



Review Article

How I Treat Febrile Neutropenia

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Abstract. The management of febrile neutropenia is a backbone of treating patients with hematologic malignancies and has evolved over the past decades. This article reviews my approach to the evaluation and treatment of febrile neutropenic patients. Key topics discussed include antibacterial and antifungal prophylaxis, the initial workup for fever, the choice of the empiric antibiotic regimen and its modifications, and criteria for discontinuation. For each of these questions, I review the literature and present my perspective.

Keywords: Fever; Neutropenia; Febrile neutropenia; Management.

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Introduction. The management of febrile neutropenia is a backbone of the treatment of patients with hematologic malignancies. Since the introduction of the concept of empiric antibiotic therapy upon the first fever in neutropenic patients,¹ the management of febrile neutropenia has evolved, reflecting changes in the epidemiology of infection, the development of new diagnostic tools and antimicrobial agents, and changes in the treatment of the underlying malignancies. Over these years, guidelines for managing febrile neutropenia have been published, and have helped hematologists and infectious diseases clinicians to treat febrile neutropenic patients. These guidelines were built based on the available literature, experts' opinions, and were endorsed by regional and national medical societies.²⁻¹³ However, while these guidelines are of great usefulness, some recommendations may not apply because of differences in infection epidemiology in different regions. Therefore, the "blind" application of international guideline recommendations not taking into account local epidemiologic aspects may result in inappropriate use of antimicrobial agents and compromise treatment success.

In this review, I present my perspective of the

management of febrile neutropenia, based on my experience in a tertiary care university-affiliated hospital. The purpose of this review is to provide a practical approach to the management of neutropenic cancer patients, taking into consideration current recommendations, local epidemiologic aspects, and the experience in managing this complication for over 30 years. A summary of my approach to the management of febrile neutropenia is presented in **Table 1**.

The "add-on" Strategy. Over the past decades, significant advances in the management of infections have occurred, including improvements in culture methods,¹⁴ faster and more accurate identification of microorganisms and patterns of resistance,¹⁵ the incorporation of biomarkers and new diagnostic tools,¹⁶ new antimicrobial agents,¹⁷ and concepts of pharmacokinetics and pharmacodynamics guiding the choice of appropriate doses and schedules for the administration of antimicrobial agents.¹⁸ These advances represent a great challenge for hematologists because they are already overwhelmed by the multitude of new information regarding the management of the underlying

Table 1. Management of febrile neutropenia.

Action	My opinion	Comments
Antibacterial prophylaxis	Ciprofloxacin or levofloxacin	Autologous and allogeneic HCT, pre-engraftment Acute leukemia, induction Before deciding for quinolone prophylaxis, take into consideration local epidemiology and re-evaluate periodically in light of changes in the epidemiology
Antifungal prophylaxis	Fluconazole Posaconazole or voriconazole	AML induction, allogeneic HCT, pre-engraftment, low risk* AML induction, allogeneic HCT, pre-engraftment, high risk*
Workup at first fever	Medical history, physical examination, blood cultures	Additional tests on a case per case basis
Monitor for MDR Gram-negative bacteria	Anal swab on admission	Consider weekly swabs if MDR in the unit
Empiric therapy	Cefepime	Empiric regimen should be active against colonizing MDR Gram-negative if the patient is colonized
Vancomycin in the initial regimen	No	Gram-positive infection is not associated with early death
Empiric vancomycin if persistently febrile	No	Add only if documented infection by MRSA
Empiric carbapenem if persistently febrile	No	Do not change the regimen if persistent fever only
Anal or abdominal pain	Metronidazole	If typhlitis is suspected, perform abdominal CT scan
Clinical deterioration	Carbapenem	Change to carbapenem even if afebrile
Empiric antifungal therapy	No	Perform serial serum galactomannan and images, and give preemptive therapy instead
Discontinuation of empiric therapy	With neutrophil recovery No neutrophil recovery	Immediately if no documentation of infection If afebrile >3 days, provided that vital signs are normal

HCT = hematopoietic cell transplantation; AML = acute myeloid leukemia; MDR = multi-drug-resistant; MRSA = methicillin-resistant. *Staphylococcus aureus*; CT = computed tomography. * High-risk AML: see **Table 2**.

hematologic malignancy, including the incorporation of new molecular markers of disease, risk stratifications, and targeted therapies. As a consequence, hematologists use the recommendations of international guidelines to manage their febrile neutropenic patients, usually taking the help of the "add-on" strategy: a beta-lactam is started in the first fever, vancomycin is added after a few days of persistent fever, the beta-lactam is changed after a few days if the patient is still febrile, and finally, empiric antifungal therapy if started in case of persistent fever. The add-on strategy is successful in keeping the patient alive, but with the expense of overusing antimicrobial agents, with its consequences: side effects, drug interactions, selection of resistant organisms, and increased cost. In addition, the overuse of antibiotics reduces the diversity of the intestinal microbiota, increasing the risk of severe acute graft versus host disease in allogeneic hematopoietic cell transplant (HCT) recipients, with a potential increase in mortality.^{19,20} Therefore, the treatments' goal in febrile neutropenia is not just to keep the patient alive but to do it with the least exposure to antimicrobial agents possible. To do so, hematologists must abandon the add-on strategy and develop a strategy that takes into consideration the underlying disease and its status, recent chemotherapy with an estimate of the predicted duration of neutropenia, local epidemiologic features, a bedside risk assessment of infection, daily visits with special attention to subtle clinical manifestations of infection, and an aggressive attempt to diagnose infection with the

help of a good microbiology laboratory.

Should I Give Antibacterial Prophylaxis? The use of a quinolone (ciprofloxacin or levofloxacin) to afebrile neutropenic patients has been associated with a reduction in fever and bacterial infection frequency and a modest impact on mortality, as shown by randomized trials and meta-analyses.²¹⁻²⁴ However, with the emergence of infection by Gram-negative bacteria, the possibility that the use of quinolones might increase resistance rates has been a concern among experts. Recently the European Conference of Infection in Leukemia (ECIL) revisited this topic, emphasizing the impact of quinolone prophylaxis on antibiotic resistance.²⁵ The authors reviewed 18 studies, including one published by our group.²⁶ Except for three observational studies (2 from the same institution), the literature review failed to show an increase in resistance with the use of quinolones, including two randomized trials and one meta-analysis. More recently, alerts about quinolones' side effects such as mental disturbances, fatal hypoglycemia, aortic dissection and rupture of aortic aneurysm, disabling side effects on tendons muscles, joints and nerves, brought new concerns about the use of quinolones (<https://www.drugs.com/fda-alerts/672-0.html>). A reflection about the benefits and potential harms of quinolone prophylaxis should be advanced, taking into consideration local epidemiology. In addition, those who argue against the use of quinolone prophylaxis highlight the lack of survival benefit. However, while bacterial

infections may increase febrile neutropenic patients' mortality, the additional risk is not high enough to be apparent in a randomized trial or meta-analysis of quinolone prophylaxis.

My opinion. Unless there is an additional risk for potentially severe side effects, I give ciprofloxacin 500 mg BID (or levofloxacin 500 mg/d) to autologous and allogeneic HCT recipients, starting with the conditioning regimen until engraftment or until the patient develops fever requiring the initiation of empiric antibiotic therapy. I also give ciprofloxacin to patients with acute myeloid leukemia (AML) receiving consolidation chemotherapy with high-dose cytarabine. This is particularly attractive because most patients are discharged after chemotherapy and spend the period of neutropenia at home. In such situations, quinolone prophylaxis may reduce the chance of readmission to treat febrile neutropenia.

Most AML patients in induction remission are already febrile on admission. For these patients, I start empiric antibiotic therapy, even acknowledging that fever is most likely caused by the underlying leukemia. However, if there is no documentation of infection and fever resolves with chemotherapy, I discontinue empiric therapy and start ciprofloxacin. The other situation in which I consider giving quinolone prophylaxis is in induction remission for acute lymphoid leukemia (ALL). The more intensive induction remission I give, the more likely I prescribe quinolone prophylaxis. Like AML, fever in newly diagnosed ALL patients may be due to underlying leukemia,²⁷ and the same strategy as described for AML applies. It is important to emphasize that quinolone prophylaxis should be considered according to local epidemiology and a periodic re-evaluation of its benefit in light of potential changes in the epidemiology over time.

