coexistence of two mandatory criteria: a confirmed diagnosis of a hematological malignancy, and at least one documented FN episode occurring during a hospitalization within the study period. FN was defined as a single oral temperature measurement of ≥ 38.3 °C or a sustained temperature of ≥ 38.0 °C for at least one hour, together with an absolute neutrophil count (ANC) <500 cells/mm³ or an expected decline below this threshold within the following 48 hours.¹ Adult patients (≥ 18 years of age) meeting both criteria were consecutively included. FN episodes related to solid organ malignancies, patients with missing fever or laboratory data, and individuals aged <18 years were excluded.

Episodes that did not meet the conventional definition of febrile neutropenia were excluded from the primary FN cohort. These episodes occurred in patients with acute leukemia or myelodysplastic syndrome with marrow blast predominance who had an ANC ≥ 500 cells/mm³ at fever onset and did not otherwise fulfill the conventional ANC criterion for FN. Although these episodes were clinically managed as neutropenic infections because the circulating neutrophil count was considered unlikely to reflect effective neutrophil function, they were excluded from the primary analysis and included only in a sensitivity analysis.

When the same patient experienced more than one FN episode during separate hospitalizations, each episode was recorded individually. Reflecting the dual nature of the clinical question, analyses were conducted at two complementary levels:

Patient-level analyses (n=156) included only each patient's first qualifying classical FN episode (the index episode) and were used to evaluate demographic and clinical characteristics, laboratory findings, disease-category grouping, mortality outcomes, and multivariable regression analyses.

Episode-level analyses (n=226) included all classical FN episodes and were used to describe causative pathogens, antimicrobial resistance patterns, and antimicrobial treatment exposure, as these are inherently episode-level phenomena. Total antimicrobial treatment duration was reported at both analytic levels for comparability. Figure 1 illustrates the overall study flow, including the exclusion of episodes that did not meet the conventional FN definition and the disease-category grouping framework.

For descriptive and analytical purposes, patients were categorized into two diagnosis-based disease groups according to their underlying hematological malignancy. The acute leukemia/MDS group included patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and myelodysplastic syndrome (MDS). In contrast, the other hematological malignancies group included patients with Hodgkin lymphoma, diffuse large B-cell lymphoma, other non-Hodgkin lymphomas, chronic lymphocytic leukemia (CLL), multiple myeloma, and myeloproliferative neoplasms. This grouping was used solely as a disease-category classification for descriptive comparisons and analytical adjustment and was not intended to represent a validated prognostic or FN risk stratification system. Because detailed MDS-specific prognostic data were not consistently available, no assumption was made that all patients with MDS had high-risk MDS; however, all MDS patients were treated with aggressive chemotherapy, AML-like, which mostly influences the degree of neutropenia.¹⁹

Baseline clinical characteristics, laboratory findings, infection classification, clinically suspected IPA, and mortality outcomes were compared between the two

disease groups, and the association between disease group and 28-day infection-related mortality was formally examined in the regression analysis.

Operational Definitions. FN episodes were classified, according to the IDSA and EORTC frameworks, as microbiologically documented infection (MDI; significant pathogen isolation from a sterile body fluid or an infected focus), clinically documented infection (CDI; a clinical and/or radiological focus of infection in the absence of microbiological confirmation), and fever of unknown origin (FUO; an episode in which no infectious focus or causative pathogen could be identified despite appropriate evaluation).^{1,3}

Clinically suspected invasive pulmonary aspergillosis (IPA) was identified based on clinical assessment together with compatible high-resolution chest computed tomography (HRCT) findings, including nodules, halo sign, air-crescent sign, or cavitation. Although serum galactomannan testing is routinely performed at our center, the results were not systematically recorded in the study dataset. Consequently, cases could not be formally classified as proven, probable, or possible invasive fungal disease according to the 2020 EORTC/MSGERC consensus definitions.¹⁵ The beta-D-glucan assay is not available at our institution.

Data Collection. For each FN episode, the following data were retrieved: demographic characteristics (age, sex, primary hematological diagnosis, chemotherapy or transplantation status); baseline laboratory parameters at the onset of fever (white blood cell count, ANC, absolute lymphocyte count, platelet count, C-reactive protein [CRP], and procalcitonin [PCT]); duration of neutropenia; clinical sites of infection; culture and antimicrobial susceptibility results; and administered antimicrobial regimens along with their durations.

Posaconazole was the primary agent used for antifungal prophylaxis. *Pneumocystis jirovecii* prophylaxis and cytomegalovirus (CMV) monitoring were not systematically documented in the dataset and were therefore not included in the analyses.

Antibacterial prophylaxis was considered documented only when a specific prophylactic agent was identifiable in the medical records; episodes without a documented prophylactic regimen included both those in which prophylaxis was not prescribed and those for which prophylaxis information was unavailable.

For each patient, the number of separate FN episodes during the study period was also recorded.

Microbiological Investigations. Blood cultures were incubated in the automated BACTEC continuous monitoring system (Becton Dickinson, Sparks, MD, USA), and species identification was performed using matrix-assisted laser desorption ionization-time-of-flight

mass spectrometry (MALDI-TOF MS). Antimicrobial susceptibility testing and breakpoint interpretation were performed in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint versions in force during the study period. Because not all antimicrobial agents were tested against every isolate, resistance rates for each organism-antimicrobial combination were calculated using the number of isolates tested for that specific antimicrobial agent as the denominator. Extended-spectrum β -lactamase (ESBL) production was confirmed phenotypically; molecular characterization of carbapenemase production (e.g., KPC, NDM, OXA-48) was not performed, and carbapenem resistance was therefore reported solely at the phenotypic level.

Microbiological isolates were considered clinically significant when, based on the clinical presentation, presumed site of infection, and available microbiological findings, they were judged to represent true infection rather than colonization or contamination. Culture results considered to reflect contamination were excluded from the microbiological analyses.

Outcome Variables and Adjudication. The primary outcome was 28-day infection-related mortality, measured from the onset of the FN episode. Infection-related mortality was defined as death occurring during the FN episode or within 28 days of its onset, when active infection was considered the direct cause of death or a major contributing factor.

Infection-related mortality was adjudicated retrospectively through joint review of the complete medical records by a senior hematologist and a senior infectious diseases specialist, each with more than 10 years of clinical experience in the care of patients with hematological malignancies. Adjudication was based on predefined criteria: (i) death occurring during the FN episode or within 28 days of its onset; (ii) evidence of active infection at the time of death, supported by findings such as persistent fever, hemodynamic instability, positive microbiological cultures, radiological findings consistent with infection, or rising inflammatory markers; and (iii) clinical judgment that infection was either the direct cause of death or a major contributing factor, in the absence of a competing dominant cause such as disease progression, hemorrhage, or unrelated organ failure. Reviewers had access to complete medical records, including laboratory and radiological findings. They were therefore not formally blinded to candidate mortality predictors, representing a potential source of adjudication bias that is acknowledged in the Limitations. Discrepancies between the two reviewers were resolved through joint discussion and consensus; no case required arbitration by a third reviewer. Formal inter-rater agreement (Cohen's kappa) was not prospectively calculated.

