Infection and Drug Resistance

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REVIEW

Clinical Characteristics and Optimization of Empirical Antimicrobial Therapy for Febrile Neutropenia in Patients With Hematologic Malignancies

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Purpose: Since the publication of the 2011 Infectious Diseases Society of America (IDSA) guidelines for empirical treatment of febrile neutropenia (FN), there have been significant shifts in pathogen profiles and emerging challenges in treatment. These include increased prevalence of multidrug-resistant (MDR) bacteria and changes in the distribution of Gram-negative or Gram-positive bacteria (GPB). The study aims to update and optimize empirical treatment strategies for hematological malignancy (HM) patients, a population particularly vulnerable to these evolving threats.

Methods: A literature review was conducted on studies published between January 2010 and December 2023 regarding empirical treatment of FN in HM patients, focusing on pathogen characteristics, treatment regimens, and duration of therapy.

Results: Approximately one-third of HM patients with FN experience fever of unknown origin (FUO), while 40–50% have clinically documented infections (CDI), and 10–30% present with microbiologically documented infections (MDI), with a predominance of Gram-negative bacteria (GNB). Factors such as prolonged neutropenia, prior broad-spectrum antibiotic use, and previous infections with drug-resistant bacteria are associated with MDR infections. Cefepime, piperacillin/tazobactam (PTZ), and carbapenem are viable empirical treatments for high-risk HM patients, though cefepime monotherapy's advantage remains uncertain. In cases of pneumonia, shock, or suspected carbapenem-resistant infections, combination therapy, tigecycline, and newer antibiotics like ceftazidime/avibactam (CAZ/AVI) are often used. Empirical broad-spectrum antibiotics can be safely discontinued in FUO patients after 48 hours of clinical stability and apyrexia.

Conclusion: Proper selection of empirical antibiotics and determining optimal treatment duration are essential for reducing antibiotic resistance and improving outcomes in HM patients with FN. These findings underscore the need for updated clinical guidelines that address evolving pathogen profiles and the growing challenge of MDR infections.

Summary: Infection-related complications remain a leading cause of mortality in HM patients, often limiting the implementation of chemotherapy. Early and appropriate empirical therapy significantly improves outcomes in FN, reducing hospital stays and healthcare costs. Effective treatment strategies require careful evaluation of local microbial epidemiology, risk factors for drug resistance, and predictors of poor prognosis. For high-risk FN patients, first-line antibiotic options include cefepime, PTZ, and carbapenems. In cases of pneumonia, septic shock, or suspected carbapenem-resistant infections, combination therapies with antipseudomonal β-lactams, aminoglycosides, or novel agents like CAZ/AVI are recommended. In patients with FUO, discontinuing broad-spectrum antibiotics may be considered 48 hours after defervescence in clinically stable patients, though premature cessation should be avoided for those with persistent fever. Ongoing monitoring and reassessment of the patient's condition are crucial to minimizing the risks of treatment failure. Timely, evidence-based empirical therapy remains critical for improving outcomes in FN, and continued advancements in antimicrobial strategies are essential to optimizing care for this high-risk patient population.

Keywords: hematological malignancy, febrile neutropenia, multidrug-resistant bacteria, empirical antibiotic treatment, fever of unknown origin

Received: 29 August 2024
Accepted: 24 January 2025
Published: 7 February 2025

Introduction

Due to the use of chemotherapy regimens, hematopoietic stem cell transplantations (HSCTs) and multiple comorbidities in hematological malignancy (HM) patients, the management of febrile neutropenia (FN) was particularly challenging.[1] While the overall survival for HM patients had improved, the infectious complications remain a significant threat to both prognosis and quality of life.[2] They are highly vulnerable to bacterial bloodstream infection (BSI), primarily due to profound neutropenia, damage to mucosal barriers, and previous treatment with broad-spectrum antibiotics.[3] Additionally, the increasing use of molecularly targeted therapies and cellular immunotherapies are expanding the spectrum of infection risks, as these treatments can further lead to increased risks of immunodeficiency.[4,5]

BSI occur in 10–30% of patients with FN, greatly worsening both morbidity and mortality rates in these individuals.[6] HM patients with FN are particularly vulnerable to drug-resistant BSI. According to published reports, approximately 10% to 25% of FN patients develop BSI,[7] with the incidence rising to 13% to 60% in those undergoing HSCTs.[8] In addition, the estimated incidence of severe sepsis and septic shock is 20–30% and 5–10% in FN patients, respectively.[9,10] Due to evolving patterns of bacterial resistance, HM patients are increasingly affected by infections attributed to drug-resistant strains, especially *Enterobacterales* and non-fermenting Gram-negative bacteria (GNB). The prevalence of multidrug-resistant (MDR) organisms has steadily increased. A study in Italy reported a six-fold increase in BSIs caused by carbapenem-resistant (CR) *Klebsiella pneumoniae* (KP) in HSCT patients from 2010 to 2013.[11] Furthermore, a ten-year retrospective study of HM patients with FN found that GNB accounted for 81% of infections, with approximately 41% of *Enterobacterales* producing extended-spectrum beta-lactamase (ESBL), and 18% of isolates being CR or MDR.[12]

The rise in drug-resistant GNB has led to increased mortality rates, particularly among HM patients. And it also linked to an increased likelihood of receiving inappropriate empirical antibiotic treatment (IEAT). Chen et al conducted a retrospective study of 706 KP-BSI adult patients, and found that HM patients were considered to be at high risk for carbapenem resistance, and the 28-day mortality rate was significantly higher for patients with CRKP-BSI compared to those with carbapenem-susceptible KP-BSI (42.5% vs 20.2%, P<0.001).[13] A meta-analysis also highlighted that mortality rates were higher in HM patients, with a relative risk (RR) of 3.20 (95% CI 2.54–4.03) for those with BSI caused by producing-ESBL *Enterobacterales*.[14] In a five-year retrospective study of 293 hospitalized acute leukemia (AL) patients with *Pseudomonas aeruginosa* (PA) BSI, our team identified 55 patients who received IEAT. Among them, 65.8% of those infected with MDR-PA experienced delays in appropriate therapy beyond 48 hours.[15] A case-control analysis of 105 HM patients revealed that those with CR-GNB BSI were 75% less likely to receive empirically active antibiotics compared to patients without CR-GNB. Additionally, the 30-day mortality rate for CR-GNB BSI patients was 27.2% higher than that of the control group (28.6% vs 1.4%, P<0.01).[16] Delays in initiating appropriate empirical treatment, whether due to ineffective or inappropriate therapy, are common in the context of antibiotic resistance. Early identification of high-risk patients is crucial to reduce IEAT and improve outcomes.

Since the last guidelines on high-risk FN were published over a decade ago, significant advancements have been made in its management. However, the rise in antibiotic resistance has necessitated more careful selection of empirical therapies for neutropenic patients with severe infections. The widespread use of broad-spectrum antibiotics, while initially beneficial, has contributed to increased resistance and higher mortality rates in both the general and neutropenic populations. This review summarizes recent developments in antimicrobial management for high-risk FN, focusing on updates in infection epidemiology, risk assessment, empirical treatment selection, the impact of MDR bacterial colonization, and optimal antimicrobial therapy duration.

Epidemiological Characteristics

The incidence of FN in HM patients undergoing chemotherapy or HSCT is exceedingly high. A nationwide study of acute myeloid leukemia (AML) patients, which included 357 individuals and 1053 treatment courses, found that 93% of these courses (977 of 1053) resulted in FN. In fact, over 90% of AML patients experienced FN during their treatment.[17] Similarly, a multi-center prospective cohort study in China involving 1139 neutropenic HM patients found that 68.8% developed fever, with FN occurring in 81.9% of patients, particularly those with prolonged neutropenia lasting over 21 days. The lungs were the most frequently identified sites of BSI in HM patients with FN (49.5%, n=388), followed by the