Should I Give Antifungal Prophylaxis? The frequency of invasive fungal disease (IFD) in hematologic patients increased with improvements in the outcome of patients with acute leukemia, and the expansion in the population of patients undergoing HCT. Studies published in the 1980s reported high infection rates caused by *Candida* species, and less frequently, *Aspergillus* and other molds.^{28,29} These epidemiologic features and fluconazole availability prompted investigators to test this agent as prophylaxis in neutropenic cancer patients. Compared with placebo, the best results favoring fluconazole were reported in allogeneic HCT^{30,31} and AML.³² Furthermore, a meta-analysis showed that a survival benefit was evident among patients with prolonged neutropenia in addition to a reduction in the incidence of invasive candidiasis.³³

With the widespread use of fluconazole as prophylaxis, the incidence of invasive candidiasis dropped sharply, and invasive aspergillosis became the

most frequent IFD in neutropenic patients.^{34,35} In addition, other filamentous fungi such as *Fusarium* species and the agents of mucormycosis emerged as important pathogens in neutropenic patients.^{36,37} As a consequence, primary prophylaxis with mold-active agents became an attractive strategy and has been tested in randomized clinical trials. The best evidence is for the use of posaconazole or caspofungin in AML. A study comparing posaconazole with fluconazole or itraconazole oral solution in adults showed that IFD and mortality incidence was significantly lower in posaconazole recipients.³⁸ In another study conducted in children and young adults, caspofungin use resulted in a reduction in IFD overall and aspergillosis compared with fluconazole.³⁹ In this trial, most children received a protocol consisting of four cycles of intensive chemotherapy, and the benefit of caspofungin was only apparent after the second cycle. Considering that adults with AML are usually treated with one or two cycles of intensive chemotherapy. Considering that, adults with AML are usually treated with one or two cycles of intensive chemotherapy, it is not clear if caspofungin will also benefit adults with AML receiving induction remission.

A significant benefit of anti-mold prophylaxis in the pre-engraftment period after allogeneic HCT has not been observed since two randomized trials comparing voriconazole with fluconazole or itraconazole failed to show a dramatic advantage of voriconazole in terms of a reduction in the incidence of mold infection.^{40,41} Likewise, a benefit of micafungin in reducing the incidence of invasive aspergillosis was not demonstrated in three studies.⁴²⁻⁴⁴ Finally, in ALL, where azoles' use is restricted because of prohibitive drug interactions with vincristine, a study comparing intravenous liposomal amphotericin B (5 mg/kg twice weekly) with placebo showed similar rates of IFD.⁴⁵

The choice of which antifungal prophylaxis to give in neutropenic patients influences the strategies of diagnosis and monitoring for IFD during neutropenia. Patients receiving fluconazole prophylaxis are at increased risk for invasive aspergillosis. In these patients, active monitoring with serial (2-3x/week) serum galactomannan should be strongly considered.⁴⁶ On the other hand, if posaconazole is given as prophylaxis, the rates of false-positive galactomannan increase because the pre-test probability of invasive aspergillosis is much lower.⁴⁷ In these circumstances, serum galactomannan testing is best performed upon clinical suspicion of invasive aspergillosis rather serially.⁴⁸

Another consequence of the choice of antifungal prophylaxis is the selection of non-prophylactic antifungal agents during neutropenia. If empiric or preemptive antifungal therapy is considered in patients receiving fluconazole prophylaxis, the options include an echinocandin, voriconazole, and an amphotericin B's

lipid formulation. However, if the patient receives posaconazole prophylaxis, the most likely choice is amphotericin B's lipid formulation.

Recently, new targeted therapies for the treatment of AML have emerged, including midostaurin, gilteritinib, enasidenib, ivosidenib, venetoclax, and others, with significant improvements in the outcome.^{49,50} Most of these agents are metabolized by CYP3A4 enzymes, which are strongly inhibited by both posaconazole and voriconazole.^{51,52} Incorporating these new compounds in the treatment of AML will represent a challenge for the use of mold-active azoles as prophylaxis, because the overexposure of target therapies may increase toxicity and underexposure may reduce their efficacy.⁵³ An alternative would be isavuconazole, a moderate CYP3A4 inhibitor, although there are no solid data on its efficacy as prophylaxis.

My opinion. I give antifungal prophylaxis to patients with AML receiving induction remission chemotherapy and in the pre-engraftment period of allogeneic HCT. In AML, my choice between fluconazole and posaconazole is based on a bedside risk assessment of IFD that takes into account the probability of achieving complete remission with one cycle of chemotherapy (older age, high white blood cell count, relapsed AML, and high cytogenetic and/or molecular risk),⁵⁴ co-morbidities and environmental exposure (**Table 2**).⁵⁵ I give posaconazole

to patients with high-risk AML and fluconazole to patients with intermediate or low-risk AML.

In the pre-engraftment period of allogeneic HCT, I use a risk stratification strategy that takes into account the predicted duration of neutropenia (stem cell source, conditioning regimen), T-cell depletion, co-morbidities, and environmental factors (**Table 2**). I give voriconazole or posaconazole to high-risk patients and fluconazole to low or intermediate-risk patients. In patients receiving any of the new drugs metabolized by CYP3A4, I prefer not to give a mold active azole (voriconazole or posaconazole) and consider giving an echinocandin as prophylaxis in patients at high risk for invasive aspergillosis. I also give echinocandins to high-risk patients who present increased liver enzymes during azole prophylaxis or who have severe gastrointestinal mucositis.

In both AML and allogeneic HCT, if the patient is receiving fluconazole prophylaxis, I monitor for invasive aspergillosis with serial (3x/week) serum galactomannan. In contrast, for patients receiving posaconazole, I only perform serum galactomannan (3 consecutive days) if there is any suspicion of aspergillosis or fusariosis (persistent or recurrent fever, respiratory symptoms, images, skin lesions).

What is the Workup in the First Fever? Because the clinical presentation of infection in febrile neutropenic

Table 2. Risk assessment of invasive fungal disease in acute myeloid leukemia and allogeneic hematopoietic cell transplantation.

	Low risk	Intermediate risk	High risk
Acute myeloid leukemia			
Age	<60		≥60
WBC count	<10,000/mm ³	10-50,000/mm ³	>50,000/mm ³
Type of leukemia	De novo		Post-chemotherapy or myelodysplasia
Cytogenetics	t(15;17), t(8;21), inv16	Normal karyotype	Complex karyotype, t(6;9), t(9;22)
Genetic mutations	NPM1, CEBPA	NPM1 + FLT3-ITD	FLT3-ITD, TP53
Co-morbidities	No	Diabetes, COPD, poor performance status, smoking, chronic sinusitis	
Environment	Room with HEPA filter	No HEPA filter	No HEPA filter and building construction or renovation
Allogeneic HCT			
Underlying disease	Complete remission		Active, relapsed
Conditioning regimen	Non-myeloablative		Myeloablative
Stem cell source	Peripheral blood	Bone marrow	Cord blood
HLA match	Matched		Mismatched
Donor	Related		Unrelated
T-cell depletion	No		ATG, altmtuzumab
Co-morbidities	No	Diabetes, COPD, iron overload, smoking, chronic sinusitis	
Environment	Room with HEPA filter	No HEPA filter	No HEPA filter and building construction or renovation
Prior invasive mold disease	No	Yes, past	Yes, recent

This risk stratification is based on the author's experience (detailed in [55]) and has not been prospectively validated. WBC = white blood cell; t = translocation; inv = inversion; NPM = nucleolar phosphoprotein; CEBPA = CCAAT/enhancer-binding protein alpha; FLT3 = Fms-like tyrosine kinase 3; ITD = internal tandem duplication; TP53 = tumor protein P53; COPD = chronic obstructive pulmonary disease; HEPA = high efficiency particulate air; HCT = hematopoietic cell transplantation; HLA = human leukocyte antigen; ATG = antithymocyte globulin.

