50 Evaluation and Management of Bacterial and Fungal Infections in Patients with a Hematological Malignancy: A 2018 Update

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Introduction

The treatment of hematological malignancies relies heavily on cytotoxic chemotherapy that most often places patients at risk for invasive bacterial and fungal infections due to disruptions in mucosal barrier integrity and impaired myelopoiesis. A weakened mucosal barrier permits translocation of fungi and bacteria present in the oropharynx, gastrointestinal tract, or skin to enter the body and, when this is combined with immune compromise from impaired myelopoiesis, severe infections are not uncommon. Antineoplastic therapy-associated neutropenia frequently results in a muted inflammatory response, with fever often being the sole presenting symptom. In addition to cytotoxic antineoplastic therapy, these patients often receive concomitant glucocorticoids which may altogether blunt even a febrile response [1]. This necessitates a high index of suspicion on the part of the clinician to effectively recognize infection in the neutropenic patient who might only present with hypotension or tachycardia with or without other nonspecific findings. Also known as neutropenic fever (these terms will be used interchangeably throughout this chapter), this clinical entity is defined as a single oral temperature measurement of 38.3 °C, or a temperature greater than 38.0 °C that is sustained for more than an hour in a neutropenic patient [2–4]. The generally accepted definition of neutropenia is an absolute neutrophil count (ANC) of <1500 cells/μL. Severe neutropenia is defined as an ANC of <500 cells/μL, or when there is an expected ANC nadir of <500 cells/μL within the next 48 h.

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Bacterial Infections

The pathogenesis of bacterial and fungal infections in the patient with hematologic malignancy is a complex interplay between host factors, effects of antineoplastic therapy, and changes in the host caused by the underlying malignancy (Table 50.1). As mentioned in the introduction to this chapter, the impairment of mucosal barriers and immune system dysfunction create an environment favorable to invasive microbial infections that is often compounded by frequent healthcare exposure and patients' inherent increased risk for exposure to organisms of increased virulence and drug resistance [2]. It is believed that the majority of infections in patients with hematologic malignancies are due to treatment-related muco-

Table 50.1 Risk factors associated with an increased risk of developing febrile neutropenia

Host factors
Age > 65 years
Female gender
Poor nutritional status
Poor performance status based on underlying cardiovascular, pulmonary, and renal comorbidities
Factors related to the underlying malignancy
Advanced stage of the malignancy
Myelophthisis
Lymphopenia
Elevated serum lactate dehydrogenase in patients with lymphoreticular process
Factors related to the antineoplastic therapies
Expected high dose density chemotherapy
Expected intensity of high dose chemotherapy
Lack of administration of prophylactic hematopoietic growth factor stimulants in patients with high-risk chemotherapeutic regimens

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sitis and translocation of gastrointestinal tract flora and colonizing organisms that eventually reach the bloodstream. Less common mechanisms include disruption of respiratory, genitourinary, and lymphatic barriers due to the underlying malignancy or associated with medical procedures. Of particular concern are the presence of central venous catheters (CVCs) and other indwelling catheters [5].

Epidemiology

Bacterial infection is a common cause for febrile neutropenia in patients who have received antineoplastic chemotherapy, with approximately 23% of them presenting with fever or neutropenic fever [6]. Of patients who present with febrile neutropenia, an infectious etiology is only identified in roughly one-quarter of cases, and often only through isolation of an organism causing bacteremia, which is found in up to 25% of all patients with neutropenic fever [2, 7]. Of note, the vast majority of organisms causing infections in hematological cancer patients are bacteria, followed by fungi and viruses as distant second and third place culprits. Given the principal factors that predispose to febrile neutropenia (disruption of mucosal barriers and immune suppression), translocation and infection by saprophytic flora explain the overwhelming predominance of these organisms isolated from cultures [8, 9].

The most commonly isolated organisms tend to be Gram positive bacterial organisms, with a predominance of *Staphylococcus epidermidis*, followed by a variety of other streptococci and staphylococci including *Staphylococcus aureus* [10, 11]. There has been a significant shift in the patterns of causative bacterial pathogens over time due to a variety of factors including antibiotic pressure from prophylaxis and/or treatment, the increased use of long-term indwelling catheters, and novel antineoplastic regimens [12]. Prior to the early 1990s, the majority of organisms isolated during evaluation of episodes of febrile neutropenia were Gram negative bacteria, with *Pseudomonas aeruginosa* being especially notorious [13, 14]. This trend began to turn gradually, with a growing predominance of Gram positives being most commonly isolated in the mid-1990s and into the early 2000s, when Gram negative prophylaxis was common. Approximately 80% of all isolates were Gram positive bacterial organisms [15, 16]. Today a reversal in this trend is being noted, this time the cause for the trend starting to turn back to Gram negative bacterial organisms seems to be related to the emergence of multidrug-resistant organisms (MDROs). MDRO groupings commonly referred to in practice include Gram positive bacteria [methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE)], as well as Gram negative bacteria [extended spectrum beta lactamase (ESBL), *Klebsiella pneumoniae* carbapenemase (KPC), and carbapenem-resistant enterobacteriaceae (CRE)]. Currently the overall percentage of infections due Gram positive bacterial organisms has decreased to around 60% [17–21]. Another important point is that outside of bloodstream infections, where Gram positive bacterial organisms are predominant, Gram negative bacterial organisms are the most common pathogens of infections related to the urinary, gastrointestinal, and biliary tracts [22].

The severity of bacterial infections varies due to a number of factors specific to each organism. Among the Gram positive bacterial organisms, MRSA and VRE are some of the most severe [16]. Though infrequent, anaerobes can contribute to severe, life-threatening infections such as necrotizing fasciitis, typhlitis (neutropenic enterocolitis), and sinusitis. Interestingly, though still rare, polymicrobial infections also appear to be becoming more frequent than in prior decades [19, 23, 24].

Risk Factors

Cancer patients undergoing systemic chemotherapy for hematologic malignancies often suffer significant side effects, especially effects on mucosal integrity and myeloid production and function. These will predispose to the development of infections due to translocation of gastrointestinal tract colonizing bacteria and fungi. Concomitant neutropenia results in a blunted immune response to invasion by previously colonizing organisms [25]. A thorough evaluation of the host characteristics, risk for developing febrile neutropenia, and risk assessment for serious complications associated with febrile neutropenia will guide empiric antimicrobial therapy and dictate additional workup and need for hospital admission [2]. Risk factors associated with an increased risk of developing neutropenic fever are best thought of in terms of host factors, factors related to the underlying malignancy, and those related to the antineoplastic therapies (Table 50.1). Host factors include the patients' underlying conditions and comorbidities that may alter their immune function (e.g., drug-induced neutropenia will predispose to bacterial and candidal infections, underlying cellular immunodeficiency will predispose to opportunistic viral

infections, and underlying humoral immunodeficiency will predispose to mycobacterial infections), those that predispose to infection due to anatomic and or functional abnormalities (vesicoureteral reflux, nephrolithiasis, bronchiectasis, etc.) and those that alter patients' flora (prolonged antibiotic use that causes selective pressure favoring more invasive or resistant organisms). Treatment-related factors include mucosal barrier disruption due to cytotoxic therapy's effect on high turnover cells of the lining the gastrointestinal tract, impaired myelogenous production, and decreased neutrophil phagocytic and chemotactic activity.