As a less subjective secondary outcome, 28-day all-cause mortality was also assessed, defined as death from any cause within 28 days of FN onset.

Secondary outcomes included causative pathogen distribution, antimicrobial resistance patterns, antimicrobial treatment exposure, clinically suspected IPA, and other documented fungal infections.

Statistical Analysis. All analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for distribution and summarized as median with interquartile range (IQR); mean $\pm$ standard deviation was additionally provided for descriptive purposes where appropriate. Categorical variables were expressed as counts and percentages. Comparisons between two independent groups were performed using the Mann-Whitney U test. Associations between categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate.

To explore factors associated with 28-day infection-related mortality, univariable logistic regression analyses were performed for candidate variables in the patient-level cohort (n=156). Variables with $p < 0.10$ in univariable analyses, together with disease group as a clinically relevant covariate, were entered into the multivariable logistic regression model. Given the limited number of infection-related deaths, the multivariable analysis was considered exploratory. Multicollinearity was assessed using the variance inflation factor (VIF), with a VIF > 5 considered indicative of substantial collinearity. Missing values were handled using a complete-case approach for the primary analysis. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Two sensitivity analyses were performed to evaluate the robustness of the findings from the primary multivariable analysis. First, an univariable logistic regression analysis was performed in the acute leukemia/MDS group (n=81; 10 infection-related deaths); a multivariable model was not fitted because of the limited number of outcome events. Second, the multivariable analysis was repeated in the full cohort of 169 patients, including the 13 patients whose index episode did not meet the conventional FN definition. Because of the limited number of outcome events, these analyses were considered exploratory and were interpreted primarily on the basis of effect estimates and confidence intervals rather than statistical significance alone.

Statistical significance was assessed using a two-sided α of 0.05.

Ethics Approval. The study protocol was approved by the Clinical Research Ethics Committee for Non-Drug and Non-Medical Device Research of Necmettin Erbakan

University Faculty of Medicine (Approval No: 2026/6653). Because of the retrospective design, written informed consent was waived. All research procedures were conducted in accordance with the Declaration of Helsinki.

Results

Study Cohort Overview. A total of 169 adult patients with hematological malignancies, with 239 episodes initially recorded and managed as FN during the study period,

were identified (**Figure 1**). Thirteen episodes in 13 patients did not meet the conventional FN definition because the ANC was ≥ 500 cells/mm³ at fever onset and were excluded from the primary analysis. The primary cohort therefore comprised 156 patients with 226 classical FN episodes.

Analyses were conducted at two complementary levels. Patient-level analyses (n=156), based on each patient's first qualifying classical FN episode (index episode), were used for the primary evaluation of clinical characteristics, disease-category grouping, mortality

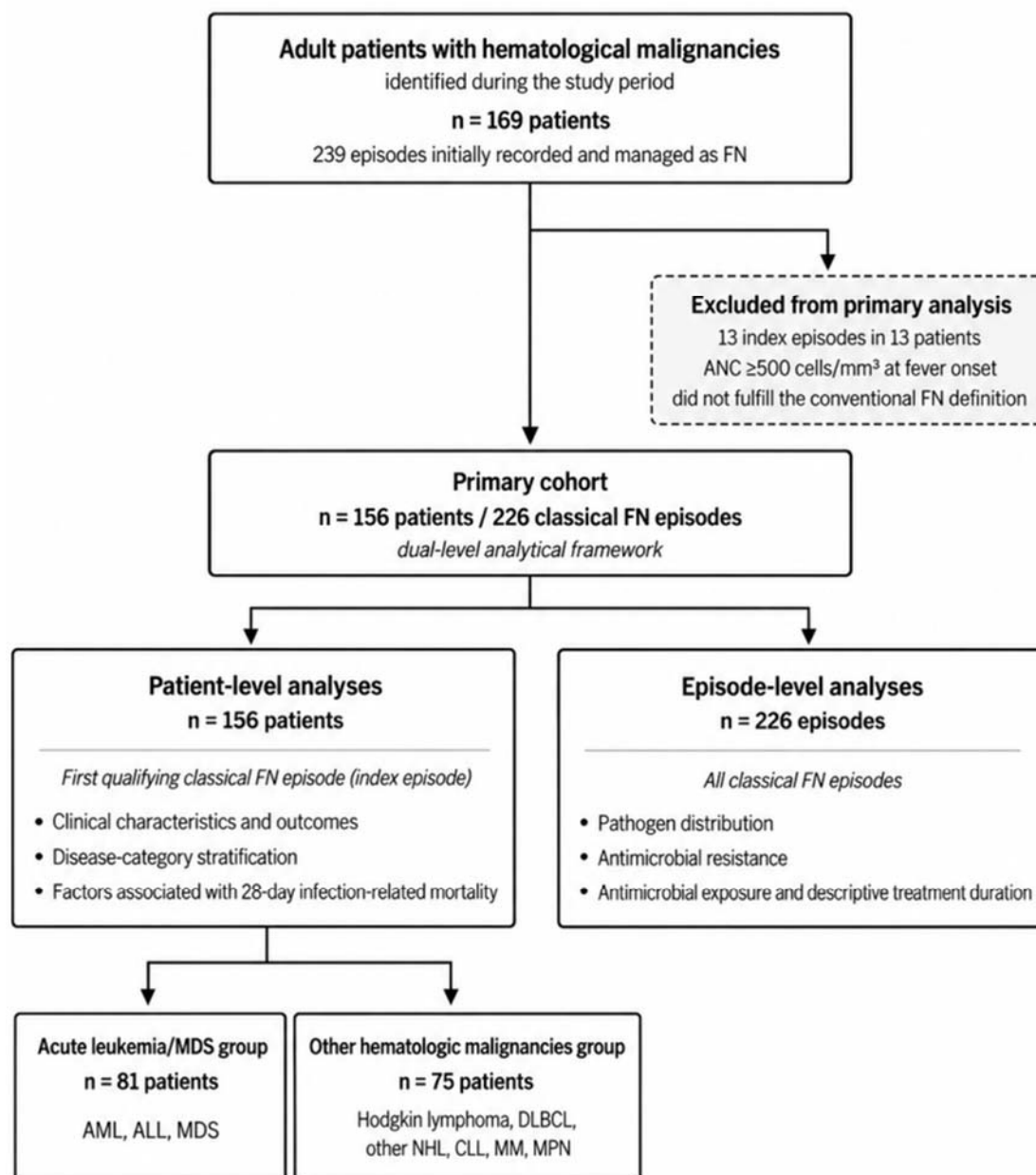


Figure 1. Study flow diagram. A total of 239 episodes initially recorded and managed as FN were identified in 169 adult patients with hematological malignancies. Thirteen index episodes in 13 patients did not fulfill the conventional neutrophil-count criterion for FN and were excluded from the primary analysis. The resulting primary cohort comprised 156 patients with 226 classical FN episodes. Patient-level analyses (n=156) were based on each patient's first qualifying classical FN episode (index episode), whereas episode-level analyses (n=226) included all classical FN episodes. Patient-level analyses were further categorized into the acute leukemia/MDS group (n=81) and the other hematological malignancies group (n=75).