upper respiratory tract (16.0%, n=159), perianal region (9.8%, n=77), and bloodstream (7.7%, n=60). Of these, 54.7% of infections were clinically documented (CDI), 13% microbiologically documented (MDI), and 32.3% were categorized as fever of unknown origin (FUO).[18] Another retrospective study from Korea, involving 687 HM patients with FN, showed that nearly one-third of patients (n=219) had FUO, with MDI and CDI accounting for 28.4% and 39.7%, respectively.[19] The Infectious Diseases International Research Initiative conducted a prospective observational study of 461 FN patients with BSI across 41 centers in 16 countries. Among these, 361 patients had HM, and the primary sources of infection included the lungs (9.2%, n=41), catheter-related BSI (9%, n=39), urinary tract infections (5.6%, n=24), skin and soft tissue infections (4.6%, n=20), and abdominal infections (2.8%, n=12). The distribution of pathogens in HM patients with FN varies, with GNB generally more prevalent than Gram-positive bacteria (GPB). A study by Erdem et al found that GNB accounted for 71.9% of infections (n=310), compared to 28.1% for GPB (n=121). The most common GNB identified were *Escherichia coli* (27.1%, n=120), KP (22.7%, n=98), PA (14.1%, n=61), and *Acinetobacter baumannii* (2.3%, n=12). Common GPB included *coagulase-negative staphylococci* (CONS) (13.2%, n=57), *Staphylococcus aureus* (7%, n=30), *Enterococci* (4.9%, n=21), and *Streptococci* (2.6%, n=11).[20] A study in India reported 393 episodes of FN in 123 patients, with 20.6% classified as MDI. GPB and GNB accounted for 41.9% and 46.9% of blood culture-positive bacteria, respectively. Among the GNB, *Klebsiella* species were the most common (39.47%), followed by *Pseudomonas* species (23.68%) and *Escherichia coli* (13.15%). The most frequently identified GPB were CONS, which accounted for 67.64% of isolates, with methicillin-resistant *Staphylococcus aureus* (MRSA) making up 8.8%. Lower respiratory tract infections were the most common CDI, affecting 47.15% of patients, followed by abdominal sepsis in 9.75%. Additionally, 38.21% of patients presented with FUO.[21] Overall, the bloodstream and lungs emerge as the predominant sites of infection among FN patients, with GNB representing the most frequently encountered pathogens. Nearly one-third of patients experience FUO. The increasing prevalence of MDR bacteria, including producing-ESBL *Enterobacterales*, CRPA, carbapenem-resistant *Acinetobacter baumannii*, vancomycin-resistant *enterococci* (VRE), and MRSA, has posed significant challenges in selecting appropriate empirical treatment of FN patients.

Risk Factors for Drug-Resistant Infection

The drug-resistant bacterial infection were mainly associated with prolonged neutropenia, prior infection or colonization with drug-resistant bacteria, advanced age, indwelling central venous catheters, and previous exposure to broad-spectrum antibiotics. Table 1 summarized the risk factors for drug-resistant infection in patients with HMs. A case-control study involving 105 HM patients identified several factors significantly associated with CR-GNB BSI. These included induction chemotherapy (P<0.01), intensive care unit (ICU) admission (P<0.01), prolonged neutropenia (P<0.01), and a history of CR-GNB infection in the previous year (P<0.01). Patients undergoing induction chemotherapy often had a more severe tumor burden, which may increase their susceptibility to CR-GNB infections.[16] Rosa et al conducted a prospective cohort study with 307 FN patients, of whom 115 developed BSI. Among these, 33.0% were attributed to MDR organisms. Multivariate analysis identified advanced age (P=0.009), prolonged neutropenia (P=0.022), and indwelling central venous catheters (P=0.022) as significant risk factors for MDR organisms BSI. The risk of MDR organisms BSI increased by 3% for each additional year of age and 2% for each additional day of neutropenia.[22] A retrospective study of 171 patients, 89% of whom had HM, found that ICU admission (OR 20.18, 95% CI 1.03–397.35), antibiotic use exceeding 14 days within the first 90 days (OR 6.02, 95% CI 1.17–30.93), and pulmonary sources of infection (OR 13.65, CI 1.14–163.57) were significant risk factors for piperacillin/tazobactam (PTZ) resistance.[23] Furthermore, prior exposure to antibiotics was associated with an elevated risk of developing drug-resistant infections. Moghnieh et al demonstrated that the history and duration of antibiotic use prior to bacteremia were significantly linked to the development of third-generation cephalosporin resistance (3GCR) bacteremia. Specifically, the prolonged use of carbapenems, PTZ, or third- and fourth-generation cephalosporins (± aminoglycosides) for >4 days prior to bacteremia was strongly correlated with the occurrence of 3GCR bacteremia (P<0.01). Additionally, extended use of carbapenems or PTZ for more than four days was strongly linked to the development of MDR organisms (P<0.05).[24] In a study of 293 AL patients complicated by PA-BSI, we found that the previous 90-day use of carbapenems (OR 4.745, P<0.001), quinolones (OR 2.833, P=0.010), and PTZ (OR 2.466, P=0.033) were important determinants of CRPA BSI.[15] Additionally, we identified risk factors for MDR-PA BSI, including previous use of carbapenems (OR

https://doi.org/10.2147/IDR.S493670

Table 1 Risk Factors for Drug-Resistant Infection in HM Patients With FN

Reference	Time Period	Design	Countries	Patients	Risk Factors (n, %)				
Schonardie et al[16]	2012–2021	Case-control	Brazil	105	Induction chemotherapy (32, 30.48%)	ICU admission (22, 20.95%)	Prolonged neutropenia	Previous CR- GNB infection (13, 12.38%)	
Rosa et al[22]	2009–2011	Prospective	Brazil	307	Advanced age	Prolonged neutropenia	Indwelling central venous catheters (243, 79.15%)		
Marini et al[23]	2007–2013	Retrospective	USA	171	ICU admission (7, 4.09%)	Previous use PTZ (69, 40.35%)	Respiratory source (8, 4.68%)		
Moghnieh et al[24]	2009–2012	Retrospective	Lebanon	75	Carbapenems use>4 days (14, 18.67%)	PTZ use>4 days (7, 9.33%)	3rd or 4th generation cephalosporin ± AG >4 days (11, 14.67%)		
Zhao et al[25]	2014–2021	Retrospective	China	429	Previous 90-day use of carbapenems (235, 54.78%)	BSI during antibiotic treatment (62, 14.45%)	Previous 90-day use of quinolones (54, 12.59%)	Previous 90-day use of PTZ (69, 16.08%)	
Viasus et al[26]	2004–2017	Retrospective	Spain	661	Previous use of cephalosporin (85, 12.86%) and PTZ (76, 11.50%)	HM (496, 75.04%)	Nosocomial-acquired BSI (289, 43.72%)	Respiratory source (85, 12.86%)	BSI during ceftriaxone treatment (26, 3.93%)
Girmenia et al[27]	2014	Prospective	Italia	2743	Pretransplant resistant GNB colonization (259, 11.69%)	Pretransplant resistant GNB infection (34, 3.04%)			
Liu et al[28]	2017–2021	Retrospective	China	421	Advanced age	MIC of meropenem and imipenem >8μg/mL (181, 43%)	Gastrointestinal symptoms (117, 27.8%)	Minimum ANC ≤0.025 (222, 52.7%)	Chills at peak temperature (32, 7.6%)
Kirkizlar rt al[29]	2010–2016	Retrospective	Turkey	200	Invasive procedures (9, 4.5%)	Co-infected status (27, 13.5%)	VRE positivity for more than 15 days		

Abbreviations: CR, carbapenem-resistant; GNB, Gram-negative bacteria; PTZ, piperacillin/tazobactam; AG, Aminoglycosides; BSI, bloodstream infection; HM, hematological malignancy; ANC, absolute neutrophil count.

2.066, P=0.043), quinolones (OR 2.275, P=0.046), PTZ (OR 2.500, P=0.019), and BSI during antibiotic treatment (OR 12.957, P<0.001). The factor of occurrence PA-BSI during antibiotic treatment was assigned 4 points, and the other three factors were assigned 1 point respectively. Based on these risk factors, a predictive model for MDR-PA BSI was developed. The findings indicated that patients with a score of ≥6 had a positive predictive value for MDR-PA BSI as high as 86.7%, with a corresponding negative predictive value of 89.1%.[25] In addition to previous use of cephalosporin and PTZ, HM, nosocomial-acquired BSI, respiratory infections and BSIs developing under ceftriaxone treatment were also found to be related to the occurrence of MDR-PA BSI.[26]

It is worth noting that patients with a prior carbapenem-resistant *Enterobacterales* (CRE) infection or colonization are at an increased likelihood of experiencing subsequent CRE infections. A multi-center prospective study highlighted a significant correlation between pretransplant colonization or prior infection with resistant GNB, particularly CRKP and MDR-PA. The study found that 32.5% of patients in the colonized group had CRKP, compared to just 0.1% in the non-colonized group (P<0.001), and 28.6% had MDR-PA, compared to 0.6% in the non-colonized group (P<0.001). These findings underscore the increased risk of developing resistant GNB BSIs prior to transplantation in allogeneic HSCT (allo-HSCT) patients.[27] In our team's analysis of intestinal CRE colonization in 421 HM patients, we identified several independent risk factors for CRE BSI: age, minimum inhibitory concentration (MIC) of meropenem and imipenem >8 μg/mL, presence of gastrointestinal symptoms, minimum absolute neutrophil count (ANC) ≤0.025 (10^9/L), and chills at peak temperature. Using these factors, we developed a predictive model with an optimal cutoff value of 0.215. The high-risk group for CRE colonization had a 47.5% likelihood of developing CRE BSI, while the low-risk group had a CRE BSI incidence rate of only 3.7% (P<0.001).[28] A retrospective study analyzed adult AL patients with FN who were colonized with VRE. The study found a VRE colonization rate of 15.2% among hospitalized HM patients. Multivariate logistic regression revealed several independent risk factors for VRE infection, including exposure to invasive procedures, co-infection, and VRE colonization lasting more than 15 days. In HM patients, VRE colonization may increase the risk of VRE BSIs due to impaired innate immunity, alterations in gut microbiota, and the promotion of VRE dissemination into the bloodstream by broad-spectrum antibiotics and chemotherapy.[29]