Patients with hematologic malignancy presenting with neutropenic fever should be risk stratified according to their risk of developing serious complications (Table 50.2), which in turn guides the need for hospital admission, parenteral antimicrobial therapy, and prolonged hospitalization (Fig. 50.1).

Table 50.2 Risk of medical complications of febrile neutropenia

Patient Risk Category	National Comprehensive Cancer Network	Infectious Disease Society of America
High	– Developing fever while inpatient	– Anticipated ANC ≤100 cells/μL for >7 days
	– Significant comorbidity or clinical instability	– ALT >5x normal or CrCl <30 mL/min
	– Anticipated ANC ≤100 cells/μL for >7 days	– Concurrent clinical conditions such as: Hemodynamic instability, intravascular catheter infection, encephalopathy, respiratory failure, mucositis or other gastrointestinal symptoms, underlying chronic lung disease and or hypoxia/ infiltrates
	– ALT >5x normal or CrCl <30 mL/min	
	– Leukemia not in complete remission or non-leukemia cancer with evidence of disease progression after >2 courses of therapy	
	– Presentation with pneumonia or other complex infection	
	– Alemtuzumab in prior 2 months	
	– Grade 3 or 4 mucositis	
	– MASCC score ≤ 20	
Medium	– Expected 7 to 10-day duration of neutropenia	
	– Lymphoma	
	– CML	
	– Autologous HCT	
	– Purine analog therapy	
Low	– No High Risk features and most of the following criteria are present:	– Anticipated ANC ≤100 cells/μL for <7 days
	– Outpatient at onset of fever	– Absence of renal and hepatic dysfunction
	– No associated acute concurrent condition requiring hospitalization or close observation	– No comorbidities
	– Anticipated ANC ≤100 cells/μL for <7 days	
	– Absence of renal and hepatic dysfunction	
	– Good performance status (ECOG 0–1)	
	– MASCC score ≥ 21	

Adapted from:Baden LR, Swaminathan S, Angarone M, Blouin G, Camins BC, Casper C, et al. Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2016;14(7):882-913Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):e56-93

ANC absolute neutrophil count, *ALT* alanine aminotransferase, *CrCl* creatinine clearance, *MASCC* Multinational Association for Supportive Care in Cancer, *CML* chronic myelogenous leukemia, *SCT* hematopoietic stem cell transplant, *ECOG* Eastern Cooperative Oncology Group

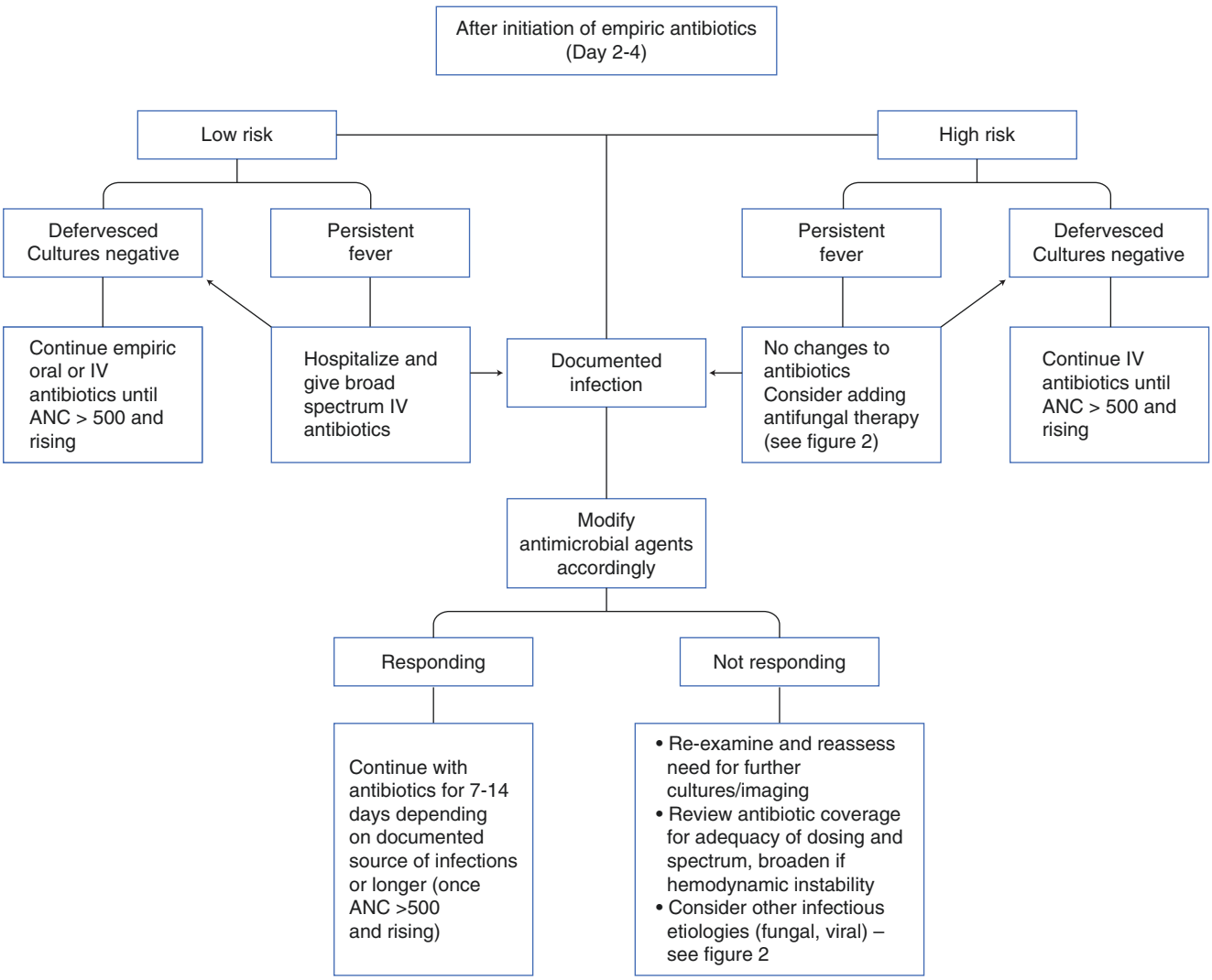

Fig. 50.1 Initial treatment algorithm for febrile neutropenia

Diagnosis

The clinical manifestations of bacterial infections in the patient with hematological malignancies can be very nonspecific due to impaired inflammatory processes. Though much emphasis so far in this chapter has been placed on febrile neutropenia, it is not uncommon for these patients to present with nonspecific findings and be infected despite the absence of fever, or conversely to have a fever as the sole presenting symptom. For the hematological malignancy patient presenting with neutropenic fever, or thought to be otherwise infected, it is imperative to conduct a rapid and thorough workup that focuses on the prompt collection of cultures, especially blood cultures, to enable rapid initiation of broad spectrum empiric antibiotic therapy without compromising their diagnostic yield. The sooner appropriate empiric antimicrobial therapy is initiated the better, as delays in administration correlate with mortality [26, 27].