patients is subtle, any sign or symptom must be seriously taken into account.⁵⁶ Specifically, pain, fever, and erythema should prompt a thorough workup for infection. The most common sites of infection are the skin, and the respiratory and gastrointestinal tract. The workup for the first fever comprises history, physical examination and blood cultures. The routine performance of chest X-ray is not indicated.⁵⁷ On the other hand, reports of invasive aspergillosis occurring before the start of treatment in AML⁵⁸⁻⁶⁰ brought the discussion of obtaining a chest CT scan before induction chemotherapy. Indeed, a web-based questionnaire, answered by 142 physicians from 43 countries, reported that 24% obtained baseline chest CT scan routinely.⁶¹

My opinion. My working definition of fever is any axillary temperature $\geq 38^{\circ}\text{C}$. Occasionally, the patient presents signs of infection (e.g., abdominal pain in the context of gastrointestinal mucositis or cellulitis) without fever. In these situations, I trigger the workup and the initiation of empiric antibiotic therapy, regardless of body temperature. My workup starts with a detailed medical history that includes co-morbidities and prior infections (e.g., chronic lung disease, sinusitis, diabetes, smoking habit, herpes virus infection, varicella, tuberculosis), underlying disease and its status, past and recent treatment for the underlying disease, prior episodes of febrile neutropenia with information about the documentation of infection and colonization by resistant organisms, concomitant medications, and symptoms of infection. On the basis of the status of the underlying disease and recent treatment (type and date), I estimate the probable duration of neutropenia and anticipate potential non-infectious complications that may mimic infection (e.g., engraftment syndrome after HCT⁶² and differentiation syndrome in AML patients receiving retinoic acid, ivosidenib or enasidenib).^{63,64} This approach is essential for the correct interpretation of clinical signs of infection throughout neutropenia.

I perform a physical examination with particular attention to the skin, nails, and respiratory and digestive tracts. I obtain at least two sets of blood cultures (aerobic, anaerobic, and fungal bottles), one from a peripheral vein and another from a catheter. I only order additional tests such as computed tomography (CT) scans or cultures from other sites if clinically indicated. These tests include PCR panel for respiratory viruses and PCR panel for diarrhea in patients with such symptoms.

What is the Empiric Antibiotic Regimen for the First Fever? Over the past decades, various antibiotic regimens have been tested as empiric therapy for febrile neutropenic patients. In early studies, combinations of two or three antibiotics were usually given,^{1,65} but since the late 1990s, monotherapy with a beta-lactam has been

preferred, usually cefepime, piperacillin-tazobactam, or a carbapenem.^{66,67} The addition of vancomycin is not recommended routinely since a meta-analysis of randomized trials comparing regimens with or without vancomycin did not show any advantage of vancomycin in the initial empiric regimen.^{68,69} However, the use of vancomycin in the initial empiric antibiotic regimen is recommended by guidelines in certain circumstances such as suspected catheter-related infection, skin and soft tissue infection, pneumonia, or hemodynamic instability.^{10,12} However, the level of evidence is weak, reflecting the lack of clinical data supporting these recommendations.

The main objective of empiric antibiotic therapy in febrile neutropenic patients is to prevent early death, an event that occurs mostly with Gram-negative bacteremia.⁷⁰ We have recently analyzed 1,305 febrile neutropenia episodes looking at factors associated with early death and shock.⁷¹ None of the circumstances in which guidelines recommend the use of vancomycin was associated with shock or early death, including bacteremia due to Gram-positive organisms, catheter-related infection, skin or soft tissue infection, or inadequate Gram-positive coverage, suggesting that the empiric use of vancomycin in the first fever in neutropenic patients is likely unnecessary in the overwhelming majority of cases. Another study evaluated the impact of inappropriate antibiotic coverage at first fever in 1,605 episodes of bloodstream infections in neutropenic patients. While the mortality rate was significantly higher in episodes of Gram-negative bacteremia with inappropriate antibiotic coverage, there was no difference in mortality in Gram-positive bacteremia.⁷² In other study, the implementation of a rapid microbial identification via MALDI-TOF (matrix-assisted laser desorption ionization time of flight) reduced mortality in bacteremia caused by Gram-negative but not Gram-positive bacteria, further indicating that Gram-positive infections do not result in early death in febrile neutropenic patients.⁷³

The empiric antibiotic regimen must cover the most frequent Gram-negative bacteria causing bloodstream infection in febrile neutropenic patients, taking into account local epidemiology. The emergence of infection caused by multi-drug resistant (MDR) Gram-negative bacteria has brought a great challenge for the management of febrile neutropenic patients because they are associated with high mortality rates.⁷⁴ Strategies to overcome this problem include active screening with weekly (or on admission) rectal swabs and the initiation of an empiric antibiotic regimen active against the colonizing MDR Gram-negative bacteria.^{75,76} In addition, a de-escalation strategy is applied if the patient is stable and blood cultures are negative.¹² A study tested the time to positive blood cultures to guide early de-escalation

and found that the median time to positivity of MDR Gram-negative bacteria was 10.5 hours, and 100% of cultures turned positive in less than 24 hours.⁷⁷

My opinion. All new patients admitted to my unit are put in contact precautions and have an anal swab performed. I strongly consider repeating the swab weekly if another patient in the unit is colonized by MDR Gram-negative bacteria. Suppose the patient is colonized by MDR Gram-negative bacteria, or had a documented infection caused by MDR Gram-negative bacteria in a previous febrile neutropenia episode. In that case, I choose an antibiotic regimen with activity against the colonizing (or previously infecting) organism. On day 3 of febrile neutropenia, if blood cultures are negative and the patient is stable, I change the antibiotic regimen to cefepime, even if the patient is still febrile (**Figure 1**).

For patients without colonization by MDR Gram-negative bacteria, I give cefepime in extended infusion (3-4 hours), with the dose and schedule adjusted for the creatinine clearance. If the patient presents signs of typhlitis, I add metronidazole to cefepime. I do not give vancomycin or any other anti-Gram positive antibiotic such as teicoplanin, daptomycin, or linezolid. Instead, I wait for blood culture results and add vancomycin if the patient presents with bacteremia due to methicillin-resistant *Staphylococcus aureus* (MRSA).

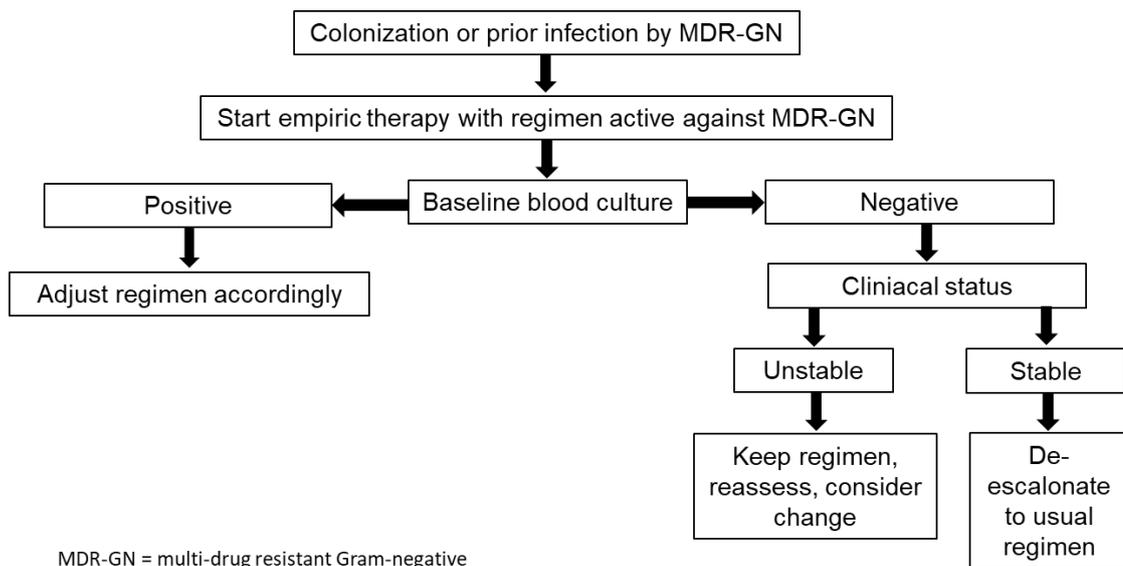
When Should I Change the Empiric Antibiotic Regimen? Persistent fever after the start of empiric antibiotic therapy is frequent and may have various causes, not necessarily indicating the need to change the antibiotic regimen. In general, it is recommended that clinical and microbiologic data should guide modifications, and persistent fever in a stable patient rarely requires changes in the empiric regimen.¹⁰ However, in practice, empiric changes in the initial

regimen are very frequent, in general, without a reasonable reason.

