Neutropenia and antibiotics: when, what, how and why?

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Purpose of review
Our aim is to review recent literature on antibiotic use in patients with neutropenia.

Recent findings
Prophylactic antibiotics are associated with risks and have limited mortality benefit. While early antibiotic use in febrile neutropenia (FN) is critical, early de-escalation or discontinuation may be safe in many patients.

Summary
With an increasing understanding of potential risks and benefits of use and improved risk assessment, paradigms of antibiotic use in neutropenic patients are changing.

Keywords
de-escalation, neutropenia, prophylaxis

INTRODUCTION

Patients with malignancy-associated neutropenia are vulnerable to infections, a major cause of morbidity and mortality. Both the degree and duration of neutropenia impacts infection risk. Patients with solid tumors usually have neutropenia for less than 7 days, and 5–30% will develop febrile neutropenia (FN). Patients with hematologic malignancies undergoing chemotherapy or hematopoietic stem cell transplantation (HSCT) are neutropenic for longer, and more than 80% will develop FN. An infectious etiology is identified in only 40–50% of neutropenic patients, with 10–30% found to be bacteremia, with translocation of enteric bacteria the most common source [1]. Antibiotic prophylaxis to abrogate bacteremia and improve outcome has been studied, and has been a standard of care at many institutions. Fluoroquinolone prophylaxis has been associated with decreased rates of infection in patients with neutropenia, though most studies do not show an overall survival benefit [2]. However, fluoroquinolone prophylaxis has been associated with the development of drug resistant infections, drug toxicities, adverse changes in the gut microbiome and increased *Clostridioides difficile* colitis rates, and adverse impacts on graft-versus-host disease (GVHD) and transplant outcomes [3–5]. Balancing infection prevention strategies with benefits and risks of antimicrobial prophylaxis is challenging. Limiting the use of prophylactic antibiotics to those at highest risk of infection and minimizing duration and spectrum of antibiotics is an admirable goal, as is developing strategies to risk-stratify patients. Here we review when antibiotics may be most appropriate, how they can be beneficial and harmful, and future strategies to guide appropriate use in this vulnerable population.

CASE

A 52-year-old woman presents with progressive fatigue and is noted to have a white blood count of 83,500 cells/μL, with 65% blasts. She is diagnosed with acute myelogenous leukemia (AML) and started on induction chemotherapy therapy with cytarabine + daunorubicin. Levofloxacin, posaconazole, and acyclovir prophylaxis are initiated. Seven days into treatment, when her absolute neutrophil count is 75 cells/μL, she develops a fever to

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KEY POINTS

- Recent literature on antibiotic use in patients with FN describes that prophylactic antibiotics are associated with risks and have limited mortality benefit.
- For patients with FN, early de-escalation and discontinuation of antibiotics may be safe for some patients.
- A personalized individual assessment that takes into account a patient's underlying disease state, co-morbidities, prior infection or colonization of drug-resistant infections, level of immunosuppression, and previous and current antimicrobial therapies is key to tailor antibiotic treatment more appropriately in patients with FN.
- Future methods to guide appropriate antibiotic use includes high frequency temperature monitoring, evaluation and manipulation of the microbiome, immunogenetic risk assessment, and machine learning.

39°C. Her physical exam is unremarkable. Blood and urine cultures are obtained and cefepime is initiated. Computed tomography scan of the sinuses, chest, abdomen, and pelvis are negative. She defervesces and at 48 h remains afebrile and clinically stable with negative cultures.

WHEN ARE ANTIBIOTICS FOR FEBRILE NEUTROPENIA APPROPRIATE?

Patients with FN require prompt evaluation and initiation of antibiotics. The Infectious Disease Society of America (IDSA), National Comprehensive Cancer Network Cancer (NCCN), and the American Society for Clinical Oncology (ASCO) [6,7] recommend risk assessment for FN-related complications utilizing clinical judgement and/or scoring systems such as Multinational Association of Supportive Care in Cancer or the Clinical Index of Stable Febrile Neutropenia, which allows clinicians to rapidly assess patients for need for inpatient care and complication risks. Our patient is deemed high risk according to IDSA and NCCN guidelines, so inpatient care and initiation of broad-spectrum antibiotics (BSA) was appropriate. Other considerations in determining most appropriate antibiotics includes prior colonization or infection with multidrug resistant organisms, infection site, local susceptibility patterns, renal or liver insufficiency, drug allergies, and prior antimicrobial therapy. Detailed algorithms exist in guidelines and should be adapted to individual facilities based on local epidemiology and antibiotic resistance trends.

SHOULD OUR PATIENT HAVE RECEIVED PROPHYLACTIC ANTIBIOTICS UPON INITIATION OF CHEMOTHERAPY? WHY SHOULD WE TRY TO LIMIT ANTIBIOTIC USE?