Risk Factors for Poor Prognosis

According to 2011 Infectious Diseases Society of America (IDSA)[7] and 4th European Conference on Infections in Leukemia (ECIL-4)[30] guidelines, neutropenic patients are ere categorized as low risk if they have neutropenia lasting less than 7 days, no comorbidities, and disease stabilization. Table 2 summarizes the risk factors for poor prognosis in HM patients. A multi-centers prospective observational study conducted in China, involving 277 HM patients, found no link between the duration of neutropenia prior to FN and patient outcomes in univariate analyses. However, prolonged neutropenia lasting more than 9 days after the onset of fever was recognized as a significant risk factor for mortality (P=0.019). Furthermore, delayed neutrophil recovery was found to significantly affect patient outcomes (P = 0.039). Patients with pulmonary infections experienced worse outcomes compared to FUO during FN (P=0.005).[31] The stage of HM also impacts prognosis. Our previous study found that complete remission of AL was related to better survival outcomes in patients with PA-BSI (P=0.018).[15] Additionally, a retrospective analysis of 362 HM patients with GNB BSIs showed that relapsed/refractory HM (OR 2.811, 95% CI 1.32–6.00) served as an independent predictor of increased 30-day mortality.[32] Bastug et al found that patients with GNB in blood cultures had higher mortality rates (P=0.005), with KP (P=0.013), *Acinetobacter baumannii* (P=0.014), producing-ESBL bacteria (P=0.004), and MDR-GNB (P=0.003) were determined to be risk factors for 30-day mortality.[33] Calik et al supported these findings by analyzing data from 164 HM patients with FN. They found that pneumonia (OR 0.040, 95% CI 0.011–0.143) and septic shock (OR 0.031, 95% CI 0.006–0.159) were related to an increased risk of mortality at day 21. Conversely, patients with GPB (P=0.005), those receiving PTZ (P=0.009), and those on empirical antibiotics for at least 72 hours (P<0.001) had a more favorable prognosis.[34] A retrospective multi-center study involving 1563 HM patients with BSI and FN revealed that individuals over the age of 70 (OR 2.4, 95% CI 1.2–4.7) had higher mortality rates.[35] Additional studies have highlighted that other clinical comorbidities are also key risk factors. Sereeaphinan et al analysed 153 cancer patients with FN and found that cardiovascular diseases (OR 22.45, 95% CI 4.90–104.78), altered consciousness at admission (OR 18.50, 95% CI 1.33–258.18), anemia (OR 4.33, 95% CI 1.20–15.65), acute kidney injury (AKI) (OR 13.15, 95% CI 3.48–49.75),

https://doi.org/10.2147/IDR.S493670

Table 2 Risk Factors for Poor Prognosis in HM Patients With FN

Reference	Time Period	Design	Countries	Patients	Risk Factors (n, %)				
Zhai et al[31]	2013	Prospective	China	277	Prolonged neutropenia (≥ 9 days)(79, 28.52%)	Delayed neutrophil recovery (25, 9.03%)	Respiratory source (114, 41.16%)		
Zhao et al[15]	2014–2019	Retrospective	China	293	Age ≥55 (47, 16%)	Perianal infection (34, 11.6%)	Respiratory source (87, 29.7%)	MDR-PA (38, 13%)	
Wang et al[32]	2015–2020	Retrospective	China	362	Septic shock (78, 21.5%)	Relapsed/refractory HMs (108, 29.8%)	Albumin <30g/l (115, 31.8%)	Platelets $<30\times10^9$/l before BSI (240, 66.3%)	IEAT (127, 35.1%)
Bastug et al[33]	2008–2013	Retrospective	Turkey	132	Prolonged neutropenia (≥ 7 days)(59.28.8%)	KP (23, 11.2%), AB infection (16, 7.8%)	Prior HSCT (34,25.8%)	IEAT (86. 42%)	
Calik et al[34]	2011–2015	Retrospective	Turkey	164	Pneumonia (39, 23.8%)	Septic shock (19, 11.58%)			
Chumbita[35]	2010–2019	Retrospective	Spain	1563	Age> 70 (48, 3.07%)	AKI	Empirical β-lactam plus aminoglycoside (101, 6.46%)	Only amikacin was active (10, 0.64%)	IEAT (471, 30%)
Sereeaphinan et al[36]	2018–2019	Retrospective	Thailand	153	Cardiovascular diseases, altered consciousness	Anemia, AKI	A confirmed pathogens, ICU admission	Septic shock	Mechanical ventilation
Marín et al[37]	2006–2013	Prospective	Spain	510	ICU admission (53, 10.39%)	Corticosteroid treatment (128,25.10%)	MDR-GNB (38,7.45%)	MASCC score <21 (150,29.41%)	Advanced neoplasm (39,7.65%)

Abbreviations: MDR-PA, multidrug-resistant Pseudomonas aeruginosa; IEAT, inappropriate empirical antibiotic treatment; KP, Klebsiella pneumoniae; HSCT, hematopoietic stem cell transplantations; AKI, acute kidney injury; MDR-GNB, multidrug-resistant Gram-negative bacteria; MASCC score, Multinational Association of Supportive Care in Cancer score.

a confirmed pathogenic organism (OR 8.68, 95% CI 1.42–52.95), ICU admission (OR 0.13, 95% CI 0.02–0.95), septic shock (OR 18.72, 95% CI 3.04–115.38), and mechanical ventilation (OR 22.65, 95% CI 4.90–104.78) were all linked to worse outcomes.[36] A prospective study from Spain involving 510 HM patients with FN also indicated that ICU admission and prior corticosteroid treatment were related to a higher risk of death.[37] HM patients are at heightened risk for drug-resistant bacterial infections and poor outcomes. Thus, early recognition of those susceptible to MDR-GNB infections and prompt initiation of empirical antibiotic therapy are essential for improving clinical prognosis.

Prophylactic Antimicrobial Therapy

The 2018 guidelines from the American Society of Clinical Oncology (ASCO) recommend oral fluoroquinolones to administer antimicrobial agents as prophylaxis in neutropenic individuals.[38] However, the extensive implementation of antibiotic prophylaxis may contribute to the emergence of antibiotic resistance. As a result, its routine use remains a subject of ongoing debate and controversy. Kern et al performed a prospective multicenter study involving patients with auto- and allo-HSCTs. The result showed that antimicrobial prophylaxis did not significantly or only slightly reduced mortality rates in patients with auto-HSCT patients (n=3602) (HR 0.64, 95% CI 0.29–1.38) and allo-HSCTs patients (n=4223) (HR 0.72, 95% CI 0.53–0.99). But it was related to a notable higher rates of occurrence of producing-ESBL *Enterobacterales* (RR 2.2, 95% CI 1.17–4.26). In contrast, prophylactic antibiotics did reduce all-cause mortality in AL patients undergoing induction chemotherapy (n=930) (HR 0.30, 95% CI 0.15–0.58), though the impact on patients in other phases of chemotherapy remains unclear.[39] A meta-analysis indicated that prophylactic fluoroquinolones may reduce the incidence of BSI (OR 0.57, 95% CI 0.43–0.74). However, no statistically significant improvement in survival rates was found for HM patients (OR 1.01, 95% CI 0.73–1.41).[40] Clerici et al assessed the impact of prophylactic fluoroquinolone on antibiotic resistance and infection-related mortality in HSCTs patients within 30 days post-transplantation. Their prospective cohort study found no cases of severe infections in either group, but the non-prophylactic group had a greatly higher prevalence of pathogens susceptible to PTZ (71% vs 30%, P=0.026), fluoroquinolones (49% vs 10%, P=0.03), and carbapenems (95% vs 50%, P=0.001).[41] Chong et al conducted a prospective study examining changes in fecal microbial composition in HM patients before and after levofloxacin prophylaxis. They observed the disappearance of quinolone-susceptible *Enterobacterales* after the initial prophylactic therapy, with quinolone-resistant CONS and *Enterococcus* becoming predominant. The prevalence of these resistant strains notably increased during subsequent courses of prophylactic therapy (P=0.003).[42] In summary, while prophylactic antibiotics in HM patients with FN may reduce infection rates, they are also associated with increased antibiotic resistance and limited improvement in clinical outcomes. The overall benefits of routine prophylaxis remain uncertain, and careful consideration is needed when selecting antimicrobial strategies.

Selection of Initial Empirical Antimicrobials

For high-risk patients with FN, intravenous broad-spectrum antibiotics should be initiated, targeting PA and other severe GNB. Commonly used agents include cefepime, PTZ, or carbapenems, either as monotherapy or in combination. In cases where clear clinical infection focuses are present, the selection of appropriate antibiotics should be guided by the relevant guidelines and consensus[43–47] (Figure 1). Following initiation of treatment, daily reassessments should be performed to monitor clinical symptoms and microbiological culture results, allowing for timely adjustments to the antimicrobial regimen.