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FN, febrile neutropenia; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPN, myeloproliferative neoplasm; NHL, non-Hodgkin lymphoma.

Table 1. Baseline demographic and clinical characteristics of the study cohort.

Characteristic	All patients (n=169)	Primary cohort (n=156)
Age (years), mean $\pm$ SD	57.72 $\pm$ 16.41	57.24 $\pm$ 16.62
Sex, n (%)		
Female	76 (45.0)	69 (44.2)
Male	93 (55.0)	87 (55.8)
Primary hematological diagnosis, n (%)		
Acute myeloid leukemia (AML)	59 (34.9)	50 (32.1)
Myelodysplastic syndrome (MDS)	25 (14.8)	25 (16.0)
Acute lymphoblastic leukemia (ALL)	9 (5.3)	7 (4.5)
Hodgkin lymphoma	4 (2.4)	4 (2.6)
Diffuse large B-cell lymphoma (DLBCL)	12 (7.1)	12 (7.7)
Non-Hodgkin lymphoma (excluding DLBCL)	27 (16.0)	27 (17.3)
Chronic lymphocytic leukemia (CLL)	6 (3.6)	6 (3.8)
Multiple myeloma (MM)	25 (14.8)	25 (16.0)
Myeloproliferative neoplasm (MPN)	2 (1.2)	1 (0.6)
Disease group, n (%)		
Acute leukemia/MDS group	93 (55.0)	81 (51.9)
Other hematological malignancies group	76 (45.0)	75 (48.1)

SD, standard deviation; ANC, absolute neutrophil count. The acute leukemia/MDS group included patients with AML, ALL, and MDS; the other hematological malignancies group included patients with Hodgkin lymphoma, DLBCL, other non-Hodgkin lymphomas, CLL, MM, and myeloproliferative neoplasms. Thirteen patients whose index episode did not meet the conventional FN definition because the ANC was ≥ 500 cells/mm³ at fever onset were excluded from the primary analytic cohort (see **Figure 1**).

outcomes, and multivariable analyses. Episode-level analyses (n=226) included all classical FN episodes and were used to describe pathogen distribution, antimicrobial resistance patterns, and antimicrobial exposure.

Of the 156 patients in the primary cohort, 114 (73.0%) had a single classical FN episode, 26 (16.7%) had two episodes, and 16 (10.3%) had three or more episodes.

Patient Characteristics. Baseline demographic and clinical characteristics of both the initial cohort (n=169) and the primary analytic cohort (n=156) are summarized **Table 2**. Clinical and laboratory features of classical FN episodes (n=226)

Characteristic	n (%) / Median (Q1-Q3)
Laboratory findings	

Neutrophil count ($\times 10^3/\mu\text{L}$)	0.07 (0.02-0.27)
Lymphocyte count ($\times 10^3/\mu\text{L}$)	0.23 (0.09-0.51)
Platelet count ($\times 10^3/\mu\text{L}$)	32 (16-72)
CRP (mg/L)	159 (95-252)
PCT (ng/mL)	0.49 (0.15-4.79)
Duration of neutropenia (days), n=159	7 (3-13)
Infection classification	
Clinically documented infection	66 (29.2)
Microbiologically documented infection	59 (26.1)
Fever of unknown origin	101 (44.7)
Focus of clinical infection (n=66)	
Pneumonia	23 (34.8)
Skin and soft tissue infection	19 (28.8)
COVID-19	9 (13.6)
Intra-abdominal infection	8 (12.1)
Upper respiratory tract infection	7 (10.6)
Concomitant invasive fungal or viral infections*	
Clinically suspected invasive pulmonary aspergillosis	18 (8.0)
Candidemia	3 (1.3)
CMV infection	2 (0.9)
Concomitant SARS-CoV-2 infection**	6 (2.7)
Antibacterial prophylaxis	
Moxifloxacin	54 (23.9)
Levofloxacin	12 (5.3)
Ciprofloxacin	1 (0.4)
No documented antibacterial prophylaxis***	159 (70.4)

CMV, cytomegalovirus; CRP, C-reactive protein; PCT, procalcitonin; Q1, first quartile; Q3, third quartile. *: Beyond the primary FN etiology. **: SARS-CoV-2 infection identified during or after the FN episode; excludes 9 episodes in which COVID-19 was the primary clinical focus (listed under "Focus of clinical infection"). *** "No documented antibacterial prophylaxis" includes episodes in which prophylaxis was not prescribed as well as those for which prophylaxis information was unavailable in the medical records.

in **Table 1**. Acute myeloid leukemia was the most common primary hematological diagnosis. In the primary cohort, 81 patients (51.9%) were classified in the acute leukemia/MDS group according to the disease-category grouping. This group includes patients who were all treated with aggressive chemotherapy, which mostly influences the degree of neutropenia.

Clinical and Laboratory Features of Classical FN Episodes. Baseline laboratory findings, infection classification, clinical foci of infection, concomitant fungal and viral infections, and antibacterial prophylaxis for the 226 classical FN episodes are summarized in

Table 3. Distribution of clinically significant microorganisms isolated in culture-positive classical FN episodes, by culture source.

Microorganism	Blood culture (n=46), n (%)	Urine culture (n=21), n (%)	Other cultures* (n=3), n (%)
<i>Escherichia coli</i>	20 (43.5)	13 (61.9)	0
<i>Klebsiella</i> spp.	13 (28.3)	3 (14.3)	2 (66.7)
<i>Pseudomonas</i> spp.	0	0	0
<i>Acinetobacter</i> spp.	3 (6.5)	1 (4.8)	0
Coagulase-negative staphylococci	3 (6.5)	0	0
MSSA	3 (6.5)	0	0
MRSA	0	0	0
<i>Enterococcus faecalis</i>	3 (6.5)	0	0
<i>Enterococcus faecium</i>	1 (2.2)	3 (14.3)	0
<i>Enterococcus</i> , species not specified	0	0	1 (33.3)
Other <i>Enterobacteriales</i>	0	1 (4.8)	0
<i>Candida</i> spp.**	3 (6.5)	0	0

Column denominators represent the number of episodes with a positive culture from the respective source. Because some episodes had positive cultures from more than one source and/or yielded more than one clinically significant organism, culture-source categories and isolate counts are not mutually exclusive. A total of 73 clinically significant isolates were recovered from 58 culture-positive episodes. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*. *: Other cultures include bronchoalveolar lavage, abscess, and catheter cultures. **: Two *Candida* isolates were identified as *Candida krusei* and one as *Candida parapsilosis*.