The time to defervescence of a febrile neutropenic patient may vary depending on the presence or absence of infection. For example, in our febrile neutropenia database with over 2,500 episodes, the median time to defervescence was three days in episodes without documented infection and four days in those with clinical or microbiological documentation. Among patients with bacteremia, the median time to defervescence was four days in Gram-negative bacteremia and five days in Gram-positive bacteremia (unpublished data). A randomized study comparing cefepime with ceftazidime plus amikacin has shown that the median time to defervescence of "responding" patients was three days. However, less than 30% of patients were afebrile after three days of antibiotics.⁷⁸ In another study comparing cefepime with or without amikacin in febrile neutropenic patients, the proportion of patients who became afebrile after 3, 7 and 10 days of antibiotics was 39%, 70% and 83%, respectively.⁷⁹ Taken these data, it is clear that the strategy of empiric change in the antibiotic regimen after 3-4 days of a patient with persistent fever and no new signs of infection is inappropriate and will likely result in the overuse of antibiotics without improving the outcome.

One of the most common actions of clinicians treating febrile neutropenia is to add an anti-Gram-positive antibiotic (usually vancomycin) in persistently febrile patients. A study randomized 165 neutropenic patients with a persistent fever after 2-3 days of piperacillin-tazobactam to receive vancomycin or placebo. No differences between the two groups were observed in time to defervescence, the proportion of afebrile patients in different time points, Gram-positive infections, or mortality.⁸⁰

Another situation in which clinicians add vancomycin



MDR-GN = multi-drug resistant Gram-negative

Figure 1. Strategy of empiric antibiotic therapy in patients with colonization or a previous episode of infection by multi-drug-resistant Gram-negative bacteria.

empirically is when there are signs of a skin infection, such as cellulitis. A useful tool to help decision making is to check the results of baseline nasal swabs usually performed on admission to detect MRSA colonization. A study analyzed the correlation between the results of 484 nasal swabs in 194 patients with AML and subsequent documentation of infection. A negative MRSA nasal swab had a 99% negative predictive value for subsequent MRSA infections.⁸¹

Another frequent empiric change in the antibiotic regimen in persistently febrile neutropenic patients is to expand Gram-negative coverage, usually switching from cefepime or piperacillin-tazobactam to meropenem. Even considering the emergence of MDR bacterial infections in neutropenic patients, this practice is not recommended for persistently febrile patients this practice is not recommended for persistently febrile patients who do not have signs of clinical deterioration. Instead, a diagnostic workup for infection and other causes of fever's persistence should be undertaken, including a thorough physical examination, repeated blood cultures, serum biomarkers of infection, and images.¹²

My opinion. I do not change the empiric regimen on the basis of just persistent fever. I perform a careful review of symptoms and physical examination, obtain additional blood cultures, and check for results of biomarkers of infection, including serum C-reactive protein and galactomannan. On the other hand, if there are new signs of infection, I change the regimen as follows: add metronidazole if there is anal or abdominal pain, and switch beta-lactam if there is any sign of clinical deterioration, even if the patient is afebrile. In addition, I check the results of baseline blood cultures and make appropriate adjustments to the antibiotic regimen accordingly, including adjusting the dose of cefepime, taking into consideration the minimal inhibitory concentration of a Gram-negative bacteria grown in blood cultures. If the patient presents signs of a skin infection, I only add vancomycin if the patient is colonized by MRSA. I give linezolid or daptomycin to patients with documented infection by vancomycin-resistant Gram-positive bacteria, such as enterococci.

I do not give empiric antifungal therapy for persistently febrile patients. Instead, I combine serum galactomannan results with images (chest and sinuses CT scan), and start antifungal therapy in a preemptive strategy. If a chest CT scan shows images suspicious of invasive mold disease (macronodules, wedge-shaped images) and serum galactomannan is negative, I perform bronchoalveolar lavage unless the patient is hypoxemic. Additional tests that I perform frequently are abdominal CT scan in patients with clinical manifestations suspicious of typhlitis, stool tests for *Clostridioides difficile* in patients with diarrhea, and skin biopsy in any

new skin nodular lesion.

When Should I Discontinue Antibiotics in Febrile Neutropenia?

In general, the parameters that guide the duration of antimicrobial therapy in febrile neutropenia are documentation of infection and neutrophil recovery. For patients with infection documentation, the usual recommendation is to define the duration of treatment based on the infection that was diagnosed, keeping the antibiotic regimen at least until neutrophil recovery.¹⁰ For patients with no infection documentation, the recommendation had been to keep the empiric regimen until neutrophil recovery. This practice was supported by a study that randomized 33 neutropenic patients who were afebrile on day 7 of antibiotics to keep (16 patients) or discontinue (17 patients) the antibiotic regimen. None of the patients who continued antibiotics until neutrophil recovery became febrile or had documentation of infection. By contrast, 7 of the 17 patients who discontinued the antibiotic regimen developed fever, with infection documentation in 5 patients (2 deaths).⁸² However, more recently, a series of studies have explored the strategy of early discontinuation of antibiotics in persistently neutropenic afebrile patients,⁸³⁻⁸⁵ including one randomized controlled study. In this multicenter trial, patients with an expected duration of neutropenia >7 days who had no documentation of infection, were afebrile after three days of empiric antibiotics and had normal vital signs (blood pressure, heart and respiratory rate, arterial oxygen saturation, and daily diuresis) were randomized to continue antibiotics until neutrophil recovery (control arm) or to discontinue the antibiotic regimen (experimental arm). The number of empiric antibiotic therapy-free days (primary endpoint) was significantly higher in the experimental arm, with no differences in the total number of days with fever or the fever recurrence rates, documentation of infection, or death.⁸⁶

My opinion. For patients who recover from neutropenia, I promptly discontinue the antibiotic regimen if there was no documentation of infection, regardless of the duration of empiric antibiotic treatment. For patients who recover from neutropenia but had documentation of infection, I adjust the antibiotic regimen to treat the documented infection for as long as it is needed (based on the type of infection that was diagnosed). For patients with are still neutropenic and have a documented infection, I adjust the regimen to cover the pathogen recovered in the documented infection but keep the beta-lactam until neutrophil recovery. If there is no infection documentation, I discontinue the empiric antibiotic regimen, provided that vital signs are normal and the patient has no oral or gastrointestinal mucositis. In some patients at high risk for infection (e.g., expected long duration of neutropenia), I discontinue the empiric

antibiotic regimen and give a quinolone. In any case, once the empiric antibiotic regimen is discontinued, I monitor the temperature very closely and reintroduce empiric antibiotic therapy if fever recurs.

Conclusions. The management of febrile neutropenia should be individualized, considering the underlying hematologic disease, prior and recent chemotherapy,

with an estimate of the duration of neutropenia, local epidemiology, and diagnostic resources in the center, and daily bedside assessment of infection. Once the patient develops a fever, an antibiotic regimen that is active against the most likely Gram-negative bacteria should be promptly initiated and further adjusted based on clinical and microbiologic parameters.