Although numerous studies attempted to evaluate the relationship between prophylactic antibiotics and infection, many were hampered by the inclusion of mixed patient populations (solid tumor, leukemia, transplant; adult or children), lack of randomization or control, and differences in outcome measures (fever, bacteremia, or mortality) making it difficult to generalize results. A number of meta-analyses have been performed to help develop a consensus approach, and two recent meta-analyses from 2014 and 2018 that evaluated the utility of fluoroquinolone prophylaxis determined prophylaxis decreases the incidence of infection, but neither found it impacted overall mortality [2,8].

Antibiotic use in cancer patients with neutropenia is associated with an increased risk of drug-resistant infections [9,10]. In patients with hematologic malignancies and HSCT, fluoroquinolone prophylaxis was associated with higher rates of colonization with resistant bacteria, and breakthrough bacteremia with meropenem-resistant *Pseudomonas aeruginosa* bacteremia [11,12]. Additionally, the use of BSA impacts the microbiome, and patients who received antibiotics during FN had decreased microbiome biodiversity [13,14], potentially increasing the risk of bacterial translocation and bacteremia [13,15,16]. Microbiome changes in HSCT recipients are also associated with risk of GVHD [17] and can serve as a predictor of mortality [18]. Fluoroquinolone use has other risks as well, including black box warnings for serious adverse reactions, including tendinitis, tendon rupture, peripheral neuropathy, and central nervous system effects. Other risks include QT prolongation, aortic aneurysm and dissection, risk of *C. difficile* colitis, and myasthenia gravis exacerbation [19].

Because of uncertainty about risk and benefits, antibacterial prophylaxis remains a controversial topic in guidelines. Both ASCO/IDSA guidelines recommend fluoroquinolone prophylaxis in high-risk patients, specifically those expected to have profound, protracted neutropenia, (<100 neutrophils/μL for more than 7 days), or other risk factors. These guidelines do not recommend prophylaxis in low-risk patients and caution potentially limited utility with reduced-intensity conditioning regimens. They also raise concerns about prophylaxis, including increasing resistance, which may lead to increased all-cause mortality. Thus, the benefits of fluoroquinolone use should be weighed against the

risks [6]. NCCN guidelines recommend considering fluoroquinolone prophylaxis during neutropenia. They too recommend caution and suggest these risks be taken into consideration when selecting prophylactic agents [7]. Neither of these guidelines take into consideration the location of the patient, an important nuance as more procedures such as autologous transplant move to the outpatient environment.

The European and Australian guidelines are more stringent in recommending antibiotic prophylaxis. Australian guidelines specify that prophylaxis in patients with neutropenia is controversial and not recommended due to a lack of evidence for mortality benefit and concerns for antimicrobial resistance. The exception is among outpatients undergoing HSCT and as a palliative measure in patients with bone marrow failure [20]. The European Society Medical Oncology acknowledges that fluoroquinolone prophylaxis reduces the infection incidence, and in some studies, infection-related mortality, but at the expense of increasing drug-resistant strains, which jeopardizes treatment in low-risk patients. Therefore, the guidelines discourage the use of fluoroquinolone prophylaxis [21]. Similarly, the European Conference on Infections in Leukemia (ECIL) notes the possible benefits of fluoroquinolone prophylaxis on bacteremia rates, but without overall mortality benefit, thus they suggest weighing the benefits against the risks of fluoroquinolone toxicity and center-specific ecology [8]. And most recently, updated ECIL guidelines from 2021 reviewed the risk of infections and FN associated with other agents including immunotherapy and molecular therapies for the treatment of AML and acute lymphocytic leukemia (ALL). They conclude that most agents do not pose a significant infection risk when used as monotherapy, but caution is recommended when combining agents. Antibacterial prophylaxis is only recommended when hypomethylating agents are combined with venetoclax [22▪▪].

While the guidelines recommend risk-assessment, in general they do not account for inpatient versus outpatient status with regards to prophylaxis. Perhaps the need for antimicrobial prophylaxis should take into consideration how quickly antibiotics can be initiated. New approaches to risk stratification for prophylaxis are needed.

WHEN CAN WE DE-ESCALATE OR STOP ANTIBIOTICS?

In our patient, BSA were indicated for FN. With no clinical or microbiologic evidence of infection after 48 h, can we consider de-escalating or stopping antibiotics altogether? Standard practice based on IDSA guidance has been to continue BSA until neutrophil recovery. NCCN suggests de-escalation or discontinuation in some settings. However, as more recent studies in children and adults demonstrated that while discontinuation of antibiotics during neutropenia may be associated with relapse of fever in some, including high-risk patients, there was no increase in mortality if antibacterials were restarted immediately if a fever recurred. As such, ECIL guidelines recommend modification of the initial regimen at 72 to 96 h based on the patient's clinical course and microbiological results. Discontinuation of antibiotics after 72 h or later may be considered in neutropenic patients with fever of unknown origin (FUO) who are hemodynamically stable and afebrile for 48 h, irrespective of neutrophil count and expected duration of neutropenia [23].