Generally, the empirical administration of additional anti-GPB drugs such as vancomycin or teicoplanin was unnecessary, except in the following specific situations (eg, hemodynamic instability, pneumonia, catheter-related infections, skin and soft tissue infections, severe mucositis, and MRSA colonization). In a meta-analysis conducted in 2014, comprising 13 trials and 2392 patients, the efficacy of empirically adding anti-GPB antibiotics on mortality in patients with FN was evaluated. The comparison between experimental and control groups indicated no notable differences in mortality (RR 0.82, 95% CI 0.56–1.20, 852 patients) and treatment failure rate (RR 1.00, 95% CI 0.79–1.27, 943 patients).[48] Beyar et al updated the meta-analysis in 2017 and similarly indicated that mortality (RR 0.90, 95% CI 0.64–1.25; 1242 patients) and overall failure rate (RR 1.00, 95% CI 0.79–1.27; 943 patients) revealed no marked differences between two groups. Currently, there is no evidence that adding anti-GPB therapy empirically to FN patients enhances prognosis.[49] In summary, the routine use of additional anti-GPB drugs in empirical treatment of FN remains unsubstantiated by evidence, and their use should be reserved for specific high-risk situations.

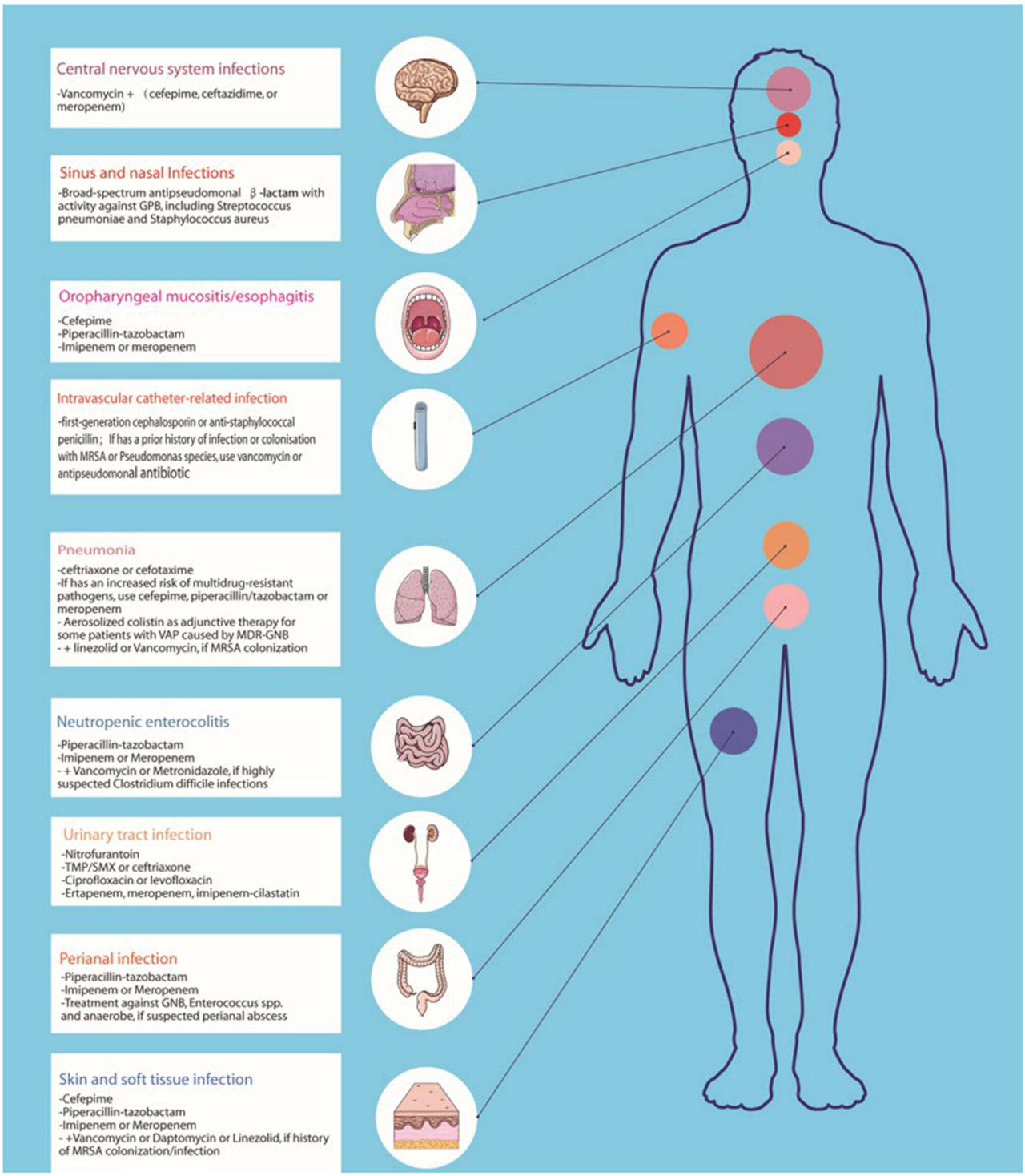

Figure 1 The selection of appropriate antibiotics at different infection sites.

Choice of Empirical Monotherapy for HM Patients With FN

Recent guidelines have identified preferred anti-pseudomonal β-lactam antibiotics for the empirical treatment of FN: cefepime, meropenem, imipenem/cilastatin, and PTZ.[50] However, with the rising rates of resistance among GNB, the efficacy of cefepime has become increasingly questionable, particularly in light of its limited activity against GPB. As a result, the role of cefepime as a first-line empirical treatment for FN remains a subject of ongoing debate within clinical practice.

In a network meta-analysis shown that patients treated with imipenem/cilastatin exhibited the lowest rate of all-cause mortality, in contrast to those receiving cefepime, who demonstrated a higher risk of all-cause mortality (OR 2.05, 95% CI 1.11–3.78).[51] However, the correlation between cefepime and increased mortality remains controversial. While several meta-analyses have suggested a potential link between cefepime and increased mortality, other studies have strongly refuted these findings.[52,53] A meta-analysis conducted in the United States, which encompassed an analysis of 24 trials involving patients with FN, did not observe a meaningful rise in mortality attributable to cefepime usage. This result highlights the importance of ongoing evaluation and deeper exploration of the potential relationship between cefepime and mortality outcomes.[54] In addition, a study[55] involving 343 patients across 13 centers in the United States found that both cefepime and PTZ remained effective as empirical treatment options for high-risk HM patients with FN. In this cohort, 70% of patients were initially treated with cefepime, 23% with PTZ, and 8% with meropenem. Cefepime showed activity against 84% of GNB, including 85% of *Escherichia coli* and 93% of PA. Similarly, PTZ was effective against 88% of GNB, including 87% of *Escherichia coli* and 92% of PA. Carbapenems, meanwhile, exhibited susceptibility to 96% of GNB, including 98% of *Escherichia coli* and 86% of PA. Despite concerns about the higher production of ESBL in HM patients, which might reduce the efficacy of cephalosporins, cefepime continues to be widely used as an empirical treatment option in the United States. These findings suggest that cefepime remains a viable choice for empirical therapy in many high-risk FN cases, although ongoing monitoring for resistance and the emergence of more potent pathogens is critical. In contrast to the findings in the United States, a recent survey of transplant centers in Europe and Asia revealed a significantly lower usage rate of cefepime for empirical therapy, with only 14.3% of centers employing it. Notably, two-thirds of the surveyed centers preferred monotherapy with PTZ as the primary empirical treatment option for FN patients.[56] A retrospective study comparing cefepime and carbapenems as empirical treatments for producing-ESBL *Escherichia coli* bacteremia found that patients treated with cefepime had an increased mortality rate. This finding suggests that cefepime may not be an effective or safe option for empirical therapy when producing-ESBL *Escherichia coli* is suspected or confirmed as the causative pathogen.[57] However, a multicenter study conducted in Europe showed no substantial increase in mortality among producing-ESBL *Enterobacterales* BSI patients who received empirical beta-lactam/beta-lactamase inhibitors (BLBLI) compared to carbapenems.[58] Producing-ESBL *Enterobacterales* are resistant to cefepime and ceftazidime but remain susceptible to carbapenems, which may explain the superiority of imipenem/cilastatin over cephalosporins in cases of producing-ESBL infections. Despite its advantages, imipenem/cilastatin is linked to an increased incidence of adverse events relative to BLBLI combinations, making it a less favorable option in certain clinical scenarios.