A thorough history with particular emphasis on pertinent host, underlying malignancy, and antineoplastic therapy factors should be performed in addition to eliciting a listing of careful relevant exposures in the context of the aforementioned factors. The physical exam should be a meticulous head-to-toe examination focused on the skin and mucosal surfaces, oropharynx and teeth, sinuses, heart and lung systems; abdominal, genital and perineal exams should not be overlooked. Peripherally Inserted Central Catheters (PICCs), implanted ports, urinary catheters, old IV sites, procedural sites such as biopsy, aspirate and surgical sites also merit careful visual inspection and palpation. The blunted immune response can manifest in a paucity of inflammatory signs and requires a high index of suspicion.

Peripheral blood counts with white blood cell (WBC) differentials should be obtained as well as at least two sets of blood cultures from the outset when infection is suspected. The hematologic tests serve to both quantify and stratify the

presence and severity of neutropenia, while the blood cultures aim to confirm an infection and identify the causative organism and subsequently determine its antimicrobial susceptibility patterns to tailor anti-infective therapy. When obtaining blood cultures, one should ideally obtain two sets of cultures of 20 mL each in the adult patient. These should be collected from two separate peripheral venipunctures in patients without indwelling venous catheters. In patients with indwelling venous catheters, one set should be from a peripheral venipuncture and one from the indwelling venous catheter. The frequency of subsequent cultures varies depending on the following variables: if fever persists after 24 h on appropriate broad spectrum anti-infective therapy, an additional 2 sets of blood cultures should be obtained and may be repeated a second time after 48 h in the presence of persistent fever. If the fever appears to have defervesced for greater than 48 h and recurs, it is reasonable to repeat blood cultures. Additionally, if initial blood cultures are positive, these should be repeated daily until bacteremia clears regardless of the fever pattern. A study published in 2013 has looked at an alternate single 40 mL sample method from central lines that seems promising, but needs further validation and cost analysis [28].

Treatment

As mentioned throughout this chapter, the prompt recognition and institution of appropriate empiric anti-infective therapy in the potentially infected neutropenic patient with hematological malignancy is life-saving. It is recommended that appropriately selected and dosed antimicrobials are received within an hour of medical contact at a maximum, with administration within 30 min being optimal [23, 26, 29, 30]. The concept of adequate antimicrobial therapy must be highlighted and contrasted with appropriate therapy, and though various somewhat different definitions have been published, we will frame the discussion in terms of the definitions set forth in the joint Infectious Disease Society of America (IDSA) and American Thoracic Society (ATS) guidelines on the management of hospital-acquired, ventilator-associated pneumonia and healthcare-associated pneumonia from 2005 and updated in 2016 [31, 32]. According to these definitions, appropriate antimicrobial therapy is the use of drugs with in vitro activity against the confirmed etiologic agent, whereas adequate treatment implies not only the use of the correct (appropriate) antimicrobial agent, but additionally administering the optimal dose as well as choosing a route for administration that allows for tissue penetration of the drug at the site of infection. In order to provide not just appropriate, but adequate, therapy to the neutropenic patient with hematologic malignancy, host factors as well those related to the underlying malignancy and antineoplastic therapy must be considered in order to determine the patient's risk of developing serious complications of neutropenic fever.

Table 50.3 Key Points: Treatment of bacterial infections

Key points: Treatment of bacterial infections
• Fever may be the only sign of a potentially life-threatening infection in immune-suppressed patients
• Start antibiotics promptly. In high-risk patients, start an antipseudomonal beta lactam agent
• Patients receiving fluoroquinolone prophylaxis should not receive empiric therapy with fluoroquinolones
• Adding vancomycin or an antibiotic with enhanced Gram positive activity empirically is not recommended
• Modifications to empiric treatment should be made based on patient's previous cultures or risks for an infection with a MDRO (e.g., MRSA, VRE, ESBL, CRE, KPC)
• Always tailor antibiotics to the underlying pathogen whenever possible
• Continue with antimicrobial therapy until neutropenia resolves

MDRO multidrug-resistant organisms, *MRSA* methicillin-resistant *Staphylococcus aureus, VRE* vancomycin-resistant enterococci, *ESBL* extended spectrum beta lactamase, *CRE* carbapenem-resistant enterobacteriaceae, *KPC Klebsiella pneumoniae* carbapenemase

In addition to this risk stratification, the patient's drug allergies, prior microbiologic culture data, antimicrobial agent exposures, and the local antibiogram need to be considered [33]. As discussed earlier in the Epidemiology section, the majority of causative organisms in neutropenic fever are Gram positive bacteria, especially skin flora; however, Gram negative bacteria tend to cause more serious clinical disease due to their virulence factors, and they are making a resurgence in terms of their frequency driven in part by the increase in MDROs. Table 50.3 summarizes key points in the treatment of bacterial infections in patients with hematological malignancy.

Those patients who are unable to tolerate oral antibiotics or who are risk stratified into the high-risk category should receive intravenous antibiotics (Fig. 50.1). A number of studies have attempted to find an ideal empiric antibiotic regimen, and no regimen has shown itself to be superior [34–39]. There are a number of acceptable monotherapy options that are as efficacious as combination regimens for empiric therapy in high-risk neutropenic fever syndromes: ceftazidime, cefepime, piperacillin-tazobactam (or other antipseudomonal beta lactam agents), imipenem-cilastatin, meropenem, etc. Combination regimens that use extended spectrum beta-lactams with fluoroquinolones, aminoglycosides, or double beta-lactams have not shown superiority and often increase toxicity [38, 39]. Furthermore, combination regimens that use a second agent to cover Gram positive bacterial organisms do not seem to confer clinical or mortality benefits and also are associated with greater toxicity and bacterial resistance [2, 7, 40–43]. The standard use of vancomycin, linezolid, and other drugs against Gram positive bacteria as part of empiric antibiotic regimens for neutropenic fever should be discouraged. These medications should be reserved for patients with presumed line infections, pneumonia, soft tissue infections, and septic shock.