Table 2. Fever of unknown origin was the most frequent infection classification (44.7%), while pneumonia and skin and soft tissue infections were the most common clinically documented foci. Nine episodes (13.6% of clinically documented infections) had COVID-19 as the primary clinical focus at FN onset, while an additional six episodes (2.7%) had concomitant SARS-CoV-2 infection identified during or after FN onset. Clinically suspected IPA was identified in 18 episodes (8.0%), while candidemia and CMV infection were identified in 3 (1.3%) and 2 (0.9%) episodes, respectively.

Fluoroquinolone-based antibacterial prophylaxis (moxifloxacin, levofloxacin, or ciprofloxacin) was documented in 67 episodes (29.6%). No specific antibacterial prophylactic regimen was documented in the remaining 159 episodes (70.4%); this category included both episodes in which prophylaxis was not prescribed and those for which prophylaxis information was unavailable in the medical records.

Neutropenia duration was available for 159 of the 226 classical FN episodes. No statistically significant differences were observed in age, sex distribution, disease group, infection classification, clinically suspected IPA, or fungal infection between episodes with and without documented neutropenia duration (**Supplementary Table S1**).

Microbiological Findings. At least one clinically significant positive culture was identified in 58 of the 226 classical FN episodes (25.7%). Among these 58 culture-positive episodes, blood cultures were positive in 46 (79.3%), urine cultures in 21 (36.2%), and other cultures in 3 (5.2%); more than one culture source could

be positive within the same episode. Overall, 73 clinically significant isolates were recovered. Gram-negative bacteria accounted for 56 of the 73 isolates (76.7%), with *Escherichia coli* (33/73, 45.2%) and *Klebsiella* spp. (18/73, 24.7%) being the most frequently identified pathogens. No *Pseudomonas* spp. or MRSA were identified. Three *Candida* isolates were recovered, all from blood cultures. The distribution of clinically significant isolates according to culture source is shown in **Table 3**.

Antimicrobial Resistance Patterns. Antimicrobial resistance profiles are summarized in Table 4. Among *E. coli* isolates, resistance to ceftriaxone was observed in 18/33 (54.5%), to piperacillin-tazobactam in 8/33 (24.2%), to meropenem in 2/33 (6.1%), and to ceftazidime-avibactam in 1/33 (3.0%). Among *Klebsiella* spp. isolates, the corresponding resistance rates were 15/18 (83.3%), 14/18 (77.8%), 14/18 (77.8%), and 6/18 (33.3%), respectively. Concurrent resistance to ciprofloxacin and levofloxacin was detected in 25/33 (75.8%) *E. coli* and 17/18 (94.4%) *Klebsiella* spp. isolates. All three *Candida* isolates were fluconazole-resistant (**Table 4**). No MRSA was recovered, and no vancomycin resistance was detected among the Gram-positive isolates tested for vancomycin.

Antimicrobial Treatment and Treatment Duration. Antimicrobial agents administered during the 226 classical FN episodes are summarized in **Table 5**. Meropenem and piperacillin-tazobactam were administered in 158 (69.9%) and 123 (54.4%) episodes, respectively. Glycopeptides were administered in 88 of

Table 4. Antimicrobial resistance profiles of isolated microorganisms.

Antimicrobial agent	<i>E. coli</i> (n=33)	<i>Klebsiella</i> spp. (n=18)	<i>Acinetobacter</i> spp. (n=4)	CoNS (n=3)	MSSA (n=3)	<i>E. faecalis</i> (n=3)	<i>E. faecium</i> (n=4)	<i>Candida</i> spp. (n=3)
Ampicillin	—	—	—	—	—	0/2 (0.0)	1/1 (100.0)	—
Oxacillin	—	—	—	1/1 (100.0)	0/3 (0.0)	—	—	—
Ceftriaxone	18/33 (54.5)	15/18 (83.3)	1/1 (100.0)	—	—	—	—	—
Piperacillin-tazobactam	8/33 (24.2)	14/18 (77.8)	0/1 (0.0)	—	—	—	—	—
Meropenem	2/33 (6.1)	14/18 (77.8)	0/1 (0.0)	—	—	—	—	—
Amikacin	1/33 (3.0)	9/18 (50.0)	0/1 (0.0)	—	—	—	—	—
Fluoroquinolones*	25/33 (75.8)	17/18 (94.4)	0/1 (0.0)	1/1 (100.0)	0/1 (0.0)	2/2 (100.0)	3/3 (100.0)	—
Tigecycline	1/33 (3.0)	1/18 (5.6)	0/1 (0.0)	—	—	0/1 (0.0)	1/2 (50.0)	—
Colistin	0/33 (0.0)	1/18 (5.6)	0/1 (0.0)	—	—	—	—	—
Ceftazidime-avibactam	1/33 (3.0)	6/18 (33.3)	0/1 (0.0)	—	—	—	—	—
Vancomycin	—	—	—	0/1 (0.0)	0/3 (0.0)	0/2 (0.0)	0/1 (0.0)	—
Fluconazole	—	—	—	—	—	—	—	3/3 (100.0)

CoNS, coagulase-negative staphylococci; MSSA, methicillin-susceptible *Staphylococcus aureus*. Values are expressed as number of resistant isolates / number of isolates tested (%). Not all antimicrobial agents were tested against every isolate; therefore, denominators vary across organism-antimicrobial combinations. *: Fluoroquinolone resistance was defined as shared resistance to both ciprofloxacin and levofloxacin.

Table 5. Antimicrobial treatment agents used in classical FN and total treatment duration.

Part A. Antimicrobial agents administered during classical FN episodes (n=226)	
Antimicrobial agent	Episodes, n (%)
β-lactam antibiotics	
Meropenem	158 (69.9)
Piperacillin-tazobactam	123 (54.4)
Ceftriaxone	1 (0.4)
Glycopeptides and other Gram-positive agents	
Teicoplanin	77 (34.1)
Vancomycin	11 (4.9)
Linezolid	4 (1.8)
Fluoroquinolones	20 (8.8)
Aminoglycosides	
Amikacin	6 (2.7)
Agents used for resistant Gram-negative infections	
Tigecycline	25 (11.1)
Polymyxin B	16 (7.1)
Colistin	8 (3.5)
Ceftazidime-avibactam	5 (2.2)
Fosfomycin	5 (2.2)
Other antibacterial agents	
Metronidazole	15 (6.6)
Trimethoprim-sulfamethoxazole	4 (1.8)
Antifungal agents	
Caspofungin	28 (12.4)

Amphotericin B	18 (8.0)
Voriconazole	11 (4.9)
Posaconazole	3 (1.3)
Antiviral agents	
Oseltamivir	6 (2.7)
Ganciclovir	1 (0.4)
Part B. Total duration of antimicrobial therapy	
Episode-level (n=226)	13 (10-17)
Patient-level, index episode (n=156)	12.5 (10-16)

More than one antimicrobial agent could be administered during the same FN episode; therefore, percentages are not mutually exclusive and their sum exceeds 100%.