It is imperative to assess the efficacy of cefepime and PTZ as empirical treatments for HM patients with infections caused by producing-ESBL *Escherichia coli*. A recent international multicenter study compared the effectiveness of BLBLI therapy with carbapenems in treating HM patients who developed FN and BSI caused by producing-ESBL *Escherichia coli*. The study found that both treatment regimens resulted in similar 14-day mortality rates.[59] Benanti et al conducted a study involving 103 HM patients, in which 40 patients received empirical treatment with cefepime, 21 with PTZ, and 42 with carbapenems. Despite clinically significant outcomes such as persistent fever and bacteremia being more common among patients treated with cefepime or PTZ, the empirical therapy with these antibiotics demonstrated no increase in mortality rates when compared with carbapenem treatment (HR 0.57; 95% CI 0.14–2.26).[60] These findings support that cefepime and PTZ remain viable empirical treatment options. Additionally, Ram et al performed a RCT that demonstrated the continuous infusion of anti-pseudomonal beta-lactam drugs was more effective in high-risk FN patients, particularly those with CDI. The overall response rate was greatly higher in the continuous infusion group (68.4%) compared to the intermittent infusion group (35.7%, P=0.039).[61] However, the emergence of extensively drug-resistant GNB, such as *Acinetobacter* spp., PA, and carbapenemase-producing KP, has reduced the efficacy of certain third-generation cephalosporins and carbapenems as monotherapy. Therefore, optimizing initial empirical monotherapy for FN patients remains a critical challenge.

Choice of Empirical Combination Therapy for HM Patients With FN

There are some controversies about monotherapy and combination therapy in empirical treatment of FN patients. A Cochrane review[62] show no survival benefits for combination therapy (RR 0.80, 95% CI 0.64–0.99) compared to monotherapy. However, Albasanz et al conducted a multicenter retrospective cohort study and suggested that while the combined treatment

group had a higher proportion of patients with PA-BSI and MDR-PA BSI, the addition of aminoglycosides to the initial empirical treatment regimen led to a significant decrease in 7-day mortality (OR 0.33, 95% CI 0.13–0.82) among HM patients with FN. And short-course aminoglycoside therapy did not lead to a significant rise in renal dysfunction (OR 1.12, 95% CI 0.26–4.87) or multidrug resistance rates (28.2% vs 27%, P=0.95).[63] Patients with FN complicated by pulmonary infections are known to have higher mortality. A retrospective study analyzed the 1017 neutropenic HM patients with PA BSI, and indicated a notable rise in 30-day mortality in patients with pneumonia (55.1% vs 31.4%, P<0.001). The study also revealed that a combination therapy involving aminoglycosides and other medications independently improved survival (HR 0.46, 95% CI 0.27–0.78) in patients with PA pneumonia, whereas monotherapy did not reduce the mortality at 30 days (HR 1.25, 95% CI 0.76–2.05).[64] Chumbita et al also noted a significant survival benefit when combining aminoglycosides with beta-lactam drugs in septic shock patients. In a study involving amikacin monotherapy, mortality was 90%, whereas the addition of beta-lactams reduced mortality to 66%. However, the combined administration of both drugs demonstrated a notable survival benefit (OR 0.32, 95% CI 0.18–0.57)[35]. However, the nephrotoxic potential of aminoglycosides, which may limit their clinical utility, must be carefully considered. Careful assessment of renal function is essential to minimize the risk of nephrotoxicity during treatment.

In summary, empirical monotherapy targeting PA and other GNB remains the standard treatment for FN. However, in cases with high suspicion of carbapenem-resistant infections, utilizing the previously described scoring system for predicting CRPA BSI or CRE BSI, and in severe infections such as pneumonia and septic shock, combination therapy involving antipseudomonal beta-lactams and aminoglycosides, along with novel antibiotics like tigecycline or ceftazidime/avibactam (CAZ/AVI), may be warranted.

Duration of Treatment for Neutropenic Patients With FUO

Determining the appropriate timing for discontinuing antibiotics in FN patients is a key clinical consideration. The duration of treatment varies depending on the specific pathogen and infection site, such as in cases of CDI or MDI. However, standardized criteria for determining the length of antibiotic therapy in febrile neutropenia with FUO remain lacking. A comprehensive overview of antibiotic treatment duration for neutropenic patients with FUO since 2016 is provided in Table 3. The 2011 IDSA guidelines recommend continued administration of antimicrobials until the neutrophil count reaches≥0.5×10^9/L.[7] Conversely, the ECIL-4 guidelines recommended that FUO patient could discontinue empirical broad-spectrum antimicrobial therapy after more than 72 hours of use, without considering neutrophil count or the estimated duration of neutropenia, if they have stable hemodynamics and been afebrile for at least 48 hours.[30] Several studies had demonstrated that early discontinuation of broad-spectrum antibiotics can shorten the length of antibiotic treatment,[65–67] minimize ICU admissions, and decrease the risk of mortality in FUO patients.[68,69] In a RCT involving 157 patients with FUO, Aguilar-Guisado et al did not observe a significant difference in recurrent fever (11 vs 14, P=0.54) and 28-day mortality (1.3% vs 3.8%, P=0.62) between experimental group (discontinuation of broad-spectrum antibiotics after 48 hours apyrexia and clinical stability) (n=78) and the control group (until neutrophil recovery) (n=79).[70] Stern et al conducted a meta-analysis involving 8 RCTs and 662 FUO neutropenic patients, revealing no significant difference in all-cause mortality (RR 1.38, 95% CI 0.73–2.62), clinical failure rates (RR 1.23, 95% CI 0.85–1.77), incidence of bacteremia (RR 1.56, 95% CI 0.91–2.66) between the short-term and prolonged-term antibiotic regimens. And the short-term antibiotic group exhibited a reduction in total antibiotic days by 3 to 7 days compared to the prolonged-term group.[71] Recently, a retrospective multicenter observational study assess the risk of early stopping antibiotics in FUO HM patients undergoing induction chemotherapy or HSCT. Compared with the control group (n=178) (discontinuation of antibiotics until neutrophil recovery), it was observed no significant difference in ICU admission (6.5% vs 11.2%, P=0.17), 30-day mortality (1.4% vs 2.7%, P=0.68) and incidence of septic shock (0.6% vs 3.9%, P=0.07) in the early discontinuation group (n=147) (discontinuation of antibiotics after 72 h or later when afebrile for at least 48 h). Early discontinuation strategies were found to be correlated with a reduction in the average duration of antibiotic use (15.5 days vs 19.9 days, P <0.001), but an increase incidence of bacteremia recurrence (27.1% vs 11.8%, P <0.001).[72] Given the retrospective nature of this study, additional prospective studies or RCTs are necessary to validate its findings. It was important to emphasize that close monitoring of body temperature is necessary after discontinuing empiric antibiotics, and antibiotics should be reinstated if fever recurs.

Table 3 A Comprehensive Overview of Antibiotic Treatment Duration for Neutropenic Patients With FUO

Study (Author, Year, Country)	Design	Population	Intervention	Days of Antibiotics	Mortality	Febrile Recurrences	Rate of Bacteremia	Other Results
Fuller, 2020, USA[65]	Single-center, Retrospective cohort	AML patients with FN of unknown origin	E: prior to neutrophil recovery (n=38) C: until neutrophil recovery (n=39)	E: 9; C: 15; P < 0.01	E:3%; C:10%; P = 0.40	HR 0.54 (95% CI 0.34–0.88)		
Ishikawa, 2023, Japan[66]	Meta-analysis: 11 RCTs (1977–2022)	1128 HM patients with unknown origin FN	E: short-term (n=526) C: long-term (n=543)	NA	RR 1.43 (95% CI 0.81–2.53)		RR 1.32 (95% CI 0.87–2.01)	Clinical failure: (RR 1.14, 95% CI 0.86–1.49)
Rearigh, 2020, USA[67]	Single-center, retrospective	HSCT recipients with FN of unknown origin	E: ECIL-4 (n=83) C: until neutrophil recovery (n=214)	E: 3.86; C: 4.62; P =0.03	E: 0; C: 0.4%; P =1		13.2% (E) vs 8.4% (C), P = 0.27	
Snyder, 2017, USA[68]	Single-center, Retrospective cohort	Allo-HSCT with FN of unknown origin	E: ECIL-4 (n=46) C: until neutrophil recovery (n=74)	E: 8.3; C: 10.1; P = 0.028	E: 0; C: 4%; P = 0.285	15% (E) vs 19% (C), P = 0.026		ICU admission: 0% (E) vs 3% (C), P = 0.52
Petteys, 2020, USA[69]	Single-center, Retrospective cohort	HSCT with FN of unknown origin	E: ECIL-4 (n=24) C: until neutrophil recovery (n=83)	E: 8 (3–25); C: 7 (2–6); P = 0.34	E: 0; C: 0;	4.2% (E) vs 7.2% (C), P = 0.85		Re-escalation of therapy: 4.2% (E) vs 4.8% (C), P = 0.64
Aguilar-Guisado, 2017, Spain[70]	Multi-center, Open-label RCT	HM or HSCT with high-risk FN without aetiological diagnosis	E: ECIL-4 (n=78) C: until neutrophil recovery (n=79)	E:16.1; C: 13.6; P = 0.026	E: 1.3%; C: 3.8%; P = 0.62	71.2% (E) vs 71.3% (C), P = 0.97		Days of fever: 5.7 (E) vs 6.3 (C), P = 0.53
Stern, 2019, Israel[71]	Meta-analysis: 8 RCTs (1973–2017)	662 episodes of unknown origin FN	E: short-term (n=285) C: long-term (n=318)	Less total antibiotics in E by 3–7 d	RR 1.38 (95% CI 0.73–2.62)		RR 1.56 (95% CI 0.91–2.66)	Antibiotic resistance (RR 1.49, 95% CI 0.62–3.61);
Paret, 2022, France[72]	Retrospective, multi-center observational	HM or HSCT with FN	E: ECIL-4 (n=147) C: until neutrophil recovery (n=178)	E:15.5; C: 19.9; P < 0.001	E: 1.4%; C: 2.7%; P = 0.084		27.1% (E) vs 11.8% (C), P < 0.01	ICU admission: 6.5% (E) vs 11.2% (C), P = 0.17
Le Clech, 2018, France[73]	Single-center, prospective observational	HM patients with FN of unknown origin	E: ECIL-4 (n=45) C: discontinuation by day 5 (n=37)	E: 7 (5–12); C: 5 (4–5.5); P = 0.0002	E: 2.2%; C: 5.4%; P = 0.80	20% (E) vs 21.6% (C), P = 0.82		ICU admission: 2.2% (E) vs 13.5% (C), P = 0.48
De Jonge, 2022, The Netherlands[74]	Open-label, multi-center, RCT	HM patients with FN of unknown origin, high-risk neutropenia expected for >7 days	E: antibiotics 72 h (n=144) C: until afebrile 5 days or neutrophil recovery (n=137)	E: 6; C: 8; P=0.2	E: 2.1%; C: 0.7%; P>0.05			Adverse events: 16% (E) vs 10% (C), P<0.0001 ICU admission: 4% (E) vs 3% (C), P=0.19
Schauwvliegh, 2021, The Netherlands and Belgium[75]	Multi-center, Retrospective cohort	AML/MDS patients with FN of unknown origin	E: meropenem 72 h (n=305) C: until neutrophil recovery (n=270)	E: 9 (5–13); C: 19 (13–25); P < 0.001	E: 8.5%; C:4.4%; P = 0.049			Adverse events: 12.5% (E) vs 8.9% (C), P = 0.17

