



Antibiotic Management of Patients with Hematologic Malignancies: From Prophylaxis to Unusual Infections

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Abstract

Purpose of Review Patients with hematological malignancies are recognized for their high susceptibility and increased risk of developing infections associated with immunosuppression that can be caused by the infection itself or by the treatments that condition a decrease in the humoral and T lymphocyte response, so this review attempts to gather the main bacterial, viral, parasitic, and fungal agents that affect them and give recommendations for their approach and diagnosis.

Recent Findings In recent years, with the discovery and use of new therapies including immunological and targeted treatments, it has been possible to improve the survival and response of patients with hematological malignancies; however, antimicrobial resistance has also increased; we have faced new and unknown microorganisms, such as the SARS-CoV-2 that caused the COVID-19 pandemic in the past year, and therefore, new risks and more severe infections are presented.

Summary We present a review of the different circumstances where hematological malignancies increased the risk of infections and which microorganisms affect these patients, their characteristics, and the suggested prophylaxis.

Keywords Hematologic malignancies · Hematologic diseases · Infection diseases · Prophylaxis · Immunocompromised · Neutropenia · Febrile neutropenia · Infections

Introduction

Infectious complications in patients with hematological malignancies are frequent and a common cause of morbidity and mortality; also, considering that these patients also develop defects that alter the innate and adaptive immune response, the diagnosis of early infections in these patients is challenging because of the different characteristics on the clinical presentation involved, as well as the diagnostic tools needed, which are difficult to get in some settings. The overuse of antibiotics in some cases in recent years has also increased antimicrobial resistance and therefore the difficulty of treating the different associated infections. Therefore, the decision to start a prophylactic antibiotic treatment must always be valued and grounded according to the risk and benefit that this intervention grants, as well

as the toxicity, cost, and duration that it will require. Generally, according to the risk of infection, the initiation of a specific antimicrobial treatment is decided, as well as the knowledge of local resistance, the patient's history in relation to previous infections, exposure to antibiotic schemes, type of underlying disease, characteristics of chemotherapy, and associated complications [1, 2••].

Humoral immune defects, including hypogammaglobulinemia, are common in patients with hematologic malignancies; this state increases the risk for bacteremia, respiratory tract infections, meningitis, and skin infections caused by encapsulated bacteria [3]. Furthermore, humoral immune defects prevent the development of fully protective antibody responses to different vaccines, such as the anti-pneumococcal vaccine, and according to recent studies, also, to the anti-SARS-CoV-2 vaccine in where the current recommendation is to evaluate the application of a 3rd dose of an mRNA vaccine [4], although infections by these viruses are usually less severe in immunosuppressed vaccinated patients than in non-vaccinated patients [5, 6].

Patients receiving treatment with anti-CD20 antibodies have a known increased risk of reactivation of the

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hepatitis B virus (HBV) and those treated with protease inhibitors an increased risk of varicella-zoster virus reactivation [7•].

Lymphocyte-mediated immunity is altered in post-transplant patients secondary to the immunosuppressive treatment they receive, as well as prophylaxis of graft-versus-host disease, and in many cases of patients with hematologic malignancies. In these patients, there is an increase in the incidence of infections associated with intracellular organisms (*Mycobacteria*, *Legionella*, *Nocardia*, and *Strongyloides*) and infections by *Pneumocystis*, fungi, and herpes viruses, mainly cytomegalovirus, which, in turn, is the latter, a predisposing factor to later opportunistic infections.

Febrile Neutropenia

Severe neutropenia is defined as an absolute peripheral neutrophil count (ANC) of less than 500 cells/mL; patients with severe neutropenia especially those with ANC of 100 cells/mL or less are at great risk of polymicrobial infections [8].

Patients that receive chemotherapy, radiotherapy, or glucocorticoids as well as those that have functional granulocytopenia (myeloid neoplasm) have a great risk for developing severe neutropenia. Chemotherapy impairs phagocytic capacity, those impairing the ability to destroy microorganisms; they also affect myelopoiesis and the developmental integrity of the gastrointestinal mucosa [9].

Other populations at risk beyond the ones mentioned above are patients with hyperglycemia. Hyperglycemia disrupts antioxidant-dependent intercellular microbial elimination, those predisposing to bacterial and fungal infection; these patients do not appear to be neutropenic, but have a functional neutropenic as patients with myeloid neoplasm [10].

This population is at great risk of presenting polymicrobial infections; it has been previously reported that 15–20% of infections in high-risk cancer patients are due to multiple microorganisms [11]. In the first week of neutropenia, bacterial infections are more frequently observed especially those caused by gram-positive cocci (*Staphylococcus*), with high mortality. In this case, mucositis, fluoroquinolone prophylaxis, and indwelling vascular access are the principal risk factors [12, 13].