Since those guidelines have been released there have been many studies looking at outcomes associated with either de-escalation or stopping BSA in high-risk patients with FN (Table 1). Among the trials that looked at de-escalation of BSA to prophylactic antibiotics in patients without known infections, there were no differences in clinical decompensation, sepsis, or mortality [24–26]. One single-center, pre-post, quasiexperimental study noted similar outcomes and found that the de-escalation group had significantly fewer episodes of *C. difficile* colitis [27▪]. Another single-center retrospective study of 101 HSCT recipients evaluated antibiotic de-escalation prior to neutrophil engraftment. De-escalation was defined as narrowing the spectrum of antibiotics either within (early) or after (late) 96 h from starting antibiotics and included discontinuation of antibiotics. Early de-escalation mostly consisted of reducing the spectrum of β-lactam antibiotics. There were failures of both early and late de-escalation due to infectious complications, but no recurrences of previous infections. All failures were successfully treated with no cases of septic shock or death [28].

Since ECIL guidelines were published, studies have compared outcomes between those who were maintained on standard BSA and those in whom ECIL guidelines were followed, where antibiotics were discontinued without an infection. These studies further demonstrate that implementation of ECIL guidelines in high-risk neutropenic patients was safe and feasible. Several of these studies demonstrated a significant reduction in BSA use, yet no differences in ICU transfers, bacteremia incidence, infection relapses, or mortality [29–32]. While two studies observed a higher bacteremia incidence in patients that followed ECIL-guidelines [33▪,34], two also showed a decreased risk of ICU [35▪] admission and death [34,35▪]. The ANTIBIOSTOP trial was a

Table 1. Literature addressing antibiotic de-escalation and discontinuation strategies for febrile neutropenia. This table includes a review of the literature over the past seven years that evaluates antibiotic de-escalation and discontinuation in patients with febrile neutropenia

Author, Year, Location	Type of Study, Sample sizes, Definitions	Findings
Kroll 2016 [24] USA	• Single-center, retrospective, 52 adults with FN • De-escalation group with BSA for 14 days, then de-escalated to levofloxacin until ANC recovery vs. continued BSA until ANC recovery.	• No difference between de-escalation and comparator group • Comparator group: 61.5% of met primary endpoint (remained afebrile without escalation of antibiotics for at least 72 h after BSA) vs. De-escalation group 80.7%. • Decreased BSA in de-escalation group.
Snyder 2017 [26] USA	• Single-center, retrospective, 120 adult HSCT recipients. • Early de-escalation group: after $\geq$ 5 days of BSA, de-escalated to prophylaxis until ANC recovery vs. continued BSA until ANC recovery.	• No difference in rate of recurrent fever, ICU admission, LOS, re-escalation, bacteremia or in-house mortality between groups. • De-escalation group: significantly less gram-positive BSA, trends toward lower gram-negative BSA, lower costs.
Gustinetti 2018 [28] Italy	• Single-center, retrospective observational study • De-escalation changed to narrower-spectrumβ-lactam or stopped any antibiotic; early: within 96 h, late: after 96 h of antibiotics, before engraftment. • Discontinuation: stopped empiric therapy and resumed prophylaxis until ANC recovery.	• Median savings of antibiotics in de-escalation/ discontinuation groups vs. escalation group: 10 days meropenem, 8 days pipercillin/tazobactam, 7 days vancomycin. • Some failures in de-escalation group but no recurrences of previous infections, no cases of septic shock or death, and all successfully treated with antibiotic escalation.
Le Clech 2018 [36] France	• Single-center, prospective, nonrandomized, observational of 238 episodes of FN in 123 adults. • 1st phase stopped BSA within 48 h apyrexia. • 2nd phase stopped on day 5 regardless of body temperature or WBC.	• No difference in composite endpoint, in-hospital mortality, ICU admission, relapse of infection $\leq$ 48 h after discontinuation of antibiotics. • No deaths after antibiotic discontinuation, 2 ICU admissions after antibiotic discontinuation, unrelated to FUO
Santolaya 2017 [39] Chile[a]	• Randomized, prospective, multicenter trial, 176 children with FN with clinical improvement after 48 h of antibiotics. • De-escalation group (84): BSA discontinued. • Comparator group (92): continued BSA until ANC recovery.	• Fewer antibiotic days in de-escalation group vs. standard group. • No significant difference in frequency of uneventful resolution, similar number of days of fever, LOS, and bacterial infections. • No deaths.
Aguilar-Guisado 2017 [40] Spain[a]	• Superiority, open-label, randomized, controlled phase 4 clinical trial in 157 adults. • Experimental group: empiric BSA withdrawn after 72 h or more of apyrexia plus clinical recovery. Control group: extended BSA until ANC recovery.	• Decreased BSA in experimental group vs. control group. • No difference in fever, bacteremia, or mortality. • No deaths due to bacterial infection. • More adverse events (mostly mild) in the experimental group (341 vs. 295 in control group).
La Martire 2018 [29] France	• Interrupted time series analysis before and after implementation of antimicrobial stewardship intervention in single center hematology ward based on ECIL guidelines, $N = 100$ antibiotic prescriptions for FN. • De-escalation: reduction of β-lactam spectrum and/or discontinuation of any companion antibiotic, based on infection type and in vitro susceptibilities. • Day 5: minimal duration of BSA if afebrile, blood cultures negative.	• Significant reduction in carbapenem consumption during intervention period. • Applicability and acceptability of flow charts were high. • No differences incidence of ICU transfers, bacteremia, mortality, *C. difficile*. • No infection relapses. • Decrease antibiotic expense during intervention period.
Stern 2019 [37]	• Meta-analysis: 8 studies (1973–2017), 662 episodes of FN randomly assigned to a t reatment group (short versus long antibiotic treatment).	• No significant difference between short vs. long antibiotic therapy for all-cause mortality, low certainty of evidence. • Number of fever-free days significantly lower in short-antibiotic treatment arm. • Less total antibiotics in shorter treatment arm by 3–7 days. • No difference in rates of clinical failure, incidence of bacteremia. • Incidence of documented infections slightly higher in short-antibiotic therapy arm. • No significant difference in antibiotic resistance.