The importance of knowing the patient's colonization status of resistant bacteria (MRSA, VRE, and other MDROs) and previous culture results cannot be overstated, as many patients with hematologic malignancies are colonized with resistant Gram positive organisms. Once appropriate empiric antibiotic therapy has been instituted in a timely fashion, close attention must be paid to clinical response and the progress of culture (with susceptibility data) to determine adequate therapy. Patients with a persistent unexplained neutropenic fever syndrome, who are clinically stable or improving, do not always require a change in antibiotic therapy for their ongoing fever (Fig. 50.2). Among oncology patients with solid tumors and tumor fever, neutropenic fever usually resolves within 48 h of empiric antibiotics; neutropenic fever among patients with hematologic malignancies can take up to an average of 5 days after initiation of treatment to defervesce [2].

Central line associated bloodstream infections (CLABSIs) are frequently the cause of neutropenic fever in hematologic malignancy patients, and adequate antibiotic administration alone is insufficient to treat these patients, with removal of the offending line being necessary. The exception to this rule is CLABSI due to coagulase negative staphylococci, in which case it may be reasonable to treat through the infection [2]. Catheter removal is recommended for infections with *Pseudomonas aeruginosa*, *Staphylococcus aureus*, fast growing atypical mycobacteria, and *Candida* spp., and with less certainty for other fungal species [2, 44–48]. In these cases, antibiotics should be continued for a minimum of 2 weeks after clearance of bacteremia and removal of the CVC, whichever occurred last. Complicated CLABSIs such as those occurring with deep tissue infections (catheter tunnel tract or port pockets), septic thrombosis or embolisms, endocarditis, or persistent bacteremia (defined as greater than 72 h after initiation of adequate therapy), warrant extended courses of antibiotics in the 4- to 6-week duration range. See Fig. 50.3 for recommendations for management of infected long-term venous access catheters.

In general, the presence of infected material (such as an abscess, a CVC, or a urolith) necessitates both antibiotic penetration and activity to treat the infection. In cases where the drug activity and penetration are suboptimal, removal of the infected material is paramount to achieving control of the infection. Source control requires the removal of infected hardware, drainage of infected fluid collections, or removal of infected tissue or other material. The indications and risk benefit for the interventions already discussed are beyond the scope of this chapter and merit the consultation of infectious diseases specialists, surgeons, or interventional radiologists as clinically dictated.