Beyond gram positive, some gram-negative multidrug-resistant bacteria are observed in these patients, such as *Escherichia coli* and *Pseudomonas aeruginosa* [14].

After the first week, ID specialist should search for fungal infections especially *Candida* species [12].

Bacterial Infections

Previous to the quinolone prophylaxis era, gram-negative bacilli especially *Pseudomonas aeruginosa* were the most common cause of bacterial infections in immunocompromised hosts. After the 1980s, a trend towards infections caused by gram-positive cocci was observed. This was caused by the introduction of central venous lines for the administration of chemotherapy and the use of quinolones as mentioned above [15]. The use of central venous catheters is extremely frequent and necessary for the treatment of patients with hematological malignancies. However, this carries a high risk of catheter-related bloodstream infections that can result in increased morbidity, mortality, and costs associated with medical care. Gram-positive bacteria, particularly those caused by *Staphylococcus*, remain the leading cause of catheter-related bloodstream infection, although an increase in gram-negative bacteria has been observed as a causative agent. Proper management as well as the precise approach to differentiate catheter-related infection bacteremia from infections associated with damage to the mucosal barrier in patients with myeloablative treatments as well as the early identification of the causative microorganisms is essential to define the antimicrobial coverage and decide whether or not the removal of the catheter is necessary.

The ratio of gram-positive to gram-negative bacteria as the cause of bacteremia in cancer patients remains at approximately 60:40; this was observed in the MASCC Trial, where they found an incidence of bacteremia of 23%, of which gram-positive organisms accounted for 57 percent of cases, gram-negative organisms for 34 percent, and polymicrobial bacteremia for 10 percent [16].

Common gram-positive cocci include *Staphylococcus epidermidis* (by far the most common), *Staphylococcus aureus*, and streptococci; less common gram-positive organisms include *Corynebacterium jeikeium*, *Bacillus* spp., *Leuconostoc* spp., *Lactobacillus* spp., *Cutibacterium* (formerly Propionibacterium) *acnes*, and *Rhodococcus* spp. [17].

From bacterial infections, *P. aeruginosa* is the most aggressive [18]; among gram-positive bacteria, methicillin-resistant *S. aureus* and enterococci can cause serious infections [15].

Initial regimen selection should be guided by the patient's history, allergies, symptoms, signs, recent antimicrobial agent use and culture data, and awareness of the susceptibility patterns of institutional nosocomial pathogens. Based on epidemiological data, empiric treatment should include broad coverage against MRSA and multidrug-resistant *Pseudomonas aeruginosa* [19]. In our practice,

Table 1 Proposed antimicrobial prophylactic treatment in patients with hematological malignancies

Disease	Prophylaxis
Neutropenic	Quinolone: ciprofloxacin 500 mg PO BID, levofloxacin 500–750 mg PO daily Consider according to local resistance: carbapenems with antipseudomonal activity • Meropenem 1 g IV TID • Imipenem 1 g IV QID
Non-neutropenic	Quinolone: ciprofloxacin 500 mg PO BID, levofloxacin 500–750 mg PO daily or TMP-SMX 800 mg/160 mg PO daily
<i>Clostridioides difficile</i> diarrhea	Vancomycin 125–250 mg PO QID or metronidazole 500 mg PO TID; if prior history
Fungal	
Disease	Prophylaxis
Invasive candidiasis	Fluconazole: 200–400 mg PO daily Consider according to local resistance and patient characteristics: • Caspofungin 70 mg IV loading dose and then 50 mg/day IV • Anidulafungin 200 mg IV loading dose and then 100 mg/day IV • Itraconazole oral solution 200 mg PO 2x/day • Posaconazole DR tabs 300 mg PO daily • Liposomal amphotericin B 3–5 mg/kg/day
Invasive aspergillosis	Posaconazole 200 mg TID for oral solution or 300 mg BID on day 1 followed by 300 mg once daily or voriconazole 200 mg PO BID Itraconazole 200 mg PO BID Inhaled amphotericin B 12.5 mg on 2 consecutive days/week
<i>Pneumocystis jirovecii</i> pneumonia	TMP-SMX 800 mg/160 mg PO daily or 2x/week or dapsone 100 mg PO daily or atovaquone 1500 mg PO daily
Virus	
Herpes simplex	Acyclovir 200–400 mg PO BID or TID or valacyclovir 500 mg PO TID or famciclovir 500 mg PO TID
Herpes zoster	Acyclovir 400 mg PO BID or TID or valacyclovir 500 mg PO TID or famciclovir 250 mg PO BID or TID
Cytomegalovirus	Ganciclovir 5 mg/kg IV BID or valganciclovir 900 mg/d PO or foscarnet 60 mg/kg IV BID
Influenza virus	Oseltamivir 75 mg PO daily for the duration of the influenza season
COVID-19	No prophylaxis available to date
Others	
Tuberculosis	Isoniazid—300 mg PO daily