Table 1 (*Continued*)

Author, Year, Location	Type of Study, Sample sizes, Definitions	Findings
Van de Wyngaert 2019 [30] France	• Prospective cohort trial, single-center, 75 patients with FN. • Based on ECIL-4 recommendation, policy compliant group ($n=62$): discontinued antibiotics after preestablished duration. Standard group: $n=13$. • Included: FUO, primary bacteremia, focal infections, those with orthopedic implants, prior history of ICU admission, septic shock, colonization with MDRO bacteria.	• Antimicrobial therapy longer in control group than policy compliant group. • After antibiotic discontinuation 20% patients experienced fever recurrence within 5.5 days, none severe. • No deaths at day 30.
Rearigh 2020 [25] USA	• Single-center, retrospective trial HSCT recipients with FN and negative infectious work-up, $n=297$. • De-escalation group: ($n=83$) fever free for 48 h, de-escalated to fluoroquinolone prophylaxis. • Standard of care group ($n=214$) remained on BSA until count recovery.	• Duration of BSA shorter in the de-escalation cohort. • No difference in mortality rates, clinical decompensation requiring ICU admission, new infections.
Nissen 2020 [31] The Netherlands	• Retrospective, single-center, before-after study. • Period 1: before restrictive empiric antibiotic therapy; carbapenem until 5 days afebrile or continuation of BSA depending upon physician preference). • Period 2: after restrictive empiric antibiotic therapy, discontinuation of carbapenem after 3 days if stable, no positive cultures, no antibacterial prophylaxis.	• Decreased carbapenem, vancomycin and overall reduction of antibiotic use in period 2 group • No deaths related to early discontinuation, no difference in ICU-admission or positive blood cultures.
Schauwylieghe 2021 [32] The Netherlands and Belgium	• Retrospective comparative cohort comparing 2 tertiary care hospitals with different strategies regarding antibiotic therapy for FN. • Hospital 1: ($n=305$ pts) BSA stopped after 3 days of FN in absence of clinically, microbiologically documented infection. • Hospital 2: ($n=270$ pts), prolonged BSA until neutrophil recovery.	• Fewer days of BSA given in hospital 1 vs. hospital 2. • No difference in serious medical complications, episodes of bacteremia, or mortality between hospitals.
Ram 2021 [41] Israel[b]	• Single-center, prospective, unblinded randomized study of patients after HCT or CAR-T therapy. 110 patients, 91 pts developed FN. • Control group (51 patients): received standard BSA until count recovery. • Intervention group (59 patients): BSA discontinued after 48–72 h if no evidence of clinical or microbiologic infection.	• Fraction of antibiotic-free neutropenia days significantly higher in intervention group compared to control group. • No difference in success rate between 2 groups; 30-day mortality rate similarly low in both groups
Alegria 2022 [27▪] USA	• Single-center, pre-post quasiexperimental study in adult patients with AML and FN. $N=93$. • De-escalation guideline: Afebrile 48 h, clinically stable, then categorized into 3 groups: 1-low suspicion bacterial infection (de-escalate to fluroquinolone prophylaxis); 2-suspected bacterial infection (tailor therapy to targeted suspicious infection then de-escalate to fluoroquinolone prophylaxis); 3-documented bacterial infection (tailor antibiotics based on susceptibilities, then de-escalate to fluoroquinolone prophylaxis).	• Fewer days of BSA in intervention group. • No difference between the groups in development of suspected or documented infection, 30-day all-cause mortality, LOS. • Intervention group: significantly fewer episodes *C. difficile* colitis
Paret 2022 [33▪] France	• Retrospective, multicenter observational study, in FN after induction chemotherapy or HSCT, compared to a historical cohort, $n=325$. • Patients included if empiric BSA were discontinued early during FUO according to ECIL-4 recommendations: at least 72 h of BSA if patient had been afebrile for $\geq$ 48 h and stable. Excluded patients with infectious source of fever.	• No significant differences in febrile recurrences, ICU admissions, septic shock, and 30-day mortality. • In ECIL-4 cohort group bacteremia rate was higher and antibiotic consumption was significantly lower. No sepsis-related mortality. • After early antibiotic discontinuation in ECIL-4 cohort, febrile recurrence was higher among patients with enterocolitis and mucositis; additionally, the only factor associated with bacteremia was presence of stage III-IV oral mucositis.