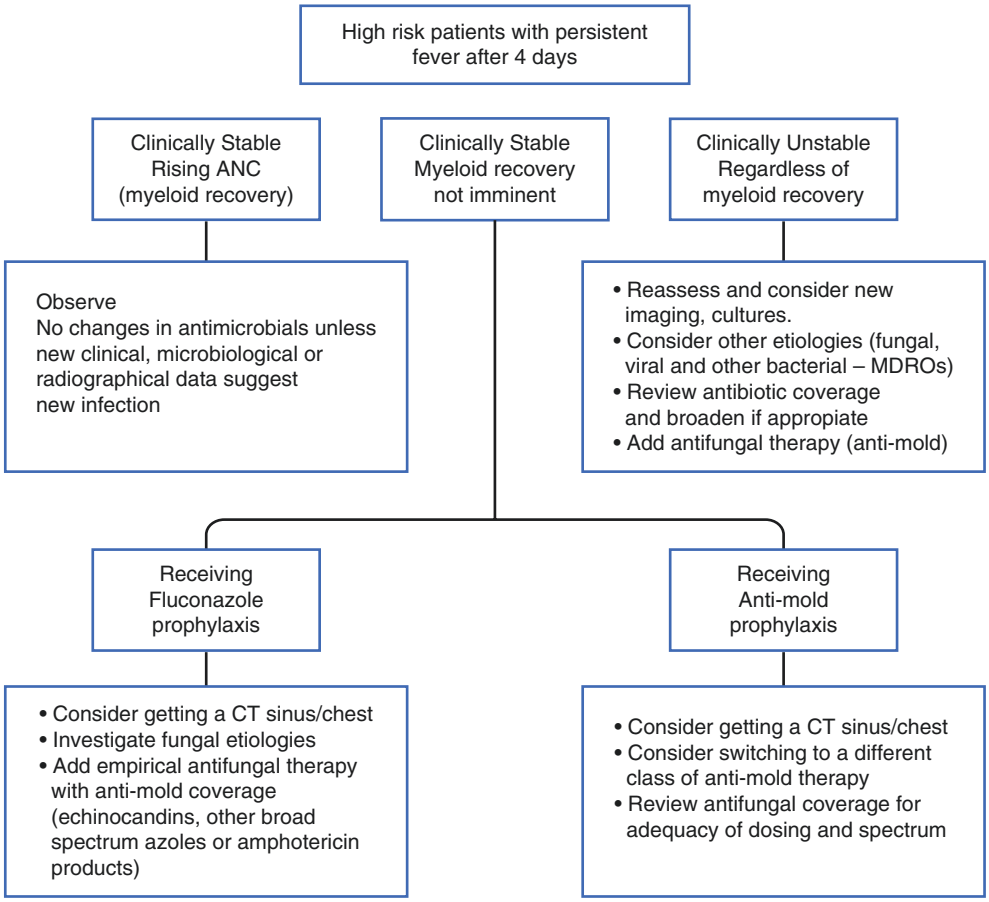

Fig. 50.2 Treatment algorithm for patient with high-risk febrile neutropenia

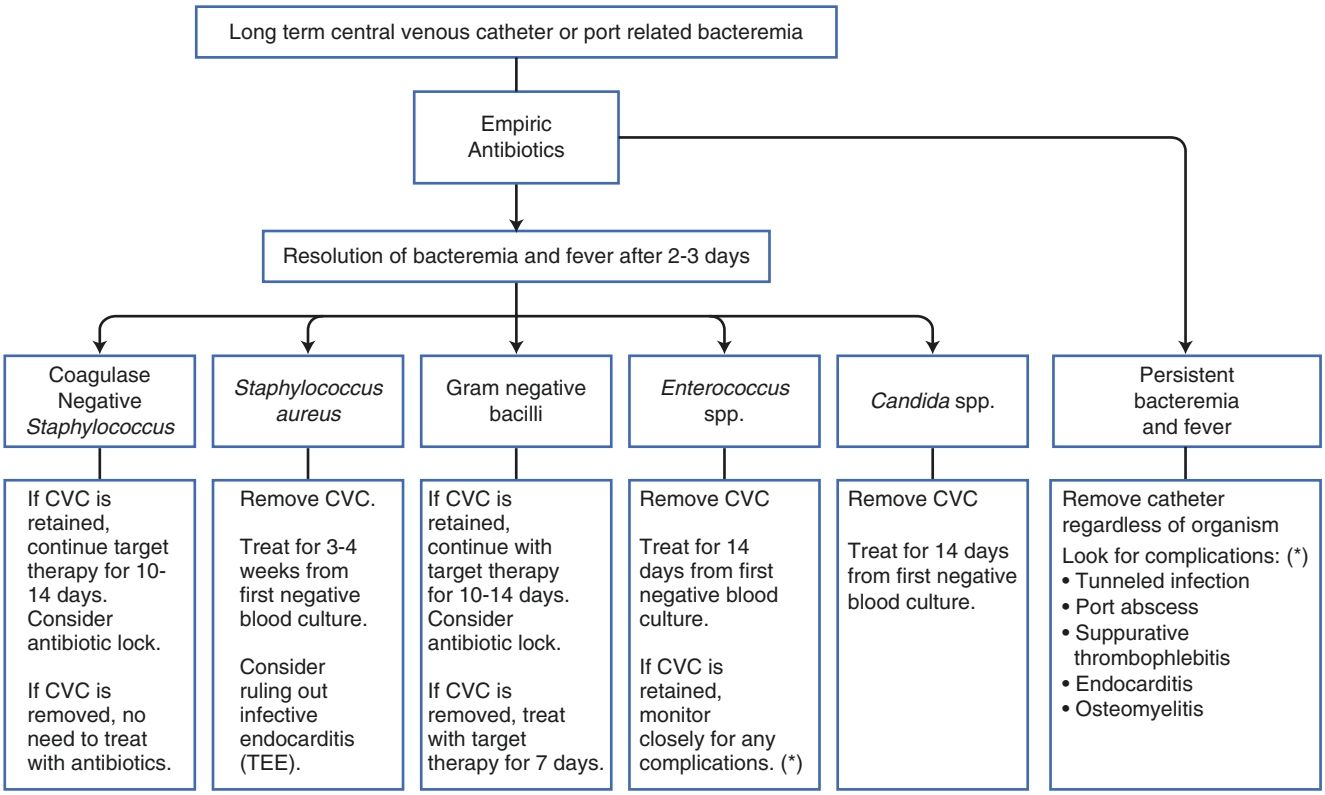

Fig. 50.3 Management of long-term indwelling venous access catheters

Bacterial Prophylaxis

Several studies have demonstrated the utility of antimicrobial prophylaxis to prevent neutropenic fever and infectious complications, especially among high-risk patients [49, 50]. A Cochrane Review meta-analysis in 2012 showed that antibiotic prophylaxis was associated with lower all-cause mortality when compared to placebo or no treatment. Prophylaxis was also associated with significantly reduced occurrence of fever, fewer clinically documented and microbiologically documented infections, and lower risk of infection-related death [49]. Fluoroquinolones (levofloxacin and ciprofloxacin) have been extensively studied given their broad spectrum (covering Gram negative bacteria including *Pseudomonas aeruginosa*, as well as Gram positive bacteria) and good oral bioavailability. Fluoroquinolone prophylaxis reduces the risk for all-cause mortality as well as infection-related mortality [2]. A combination of a fluoroquinolone plus an antibiotic with enhanced Gram positive activity is not recommended [2]. Some studies have shown that this approach may reduce infections caused by *Staphylococcus* and *Streptococcus* spp., but they do not affect infection-related mortality and may increase the rated of resistant bacteria [51–54]. See Table 50.4 for suggested empiric antibiotic regimens for high-risk patients.

There are concerns about toxicities and antimicrobial resistance [52, 55], especially among patients concurrently

Table 50.4 Empiric antibiotic regimens in high-risk patients with febrile neutropenia

Monotherapy options	
Piperacillin/Tazobactam	
Cefepime	
Ceftazidime[a]	
Carbapenems (except Ertapenem since no antipseudomonal coverage)[b]	
Add these antimicrobials based on culture data or specific clinical scenarios	
Vancomycin	If suspected MRSA infection such as cellulitis and/or pneumonia
Linezolid	If suspected VRE infection
Daptomycin	If suspected MRSA or VRE infection, although cannot be used for pulmonary infections as it is inactivated by surfactant
Aminoglycoside/Colistin	If suspected Gram negative MDRO involvement (ESBL, CRE, KPC)
Metronidazole	If suspected intraabdominal infection

[a]Ceftazidime monotherapy has been used for many years, however has less Gram positive coverage than cefepime
[b]Use Carbapenems for patients at high risk of MDROs
MRSA methicillin-resistant *Staphylococcus aureus, VRE* vancomycin-resistant enterococci, *MDRO* multidrug-resistant organisms, *ESBL* extended spectrum beta lactamase, *CRE* carbapenem-resistant enterobacteriaceae, *KPC Klebsiella pneumoniae* carbapenemase

using QT prolonging medications such as amiodarone or voriconazole. In 2016, the Food and Drug Administration (FDA) issued safety warnings about fluoroquinolones causing acute tendonitis, neuropathy, and central nervous system side effects, which has led to a revision of the package inserts for these medications.

The optimal timing for initiation and duration of antimicrobial prophylaxis has not been well studied. Some clinicians will start prophylaxis on the first day of cytotoxic chemotherapy even for those patients not yet neutropenic, while others will do so on the last day of chemotherapy. It is common to discontinue prophylaxis when the neutropenia has resolved.

Fungal Infections

Invasive fungal infections (IFIs) cause significant morbidity in patients with hematological malignancies and stem cell transplants. This section will elaborate on the epidemiology, clinical syndromes, diagnosis, and treatment of the most common IFIs in this population. IFIs are categorized into those caused by yeasts or molds, of which a basic microbiologic understanding is useful when we think about the syndromes and the term "mold active" antifungal agent. Yeasts are single cell organisms that reproduce by budding and include genera such as *Candida* or *Cryptococcus*, among others. Mold organisms have a filamentous growth stage that allows them to elongate by branching with longitudinal extension, and can be further categorized as opportunistic or endemic infections. The morphology of filamentous hyphae on pathology specimens plays an essential part in diagnosis and early management of mold infections. The most common opportunistic mold organisms include *Aspergillus*, *Mucor*, *Rhizopus*, and *Fusarium* species, while *Histoplasma*, *Blastomyces*, and *Coccidioidomyces* species comprise most of the common endemic fungi.