226 episodes (38.9%), including teicoplanin in 77 episodes and vancomycin in 11 episodes. Tigecycline, polymyxin B, colistin, ceftazidime-avibactam, and fosfomycin were administered in 11.1%, 7.1%, 3.5%, 2.2%, and 2.2% of episodes, respectively. Antifungal agents included caspofungin (12.4%), amphotericin B (8.0%), voriconazole (4.9%), and posaconazole (1.3%). The median total duration of antimicrobial therapy was 13 days at the episode level (IQR, 10-17 days) and 12.5 days at the patient-level index episode (IQR, 10-16 days).

Patient-Level Outcomes. In the patient-level cohort of 156 patients, clinically suspected IPA was identified in 8 patients (5.1%). The 28-day infection-related mortality rate was 10.3% (16/156), and the 28-day all-cause mortality rate was 12.8% (20/156).

Table 6. Clinical characteristics and outcomes according to disease group in the patient-level cohort (n=156).

Characteristic	Acute leukemia/MDS group (n=81), n (%)	Other hematological malignancies group (n=75), n (%)	p
Sex			
Female	42 (51.9)	27 (36.0)	0.046 ^a
Male	39 (48.1)	48 (64.0)	
Infection classification			
Clinically documented infection	19 (23.5)	28 (37.3)	0.139 ^a
Microbiologically documented infection	22 (27.2)	14 (18.7)	
Fever of unknown origin	40 (49.4)	33 (44.0)	
Clinically suspected IPA	7 (8.6)	1 (1.3)	0.065 ^b
Infection-related mortality	10 (12.3)	6 (8.0)	0.371 ^a
28-day all-cause mortality	12 (14.8)	8 (10.7)	0.439 ^a
	Median (Q1-Q3)	Median (Q1-Q3)	
Age (years)	62 (44-71)	61 (50.5-66.5)	0.862 ^c
Neutrophil count ($\times 10^3/\mu\text{L}$)	0.07 (0.02-0.34)	0.12 (0.02-0.30)	0.696 ^c
Lymphocyte count ($\times 10^3/\mu\text{L}$)	0.36 (0.13-0.79)	0.21 (0.06-0.37)	0.003^c
Platelet count ($\times 10^3/\mu\text{L}$)	26 (16.5-51.5)	62 (23.5-111)	<0.001^c
CRP (mg/L)	153 (89.5-222)	163 (108-280)	0.339 ^c
PCT (ng/mL)	0.54 (0.19-5.52)	0.40 (0.13-5.17)	0.393 ^c
Duration of neutropenia (days)*	8 (4-21) (n=60)	3.5 (2-8) (n=50)	<0.001^c

Bold p values indicate statistical significance ($p < 0.05$). *Neutropenia duration was available for 60 patients in the acute leukemia and MDS group and 50 patients in the other hematological malignancies group. CRP, C-reactive protein; PCT, procalcitonin; IPA, invasive pulmonary aspergillosis. ^a Pearson chi-square test. ^b Fisher's exact test. ^c Mann-Whitney U test.

Outcomes According to Disease Group. Clinical characteristics and outcomes according to disease group are summarized in **Table 6**. Female sex was more frequent in the acute leukemia/MDS group than in the other hematological malignancies group (51.9% vs 36.0%; $p = 0.046$). Compared with the other hematological malignancies group, patients in the acute leukemia/MDS group had lower baseline platelet counts (median, 26 vs 62 $\times 10^3/\mu\text{L}$; $p < 0.001$), higher absolute lymphocyte counts (median, 0.36 vs 0.21 $\times 10^3/\mu\text{L}$; $p = 0.003$), and longer neutropenia duration (median, 8 vs 3.5 days; $p < 0.001$). No statistically significant differences were observed between the disease groups in infection classification, clinically suspected IPA, 28-day infection-related mortality, or 28-day all-cause mortality.

Factors Associated with Infection-Related Mortality. **Table 8** presents univariable and multivariable logistic regression analyses of factors associated with 28-day infection-related mortality, while **Table 7** summarizes categorical characteristics by mortality status. In univariable logistic regression, female sex (OR=3.110, 95% CI 1.026-9.432; $p = 0.045$) and lower baseline platelet count (OR=0.978 per 1 $\times 10^3/\mu\text{L}$ increase, 95% CI 0.957-0.999; $p = 0.037$) were associated with

infection-related mortality. In the acute leukemia/MDS group, age, baseline neutrophil and lymphocyte counts, CRP, PCT, neutropenia duration, and clinically suspected IPA were not significantly associated with the outcome.

In the exploratory multivariable model, female sex (adjusted OR=2.661, 95% CI 0.851-8.316; $p = 0.092$), platelet count (adjusted OR=0.979, 95% CI 0.958-1.000; $p = 0.053$), and acute leukemia/MDS group (adjusted OR=0.943, 95% CI 0.303-2.935; $p = 0.920$) were not statistically significantly associated with 28-day infection-related mortality. Thus, no statistically significant independent association was identified in the multivariable analysis. Given the limited number of infection-related deaths ($n = 16$), the multivariable findings should be interpreted as exploratory.

Sensitivity Analysis. Two sensitivity analyses were performed. First, univariable logistic regression was repeated in the acute leukemia/MDS group ($n = 81$; 10 infection-related deaths). None of the evaluated variables showed a statistically significant association with 28-day infection-related mortality in this subgroup (**Supplementary Table S2**). Given the limited number of events, a multivariable model was not constructed.

Table 7. Categorical clinical characteristics according to 28-day infection-related mortality status in the patient-level cohort (n=156).

Characteristic	No mortality (n=140), n (%)	Mortality (n=16), n (%)	p
Sex			
Female	58 (41.4)	11 (68.8)	0.037^a
Male	82 (58.6)	5 (31.2)	
Acute leukemia/MDS group			
No	69 (49.3)	6 (37.5)	0.371 ^a
Yes	71 (50.7)	10 (62.5)	
Infection classification			
Clinically documented infection	42 (30.0)	5 (31.2)	
Microbiologically documented infection	30 (21.4)	6 (37.5)	0.295 ^b
Fever of unknown origin	68 (48.6)	5 (31.2)	
Clinically suspected IPA			
No	134 (95.7)	14 (87.5)	0.192 ^b
Yes	6 (4.3)	2 (12.5)	

Bold p values indicate statistical significance ($p < 0.05$). Continuous variables (age, laboratory parameters, and neutropenia duration) are reported in Table 8 with corresponding odds ratios. IPA, invasive pulmonary aspergillosis. ^a Pearson chi-square test. ^b Fisher's exact test.