Table 1 (*Continued*)

Author, Year, Location	Type of Study, Sample sizes, Definitions	Findings
Rainess 2022 [52▪] USA	• Retrospective observational cohort study, single-center, 123 adult patients. • Conventional group ($n=89$) compared to de-escalation group ($n=34$): antibiotics de-escalated based on bacterial culture results.	• No difference in fever recurrence or antibiotic escalation due to fever. • No difference incidence of *C. difficile*. • No difference in development of MDRO. • Fewer days of BSA in de-escalation group. • No cases of mortality in de-escalation group.
Contejean 2022 [35▪] France	• Single-center, retrospective, observational study in FN, included hematologic malignancies and HSCT recipients. • ECIL-4 based guideline for de-escalation and discontinuation implemented and compared preintervention ($n=164$) vs. postintervention periods ($n==148$).	• After implementation of antimicrobial stewardship, glycopeptide use decreased by 85%, carbapenem use decreased by 72%. • Risk of transfer to ICU/death decreased significantly after implementation of antimicrobial stewardship program
Verlinden 2022 [34] Belgium	• Single-center interventional study without concurrent controls in FN, hematologic malignancy or HSCT. • Studied 446 admissions after introduction of ECIL-4 based protocol in comparison to a historical cohort of 512 admissions.	• Bacteremia occurred more frequently in ECIL-4 group. • No difference in incidence of septic shock, infection-related ICU admissions. • Overall mortality was lower in ECIL-4 group due to a decrease in infection-related mortality. • Antibiotic consumption significantly reduced by a median of 2 days in ECIL-4 cohort.
de Jonge 2022 [42▪] The Netherlands	• Noninferiority, open-label, multicenter, randomized trial in 6 hospitals. Adult patients with intensive chemotherapy or HSCT had FUO, high-risk neutropenia expected for $\geq$7 days. After onset FN patients received either carbapenem and were placed into one of two groups. • Short treatment group ($N=144$): antibiotics 72 h. • Extended treatment group ($N=137$): >9 days until afebrile 5 days or neutrophil recovery.	• No difference in treatment failure in both intention-to-treat and per-protocol analysis. • Number of serious adverse events higher in short treatment arm vs. extended treatment arm due to increased readmission. • Death < 30 days after ANC recovery occurred in 3% short treatment arm vs. 1% in extended treatment arm.
Ishikawa 2023 [38▪]	• Meta-analysis of 11 RCTs. • 1128 patients with FN (1977–2022). • Compared short- and long-term antibiotics for FN and cancer. • 8/11 of these articles were also included in meta-analysis by Stern 2019.	• No significant differences in mortality, bacteremia, or clinical failure. • A low certainty of evidence was observed.

[a]included in Stern[53] and Ishikawa [38▪] meta-analyses.
[b]included in Ishikawa [38▪] meta-analysis.
ANC, absolute neutrophil count; BSA, broad-spectrum antibiotics, ECIL, European Conference on Infections in Leukemia; FUO, fever of unknown origin; FN, febrile neutropenia; HSCT, hematopoietic stem cell transplantation; ICU, intensive care unit; LOS, length of stay; RCT, randomized controlled trials; WBC, white blood count.

single-center, prospective, observational trial including 238 episodes of FN in 123 patients, where antibiotics were stopped after 48 h versus five days for all patients without an identifiable infection. There was no difference in ICU admission, infection relapse, or in-hospital mortality between the two groups [36].

Additionally, two large meta-analyses [37,38▪] included recent prospective trials evaluating stopping antibiotics in patients with FN [39,40,41,42▪]. A Cochrane Review included eight randomized controlled trials that compared a short antibiotic therapy course in which discontinuation of antibiotics was guided by protocols regardless of the neutrophil count to a long course in which antibiotics were continued until resolution of neutropenia. There were 662 episodes of FN in adults and children, and all studies excluded people with documented microbiological infections. There were no significant differences in all-cause mortality, clinical failure, or episodes of bacteremia between the short-antibiotic and long-antibiotic therapy arms. The number of fever-free days was significantly lower in the short versus the long-antibiotic treatment arm. There were fewer days of antibiotic use in the short-antibiotic arm by three to seven days compared to the long antibiotic therapy arm. There was a higher incidence of documented infections in the short antibiotic arm, but this finding was noted in older studies between 1973 to 2000; the more

recent studies [39,40] did not find a significant increased risk of infections. The authors however concluded that the overall certainty of evidence was low or very low as most of the included studies were old or inadequately designed with differences in definitions, inclusion criteria, and study design. A second review of those same eight trials, with three additional trials, now including 1128 patients with FN between 1977 and 2022, similarly noted no significant differences in mortality, clinical failure, or bacteremia between groups, but again noted a low certainty of evidence [38▪].