Abbreviations: FN, febrile neutropenia; HM, hematologic malignancy; RCT, randomized controlled trial; HSCT, hematopoietic stem cell transplantation; E: Experimental group; C: Control group; ECIL-4, discontinuation of antibiotics after 72 h or later when hemodynamically stable and afebrile for at least 48 h, irrespective of neutrophil count and expected duration of neutropenia.

Persistent fever was common after initiation of empiric antibiotic therapy, necessitating a reevaluation of its underlying cause within 3–4 days of treatment. This reassessment should involve a comprehensive physical examination, regular blood cultures every 2–3 days, and testing for infection-related biomarkers. If there were any signs of clinical deterioration, the antibiotic regimen should be adjusted promptly, with broad coverage of GPB, GNB, and fungi if necessary. However, if patients remain clinically stable, there is no need to alter the initial antimicrobial therapy solely for persistent fever. Several studies have explored the feasibility and safety of early cessation of broad-spectrum antibiotics in FUO patients with persistent fever. Clech et al comparing two discontinuation strategies in FUO patients: 1) discontinuation of empirical antibiotics after 48 hours of fever resolution, following ECIL-4 guidelines (group 1); and 2) discontinuation on day 5, irrespective of persistent fever and neutrophil recovery (group 2). The study found no statistically differences in in-hospital mortality (HR 0.70, P = 0.80), ICU admissions (HR 0.38, P = 0.48), or infection recurrence (HR 0.92, P = 0.82) between the two groups. However, the duration of antibiotic treatment and neutropenia in group 2 was significantly shorter (5 days vs 7 days, P = 0.002; 12 days vs 20 days, P = 0.01). It suggested that caution should be exercised when interpreting these findings, as the shorter neutropenia duration could have influenced the outcomes.[73] A recent multicenter trial randomized FUO patients with neutropenia to short-term treatment group (72 hours of carbapenem therapy) (n=144) and extended treatment group (≥9 days of carbapenem therapy until 5 days of defervesce or neutrophil recovery) (n=137). The findings indicated that among patients with persistent fever even after 72 hours of treatment, the 30-day infection-related mortality was greatly higher in the short-term treatment group (3/81 vs 0/71, P < 0.05). However, no notable difference in 30-day infection-related mortality was observed between the two groups among afebrile patients (0/63 vs 1/66, P > 0.05).[74] In contrast, Schauwvlieghe et al conducted a multicenter retrospective cohort study to evaluate the impact of early cessation of empirical antibiotic therapy in FUO patients with neutropenia. They found early discontinuation group (treated with broad-spectrum antibiotics for 3 days regardless of fever resolution, n=305) showed a significantly shorter duration of antimicrobial use compared to the prolonged-term group (treated with antibiotics until neutrophil recovery, n=270) (9 days vs 19 days, P < 0.001). Importantly, the findings indicated no major differences in serious complications across the two groups, including 30-day mortality and ICU admissions. The authors concluded that early discontinuation of antibiotics after more than 48 hours of defervescence and clinical stabilization could be considered in FUO patients, but emphasized that in cases of persistent fever, premature cessation of antibiotics may worsen the prognosis.[75] In summary, while early cessation of antibiotics may reduce the duration of antimicrobial therapy in neutropenic FUO patients, this approach should be cautiously considered in the context of persistent fever.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; SZF gave final approval of the version to be published; XL have agreed on the journal to which the article has been submitted; and YQC agree to be accountable for all aspects of the work.

Funding

This study was supported by the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2021-I2M-1-017; 2023-I2M-2-007), Tianjin Municipal Science and Technology Commission Grant (21JCZDJC01170).

Disclosure

The authors have no conflicts of interest to disclose.

References

1. Peseski AM, Mcclean M, Green SD, et al. Management of fever and neutropenia in the adult patient with acute myeloid leukemia[J]. *Expert Rev Anti Infect Ther*. 2021;19(3):359–378. doi:10.1080/14787210.2020.1820863
2. Christopeit M, Schmidt-Hieber M, Sprute R, et al. Prophylaxis, diagnosis and therapy of infections in patients undergoing high-dose chemotherapy and autologous haematopoietic stem cell transplantation. 2020 update of the recommendations of the Infectious diseases working party (AGIHO) of the German society of hematology and medical oncology (DGHO)[J]. *Ann Hematol*. 2021;100(2):321–336. doi:10.1007/s00277-020-04297-8
3. Logan C, Koura D, Taplitz R. Updates in infection risk and management in acute leukemia[J]. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):135–139. doi:10.1182/hematology.2020000098