Table 8. Univariable and multivariable logistic regression analysis of factors associated with 28-day infection-related mortality (n=156).

Variable	Univariable OR (95% CI)	p	Adjusted OR (95% CI)	p
Female sex (ref: male)	3.110 (1.026-9.432)	0.045	2.661 (0.851-8.316)	0.092
Age (years)	1.014 (0.981-1.048)	0.416	—	—
Acute leukemia/MDS group (ref: other hematological malignancies)	1.620 (0.558-4.699)	0.375	0.943 (0.303-2.935)	0.920
Absolute neutrophil count ($\times 10^3/\mu\text{L}$)	0.449 (0.035-5.719)	0.538	—	—
Absolute lymphocyte count ($\times 10^3/\mu\text{L}$)	0.315 (0.061-1.626)	0.168	—	—
Platelet count ($\times 10^3/\mu\text{L}$)	0.978 (0.957-0.999)	0.037	0.979 (0.958-1.000)	0.053
CRP (mg/L)	0.999 (0.995-1.004)	0.807	—	—
PCT (ng/mL)	1.002 (0.990-1.013)	0.667	—	—
Duration of neutropenia (days) ^a	1.005 (0.980-1.031)	0.677	—	—
Clinically suspected IPA (ref: no)	3.190 (0.587-17.331)	0.179	—	—

Bold values indicate statistical significance ($p < 0.05$). CRP, C-reactive protein; PCT, procalcitonin; IPA, invasive pulmonary aspergillosis. Hosmer-Lemeshow $\chi^2=4.27$, $df=8$, $p=0.830$; Nagelkerke $R^2=0.141$. Variables entered into the multivariable model were those reaching $p < 0.10$ in univariable analyses (female sex and platelet count), together with the acute leukemia/MDS disease-category group, which was included as a clinically relevant covariate. The acute leukemia/MDS group comprised patients with AML, ALL, and MDS; other hematological malignancies served as the reference category. ^a Neutropenia duration was available for 110 patients (13 mortality events); univariable analysis restricted to this subset.

Second, the multivariable analysis was repeated in the full cohort of 169 patients, including the 13 patients whose index episode did not meet the conventional FN definition. In this analysis, female sex (adjusted OR=1.800, 95% CI 0.646-5.015; $p=0.261$), platelet count (adjusted OR=0.987, 95% CI 0.971-1.003; $p=0.103$), and acute leukemia/MDS group (adjusted OR=1.218, 95% CI 0.415-3.573; $p=0.720$) were not statistically significantly associated with infection-related mortality (**Supplementary Table S3**). Although the estimates for female sex and platelet count followed the same direction as in the primary analysis, the effect

estimates were attenuated and remained statistically non-significant.

Discussion. In this retrospective single-center cohort, 239 episodes initially recorded and managed as FN were identified in 169 adults with hematological malignancies; the primary analysis included 226 classical FN episodes in 156 patients within a dual-level analytical framework. Three main findings emerged. First, Gram-negative bacteria predominated among clinically significant isolates, with high meropenem resistance in *Klebsiella* spp. and frequent concurrent

resistance to ciprofloxacin and levofloxacin in both *E. coli* and *Klebsiella* spp. Second, glycopeptide therapy was administered in more than one-third of classical FN episodes (38.9%), despite the absence of MRSA among the clinically significant isolates recovered during the study period. Third, no variable was statistically significantly associated with 28-day infection-related mortality in the exploratory multivariable analysis. These findings highlight the importance of local antimicrobial resistance surveillance and antimicrobial stewardship while underscoring the limited statistical power of the mortality analysis.

The distribution of FN episodes across clinical categories in our cohort (MDI, 26.1%; CDI, 29.2%; FUO, 44.7%) broadly matched patterns reported in patients with FN.^{1,20} The substantial proportion of FUO reflects the persistent diagnostic uncertainty encountered in patients with hematological malignancies, in whom fever may occur without an identifiable microbiological or clinical focus despite routine diagnostic evaluation. In our cohort, no causative pathogen or clinical infectious focus was identified in nearly half of the classical FN episodes. This finding reinforces the continued importance of empirical antibacterial therapy while highlighting the need for improved diagnostic approaches that increase microbiological yield and distinguish infectious from non-infectious causes of fever.

Gram-negative bacteria accounted for approximately three-quarters of clinically significant isolates in our cohort (56/73, 76.7%). This distribution is consistent with the resurgence of Gram-negative predominance reported in hematological malignancy cohorts since the early 2010s. Trecarichi et al. reported a Gram-negative rate of 56–58% in their multicenter Italian cohort,¹⁰ while Chen et al., in a more recent series of 3,014 patients, reported a rate of 64.7%.²¹ In our cohort, *E. coli* (45.2%) and *Klebsiella* spp. (24.7%) were the most frequently isolated pathogens. Notably, no *Pseudomonas* spp. was recovered during the study period. This finding contrasts with the *P. aeruginosa* rates of 5–15% typically reported in hematological malignancy cohorts.^{10,21} The retrospective, single-center design and limited number of culture-positive episodes preclude conclusions about the reasons for its absence. Larger multicenter studies are needed to determine whether this finding represents a reproducible local epidemiological pattern.

The antimicrobial resistance profile of the predominant Gram-negative isolates was notable. Among *E. coli* isolates, 54.5% (18/33) were ceftriaxone-resistant, whereas 6.1% (2/33) were meropenem-resistant. This pattern is comparable to resistance profiles reported in international cohorts of hematological malignancies.^{10,21} In contrast, *Klebsiella* spp. demonstrated high resistance rates to both ceftriaxone (83.3%; 15/18) and meropenem (77.8%;

14/18). Reported carbapenem resistance rates in *Klebsiella* from hematological malignancy cohorts vary considerably by region, ranging from about 3% in some Chinese centers to 57.9% in an Italian cohort, with comparable levels in long-term Brazilian cohorts.^{22–24} Whether this pattern reflects endemic circulation of carbapenemase-producing strains at our center remains speculative in the absence of molecular typing. Similarly high rates of carbapenem resistance have been reported in recent studies conducted among patients with hematological malignancies in Türkiye,²⁵ underscoring that our country is situated within a high antimicrobial resistance setting.

Ceftazidime-avibactam resistance was detected in 6 of 18 (33.3%) *Klebsiella* spp. isolates. The ECIL-10 guideline recommends newer β -lactam/ β -lactamase inhibitor combinations (ceftazidime-avibactam, meropenem-vaborbactam) as first-line targeted therapy in place of carbapenem-based regimens in patients with hematological malignancies and HCT recipients who develop CRE bacteremia.¹³ In a prospective multicenter study, Herrera et al. demonstrated that ceftazidime-avibactam significantly reduced 30-day mortality in neutropenic patients with KPC-producing Enterobacterales bacteremia.²⁶ However, because carbapenemase mechanisms were not molecularly characterized in our study, the basis of ceftazidime-avibactam resistance could not be determined. In addition, our study was not designed to evaluate treatment effectiveness according to susceptibility phenotype. Therefore, these findings primarily support the need for continued local resistance surveillance and susceptibility-guided treatment rather than conclusions regarding the clinical effectiveness of ceftazidime-avibactam at our center.