Though some studies did demonstrate increases in infections and bacteremia, there were no serious infection-related adverse effects, likely due to the rapid re-initiation of antibiotics. An approach to antibiotic use in high-risk patients with FN is shown in Fig. 1.

RISK-ASSESSMENT STRATEGIES AND FUTURE METHODS TO GUIDE ANTIBIOTIC USE IN PATIENTS WITH CANCER AND NEUTROPENIA

Infection risks are complex, and numerous interactions between the patient and their environment impact infection risk in patients with neutropenia. An individual risk assessment should include patient factors, ecological factors, and treatments planned or anticipated. (Fig. 2). For each patient, the location and ability to monitor for infection, along with quick access to BSA, may be considered before initiating antibiotic prophylaxis. Hospitalized patients who are closely monitored may not need prophylactic antibiotics. Currently, the degree of monitoring needed is often practical only in the inpatient setting. Mobile technologies that permit more intense monitoring in outpatient settings are becoming more available, including wearable devices with high frequency temperature monitoring. One case series described three patients who were monitored at home with a device that detected a fever even when an oral temperature was not detected by traditional methods, and two of those cases were associated with bloodstream infections. These technologies could trigger the earlier initiation of antibiotics and lead to a lower risk of severe infectious complications without the need for prophylaxis and its attendant risks [43▪,44].

Other ways to mitigate risks include evaluation or manipulation of the microbiome, as multiple studies have demonstrated that restricted diversity and intestinal domination with specific species precedes bacteremia [13,15,16]. As metagenomic analysis techniques advance to allow rapid and inexpensive testing of clinical samples, evaluation

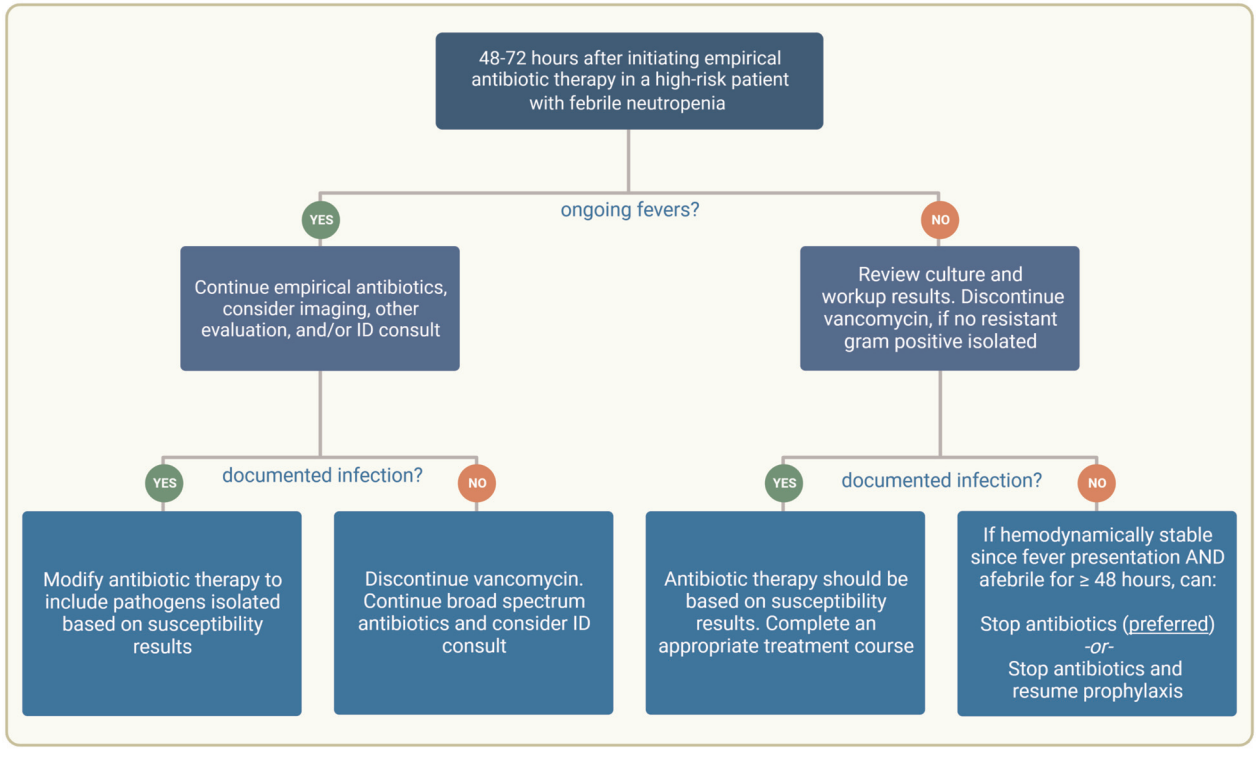

FIGURE 1. Follow-up approach to high-risk patients with fever and persistent neutropenia. Based on most recent literature, along with updated guidelines, an algorithmic approach to managing antimicrobial therapy for patients with febrile neutropenia. For some patients, de-escalation and/or discontinuation of antibiotics may be considered.