TMP-SMX trimethoprim-sulfamethoxazole, PO per os, TID three times a day, QID four times a day, BID twice a day. Clin Infect Dis 34:730, 2002; N Engl J Med 353:977, 2005; N Engl J Med 353:988, 2005; N Engl J Med 353:1052, 2005, IDSA Practice Guidelines (Clin Infect Dis 52:427, 2011)

quinolone-resistant bacteria have a high prevalence; that is why we recommend in some situations empirical treatment with carbapenemic antibiotics (e.g., meropenem) and vancomycin or linezolid for MRSA, as described in Table 1.

Community Respiratory Viruses

Patients with hematologic disease have an increased risk of lower respiratory tract infection secondary to community-acquired respiratory virus (IVR) compared to immunocompetent patients. Respiratory viruses cause more serious and complicated diseases in immunosuppressed individuals, especially those with significant T cell defects. Respiratory tract infections are among the most common types of tissue-invasive infections in immunocompromised patients, including those with hematologic malignancies, who have an increased susceptibility to

infection with organisms of little virulence in non-immunocompromised individuals or with increased severity of common infections, along with the immunosuppressive treatment. Most viral lung infections in hematological patients begin insidiously with constitutional symptoms including fever and non-productive dry cough; some patients develop tachypnea, dyspnea, and hypoxemia [20–22].

Influenza, parainfluenza, respiratory syncytial virus (RSV), metapneumovirus, and adenovirus infections are the most important.

The seasonal variability of respiratory viruses in these patients coincides with that observed in the general community. Some cases may be seen earlier in immunosuppressed individuals than in the general community as harbingers of impending outbreaks. Human metapneumovirus (hMPV) is an increasingly recognized pathogen in immunosuppressed children and adults. Disease progression from the upper to

the lower tract occurs in 7 to 50 percent of TCH recipients [23].

An extensive review is always very important in these patients to rule out the possibility of bacterial or other superinfection. Marked hypoxemia or purulent sputum may suggest coinfection. More than usual, it is of great importance obtaining samples to establish antimicrobial susceptibility testing, molecular testing (RT-PCR (real-time polymerase chain reaction, genome sequencing)), and other interventions in the diagnostic evaluation as early imaging or invasive procedures which are often necessary to establish a microbiologic diagnosis. The election of antiviral prophylaxis is suggested in Table 1.

COVID-19 symptoms could be mild vs. more severe and may overlap with treatment-related pneumonitis or associated opportunistic infections [24•] which should have a close monitoring for thromboembolic events due to higher risk [25]. In a multicenter study of 190 CLL patients who tested positive for COVID-19, 90% were hospitalized and 79% presented with severe COVID-19 (needed oxygen and/or ICU admission); they found that severe COVID-19 was more common in patients >65 years of age, hospitalizations were less frequent for patients on a BTK inhibitor, and the overall mortality was 30% for all patients, 32.5% among those in hospital [26]. Other studies suggest that older age and comorbidities increased mortality risk [27]. It is known that there is a higher risk of invasive ventilation or death in patients with cancer and COVID-19, with a CFR (Crude Fatality Rate) of 7.6% reported in a cohort of 55,924 patients [28•]. But there are some reported factors that are not associated with increased risk of severe COVID-19 in cancer patients such as use of noncytotoxic therapy (targeted agents, endocrine therapy, immunotherapy, and radiation therapy) and cytotoxic therapy and surgery within 4 weeks prior to COVID-19 diagnosis vs. no treatments within 4 weeks of diagnosis [29].

Fungal Infections

Infections due to fungi are common in neutropenic patients; nevertheless, they are not frequent in the first febrile event; thus, fungal infections should be suspected in patients with neutropenic febrile syndrome that lasts for more than 1 week, those with long period of chemotherapy (e.g., hematological malignancies), and those with high antibiotic usage and should be suspected in patients with prolonged and sustained fever [30].

Candida spp. and *Aspergillus* spp. are the most common causes of fungal infection. *Aspergillus* colonization is by inhalation of airborne spores, whereas *Candida* spp. are obtained from translocation of damaged intestinal surface [30, 31].