References:

1. Schimpff S, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *N Engl J Med.* 1971;284:1061-5.PM:4994878
<https://doi.org/10.1056/NEJM197105132841904>
PMid:4994878
2. Hughes WT, Armstrong D, Bodey GP, Brown AE, Edwards JE, Feld R, Pizzo P, Rolston KV, Shenep JL, Young LS. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. Infectious Diseases Society of America. *Clin Infect Dis.* 1997;25:551-73.PM:9314442
<https://doi.org/10.1086/513764>
PMid:9314442
3. Viscoli C, Castagnola E, Caniggia M, De SL, Garaventa A, Giacchino M, Indolfi P, Izzi GC, Manzoni P, Rossi MR, Santoro N, Zanazzo GA, Maserà G. Italian guidelines for the management of infectious complications in pediatric oncology: empirical antimicrobial therapy of febrile neutropenia. *Oncology.* 1998;55:489-500.PM:9732231
<https://doi.org/10.1159/000011901>
PMid:9732231
4. NCCN practice guidelines for fever and neutropenia. National Comprehensive Cancer Network. *Oncology (Williston Park).* 1999;13:197-257.PM:10370929
5. Wade JC, Rubenstein EB. NCCN: Fever and neutropenia. *Cancer Control.* 2001;8:16-21.PM:11760554
6. Link H, Bohme A, Cornely OA, Hoffken K, Kellner O, Kern WV, Mahlberg R, Maschmeyer G, Nowrousian MR, Ostermann H, Ruhnke M, Sezer O, Schiel X, Wilhelm M, Auner HW. Antimicrobial therapy of unexplained fever in neutropenic patients--guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society). *Ann Hematol.* 2003;82 Suppl 2:S105-S117.PM:13680173
<https://doi.org/10.1007/s00277-003-0764-4>
PMid:13680173
7. Hughes WT, Armstrong D, Bodey GP, Bow EJ, Brown AE, Calandra T, Feld R, Pizzo PA, Rolston KV, Shenep JL, Young LS. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis.* 2002;34:730-51.PM:11850858
<https://doi.org/10.1086/339215>
PMid:11850858
8. Guidelines for the use of antimicrobial agents in patients with febrile neutropenia in Taiwan. *J Microbiol Immunol Infect.* 2005;38:455-7.PM:16341349
9. de NJ, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2010;21 Suppl 5:v252-v256.PM:20555092
<https://doi.org/10.1093/annonc/mdq196>
PMid:20555092
10. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011;52:e56-e93.PM:21258094
<https://doi.org/10.1093/cid/cir073>
PMid:21258094
11. Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, Hawley DK, Kuderer NM, Langston AA, Marr KA, Rolston KV, Ramsey SD. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2013;31:794-810.PM:23319691
<https://doi.org/10.1200/JCO.2012.45.8661>
PMid:23319691
12. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, Gyssens IC, Kern WV, Klyasova G, Marchetti O, Engelhard D, Akova M. 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. *Haematologica.* 2013;98:1826-35.PM:24323983
<https://doi.org/10.3324/haematol.2013.091025>
PMid:24323983 PMCid:PMC3856957
13. Lehrmbecher T, Robinson P, Fisher B, Alexander S, Ammann RA, Beauchemin M, Carlesse F, Groll AH, Haeusler GM, Santolaya M, Steinbach WJ, Castagnola E, Davis BL, Dupuis LL, Gaur AH, Tissing WJE, Zaoutis T, Phillips R, Sung L. Guideline for the Management of Fever and Neutropenia in Children With Cancer and Hematopoietic Stem-Cell Transplantation Recipients: 2017 Update. *J Clin Oncol.* 2017;35:2082-94.PM:28459614
<https://doi.org/10.1200/JCO.2016.71.7017>
PMid:28459614
14. Opota O, Croxatto A, Prod'homme G, Greub G. Blood culture-based diagnosis of bacteraemia: state of the art. *Clin Microbiol Infect.* 2015;21:313-22.PM:25753137
<https://doi.org/10.1016/j.cmi.2015.01.003>
PMid:25753137
15. Luethy PM, Johnson JK. The Use of Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) for the Identification of Pathogens Causing Sepsis. *J Appl Lab Med.* 2019;3:675-85.PM:31639735
<https://doi.org/10.1373/jalm.2018.027318>
PMid:31639735
16. Maertens J, Theunissen K, Verhoef G, Verschakelen J, Lagrou K, Verbeken E, Wilmer A, Verhaegen J, Boogaerts M, Van EJ. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis.* 2005;41:1242-50.PM:16206097
<https://doi.org/10.1086/496927>
PMid:16206097
17. van DD, Bonomo RA. Ceftazidime/Avibactam and Ceftolozane/Tazobactam: Second-generation beta-Lactam/beta-Lactamase Inhibitor Combinations. *Clin Infect Dis.* 2016;63:234-41.PM:27098166
<https://doi.org/10.1093/cid/ciw243>
PMid:27098166 PMCid:PMC4928383
18. Goulenok T, Fantin B. Antimicrobial treatment of febrile neutropenia: pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet.* 2013;52:869-83.PM:23807657
<https://doi.org/10.1007/s40262-013-0086-1>
PMid:23807657
19. Golob JL, Pergam SA, Srinivasan S, Fiedler TL, Liu C, Garcia K, Mielcarek M, Ko D, Aker S, Marquis S, Loeffelholz T, Plantinga A, Wu MC, Celustka K, Morrison A, Woodfield M, Fredricks DN. Stool Microbiota at Neutrophil Recovery Is Predictive for Severe Acute Graft vs Host Disease After Hematopoietic Cell Transplantation. *Clin Infect Dis.* 2017;65:1984-91.PM:29020185
<https://doi.org/10.1093/cid/cix699>
PMid:29020185 PMCid:PMC5850019
20. Holler E, Butzhammer P, Schmid K, Hundsrucker C, Koestler J, Peter K, Zhu W, Sporrer D, Hehlhans T, Kreutz M, Holler B, Wolff D, Edinger M, Andreesen R, Levine JE, Ferrara JL, Gessner A, Spang R, Oefner PJ. Metagenomic analysis of the stool microbiome in patients receiving allogeneic stem cell transplantation: loss of diversity is associated with use of systemic antibiotics and more pronounced in gastrointestinal graft-