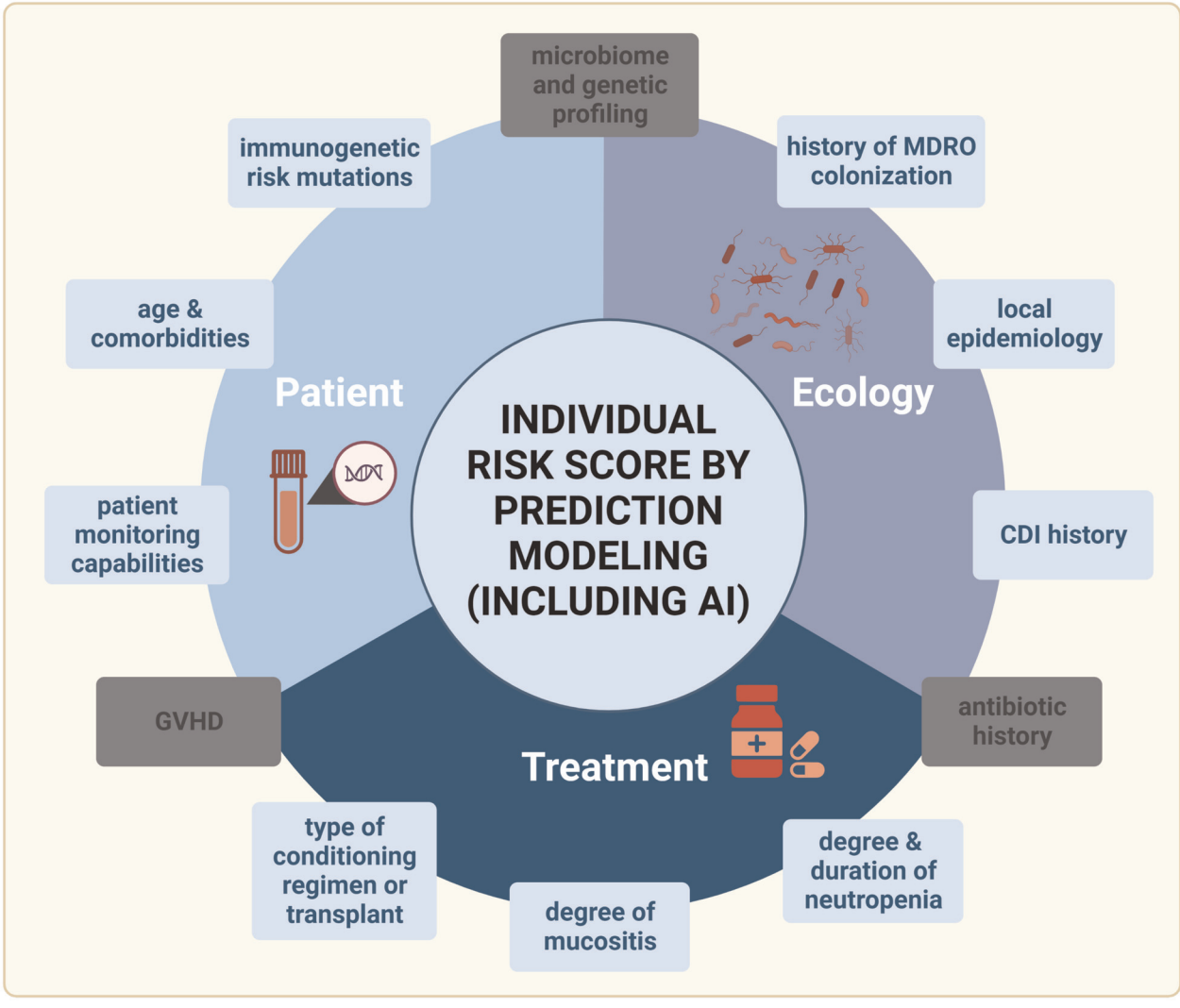

FIGURE 2. Strategic risk score for antibiotic management.

of an individual's microbiome in real time to identify adverse changes in diversity may be possible. If decreasing diversity and domination of pathogenic bacteria are identified, prophylactic antibiotics could be initiated. Other strategies may include fecal microbial transplant from the patient's own banked stool [45,46] or from a healthy donor [47], or the administration of prebiotics or probiotics [48]. Alternatively, gut-decontamination with rifaximin to preserve microbial balance may be considered as an alternative to fluoroquinolone or other BSA for prophylaxis [49].