Concurrent resistance to ciprofloxacin and levofloxacin was frequent among the predominant Gram-negative isolates, occurring in 75.8% (25/33) of *E. coli* and 94.4% (17/18) of *Klebsiella* spp. isolates. Fluoroquinolone-based antibacterial prophylaxis was documented in 29.6% of classical FN episodes; however, prophylaxis information was incomplete for a substantial proportion of episodes, and the present study did not evaluate the association between individual prior antimicrobial exposure and subsequent resistance. Accordingly, a causal relationship between local prophylactic practices and the observed fluoroquinolone resistance rates cannot be established from these data. The ECIL-4 guideline reports that fluoroquinolone resistance can reach 60–80% in hematological malignancy cohorts receiving prolonged fluoroquinolone prophylaxis.¹⁶ Nevertheless, these high resistance rates support periodic reassessment of prophylactic strategies alongside local susceptibility surveillance.

Piperacillin-tazobactam resistance was observed in 24.2% (8/33) of *E. coli* and 77.8% (14/18) of *Klebsiella* spp. isolates. Piperacillin-tazobactam was also frequently administered in our cohort; however, because antimicrobial exposure and resistance were not analyzed at the individual isolate level, the present data do not permit inference regarding selection pressure or a causal association between institutional use and resistance. These findings are consistent with the principle emphasized in ECIL guidance that prior antimicrobial exposure, colonization status, and local resistance epidemiology should be considered when selecting empirical therapy. The ECIL-10 update further emphasizes pathogen-directed empirical strategies in patients known to be colonized with resistant Gram-negative organisms such as CRE or CRAB.^{13,27}

All three *Candida* bloodstream isolates were fluconazole-resistant. The isolates were exclusively non-*albicans* *Candida* species, comprising two *Candida krusei* and one *Candida parapsilosis*. In a 14-year Turkish cohort, Hunutlu et al. showed that posaconazole prophylaxis significantly reduced the incidence of *Candida* infection, while the majority of resulting isolates consisted of azole-resistant or less-susceptible species such as *C. krusei* and *C. tropicalis*.²⁸ The very small number of *Candida* isolates in our cohort (n=3) precludes any inference regarding local species trends, antifungal selection pressure, or the effect of prophylactic strategies. These findings should therefore be regarded as descriptive.

Current international guidelines recommend empirical glycopeptide therapy in FN only when specific clinical indications are present.^{1,27} No MRSA was recovered among the clinically significant isolates in our cohort, a finding consistent with the low overall prevalence of MRSA bacteremia reported in cancer patients (global meta-analysis: 3%, 95% CI 2-5) and with the low MRSA prevalence reported in hematological malignancy and FN cohorts from Türkiye.^{29,30} Hamidi et al., evaluating 45 FN-related bacteremia episodes in 37 patients, similarly reported no MRSA isolation.³⁰ In a prospective study of 161 FN episodes in 99 patients, Aslan et al. found that coagulase-negative staphylococci accounted for a substantial proportion of Gram-positive isolates in blood cultures, while MRSA was distinctly rare.³¹ Despite this local and regional epidemiological pattern, glycopeptide therapy (teicoplanin or vancomycin) was administered in 88 of 226 classical FN episodes (38.9%). Because the indication, timing, and duration of glycopeptide therapy were not systematically captured, the appropriateness of individual prescriptions could not be assessed. Nevertheless, the combination of frequent glycopeptide exposure and the absence of MRSA among recovered isolates suggests that prospective antimicrobial stewardship evaluation of

indications, duration, and opportunities for early de-escalation may be informative.

Agents commonly used in the management of resistant Gram-negative infections were also administered during a subset of classical FN episodes, including tigecycline (11.1%), polymyxin B (7.1%), colistin (3.5%), ceftazidime-avibactam (2.2%), and fosfomycin (2.2%). These treatment exposures should be interpreted descriptively, because antimicrobial indication, timing, microbiological targeting, and treatment response were not systematically evaluated at the individual-episode level. Nevertheless, their use further illustrates the therapeutic complexity encountered in the management of FN in a setting with substantial resistance among several predominant Gram-negative isolates.

The median total duration of antimicrobial therapy was 13 days at the episode level (IQR, 10-17 days) and 12.5 days at the patient-level index episode (IQR, 10-16 days). As demonstrated in the "How Long" randomized controlled trial by Aguilar-Guisado et al., early discontinuation of empirical therapy based on clinical response can be safe in high-risk patients.¹⁷ The recent ECIL-10 guideline endorses this approach, recommending that empirical therapy can be discontinued after 72 hours in afebrile, hemodynamically stable patients without waiting for neutropenia to resolve.¹³ However, because our study was not designed to evaluate the appropriateness of treatment duration or criteria for antimicrobial discontinuation, these data should be interpreted descriptively.

We identified clinically suspected IPA in 18 of 226 classical FN episodes (8.0%) and in 8 of 156 patients (5.1%) at the patient level. As described in the Methods, we identified cases based on clinical assessment and HRCT findings compatible with IPA. Because galactomannan results were not systematically recorded in the study dataset, cases could not be formally classified as proven, probable, or possible invasive fungal disease according to the 2020 EORTC/MSGERC consensus definitions.¹⁵ Accordingly, direct comparison of the observed frequency of clinically suspected IPA with rates of consensus-defined IPA reported in hematological malignancy cohorts should be made cautiously.³² At the patient level, clinically suspected IPA was not statistically significantly associated with 28-day infection-related mortality in univariable logistic regression (OR=3.190, 95% CI 0.587-17.331; p=0.179). This finding should not be interpreted as evidence of no association, given the small number of patients with clinically suspected IPA (n=8), the limited number of infection-related deaths (n=16), and the resulting wide confidence interval. Larger studies using standardized consensus-based diagnostic classification are needed to more reliably evaluate the prognostic impact of invasive

fungal disease in patients with hematological malignancies and FN.