Candida

Candida yeasts are saprophytic organisms commonly found on the skin and mucosal surfaces of humans. Infections with these organisms can cause superficial (oral thrush, esophagitis, dermatitis, and vaginitis, etc.) and/or deep infections (candidemia, visceral organ abscesses, endophthalmitis, and many others). Herein we focus on the invasive forms of candidiasis (IC), which cause significant morbidity and mortality among hematologic cancer patients and stem cell transplant (SCT) recipients. Prior to the use of antifungal prophylaxis, the incidence of disseminated candidemia was approximately 17% among patients with hematologic malignancies [56, 57] and 11% after SCT [58, 59]. Mortality for patients with IC ranged from 39 to 73% [58, 59]. Autopsy studies in SCT patients from the 1980s suggest overall prevalence of *Candida* infections was 28% [60]. Table 50.5 summarizes key points in the management of *Candida* infections.

Table 50.5 Key points: *Candida* spp.

Key points: *Candida spp.*
• The incidence of non-albicans *Candida* is more common than *C. albicans*.
• Non-albicans *Candida* organisms are frequently fluconazole resistant (*C. krusei* and *C. glabrata*)
• Empiric therapy for yeast identified in the blood is an echinocandin, which is then de-escalated pending species identification

Risk Factors and Epidemiology

In addition to the risk factors for IC in the general population (CVCs, broad spectrum antibiotics, and total parenteral nutrition) [61], those with hematologic malignancies are at increased risk of disseminated disease secondary to prolonged neutropenia [62–64], use of antibacterial antibiotics [62, 64], *Candida* colonization [19, 52, 60, 65, 66], and mucosal damage from cytotoxic chemotherapy [62]. Specifically, neutropenia lasting over 15 days is a risk for hepatosplenic candidiasis [62].

Over time the incidence of infection by non-albicans *Candida* spp. is increasing [67, 68], and even surpassing the incidence of *Candida albicans* infections in the United States [68–70]. Hematology patients are at increased risk for specifically *C. glabrata* [63, 67], *C. krusei* [63, 71, 72], *C. tropicalis* [72, 73], *C. guilliermondii* [72], and emerging *Candida* spp. such as *C. dubliniensis* and *C. kefyr* [72]. This evolution of epidemiology is important as these species can be resistant to fluconazole and to a lesser extent voriconazole [72].

Clinical Presentation

The most common clinical presentation of IC in hematologic malignancy patients is fever. Acute disseminated candidiasis can result in severe sepsis and multiorgan failure. Early descriptions of IC from autopsy studies in the 1980s (prior to the use of antifungal prophylaxis in the 1990s) in subjects with acute leukemia report fever refractory to antibiotics or a second episode of fever. At autopsy, often multiple organs were involved [65, 74]. By the late 1990s fever was being reported in 99% patients with malignancies and was most often it was low grade [75].

Chronic disseminated candidiasis or hepatosplenic candidiasis deserves special attention as this entity occurs almost exclusively among patients with acute leukemia. Epithelial damage that occurs along the gastrointestinal mucosa from cytotoxic chemotherapy enables *Candida* to enter the hepatobiliary circulation, resulting in hepatic and splenic microabscesses. Symptoms of disease develop later into the course

of infection, usually just after neutrophil recovery, when neutrophils can migrate to the sites of the microabscesses. As with acute IC, persistent fever is the most common manifestation, sometimes accompanied by right upper quadrant abdominal pain, tenderness, and an elevated alkaline phosphatase. An immune reconstitution-like syndrome has been hypothesized given the timing of symptoms following neutrophil recovery [76].

Diagnosis

There is no true gold standard for the diagnosis of IC, and limitations of culture and non-culture diagnostic tests make this challenging. While diagnosis often relies on positive blood cultures, and blood culture technology has improved over the decades, overall sensitivity of blood culture has been estimated to remain approximately 50% [77]. IC can be divided into three groups: candidemia in the absence of deep-seated infection, candidemia associated with deep-seated infection, and deep-seated candidiasis that is not associated with candidemia. Blood culture systems, while as sensitive as PCR in vitro, may capture 75% of group 1 and 2 above, leading to an overall sensitivity of 50% [77]. The 2- to 3-day turnaround time of blood cultures often delays diagnosis [78]. Of note, in hepatosplenic candidiasis (the third group described above), blood cultures may be positive in only 20% of cases, with tissue culture positivity in approximately 50%.

Non-culture-based techniques include antigen/antibody testing, β-D-glucan, and PCR, which can be used adjunctively with blood cultures. There are several limitations of these non-culture-based tests, some of which include the rapid clearance of antigen/antibody from the circulation and limitations in immunocompromised hosts. β-D-Glucan (a component of the fungal cell wall) is not specific for *Candida*, has poor specificity, and false positivity among immunocompromised patients who are at risk for a number of fungal pathogens. PCR is problematic in that there is a lack of standardization in methodologies and has similar limitations to β-D-glucan testing. Currently these tests are not considered standards in making the diagnosis of invasive candidiasis [77, 78]. There are no guidelines for interpreting these non-invasive diagnostic tests, because they provide adjunctive information to blood cultures and should not be ordered in place of blood cultures.

T2Candida is a newer diagnostic modality that is being implemented into some clinical practices. T2 diagnostic testing involves a miniaturized, magnetic resonance-based diagnostic approach that measures how water molecules react in the presence of magnetic fields. The T2Candida Panel test seems to be capable of improved sensitivity compared to blood culture, using automated systems with a turnaround time of 3–5 h [79]. In some instances, the T2Candida Panel test may be positive up to a week prior to blood culture [79].

Treatment

Treatment of ICs has been extensively reviewed and updated by the IDSA in 2016 [78]. Due to the increase in non-albicans infections, with the potential for fluconazole drug resistance, it has become standard practice that echinocandins (either anidulafungin, caspofungin, or micafungin) are initiated empirically upon microbiologic diagnosis of candidemia until speciation is known. Fluconazole is used in the majority of *C. albicans* infections given the >95% sensitivity of isolates to this drug. Treatment durations range from 2- to 4-weeks on average, depending on the underlying disease [78]. Dilated retinal exams are recommended on all patients with candidemia, but can be delayed until neutrophil recovery in hematologic patients. Removal of CVCs is also widely implemented in clinical practice.

Antifungal Prophylaxis

With the advent of a well-tolerated antifungal drug (fluconazole), initial studies from the 1990s showed that prophylactic fluconazole significantly reduced *Candida* colonization [56], reduced invasive *Candida* infections [80], and decreased the incidence of superficial and systemic IC among SCT recipients, with improvements in survival [81, 82]. A randomized placebo-controlled trial of fluconazole prophylaxis in neutropenic cancer patients identified that patients who benefited most from prophylaxis included those with acute myeloid leukemia undergoing induction with anthracycline-based regimens and those receiving autologous transplants not supported with hematopoietic growth factors [57]. Low dose (200 mg daily) of fluconazole was found to be as efficacious to high dose (400 mg daily) in preventing candidal infections among SCT recipients [83]. Since those pivotal studies, the use of fluconazole prophylaxis has become standard protocol throughout many hematologic and transplant centers and is supported by the National Comprehensive Cancer Network (NCCN) guidelines. Meta-analysis studies of antifungal prophylaxis in neutropenic chemotherapy recipients [84] and stem cell transplant recipients [85] report reduced morbidity, superficial and invasive fungal infections, and fungal infection-related mortality with the use of antifungal prophylaxis [84, 85].

