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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	AML induction, allogeneic HCT, pre-engraftment, low risk*
	Posaconazole or voriconazole	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	Immediately if no documentation of infection
	No neutrophil recovery	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 (IDF) 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 AML[58-60] 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 ≥38ºC. 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 HCT[62] 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 different 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 is the patient is still febrile (**Figure 1**).

For patients without colonization by MDG 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

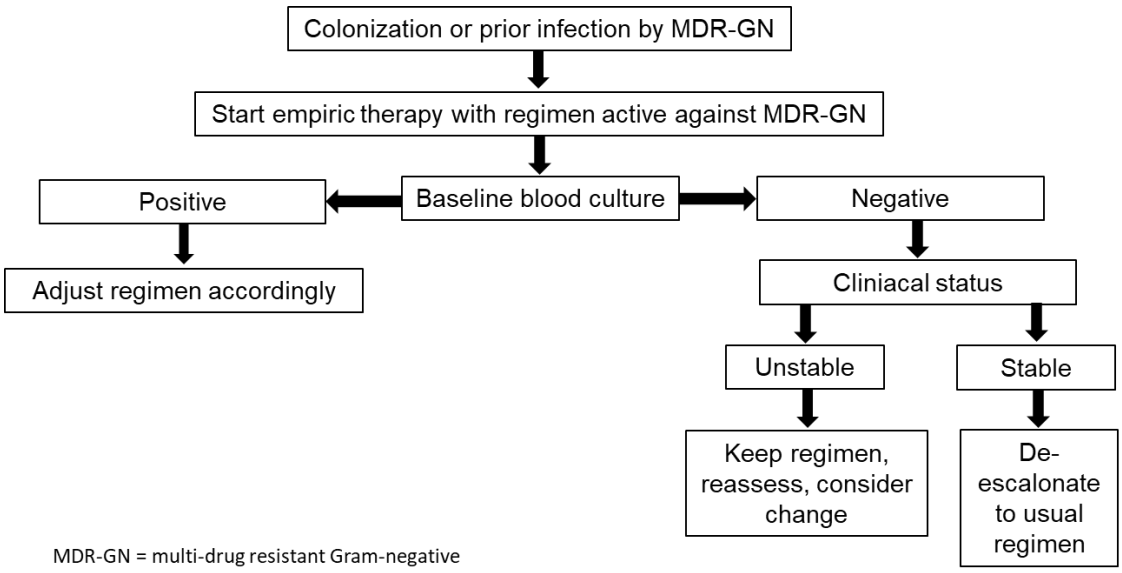

Figure 1. Strategy of empiric antibiotic therapy in patients with colonization or a previous episode of infection by multi-drug-resistant Gram-negative bacteria.

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.

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