4. Wudhikarn K, Perales MA. Infectious complications, immune reconstitution, and infection prophylaxis after CD19 chimeric antigen receptor T-cell therapy[J]. *Bone Marrow Transplant*. 2022;57(10):1477–1488. doi:10.1038/s41409-022-01756-w
5. Prosty C, Katergi K, Nguyen A, et al. Infectious complications of venetoclax treatment of hematologic malignancies: a systematic review and meta-analysis[J]. *Blood Adv*. 2023;2024:bloodadvances-–2023011964.
6. Kameda K, Kimura SI, Misaki Y, et al. Associations between febrile neutropenia-related parameters and the risk of acute GVHD or non-relapse mortality after allogeneic hematopoietic stem cell transplantation[J]. *Bone Marrow Transplant*. 2019;54(5):707–716. doi:10.1038/s41409-018-0330-2
7. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America[J]. *Clin Infect Dis*. 2011;52(4):e56–93. doi:10.1093/cid/cir073
8. Liu CY, Lai YC, Huang LJ, et al. Impact of bloodstream infections on outcome and the influence of prophylactic oral antibiotic regimens in allogeneic hematopoietic SCT recipients[J]. *Bone Marrow Transplant*. 2011;46(9):1231–1239. doi:10.1038/bmt.2010.286
9. Penack O, Becker C, Buchheidt D, et al. Management of sepsis in neutropenic patients: 2014 updated guidelines from the infectious diseases working party of the German society of hematology and medical oncology (AGIHO)[J]. *Ann Hematol*. 2014;93(7):1083–1095. doi:10.1007/s00277-014-2086-0
10. Kang CI, Song JH, Chung DR, et al. Risk factors and pathogenic significance of severe sepsis and septic shock in 2286 patients with gram-negative bacteremia[J]. *J Infect*. 2011;62(1):26–33. doi:10.1016/j.jinf.2010.10.010
11. Girmenia C, Rossolini GM, Piciocchi A, et al. Infections by carbapenem-resistant Klebsiella pneumoniae in SCT recipients: a nationwide retrospective survey from Italy[J]. *Bone Marrow Transplant*. 2015;50(2):282–288. doi:10.1038/bmt.2014.231
12. El Omri H, Padmanabhan R, Taha RY, et al. Dissecting bloodstream infections in febrile neutropenic patients with hematological malignancies, a decade-long single center retrospective observational study (2009-2019)[J]. *J Infect Public Health*. 2024;17(1):152–162. doi:10.1016/j.jiph.2023.11.017
13. Chen J, Ma H, Huang X, et al. Risk factors and mortality of carbapenem-resistant Klebsiella pneumoniae bloodstream infection in a tertiary-care hospital in China: an eight-year retrospective study[J]. *Antimicrob Resist Infect Control*. 2022;11(1):161. doi:10.1186/s13756-022-01204-w
14. Jiang AM, Liu N, Zhao R, et al. Clinical outcomes and prognostic factors in bloodstream infections due to extended-spectrum β-lactamase-producing Enterobacteriaceae among patients with malignancy: a meta-analysis[J]. *Ann Clin Microbiol Antimicrob*. 2020;19(1):53. doi:10.1186/s12941-020-00395-7
15. Zhao Y, Lin Q, Liu L, et al. Risk factors and outcomes of antibiotic-resistant pseudomonas aeruginosa bloodstream infection in adult patients with acute leukemia[J]. *Clin Infect Dis*. 2020;71(Suppl 4):S386–s393. doi:10.1093/cid/ciaa1522
16. Schonardie AP, Beck E, Rigatto MH. Prevalence of bloodstream infection pathogens in hemato-oncological patients and predictors of carbapenem-resistant gram-negative bacterial infections during febrile neutropenia[J]. *Braz J Infect Dis*. 2023;27(2):102758. doi:10.1016/j.bjid.2023.102758
17. Kolonen A, Sinisalo M, Huttunen R, et al. Bloodstream infections in acute myeloid leukemia patients treated according to the Finnish leukemia group AML-2003 protocol - a prospective nationwide study[J]. *Infect Dis*. 2017;49(11–12):799–808. doi:10.1080/23744235.2017.1347814
18. Yan CH, Xu T, Zheng XY, et al. Epidemiology of febrile neutropenia in patients with hematological disease-a prospective multicentre survey in China][J]. *Zhonghua Xue Ye Xue Za Zhi*. 2016;37(3):177–182. doi:10.3760/cma.j.issn.0253-2727.2016.03.001
19. Nam EY, Song KH, Kim NH, et al. Differences in characteristics between first and breakthrough neutropenic fever after chemotherapy in patients with hematologic disease[J]. *Int J Infect Dis*. 2016;44:4–7. doi:10.1016/j.ijid.2016.01.006
20. Erdem H, Kocoglu E, Ankarali H, et al. Prospective analysis of febrile neutropenia patients with bacteraemia: the results of an international ID-IRI study[J]. *Int J Antimicrob Agents*. 2023;62(3):106919. doi:10.1016/j.ijantimicag.2023.106919
21. Ghosh S, Chakraborty M, Samanta S, et al. Analysis of blood stream infections, antibiograms and clinical outcomes in haematological patients with febrile neutropenia: data from a tertiary care haematology institute in India[J]. *Ann Hematol*. 2021;100(2):395–403. doi:10.1007/s00277-020-04324-8
22. Rosa RG, Goldani LZ, Dos Santos RP. Risk factors for multidrug-resistant bacteremia in hospitalized cancer patients with febrile neutropenia: a cohort study[J]. *Am J Infect Control*. 2014;42(1):74–76. doi:10.1016/j.ajic.2013.06.025
23. Marini BL, Hough SM, Gregg KS, et al. Risk factors for piperacillin/tazobactam-resistant Gram-negative infection in hematology/oncology patients with febrile neutropenia[J]. *Support Care Cancer*. 2015;23(8):2287–2295. doi:10.1007/s00520-014-2582-8
24. Moghnieh R, Estaitieh N, Mugharbil A, et al. Third generation cephalosporin resistant Enterobacteriaceae and multidrug resistant gram-negative bacteria causing bacteremia in febrile neutropenia adult cancer patients in Lebanon, broad spectrum antibiotics use as a major risk factor, and correlation with poor prognosis[J]. *Front Cell Infect Microbiol*. 2015;5:11. doi:10.3389/fcimb.2015.00011
25. Zhao Y, Lin Q, Zhang T, et al. Pseudomonas aeruginosa bloodstream infection in patients with hematological diseases: clinical outcomes and prediction model of multidrug-resistant infections[J]. *J Infect*. 2023;86(1):66–117. doi:10.1016/j.jinf.2022.08.037
26. Viasus D, Puerta-Alcalde P, Cardozo C, et al. Predictors of multidrug-resistant Pseudomonas aeruginosa in neutropenic patients with bloodstream infection[J]. *Clin Microbiol Infect*. 2020;26(3):345–350. doi:10.1016/j.cmi.2019.07.002
27. Girmenia C, Bertaina A, Piciocchi A, et al. Incidence, risk factors and outcome of pre-engraftment gram-negative bacteremia after allogeneic and autologous hematopoietic stem cell transplantation: an Italian prospective multicenter survey[J]. *Clin Infect Dis*. 2017;65(11):1884–1896. doi:10.1093/cid/cix690
28. Liu J, Zhang H, Feng D, et al. Development of a risk prediction model of subsequent bloodstream infection after carbapenem-resistant Enterobacteriaceae isolated from perianal swabs in hematological patients[J]. *Infect Drug Resist*. 2023;16:1297–1312. doi:10.2147/IDR.S400939
29. Kirkizlar TA, Akalin H, Kirkizlar O, et al. Vancomycin-resistant enterococci infection and predisposing factors for infection and mortality in patients with acute leukaemia and febrile neutropenia[J]. *Leuk Res*. 2020;99:106463. doi:10.1016/j.leukres.2020.106463
30. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia[J]. *Haematologica*. 2013;98(12):1826–1835. doi:10.3324/haematol.2013.091025
31. Zhai W, Zhang X, Wei J, et al. A prospective observational study of antibiotic therapy in febrile neutropenia patients with hematological malignances from multiple centers in Northeast China. *Int J Infect Dis*. 2015;37:97–103. doi:10.1016/j.ijid.2015.04.015
32. Wang J, Wang M, Zhao A, et al. Microbiology and prognostic prediction model of bloodstream infection in patients with hematological malignancies[J]. *Front Cell Infect Microbiol*. 2023;13:1167638. doi:10.3389/fcimb.2023.1167638