The 28-day infection-related mortality rate in the patient-level cohort was 10.3% (16/156), while 28-day all-cause mortality was 12.8% (20/156), broadly within the range reported in previous hematological malignancy cohorts.^{25,33} In the exploratory multivariable analysis, none of the evaluated variables were statistically significantly associated with 28-day infection-related mortality. Female sex (adjusted OR=2.661, 95% CI 0.851-8.316; $p=0.092$), platelet count (adjusted OR=0.979, 95% CI 0.958-1.000; $p=0.053$), and acute leukemia/MDS group (adjusted OR=0.943, 95% CI 0.303-2.935; $p=0.920$) did not meet conventional criteria for statistical significance. These findings should be interpreted in the context of the limited number of infection-related deaths. With only 16 outcome events, the multivariable analysis had limited capacity to provide precise estimates, as reflected by the relatively wide confidence intervals for several variables. In the sensitivity analysis including the full cohort of 169 patients, the estimates for female sex and platelet count remained statistically non-significant, and differences were attenuated compared with those in the primary analysis. Accordingly, the present findings should be considered exploratory and hypothesis-generating rather than evidence of independent prognostic associations. Although thrombocytopenia has been associated with adverse outcomes in sepsis and hematological malignancy cohorts,³⁴ our analysis did not demonstrate an independent association between baseline platelet count and infection-related mortality.

Several variables previously associated with adverse outcomes in patients with hematological malignancies and FN, including prolonged neutropenia and lymphopenia, were not statistically significantly associated with infection-related mortality in our cohort.^{33,35} Similarly, the acute leukemia/MDS group and clinically suspected IPA were not significantly associated with the outcome. These negative findings should not be interpreted as evidence that these factors lack prognostic relevance, particularly given the limited number of outcome events and the incomplete availability of neutropenia-duration data. Previous studies of similarly sized hematological malignancy cohorts have also reported substantial variability in mortality-associated factors, with some candidate variables losing statistical significance after multivariable adjustment.^{36,37} This heterogeneity highlights the difficulty of identifying robust prognostic factors in clinically diverse FN populations and supports the need for larger, multicenter cohorts with sufficient numbers of outcome events.

Neither CRP nor PCT was statistically significantly associated with 28-day infection-related mortality in univariable logistic regression (CRP: OR=0.999, 95% CI

0.995-1.004; $p=0.807$; PCT: OR=1.002, 95% CI 0.991-1.013; $p=0.667$). These findings should be interpreted cautiously given the limited number of outcome events and do not exclude a potential role for inflammatory biomarkers in broader clinical risk assessment. In a hematological malignancy cohort of 614 episodes, Yang et al. reported that the discriminative power of CRP for bacteremia in FN episodes was at the level of chance, while PCT contributed independently of neutropenia to the differentiation of bacteremia.³⁸ Therefore, inflammatory biomarkers should be interpreted alongside clinical and microbiological findings rather than in isolation.

Fluoroquinolone-based antibacterial prophylaxis was documented in 67 of 226 classical FN episodes (29.6%), most commonly with moxifloxacin ($n=54$), followed by levofloxacin ($n=12$) and ciprofloxacin ($n=1$). The preferential use of moxifloxacin at our center has previously been evaluated by our group in patients with AML.³⁹ However, the remaining 159 episodes (70.4%) did not document a specific antibacterial prophylactic regimen; this category included episodes where prophylaxis was not prescribed and those where prophylaxis information was unavailable. Consequently, the present study cannot reliably compare outcomes or resistance patterns according to specific prophylactic regimens. Given the high observed fluoroquinolone resistance rates, institutional prophylaxis strategies should be periodically reassessed in conjunction with local susceptibility data and current guideline recommendations.^{40,41}

Several limitations should be considered when interpreting our findings. First, the retrospective, single-center design limits the generalizability of the results, and the relatively small number of isolates in some pathogen subgroups, particularly *Acinetobacter* spp. ($n=4$) and *Candida* spp. ($n=3$), limits the precision of subgroup-specific resistance estimates. Second, the mortality analysis was constrained by the limited number of outcome events. Only 16 infection-related deaths occurred in the patient-level cohort of 156 patients, resulting in limited statistical power and imprecise estimates in the exploratory multivariable model. Accordingly, the absence of statistically significant associations should not be interpreted as evidence that the evaluated variables lack prognostic relevance.

Third, infection-related mortality was adjudicated retrospectively by two experienced clinicians who had access to the complete medical records and were not formally blinded to candidate prognostic variables. Although we resolved discrepancies by consensus, we did not prospectively assess formal inter-rater agreement. To provide a less subjective complementary outcome, 28-day all-cause mortality was also reported. Fourth, several clinically relevant variables were not systematically available, including disease status

(remission, relapsed, or refractory), treatment intensity, timing and appropriateness of antimicrobial therapy, shock, organ dysfunction, ICU admission, and detailed hematopoietic cell transplantation-related characteristics. In addition, established clinical risk scores such as MASCC and CISNE and the Charlson comorbidity index were not available. Residual confounding therefore cannot be excluded. Fifth, not all antimicrobial agents were tested against every isolate, resulting in variable denominators across organism-antimicrobial combinations. Molecular characterization of carbapenemase mechanisms was not performed; therefore, resistance findings were interpreted on a phenotypic basis, and the mechanisms underlying meropenem or ceftazidime-avibactam resistance could not be determined. Sixth, clinically suspected IPA was identified using clinical assessment and compatible HRCT findings. Still, galactomannan results were not systematically recorded, and beta-D-glucan testing was not available at our institution. Consequently, cases could not be formally classified according to the 2020 EORTC/MSGERC consensus definitions. Seventh, antibacterial prophylaxis could not be fully characterized. A specific fluoroquinolone prophylactic regimen was documented in 67 of 226 classical FN episodes, whereas no specific prophylactic regimen was documented in the remaining 159 episodes; the latter category included both episodes in which prophylaxis was not prescribed and those for which prophylaxis information was unavailable. This limitation precluded reliable evaluation of associations between specific prophylactic strategies, antimicrobial resistance, and clinical outcomes. Similarly, systematic data on colonization status and recent antimicrobial exposure were unavailable, limiting assessment of risk factors for acquisition of resistant organisms. Finally, neutropenia duration was

unavailable for 67 of the 226 classical FN episodes. Although a descriptive comparison of episodes with and without documented neutropenia duration did not reveal major differences across several measured clinical characteristics, informative missingness related to unmeasured factors cannot be excluded.

Conclusions. Gram-negative bacteria predominated among clinically significant isolates in patients with hematological malignancies and FN, with high meropenem resistance among *Klebsiella* spp. and frequent concurrent resistance to ciprofloxacin and levofloxacin in both *E. coli* and *Klebsiella* spp. Ceftazidime-avibactam resistance was also detected among *Klebsiella* spp. isolates, underscoring the importance of ongoing local antimicrobial resistance surveillance and susceptibility-guided treatment. Glycopeptides were administered in more than one-third of classical FN episodes despite no MRSA among recovered isolates, highlighting the value of prospective stewardship to evaluate treatment indications and opportunities for de-escalation. No variable was statistically significantly associated with 28-day infection-related mortality in the exploratory multivariable analysis, and the limited number of outcome events precludes firm conclusions regarding prognostic factors. Larger multicenter studies incorporating detailed antimicrobial exposure, colonization data, and molecular resistance characterization are warranted.

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