Candida albicans is the most frequent cause of candidemia, followed by *C. glabrata*, *C. tropicalis*, and other *Candida* spp. Candidemia manifests as fever and in some patients with macronodular skin nodules. The median time of candidemia after remission chemotherapy (especially for acute myeloid leukemia) is 16 days. Patients with candidemia are at high risk of hepatosplenic involvement, especially 26 days after remission chemotherapy [31].

On the other hand, *Aspergillus* mainly manifests as lung damage, due to the colonization mechanism by inhalation of spores. It manifests as pneumonia or sinusitis, and a CT scan is always necessary when the suspicion is high. There are also reports of neurological and cutaneous damage [32].

Mucormycosis is frequently observed in hyperglycemic patients; thus, apparent neutropenia is not always observed in this population. The main damage is rhino-orbital-cerebral, pulmonary, and disseminated, with a high mortality. Biopsy of damaged tissue is always necessary for diagnosis, where vascular involvement is observed [32].

Other infections should be considered in these populations like *Fusarium* spp. and some endemic fungal infections like *Histoplasma capsulatum*, *Blastomyces dermatitidis*, and *Coccidioides* spp.

Empiric fungal treatment should be started in patient with persistent fever after 4 to 7 days of broad coverage antibiotic regime; treatment should be directed against *Candida* spp. and *Aspergillus* spp. In patients without lung damage, *Candida* spp. should be suspected and caspofungin should be started [33]. If lung nodular damage is observed, coverage against molds (*Aspergillus*) should be initiated especially with voriconazole; also, bronchoalveolar lavage with cultures, stains, and *Aspergillus* galactomannan antigen should be performed. The choice of voriconazole over caspofungin is due to higher failure rates with caspofungin in treating invasive aspergillosis. The selection of different suggested regimens of antifungal prophylaxis is noted in Table 1 [34].

Viral Disseminated Infections

Cytomegalovirus (CMV) is one of the viruses of the greatest concern, especially in post-transplant patients. The greatest risk of CMV pneumonitis after hematopoietic cell transplantation (HCT) occurs in the seropositive recipient of seronegative stem cells. The incidence of CMV disease is related to the intensity of immunosuppressive therapy, particularly treatments that deplete T lymphocytes [35].

In the absence of antiviral prophylaxis, CMV pneumonitis appears between one and four months after transplantation [21]. However, late infection can occur after completion of antiviral prophylaxis or with treatment for graft rejection.

Patients with skin infections associated with the herpes simplex virus and varicella-zoster have up to 10% higher risk of viral spread to the liver, lungs, brain, or

gastrointestinal tract. When pulmonary involvement occurs, the reported mortality is close to 20%, and in these patients, it should be considered an emergency since it can be fatal. Atypical skin eruptions and disseminated infection in the absence of skin lesions can be frequent in these patients; the preexisting antibody does not prevent VZV reactivation, but has been associated with a mild clinical course. The treatment suggested in immunocompromised individuals is different from the conventional scheme; it is recommended to administer high-dose acyclovir intravenously (IV) from 5 to 12.5 mg/kg every 8 hours for a total duration of 7 to 10 days [36, 37].

Latent TB

Routine LTBI testing is warranted for patients with hematologic malignancies, given substantially increased risk for reactivation. There is no clear advantage of performing an IGRA or TST to predict the risk of active TB; test selection should be based on cost and availability. However, in very high-risk populations, such as patients with hematological diseases, positive IGRAs have higher rates of active TB than those with positive TST [38]. In the case of using TST, the highest specificity was found using a TST of 15 mm as a criterion for a positive test [39].

In the case of mixing the different tests, a discordant result in the second test implies a greater risk of disease than the concordant negative tests. The risk of tuberculosis disease is highest with concordant positive results, lowest with concordant negative results, and intermediate with discordant results [40].

Biologic drugs have revolutionized the treatment of certain hematologic, autoimmune, and malignant diseases, but unfortunately, they may put patients at risk for reactivation or acquisition of tuberculosis. This risk is the highest with the tumor necrosis factor-alpha (TNF- α) inhibitors [41].

TNF- α is a cytokine involved in inflammatory and immune responses through its regulation of immune cell proliferation and differentiation; it is known that TNF- α is important in the pathogenesis of TB infection, due to the inability to control intracellular TB growth in macrophages and maintain granulomas [42, 43].

The Janus kinases (JAKs) are involved in the intracellular signaling for many cytokines that mediate TNF- α effects (ruxolitinib, tofacitinib and upadacitinib, and filgotinib); of these kinds of therapies, more cases of Tb reactivation have been reported with the use of tofacitinib [44].