- versus-host disease. *Biol Blood Marrow Transplant.* 2014;20:640-5.PM:24492144
<https://doi.org/10.1016/j.bbmt.2014.01.030>
 PMid:24492144 PMCid:PMC4973578
21. Bucaneve G, Micozzi A, Menichetti F, Martino P, Dionisi MS, Martinelli G, Allione B, D'Antonio D, Buelli M, Nosari AM, Cilloni D, Zuffa E, Cantaffa R, Specchia G, Amadori S, Fabbiano F, Deliliers GL, Lauria F, Foa R, Del FA. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med.* 2005;353:977-87.PM:16148283
<https://doi.org/10.1056/NEJMoa044097>
 PMid:16148283
 22. Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P, Stuart N, Rea D, Bower M, Fernando I, Huddart R, Gollins S, Stanley A. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med.* 2005;353:988-98.PM:16148284
<https://doi.org/10.1056/NEJMoa050078>
 PMid:16148284
 23. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med.* 2005;142:979-95.PM:15968013
https://doi.org/10.7326/0003-4819-142-12_Part_1-200506210-00008
 PMid:15968013
 24. Leibovici L, Paul M, Cullen M, Bucaneve G, Gafter-Gvili A, Fraser A, Kern WV. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. *Cancer.* 2006;107:1743-51.PM:16977651
<https://doi.org/10.1002/cncr.22205>
 PMid:16977651
 25. Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T, Ceppi M, Bruzzi P, Viscoli C. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *J Infect.* 2018;76:20-37.PM:29079323
<https://doi.org/10.1016/j.jinf.2017.10.009>
 PMid:29079323
 26. Garnica M, Nouer SA, Pellegrino FL, Moreira BM, Maiolino A, Nucci M. Ciprofloxacin prophylaxis in high risk neutropenic patients: effects on outcomes, antimicrobial therapy and resistance. *BMC Infect Dis.* 2013;13:356.PM:23899356
<https://doi.org/10.1186/1471-2334-13-356>
 PMid:23899356 PMCid:PMC3729823
 27. Khurana M, Lee B, Feusner JH. Fever at Diagnosis of Pediatric Acute Lymphoblastic Leukemia: Are Antibiotics Really Necessary? *J Pediatr Hematol Oncol.* 2015;37:498-501.PM:26376233
<https://doi.org/10.1097/MPH.0000000000000417>
 PMid:26376233
 28. DeGregorio MW, Lee WM, Linker CA, Jacobs RA, Ries CA. Fungal infections in patients with acute leukemia. *Am J Med.* 1982;73:543-8.PM:7124778
[https://doi.org/10.1016/0002-9343\(82\)90334-5](https://doi.org/10.1016/0002-9343(82)90334-5)
 29. Bodey G, Bueltmann B, Duguid W, Gibbs D, Hanak H, Hotchi M, Mall G, Martino P, Meunier F, Milliken S, . Fungal infections in cancer patients: an international autopsy survey. *Eur J Clin Microbiol Infect Dis.* 1992;11:99-109.PM:1396746
<https://doi.org/10.1007/BF01967060>
 PMid:1396746
 30. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, Meyers JD, Bowden RA. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation--a prospective, randomized, double-blind study. *J Infect Dis.* 1995;171:1545-52.PM:7769290
<https://doi.org/10.1093/infdis/171.6.1545>
 PMid:7769290
 31. Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H, Shaddock RK, Shea TC, Stiff P, Friedman DJ, . A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med.* 1992;326:845-51.PM:1542320
<https://doi.org/10.1056/NEJM199203263261301>
 PMid:1542320
 32. Winston DJ, Chandrasekar PH, Lazarus HM, Goodman JL, Silber JL, Horowitz H, Shaddock RK, Rosenfeld CS, Ho WG, Islam MZ, Buell DN. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. *Ann Intern Med.* 1993;118:495-503.PM:8442620
<https://doi.org/10.7326/0003-4819-118-7-199304010-00003>
 PMid:8442620
 33. Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. *Cancer.* 2002;94:3230-46.PM:12115356
<https://doi.org/10.1002/cncr.10610>
 PMid:12115356
 34. Pagano L, Caira M, Candoni A, Offidani M, Fianchi L, Martino B, Pastore D, Picardi M, Bonini A, Chierichini A, Fanci R, Caramatti C, Invernizzi R, Mattei D, Mitra ME, Melillo L, Aversa F, Van Lint MT, Falcucci P, Valentini CG, Girmenia C, Nosari A. The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Haematologica.* 2006;91:1068-75.PM:16885047
 35. Pagano L, Caira M, Nosari A, Van Lint MT, Candoni A, Offidani M, Aloisi T, Irrera G, Bonini A, Picardi M, Caramatti C, Invernizzi R, Mattei D, Melillo L, de WC, Reddiconto G, Fianchi L, Valentini CG, Girmenia C, Leone G, Aversa F. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study--Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. *Clin Infect Dis.* 2007;45:1161-70.PM:17918077
<https://doi.org/10.1086/522189>
 PMid:17918077
 36. Nucci M, Garnica M, Gloria AB, Lehueur DS, Dias VC, Palma LC, Cappellano P, Fertrin KY, Carlesse F, Simoes B, Bergamasco MD, Cunha CA, Seber A, Ribeiro MP, Queiroz-Telles F, Lee ML, Chauffaille ML, Silla L, De Souza CA, Colombo AL. Invasive fungal diseases in haematopoietic cell transplant recipients and in patients with acute myeloid leukaemia or myelodysplasia in Brazil. *Clin Microbiol Infect.* 2013;19:745-51.PM:23009319
<https://doi.org/10.1111/1469-0691.12002>
 PMid:23009319
 37. Pagano L, Offidani M, Fianchi L, Nosari A, Candoni A, Piccardi M, Corvatta L, D'Antonio D, Girmenia C, Martino P, Del FA. Mucormycosis in hematologic patients. *Haematologica.* 2004;89:207-14.PM:15003897
 38. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med.* 2007;356:348-59.PM:17251531
<https://doi.org/10.1056/NEJMoa061094>
 PMid:17251531
 39. Fisher BT, Zaoutis T, Dvorak CC, Nieder M, Zerr D, Wingard JR, Callahan C, Villaluna D, Chen L, Dang H, Esbenshade AJ, Alexander S, Wiley JM, Sung L. Effect of Caspofungin vs Fluconazole Prophylaxis on Invasive Fungal Disease Among Children and Young Adults With Acute Myeloid Leukemia: A Randomized Clinical Trial. *JAMA.* 2019;322:1673-81.PM:31688884
<https://doi.org/10.1001/jama.2019.15702>
 PMid:31688884 PMCid:PMC6865545
 40. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Baden LR, Gersten ID, Mendizabal AM, Leather HL, Confer DL, Maziarz RT, Stadtmauer EA, Bolanos-Meade J, Brown J, DiPersio JF, Boeckh M, Marr KA. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood.* 2010;116:5111-8.PM:20826719
<https://doi.org/10.1182/blood-2010-02-268151>
 PMid:20826719 PMCid:PMC3012532
 41. Marks DI, Pagliuca A, Kibbler CC, Glasmacher A, Heussel CP, Kantecki M, Miller PJ, Ribaud P, Schlamm HT, Solano C, Cook G. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol.* 2011;155:318-27.PM:21880032
<https://doi.org/10.1111/j.1365-2141.2011.08838.x>
 PMid:21880032 PMCid:PMC3253339
 42. Park S, Kim K, Jang JH, Kim SJ, Kim WS, Chung DR, Kang CI, Peck KR, Jung CW. Randomized trial of micafungin versus fluconazole as prophylaxis against invasive fungal infections in hematopoietic stem cell transplant recipients. *J Infect.* 2016;73:496-505.PM:27394404
<https://doi.org/10.1016/j.jinf.2016.06.011>
 PMid:27394404
 43. Huang X, Chen H, Han M, Zou P, Wu D, Lai Y, Huang H, Chen X, Liu T, Zhu H, Wang J, Hu J. Multicenter, randomized, open-label study comparing the efficacy and safety of micafungin versus itraconazole for prophylaxis of invasive fungal infections in patients undergoing hematopoietic stem cell transplant. *Biol Blood Marrow Transplant.* 2012;18:1509-16.PM:22469884
<https://doi.org/10.1016/j.bbmt.2012.03.014>
 PMid:22469884
 44. van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, Bunin N, Wall DA, Hiemenz JW, Satoi Y, Lee JM, Walsh TJ.

- Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis.* 2004;39:1407-16.PM:15546073
<https://doi.org/10.1086/422312>
PMid:15546073
45. Cornely OA, Leguay T, Maertens J, Vehreschild MJGT, Anagnostopoulos A, Castagnola C, Verga L, Rieger C, Kondakci M, Harter G, Duarte RF, Allione B, Cordonnier C, Heussel CP, Morrissey CO, Agrawal SG, Donnelly JP, Bresnik M, Hawkins MJ, Garner W, Gokbuget N. Randomized comparison of liposomal amphotericin B versus placebo to prevent invasive mycoses in acute lymphoblastic leukaemia. *J Antimicrob Chemother.* 2017;72:2359-67.PM:28575414
<https://doi.org/10.1093/jac/dkx133>
PMid:28575414 PMCID:PMC5890735
 46. Maertens J, Theunissen K, Verhoef G, Verschakelen J, Lagrou K, Verbeken E, Wilmer A, Verhaegen J, Boogaerts M, Van EJ. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis.* 2005;41:1242-50.PM:16206097
<https://doi.org/10.1086/496927>
PMid:16206097
 47. Duarte RF, Sanchez-Ortega I, Cuesta I, Arnan M, Patino B, Fernandez de SA, Gudiol C, Ayats J, Cuenca-Estrella M. Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective antimold prophylaxis. *Clin Infect Dis.* 2014;59:1696-702.PM:25165088
<https://doi.org/10.1093/cid/ciu673>
PMid:25165088
 48. Girmenia C, Micozzi A, Gentile G, Santilli S, Arleo E, Cardarelli L, Capria S, Minotti C, Cartoni C, Brocchieri S, Guerrisi V, Meloni G, Foa R, Martino P. Clinically driven diagnostic antifungal approach in neutropenic patients: a prospective feasibility study. *J Clin Oncol.* 2010;28:667-74.PM:19841328
<https://doi.org/10.1200/JCO.2009.21.8032>
PMid:19841328
 49. Bewersdorf JP, Stahl M, Zeidan AM. Are we witnessing the start of a therapeutic revolution in acute myeloid leukemia? *Leuk Lymphoma.* 2019;60:1354-69.PM:30652518
<https://doi.org/10.1080/10428194.2018.1546854>
PMid:30652518
 50. Kucukyurt S, Eskazan AE. New drugs approved for acute myeloid leukemia (AML) in 2018. *Br J Clin Pharmacol.* 2019.PM:31469910
<https://doi.org/10.1111/bcp.14105>
PMid:31469910 PMCID:PMC6955409
 51. Agarwal SK, DiNardo CD, Potluri J, Dunbar M, Kantarjian HM, Humerickhouse RA, Wong SL, Menon RM, Konopleva MY, Salem AH. Management of Venetoclax-Posaconazole Interaction in Acute Myeloid Leukemia Patients: Evaluation of Dose Adjustments. *Clin Ther.* 2017;39:359-67.PM:28161120
<https://doi.org/10.1016/j.clinthera.2017.01.003>
PMid:28161120
 52. Dutreix C, Munarini F, Lorenzo S, Roesel J, Wang Y. Investigation into CYP3A4-mediated drug-drug interactions on midostaurin in healthy volunteers. *Cancer Chemother Pharmacol.* 2013;72:1223-34.PM:24085261
<https://doi.org/10.1007/s00280-013-2287-6>
PMid:24085261 PMCID:PMC3834177
 53. Agarwal S, Gopalakrishnan S, Mensing S, Potluri J, Hayslip J, Kirschbrown W, Friedel A, Menon R, Salem AH. Optimizing venetoclax dose in combination with low intensive therapies in elderly patients with newly diagnosed acute myeloid leukemia: An exposure-response analysis. *Hematol Oncol.* 2019;37:464-73.PM:31251400
<https://doi.org/10.1002/hon.2646>
PMid:31251400
 54. Estey EH. Acute myeloid leukemia: 2019 update on risk-stratification and management. *Am J Hematol.* 2018;93:1267-91.PM:30328165
<https://doi.org/10.1002/ajh.25214>
PMid:30328165
 55. Nucci M, Anaissie E. How we treat invasive fungal diseases in patients with acute leukemia: the importance of an individualized approach. *Blood.* 2014;124:3858-69.PM:25339358
<https://doi.org/10.1182/blood-2014-04-516211>
PMid:25339358
 56. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. *Ann Intern Med.* 1966;64:328-40.PM:5216294
<https://doi.org/10.7326/0003-4819-64-2-328>
PMid:5216294
 57. Estacio O, Loh Z, Baker A, Chong G, Grigg A, Churilov L, Hawkes EA. Limited utility of routine chest X-ray in initial evaluation of neutropenic fever in patients with hematological diseases undergoing chemotherapy. *Intern Med J.* 2018;48:556-60.PM:29227565
<https://doi.org/10.1111/imj.13712>
PMid:29227565
 58. Bitterman R, Hardak E, Guralnik L, Paul M, Oren I. Reply to Nucci. *Clin Infect Dis.* 2020;70:347-9.PM:31075162
<https://doi.org/10.1093/cid/ciz382>
PMid:31075162
 59. Bitterman R, Hardak E, Raines M, Stern A, Zuckerman T, Ofra Y, Lavi N, Guralnik L, Frisch A, Nudelman O, Paul M, Oren I. Baseline Chest Computed Tomography for Early Diagnosis of Invasive Pulmonary Aspergillosis in Hemato-oncological Patients: A Prospective Cohort Study. *Clin Infect Dis.* 2019;69:1805-8.PM:30855077
<https://doi.org/10.1093/cid/ciz194>
PMid:30855077
 60. Nucci M. Is Early Invasive Pulmonary Aspergillosis Coming of Age? *Clin Infect Dis.* 2020;70:347.PM:31075161
<https://doi.org/10.1093/cid/ciz381>
PMid:31075161
 61. Stemler J, Bruns C, Mellinghoff SC, Alakel N, Akan H, Ananda-Rajah M, Auberger J, Brojko P, Chandrasekar PH, Chayakulkeeree M, Cozzi JA, de Kort EA, Groll AH, Heath CH, Henze L, Hernandez JM, Kanj SS, Khanna N, Koldehoff M, Lee DG, Mager A, Marchesi F, Martino-Bufarull R, Nucci M, Oksi J, Pagano L, Phillips B, Prattes J, Pyrasopoulou A, Rabitsch W, Schalk E, Schmidt-Hieber M, Sidharthan N, Soler-Palacin P, Stern A, Weinbergerova B, El ZA, Cornely OA, Koehler P. Baseline Chest Computed Tomography as Standard of Care in High-Risk Hematology Patients. *J Fungi (Basel).* 2020;6.PM:32183235
<https://doi.org/10.3390/jof6010036>
PMid:32183235 PMCID:PMC7151030
 62. Maiolino A, Biasoli I, Lima J, Portugal AC, Pulcheri W, Nucci M. Engraftment syndrome following autologous hematopoietic stem cell transplantation: definition of diagnostic criteria. *Bone Marrow Transplant.* 2003;31:393-7.PM:12634731
<https://doi.org/10.1038/sj.bmt.1703855>
PMid:12634731
 63. Montesinos P, Bergua JM, Vellenga E, Rayon C, Parody R, De la Serna J, Leon A, Esteve J, Milone G, Deben G, Rivas C, Gonzalez M, Tormo M, Diaz-Mediavilla J, Gonzalez JD, Negri S, Amutio E, Brunet S, Lowenberg B, Sanz MA. Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. *Blood.* 2009;113:775-83.PM:18945964
<https://doi.org/10.1182/blood-2008-07-168617>
PMid:18945964
 64. Norsworthy KJ, Mulkey F, Scott EC, Ward AF, Przepiorka D, Charlab R, Dorff SE, Deisseroth A, Kazandjian D, Sridhara R, Beaver JA, Farrell AT, de Claro RA, Pazdur R. Differentiation Syndrome with Ivosidenib and Enasidenib Treatment in Patients with Relapsed or Refractory IDH-Mutated AML: A U.S. Food and Drug Administration Systematic Analysis. *Clin Cancer Res.* 2020;26:4280-8.PM:32393603
<https://doi.org/10.1158/1078-0432.CCR-20-0834>
PMid:32393603
 65. Calandra T, Klastersky J, Gaya H, Glauser MP, Meunier F, Zinner SH. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. *N Engl J Med.* 1987;317:1692-8.PM:2892130
<https://doi.org/10.1056/NEJM198712313172703>
PMid:2892130
 66. Paul M, Dickstein Y, Schlesinger A, Grozinsky-Glasberg S, Soares-Weiser K, Leibovici L. Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. *Cochrane Database Syst Rev.* 2013;CD003038.PM:23813455
<https://doi.org/10.1002/14651858.CD003038.pub2>
PMid:23813455 PMCID:PMC6457814
 67. Pizzo PA, Hathorn JW, Hiemenz J, Browne M, Commers J, Cotton D, Gress J, Longo D, Marshall D, McKnight J, . A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *N Engl J Med.* 1986;315:552-8.PM:3526155
<https://doi.org/10.1056/NEJM198608283150905>
PMid:3526155
 68. Paul M, Borok S, Fraser A, Vidal L, Leibovici L. Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic

- review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* 2005;55:436-44.PM:15722392
<https://doi.org/10.1093/jac/dki028>
PMid:15722392
69. Beyar-Katz O, Dickstein Y, Borok S, Vidal L, Leibovici L, Paul M. Empirical antibiotics targeting gram-positive bacteria for the treatment of febrile neutropenic patients with cancer. *Cochrane Database Syst Rev.* 2017;6:CD003914.PM:28577308
<https://doi.org/10.1002/14651858.CD003914.pub4>
PMid:28577308 PMCID:PMC6481386
70. Gustinetti G, Mikulska M. Bloodstream infections in neutropenic cancer patients: A practical update. *Virulence.* 2016;7:280-97.PM:27002635
<https://doi.org/10.1080/21505594.2016.1156821>
PMid:27002635 PMCID:PMC4871679
71. Guarana M, Nucci M, Nouer SA. Shock and Early Death in Hematologic Patients with Febrile Neutropenia. *Antimicrob Agents Chemother.* 2019.PM:31405857
<https://doi.org/10.1128/AAC.01250-19>
PMid:31405857 PMCID:PMC6811434
72. Martinez-Nadal G, Puerta-Alcalde P, Gudiol C, Cardozo C, Albasanz-Puig A, Marco F, Laporte-Amargos J, Moreno-Garcia E, Domingo-Domenech E, Chumbita M, Martinez JA, Soriano A, Carratala J, Garcia-Vidal C. Inappropriate Empirical Antibiotic Treatment in High-risk Neutropenic Patients With Bacteremia in the Era of Multidrug Resistance. *Clin Infect Dis.* 2020;70:1068-74.PM:31321410
<https://doi.org/10.1093/cid/ciz319>
PMid:31321410
73. Zadka H, Raykhshtat E, Urlev B, Bishouty N, Weiss-Meilik A, Adler A. The implementation of rapid microbial identification via MALDI-ToF reduces mortality in gram-negative but not gram-positive bacteremia. *Eur J Clin Microbiol Infect Dis.* 2019;38:2053-9.PM:31359256
<https://doi.org/10.1007/s10096-019-03640-w>
PMid:31359256
74. Righi E, Peri AM, Harris PN, Wailan AM, Liborio M, Lane SW, Paterson DL. Global prevalence of carbapenem resistance in neutropenic patients and association with mortality and carbapenem use: systematic review and meta-analysis. *J Antimicrob Chemother.* 2017;72:668-77.PM:27999023
<https://doi.org/10.1093/jac/dkw459>
PMid:27999023
75. Forcina A, Baldan R, Marasco V, Cichero P, Bondanza A, Noviello M, Piemontese S, Soliman C, Greco R, Lorentino F, Giglio F, Messina C, Carrabba M, Bernardi M, Peccatori J, Moro M, Biancardi A, Nizzero P, Scarpellini P, Cirillo DM, Mancini N, Corti C, Clementi M, Ciceri F. Control of infectious mortality due to carbapenemase-producing *Klebsiella pneumoniae* in hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2017;52:114-9.PM:27668762
<https://doi.org/10.1038/bmt.2016.234>
PMid:27668762
76. Nouer SA, Nucci M, Anaissie E. Tackling antibiotic resistance in febrile neutropenia: current challenges with and recommendations for managing infections with resistant Gram-negative organisms. *Expert Rev Hematol.* 2015;8:647-58.PM:26115679
<https://doi.org/10.1586/17474086.2015.1060576>
PMid:26115679
77. Puerta-Alcalde P, Cardozo C, Suarez-Lledo M, Rodriguez-Nunez O, Morata L, Feher C, Marco F, Del RA, Martinez JA, Mensa J, Rovira M, Esteve J, Soriano A, Garcia-Vidal C. Current time-to-positivity of blood cultures in febrile neutropenia: a tool to be used in stewardship de-escalation strategies. *Clin Microbiol Infect.* 2019;25:447-53.PM:30096417
<https://doi.org/10.1016/j.cmi.2018.07.026>
PMid:30096417
78. Erman M, Akova M, Akan H, Kortzen V, Ferhanoglu B, Koksali I, Cetinkaya Y, Uzun O, Unal S. Comparison of cefepime and ceftazidime in combination with amikacin in the empirical treatment of high-risk patients with febrile neutropenia: a prospective, randomized, multicenter study. *Scand J Infect Dis.* 2001;33:827-31.PM:11760163
<https://doi.org/10.1080/00365540110076679>
PMid:11760163
79. Tamura K, Imajo K, Akiyama N, Suzuki K, Urabe A, Ohyashiki K, Tanimoto M, Masaoka T. Randomized trial of cefepime monotherapy or cefepime in combination with amikacin as empirical therapy for febrile neutropenia. *Clin Infect Dis.* 2004;39 Suppl 1:S15-S24.PM:15250016
<https://doi.org/10.1086/383046>
PMid:15250016
80. Cometta A, Kern WV, de BR, Paesmans M, Vandenberghe M, Crokaert F, Engelhard D, Marchetti O, Akan H, Skoutelis A, Kortzen V, Vandercam M, Gaya H, Padmos A, Klastersky J, Zinner S, Glauser MP, Calandra T, Viscogli C. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis.* 2003;37:382-9.PM:12884163
<https://doi.org/10.1086/376637>
PMid:12884163
81. Perreault SK, Binks B, McManus DS, Topal JE. Evaluation of the negative predictive value of methicillin-resistant *Staphylococcus aureus* nasal swab screening in patients with acute myeloid leukemia. *Infect Control Hosp Epidemiol.* 2020;1-4.PM:33228818
<https://doi.org/10.1017/ice.2020.1299>
PMid:33228818
82. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG, Levine AS, Deisseroth AB, Glaubiger DL, MacLowry JD, Magrath IT, Poplack DG, Simon RM. Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. *Am J Med.* 1979;67:194-200.PM:380336
[https://doi.org/10.1016/0002-9343\(79\)90390-5](https://doi.org/10.1016/0002-9343(79)90390-5)
83. Le CL, Talarmin JP, Couturier MA, Ianotto JC, Nicol C, Le CR, Dos SS, Hutin P, Tande D, Cogulet V, Berthou C, Guillemin G. Early discontinuation of empirical antibacterial therapy in febrile neutropenia: the ANTIBIOSTOP study. *Infect Dis (Lond).* 2018;50:539-49.PM:29451055
<https://doi.org/10.1080/23744235.2018.1438649>
PMid:29451055
84. Van de Wyngaert Z, Berthon C, Debarri H, Bories C, Bonnet S, Nudel M, Carpentier B, Legrand C, Barbieux S, Chauvet P, Simonnet A, Willaume A, Bossard JB, Renaud L, Wattebled KJ, Escure G, Branche N, Arib I, Titecat M, Quesnel B, Alfandari S. Discontinuation of antimicrobial therapy in adult neutropenic haematology patients: A prospective cohort. *Int J Antimicrob Agents.* 2019;53:781-8.PM:30831232
<https://doi.org/10.1016/j.ijantimicag.2019.02.020>
PMid:30831232
85. Niessen FA, van Mourik MSM, Bruns AHW, Raijmakers RAP, de Groot MCH, van der Bruggen T. Early discontinuation of empirical antibiotic treatment in neutropenic patients with acute myeloid leukaemia and high-risk myelodysplastic syndrome. *Antimicrob Resist Infect Control.* 2020;9:74.PM:32460887
<https://doi.org/10.1186/s13756-020-00729-2>
PMid:32460887 PMCID:PMC7251665
86. Aguilar-Guisado M, Espigado I, Martin-Pena A, Gudiol C, Royo-Cebrecos C, Falantes J, Vazquez-Lopez L, Montero MI, Rosso-Fernandez C, de la Luz MM, Parody R, Gonzalez-Campos J, Garzon-Lopez S, Calderon-Cabrera C, Barba P, Rodriguez N, Rovira M, Montero-Mateos E, Carratala J, Perez-Simon JA, Cisneros JM. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol.* 2017;4:e573-e583.PM:29153975
[https://doi.org/10.1016/S2352-3026\(17\)30211-9](https://doi.org/10.1016/S2352-3026(17)30211-9)