33. Bastug A, Kayaaslan B, Kazancioglu S, et al. Emergence of multidrug resistant isolates and mortality predictors in patients with solid tumors or hematological malignancies[J]. *J Infect Dev Ctries*. 2015;9(10):1100–1107. doi:10.3855/jidc.6805
34. Calik S, Ari A, Bilgir O, et al. The relationship between mortality and microbiological parameters in febrile neutropenic patients with hematological malignancies[J]. *Saudi Med J*. 2018;39(9):878–885. doi:10.15537/smj.2018.9.22824
35. Chumbita M, Puerta-Alcalde P, Gudiol C, et al. Impact of empirical antibiotic regimens on mortality in neutropenic patients with bloodstream infection presenting with septic shock[J]. *Antimicrob Agents Chemother*. 2022;66(2):e0174421. doi:10.1128/AAC.01744-21
36. Sereeaphinan C, Kanchanasuwan S, Julamanee J. Mortality-associated clinical risk factors in patients with febrile neutropenia: a retrospective study[J]. *IJID Reg*. 2021;1:5–11. doi:10.1016/j.ijregi.2021.09.002
37. Marín M, Gudiol C, Ardanuy C, et al. Factors influencing mortality in neutropenic patients with haematologic malignancies or solid tumours with bloodstream infection[J]. *Clin Microbiol Infect*. 2015;21(6):583–590. doi:10.1016/j.cmi.2015.01.029
38. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update[J]. *J Clin Oncol*. 2018;36(14):1443–1453. doi:10.1200/JCO.2017.77.6211
39. Kern WV, Weber S, Dettenkofer M, et al. Impact of fluoroquinolone prophylaxis during neutropenia on bloodstream infection: data from a surveillance program in 8755 patients receiving high-dose chemotherapy for haematologic malignancies between 2009 and 2014[J]. *J Infect*. 2018;77(1):68–74. doi:10.1016/j.jinf.2018.05.004
40. Mikulska M, Averbuch D, Tissot F, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines[J]. *J Infect*. 2018;76(1):20–37. doi:10.1016/j.jinf.2017.10.009
41. Clerici D, Galli L, Greco R, et al. Levofloxacin prophylaxis vs no prophylaxis in patients with neutropenia within an endemic country for carbapenem-resistant GNB[J]. *Blood Adv*. 2023;7(9):1621–1634. doi:10.1182/bloodadvances.2022008226
42. Chong Y, Shimoda S, Miyake N, et al. Incomplete recovery of the fecal flora of hematological patients with neutropenia and repeated fluoroquinolone prophylaxis[J]. *Infect Drug Resist*. 2017;10:193–199. doi:10.2147/IDR.S133333
43. Gudiol C, Aguilar-Guisado M, Azanza JR, et al. Executive summary of the consensus document of the Spanish society of infectious diseases and clinical microbiology (SEIMC), the Spanish network for research in infectious diseases (REIPI) and the Spanish society of haematology and haemotherapy (SEHH) on the management of febrile neutropenia in patients with hematological malignancies[J]. *Enferm Infecc Microbiol Clin*. 2020;38(4):174–181. doi:10.1016/j.eimc.2019.01.013
44. Tunkel AR, Hasbun R, Bhimraj A, et al. Infectious diseases society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis[J]. *Clin Infect Dis*. 2017;64(6):e34–e65. doi:10.1093/cid/ciw861
45. Chow KM, Li PK, Cho Y, et al. ISPD catheter-related infection recommendations: 2023 update[J]. *Perit Dial Int*. 2023;43(3):201–219. doi:10.1177/08968608231172740
46. Pintado V, Ruiz-Garbajosa P, Aguilera-Alonso D, et al. Executive summary of the consensus document of the Spanish society of infectious diseases and clinical microbiology (SEIMC) on the diagnosis and antimicrobial treatment of infections due to carbapenem-resistant Gram-negative bacteria[J]. *Enferm Infecc Microbiol Clin*. 2023;41(6):360–370. doi:10.1016/j.eimc.2022.06.004
47. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious diseases society of America 2022 guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), Carbapenem-resistant enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-P. aeruginosa)[J]. *Clin Infect Dis*. 2022;75(2):187–212. doi:10.1093/cid/ciac268
48. Paul M, Dickstein Y, Borok S, et al.Empirical antibiotics targeting Gram-positive bacteria for the treatment of febrile neutropenic patients with cancer[J]. *Cochrane Database Syst Rev*. 2014;(1):Cd003914. doi:10.1002/14651858.CD003914.pub3
49. Beyar-Katz O, Dickstein Y, Borok S, et al. Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer[J]. *Cochrane Database Syst Rev*. 2017;6(6):Cd003914. doi:10.1002/14651858.CD003914.pub4
50. Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, version 2.2016, NCCN clinical practice guidelines in oncology[J]. *J Natl Compr Canc Netw*. 2016;14(7):882–913. doi:10.6004/jnccn.2016.0093
51. Horita N, Shibata Y, Watanabe H, et al. Comparison of antipseudomonal β-lactams for febrile neutropenia empiric therapy: systematic review and network meta-analysis[J]. *Clin Microbiol Infect*. 2017;23(10):723–729. doi:10.1016/j.cmi.2017.03.024
52. Leibovici L, Yahav D, Paul M. Meta-analysis of a possible signal of increased mortality associated with cefepime use[J]. *Clin Infect Dis*. 2010;51(11):1350–1351. doi:10.1086/657247
53. Andreatos N, Flokas ME, Apostolopoulou A, et al. The dose-dependent efficacy of cefepime in the empiric management of febrile neutropenia: a systematic review and meta-analysis[J]. *Open Forum Infect Dis*. 2017;4(3):ofx113. doi:10.1093/ofid/ofx113
54. Kim PW, Wu YT, Cooper C, et al. Meta-analysis of a possible signal of increased mortality associated with cefepime use[J]. *Clin Infect Dis*. 2010;51(4):381–389. doi:10.1086/655131
55. Zimmer AJ, Stohs E, Meza J, et al. Bloodstream infections in hematologic malignancy patients with fever and neutropenia: are empirical antibiotic therapies in the United States still effective?[J]. *Open Forum Infect Dis*. 2022;9(7):ofac240. doi:10.1093/ofid/ofac240
56. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial resistance in gram-negative rods causing bacteremia in hematopoietic stem cell transplant recipients: intercontinental prospective study of the infectious diseases working party of the European bone marrow transplantation group[J]. *Clin Infect Dis*. 2017;65(11):1819–1828. doi:10.1093/cid/cix646
57. Arizpe A, Reveles KR, Patel SD, et al. Updates in the management of cephalosporin-resistant gram-negative bacteria[J]. *Curr Infect Dis Rep*. 2016;18(12):39. doi:10.1007/s11908-016-0552-7
58. Gutiérrez-Gutiérrez B, Pérez-Galera S, Salamanca E, et al. A multinational, preregistered cohort study of β-lactam/β-lactamase inhibitor combinations for treatment of bloodstream infections due to extended-spectrum-β-lactamase-producing Enterobacteriaceae[J]. *Antimicrob Agents Chemother*. 2016;60(7):4159–4169. doi:10.1128/AAC.00365-16
59. Gudiol C, Royo-Cebrecos C, Abdala E, et al. Efficacy of β-lactam/β-lactamase inhibitor combinations for the treatment of bloodstream infection due to extended-spectrum-β-lactamase-producing Enterobacteriaceae in hematological patients with neutropenia[J]. *Antimicrob Agents Chemother*. 2017;61(8). doi:10.1128/AAC.00164-17.
60. Benanti GE, Brown ART, Shigle TL, et al. Carbapenem versus cefepime or piperacillin-tazobactam for empiric treatment of bacteremia due to extended-spectrum-β-lactamase-producing Escherichia coli in patients with hematologic malignancy[J]. *Antimicrob Agents Chemother*. 2019;63(2). doi:10.1128/AAC.01813-18.

61. Ram R, Halavy Y, Amit O, et al. Extended vs bolus infusion of broad-spectrum β-lactams for febrile neutropenia: an unblinded, randomized trial[J]. *Clin Infect Dis*. 2018;67(8):1153–1160. doi:10.1093/cid/ciy258
62. Paul M, Dickstein Y, Schlesinger A, et al. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia[J]. *Cochrane Database Syst Rev*. 2013;2013(6):Cd003038. doi:10.1002/14651858.CD003038.pub2
63. Albasanz-Puig A, Gudiol C, Puerta-Alcalde P, et al. Impact of the inclusion of an aminoglycoside to the initial empirical antibiotic therapy for gram-negative bloodstream infections in hematological neutropenic patients: a propensity-matched cohort study (AMINOLACTAM Study)[J]. *Antimicrob Agents Chemother*. 2021;65(8):e0004521. doi:10.1128/AAC.00045-21
64. Albasanz-Puig A, Durà-Miralles X, Laporte-Amargós J, et al. Effect of combination antibiotic empirical therapy on mortality in neutropenic cancer patients with pseudomonas aeruginosa pneumonia[J]. *Microorganisms*. 2022;10(4):733. doi:10.3390/microorganisms10040733
65. Fuller R, Moshier E, Jacobs SE, et al. Practicing antimicrobial stewardship: de-escalating antibiotics in patients with acute myeloid leukemia and neutropenic fever[J]. *Open Forum Infect Dis*. 2020;7(5):ofaa138. doi:10.1093/ofid/ofaa138
66. Ishikawa K, Masaki T, Kawai F, et al. Systematic review of the short-term versus long-term duration of antibiotic management for neutropenic fever in patients with cancer[J]. *Cancers*. 2023;15(5):1611. doi:10.3390/cancers15051611
67. Rearigh L, Stohs E, Freifeld A, et al. De-escalation of empiric broad spectrum antibiotics in hematopoietic stem cell transplant recipients with febrile neutropenia[J]. *Ann Hematol*. 2020;99(8):1917–1924. doi:10.1007/s00277-020-04132-0
68. Snyder M, Pasikhova Y, Baluch A. Early antimicrobial de-escalation and stewardship in adult hematopoietic stem cell transplantation recipients: retrospective review[J]. *Open Forum Infect Dis*. 2017;4(4):ofx226. doi:10.1093/ofid/ofx226
69. Petteys MM, Kachur E, Pillinger KE, et al. Antimicrobial de-escalation in adult hematopoietic cell transplantation recipients with febrile neutropenia of unknown origin[J]. *J Oncol Pharm Pract*. 2020;26(3):632–640. doi:10.1177/1078155219865303
70. Aguilar-Guisado M, Espigado I, Martín-Peña A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled Phase 4 trial[J]. *Lancet Haematol*. 2017;4(12):e573–e583. doi:10.1016/S2352-3026(17)30211-9
71. Stern A, Carrara E, Bitterman R, et al. Early discontinuation of antibiotics for febrile neutropenia versus continuation until neutropenia resolution in people with cancer[J]. *Cochrane Database Syst Rev*. 2019;1(1):Cd012184. doi:10.1002/14651858.CD012184.pub2
72. Paret R, Le Bourgeois A, Guillerm G, et al. Safety and risk of febrile recurrence after early antibiotic discontinuation in high-risk neutropenic patients with haematological malignancies: a multicentre observational study[J]. *J Antimicrob Chemother*. 2022;77(9):2546–2556. doi:10.1093/jac/dkac190
73. Le Clech L, Talarmin JP, Couturier MA, et al. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study[J]. *Infect Dis*. 2018;50(7):539–549. doi:10.1080/23744235.2018.1438649
74. De Jonge NA, Sikkens JJ, Zweegman S, et al. Short versus extended treatment with a carbapenem in patients with high-risk fever of unknown origin during neutropenia: a non-inferiority, open-label, multicentre, randomised trial[J]. *Lancet Haematol*. 2022;9(8):e563–e572. doi:10.1016/S2352-3026(22)00145-4
75. Schauwvlieghe A, Dunbar A, Storme E, et al. Stopping antibiotic therapy after 72 h in patients with febrile neutropenia following intensive chemotherapy for AML/MDS (safe study): a retrospective comparative cohort study[J]. *EClinicalMedicine*. 2021;35:100855. doi:10.1016/j.eclinm.2021.100855