Opportunistic Molds

The term invasive fungal disease (IFD) was coined by the European Organization for Research and Treatment of Cancer (EORTC) Invasive Fungal Infection Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (NIAID-MSG) in 2008 to describe any disease process dealing with fungi in high-risk patients [86]. The IDSA has now expanded their guidelines

to include other groups of patients at risk such as solid organ transplant and those with primary immunodeficiencies [87]. For the purposes of this section we will refer to IFD as it relates to pathogenic mold fungal infections among hematologic patients, and the discussion will be limited to *Aspergillus*, the agents of Zygomycetes infections (*Mucor*, *Rhizopus,* and *Rhizomucor*) and *Fusarium*, the most common mold infections.

These fungi are saprophytic environmental molds that propagate on decaying soil. Concomitant environmental exposure and host immune deficiency are necessary for invasive disease, of which inhalation of fungal spores is the most common portal of entry. These molds grow by longitudinal extension and branching of filamentous hyphae and are angioinvasive. The morphologic appearance on pathology specimens is pivotal in diagnosing these infections (i.e., *Aspergillus* are seen as branching acute angle septate hyphae, while Zygomycetes are seen as non-septate, broad, ribbon-like hyphae).

Common Features of Invasive Fungal Diseases

There is significant overlap in the clinical and radiographic features of *Aspergillus*, Zygomycetes, and *Fusarium*. Early descriptions of invasive aspergillosis (IA) included persistent fever with pulmonary infiltrates in patients with acute leukemia [74, 88, 89], which also commonly occurs in Zygomycetes [90] and *Fusarium* [91, 92]. The range of pulmonary symptoms includes cough, hypoxemia, shortness of breath, pleuritic chest pain, and (given the angioinvasive character of these fungi) hemoptysis. Risk factors for infection have been extensively studied and include prolonged neutropenia, corticosteroids, and acute leukemia [89, 93–96]. In addition, those patients with active malignancy, persistent neutropenia at the end of treatment, and delayed initiation of treatment are associated with poor survival [97–99]. Delayed therapy for ≥10 days and 6 days has been associated with worse survival in *Aspergillus* [100] and Zygomycetes [99] infections, respectively. Utilization of high-resolution chest computed tomography (CT) scans has allowed earlier diagnosis of IFDs and hence improvement in outcomes with initiation of antifungal therapy.

After entry into the lungs, these mold infections can spread by either direct extension or systemic dissemination via the blood system and angioinvasion [101]. Pulmonary disease is the most common manifestation of infection [102–104], with lung involvement occurring in 90% of cases in one single center study [105]. IA does have a predilection to cause central nervous system disease, either through hematogenous dissemination or contiguous spread from the sinuses, however dissemination into any organ can occur [101]. Table 50.6 summarizes key points regarding invasive mold infections.

Table 50.6 Key points: Invasive fungal diseases

Key points: Invasive fungal diseases
• Invasive aspergillosis is the most common invasive fungal disease among immune-compromised patients
• Rhino-cerebral disease more commonly occurs in Zygomycetes infections
• Ribbon-like non-septate hyphae are characteristic of Zygomycetes histopathology
• Skin manifestations commonly occur in disseminated *Fusarium* infections

Epidemiology

Aspergillus

Invasive aspergillosis is the most common of the opportunistic mold infections occurring in patients with hematologic malignancies and SCT. The actual overall incidence of IA is difficult to estimate; however, the use of non-culture-based diagnostic tests has expanded the number of patients who will be defined as "possible" cases [106]. Among all causes of IFDs among immunocompromised and immunocompetent patients, IA represents approximately 70% of mold infections, with 85% of those occurring in patients with hematologic malignancies and SCT recipients [107]. The majority of IA occurs during the first course of induction chemotherapy for those with AML [108], when mold-active prophylaxis is not routinely employed. A bimodal distribution of IA has been described after SCT, with early disease being related to underlying myeloid deficiencies and late disease (after day 100) related to graft-versus-host disease, steroids, and immunosuppression [108]. *Aspergillus fumigatus* is the most common species isolated [102, 104, 107, 109], followed by *A. flavus*, *A. niger*, and *A. terreus* [102]. A history of aspergillosis during chemotherapy for AML does not preclude progression to transplantation, but the infection should be well controlled unless activity of the underlying transplant condition is the reason why aspergillosis cannot be controlled.

Survival and mortality vary significantly depending on the study and have been reported as 59% survival after hematologic malignances at 12 weeks [102], to 43–62% with hematologic malignancy or after SCT [102, 105, 110]. Factors for poor survival include SCT, progression of underlying disease [111, 112], steroid use [110, 113], neutropenia [112, 113], disseminated disease [113], and extent of pulmonary lesions [105].

Zygomycetes

Common Zygomycetes molds include organisms in the genera *Mucor*, *Rhizopus*, *Rhizomucor*, *Lichtheimia* (formerly *Absidia*), and *Cunninghamella*. Among hematologic malignancy patients, the most common presentation mimics IA; however, Zygomycetes infections do have a greater propensity

to have sinus or rhinocerebral involvement [114–116]. The presence of sinus disease favors Zygomycetes, but does not rule out IA. In the two largest prospective studies on Zygomycetes, the incidence of pulmonary disease ranged from 30 to 46%, with rhinocerebral disease occurring in 27–29% [115, 116]. Single center studies prospectively comparing IA to Zygomycetes infections in those with hematologic malignancies report that sinusitis and rhinocerebral manifestations were significantly more common in those with Zygomycetes infections compared to *Aspergillus* [96, 99]. Other independent predictors for Zygomycetes also included prior use of voriconazole [96, 114], the presence of multiple pulmonary nodules (≥10 nodules), and pleural effusions [114]. Taken together, the two most significant distinguishing factors for Zygomycetes infections include sinus disease and breakthrough IFD on voriconazole prophylaxis.

Worse outcomes have been associated with active malignancy [97, 99], delay in therapy [99], and pulmonary and disseminated disease [93, 116]. A single center retrospective study showed that delay in initiation of an amphotericin product resulted in a twofold increased mortality at 12 weeks [99], which has been confirmed in other studies [115]. Use of posaconazole [99] and neutrophil recovery are associated with favorable outcomes [90, 99]. Mortality ranges from 52% in those with hematologic malignancies to 76% after stem cell transplant [116]. Interestingly, in one small pilot study, radiographic improvement was not predictive of 90-day survival, and 50% who survived did not have improved CT or magnetic resonance imaging at the end of treatment. However, clinical response 30 days after the end of treatment was predictive of survival at 90 days after treatment [97].