Although such approaches are still exploratory, preliminary microbiome-based models to predict infection have shown good prognostic value. In a study of 28 patients, fecal microbiome sampling was done prior to HSCT which characterized 16S ribosomal RNA genes using high-throughput DNA sequencing. The study quantified bacterial taxa and used machine learning techniques to identify microbial biomarkers that predicted subsequent bloodstream infections. This technique was noted to be capable of predicting bloodstream infections with a sensitivity and specificity of 90% based only on pretreatment fecal microbiome [13].

Another potential contributor to risk stratification includes immunogenetic risk assessment. Evidence suggests that some individual risk factors may be due to specific genetic polymorphisms [50]. Identifying these genetic markers could be another method to identify high-risk patients and tailor prophylactic treatment accordingly.

Finally, machine learning models may help estimate bacterial sepsis among HSCT recipients. One prognostic study of 1943 HSCT recipients used a full risk factor and clinical factor-specific automated bacterial decision support tool to help predict bloodstream infections. This full decision support assessment had superior prognostic accuracy for high-risk bacteremia and short-term mortality. This has the

potential to inform timely sepsis detection in this patient population [51].

CONCLUSIONS

Patients with FN should be managed based on a comprehensive risk assessment that takes in to account the person's disease state, level of immunosuppression, prior and current treatments to ensure that the most appropriate prophylaxis and treatment strategies are utilized. Future tools may better stratify an individual's risk factors and help tailor best antibiotic use practices in this vulnerable patient population.

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Conflicts of interest

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- ■ of special interest
- ■■ of outstanding interest

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Updated ECIL guidelines from 2021 reviewed the risk of infections and febrile neutropenia associated with other agents including immunotherapy and molecular therapies for the treatment of AML and acute lymphocytic leukemia (ALL). They concluded that most agents do not pose a significant infection risk when used as monotherapy, but caution is recommended when combining agents. Antibacterial prophylaxis is only recommended when hypomethylating agents are combined with venetoclax.

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Single-center, prepost quasiexperimental study in adult patients with AML and febrile neutropenia. Patients underwent antibiotic de-escalation if they were afebrile for at least 48 h, clinically stable, then categorized into 3 groups: 1-low suspicion bacterial infection (deescalate to fluroquinolone prophylaxis); 2-suspected bacterial infection (tailor therapy to targeted suspicious infection then de-escalate to fluoroquinolone prophylaxis); 3-documented bacterial infection (tailor antibiotics based on susceptibilities, then de-escalate to fluoroquinolone prophylaxis. There were no differences between the groups in development of suspected or documented infection, 30-day all-cause mortality, or length of stay. The intervention group had significantly fewer episodes *C. difficile* colitis.

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Retrospective multicenter observational study in patients with febrile neutropenia after induction chemotherapy or HSCT, that compared implementation of ECIL-4 recommendations, where empiric broad spectrum antibiotics were discontinued early during fever of unknown origin if the patient had been afebrile for $\geq$ 48 h and stable, to a historical cohort. There were no significant differences in febrile recurrences, ICU admissions, septic shock, and mortality, though in the ECIL-4 cohort there was a higher rate of bacteremia.

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Single center, retrospective, observational study in febrile neutropenia, that included patients with hematologic malignancies and HSCT recipients. Compared preand post initiation of ECIL-4 based guideline for de-escalation. After implementation of ECIL-based guideline, risk of transfer to ICU and death decreased significantly.

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Meta-analysis of 11 randomized controlled trials, that included 1128 patients with febrile neutropenia between 1977–2022, that compared short- and long-term antibiotic use for febrile neutropenia and cancer. A low certainty of evidence was observed, but there were no significant differences in clinical failure, bacteremia, or mortality

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Noninferiority, open-label, multicenter, randomized trial in six hospitals, where adult patients with a fever of unknown origin were included who were receiving intensive chemotherapy or undergoing HSCT, with high-risk neutropenia expected for >7 days. A short treatment group, where patients received carbapenem antibiotics for 72 h, were compared to an extended treatment group, where patients received over nine days of antibiotics until afebrile for 5 days or until neutrophil recovery. There was no difference in treatment failure in both groups. There was a higher number of serious events in the short treatment arm due to an increased readmission rate. There were no deaths due to carbapenem-sensitive infections.

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Home-based high frequency temperature monitoring detected fevers prior to conventional thermometer and triggered earlier medical evaluation and treatment. May be potential future technology to improve infection-related outcomes for patients with febrile neutropenia.

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Retrospective, observational cohort study, single-center, adult patients with hematologic malignancy and febrile neutropenia, compared a conventional group to a group where antibiotics were de-escalated based on bacterial culture results. There were no differences in fever recurrence, antibiotic escalation due to fevers, incidence of *C. difficile*, or incidence of multidrug resistant organisms. There were no cases of mortality in the de-escalation group.