Anti-CD3 drugs (muromonab-CD3, oteelixizumab, teplizumab, and visilizumab) can render T cells anergic or induce apoptosis. Due to its effects on CD4+ T cells, patients are at risk for the same opportunistic infections as in advanced HIV, including TB [45••].

Conclusions

Hematological malignancy patients that receive treatment that inhibits myelopoietic and phagocytic functions are at high risk of developing neutropenic febrile syndrome and thus are at high risk of infection. It is important to address the risk of each patient including the previous exposure to antibiotics, the type of treatment, and the specific association with some infections as noted in Table 2, as well as if neutropenic, how many days have gone by and if the patient has fever or not, as well as the presence of central intravenous catheters or invasive hardware that could add information to the best decision-making strategies, use of the best diagnostic tools needed for the assessment, and finally the best election of antimicrobials and the follow-up required.

Bacterial infections are the most common and potentially fatal and should be suspected in any patient with neutropenic febrile syndrome; also, empiric antibiotic with coverage against *P. aeruginosa* and MRSA should be started as soon as possible in order to prevent complications.

In patients with prolonged chemotherapy and long-lasting fever, fungal infections should be suspected and adequate coverage against *Candida* spp. and *Aspergillus* spp. should be started. Lung nodular damage should be discarded since invasive aspergillosis has a higher mortality and treatment failure has been observed with equinocandins.

In patients with T cell dysfunction (either treatment induced or acquired), viral infections should be suspected and monitored.

Latent tuberculosis is observed more frequently when using treatments that include the use of monoclonal antibodies, mainly TNF inhibitors, for which it is recommended that any hematological patient in areas endemic for tuberculosis should be screened prior to the start of treatment to know its status and initiate prophylactic treatment on time.

Neutropenic febrile syndromes have a high mortality if not treated in a timely and precise way, so broad coverage is mandatory.

Patients with hematological diseases who are at risk of presenting infections should be evaluated and treated by a multidisciplinary team that includes a promptly participation of specialists in pharmacology and infectious diseases so that better clinical results are obtained and the chances of survival of patients are improved.

Table 2 Infections encountered in patients with hematological malignancies

Bacteria	Fungi	Parasites	Virus
Neutropenia			
<i>Staphylococcus aureus</i>	<i>Aspergillus</i> spp.		Herpes simplex virus I & II
<i>Streptococcus pneumoniae</i>	Non- <i>Aspergillus</i> hyalohyphomycosis such as <i>Fusarium solani</i>		Varicella-zoster virus
<i>Pseudomonas aeruginosa</i>			
<i>Pseudomonas</i> spp.	Mucorales (zygomycoses)		
<i>Enterobacteriaceae</i>	<i>Alternaria</i>		
<i>Stenotrophomonas maltophilia</i>	<i>Scedosporium apiospermum</i>		
<i>Acinetobacter</i> spp.	<i>Scedosporium prolificans</i>		
<i>Corynebacterium jeikeium</i>			
<i>Clostridioides difficile</i>			
Humoral immune dysfunction			
<i>Streptococcus pneumoniae</i>	<i>Pneumocystis jiroveci</i> (<i>P. carinii</i>)	<i>Giardia lamblia</i>	Varicella-zoster virus
<i>Haemophilus influenzae</i>		<i>Babesia microti</i>	Echovirus
<i>Neisseria meningitidis</i>			Enterovirus
<i>Capnocytophaga canimorsus</i>			
<i>Campylobacter</i>			
Linfocyte T immune dysfunction			
<i>Streptococcus pneumoniae</i>	<i>Pneumocystis jiroveci</i> (<i>P. carinii</i>)	<i>Toxoplasma gondii</i>	Influenza virus
<i>Staphylococcus aureus</i>	<i>Aspergillus</i> species	<i>Strongyloides stercoralis</i>	Parainfluenza
<i>Haemophilus influenzae</i>	<i>Candida</i> species		Respiratory syncytial virus
<i>Klebsiella pneumoniae</i>	<i>Cryptococcus neoformans</i>		Adenovirus
<i>Pseudomonas aeruginosa</i>	Mucorales (zygomycoses)		Epstein–Barr virus
<i>Enterobacter</i> species	<i>Histoplasma capsulatum</i>		Cytomegalovirus
<i>Stenotrophomonas maltophilia</i>			Varicella-zoster virus
<i>Nocardia asteroides</i> complex			COVID-19 virus
<i>Listeria monocytogenes</i>			Parvovirus
<i>Legionella</i> species			
<i>Salmonella</i> species			
** <i>Mycobacterium tuberculosis</i>			

Declarations

Conflict of Interest The authors declare no competing interests.

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