Fusarium

Notable characteristics that distinguish *Fusarium* from the above infections is the propensity for disseminated disease (not just pulmonary involvement), skin manifestations that occur in approximately 60% of infections, and the ability to grow in blood cultures in 40–55% of cases [91, 98]. The pulmonary nodules that occur in *Fusarium* infections tend to have more peripheral involvement compared to Zygomycetes or *Aspergillus* infections [117].

Fusarium solani is the most commonly reported isolate representing >50% of the *Fusarium* cases reported in the literature [92, 95, 98]. The most common skin manifestation is multiple painful erythematous papular or nodular lesions with or without central necrosis, and can also manifest as ulcerations, bullae, or ecthyma gangrenosum [118]. Skin lesions have been described to precede fungemia by 5 days [95, 119]. Early descriptions of *Fusarium* in hematologic patients reported fever refractory to antibacterial therapy with painful skin lesions in 91% of infections, with presumed pneumonia and sinusitis occurring in 84% and 26%, respectively [92].

Diagnosis

The EORTC/MSG and IDSA all support a composite definition for the diagnosis of IFD that includes host factors, clinical manifestations, and mycologic evidence of infection. Utilizing these criteria, patients are grouped as either proven, possible or probable IFD, with proven infection necessitating tissue biopsy with pathologic evidence of fungi invading tissue. Probable is the most common category in clinical practice, which includes a host factor (such as allogenic SCT, corticosteroids, T cell immune-suppression, or recent history of neutropenia >10 days), clinical features (such compatible CT imaging), and mycologic evidence (direct or indirect mycologic testing) be present [86].

Use of high-resolution CT imaging and non-culture-based diagnostic testing improves early diagnosis of IFD in hematologic patients, which in turn impacts outcome. There are several classic patterns of IFD on high-resolution CT of the lung, including the halo, air-crescent, or reverse halo sign [120]. The macronodule is the most common manifestation of IA [121]. A macronodule surrounded by ground glass (the halo sign) pathologically represents an area of fungal tissue invasion surrounded by alveolar hemorrhage [87, 120, 122]. The halo sign occurs early in the course of IFD, and while not specific for IA, it commonly occurs among hematologic patients with invasive aspergillosis (92–95% of patients in small series) [120, 123, 124]. The reverse halo sign, a focal area of ground glass opacity surrounded by a ring of consolidation, also occurs early in the course of IFD, but is more associated with infections caused by the agents of Zygomycetes rather than *Aspergillus* [120]. As neutrophils recover, cavitation and gas formation may occur, denoting the air-crescent sign.

Treatment

Azole antifungal agents (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) are the most commonly used class of agents used to treat IFD infection, given their improved tolerability profile over amphotericin products. Table 50.7 expands upon the different antifungal agents, with expanded coverage of the higher generation azole antifungal agents. Echinocandins (micafungin, caspofungin, and anidulafungin) have good *Aspergillus* coverage, but lack activity against the agents of Zygomycetes and *Fusarium*. These are often used along with an azole for dual drug or salvage therapy for *Aspergillus*. Finally, amphotericin products do have a broad spectrum, but are most commonly used to treat Zygomycetes infections. Nephrotoxicity and infusion-related reactions are the most common limiting factors in using these agents. Knowledge of the antifungal spectrum that is used for prophylaxis is essential in making early treatment choices for suspected IFDs and breakthrough fungal infections.

Therapy for *Aspergillus*: In 2002 a randomized clinical control trial showed better treatment responses and improved

Table 50.7 Key points: Commonly used Antifungal agents

Class of antifungal agent	Route of administration	Individual antifungal agent	Characteristic
Azole (Liver metabolism effects)	Water soluble	Fluconazole	– Most activity with *Candida albicans* and *Candida parapsilosis*
	IV and enteral		
		Voriconazole	– Predictable visual side effects
		Isavuconazole	– Zygomycetes activity
			– Administered as a prodrug
	Lipid soluble	Itraconazole	– Absorption variable
	For the most part, used enterally		– Enteral agent only
		Posaconazole	– Zygomycetes activity
			– Extended release form with reliable absorption
Echinocandin	IV only	Anidulafungin	– None of these agents cover *Cryptococcus* or Zygomycetes
		Caspofungin	
		Micafungin	
Polyene	For the most part, used IV	Amphotericin products	– Zygomycetes activity
			– Considered fungicidal
			– Nephrotoxicity common
			– Infusion-related side effects
		Nystatin	Topical agent only

IV intravenous

survival with voriconazole as compared to amphotericin-B [109], which has been confirmed by two superseding studies [105, 113]. Given the high mortality of IA in immune-compromised patients, combination antifungal therapy is often considered for patients with a high risk of death and for critically ill patients. This usually consists of voriconazole plus an echinocandin. A randomized, controlled trial of voriconazole monotherapy versus combination therapy was published in 2015 [125]. There was a trend toward improved mortality at 6 weeks with combination therapy in patients with hematological malignancy or SCT, although statistical significance was not obtained.

Therapy for Zygomycetes: Mold active agents with activity against Zygomycetes include amphotericin, posaconazole, and isavuconazole. Double coverage of amphotericin and posaconazole is the most common regimen used early in the course of therapy. Surgical debridement in those with sino-cerebral disease is an important part of therapy and improves outcomes [90, 93, 126]. Hyperbaric oxygen and granulocyte transfusions are often considered in those with severe disease.

Therapy for *Fusarium*: The most common regimens for therapy include voriconazole with or without amphotericin, and therapy should be based on the isolate's sensitivities. Neutrophil recovery is essential for recovery from *Fusarium* infections [63, 91], with some series reporting 0% survival without recovery from myelosuppression [92]. Granulocyte transfusions can be considered as an adjunct to antifungal therapy, working as a bridge until recovery from myelosuppression. Steroid use is also associated with poor outcome [91].

Summary

The evaluation of potential bacterial and fungal infections in patients with hematological malignancies necessitates a careful understanding of host, underlying disease, and antineoplastic therapy factors. The likelihood of infections that one is likely to encounter will influence the types of diagnostic testing and empiric treatment that should be ordered. Additionally, empiric and targeted treatments are influenced by the current knowledge of local microbial prevalence and antimicrobial resistance patterns. Providers managing these patients need to have a good understanding of these concepts and are encouraged to involve infectious diseases experts in the management of these complex patients, especially when facing poor clinical response to anti-infective therapy, MDROs, and fungal infections. To be certain, this is a constantly changing field, if nothing else due to microorganisms' ability to constantly evolve and adapt; therefore, we must remain flexible, observant, and willing to adapt as well.

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