Fungal Infections in Cancer Patients

Michael Angarone

Abstract

Invasive fungal infections (IFI) have become a leading cause of morbidity and mortality in cancer patients. Infections with these organisms are often difficult to diagnose and treat. Appropriate and timely diagnosis requires a high index of suspicion and invasive procedures, including biopsy, to confirm the diagnosis. Treatment may be difficult, secondary to variable susceptibility and difficulty with exact and specific characterization of the fungal pathogen. The pathogens that are seen range from yeasts to invasive molds. Fortunately newer, noninvasive diagnostic techniques are available to aid in the diagnosis and treatments have become better tolerated and more efficacious.

Keywords

Malignancy · *Candida* species · Aspergillosis · Mucormycosis

Contents

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Invasive fungal infections (IFI) are recognized as a leading cause of morbidity and mortality in cancer patients. The highest risk has been seen in those individuals undergoing hematopoietic stem cell transplantation (HSCT); however, these infections are now recognized as significant sequelae in patients with cancer receiving chemotherapy alone. Infections with these organisms are often difficult to diagnose and require a high index of suspicion and invasive procedures with tissue biopsy are often needed to confirm the diagnosis. Treatment of these infections continues to be a challenge as many of these organisms have variable susceptibility to the available antifungal agents, and treatment is often empiric as the causative agent is being identified. This empiric treatment often requires multiple agents or agents with a higher side effect profile, placing the patient at risk for drug-induced complications. In response to these limitations, newer diagnostic protocols, noninvasive testing, and broader spectrum antifungals have been developed to aid in the diagnosis and management of these infections [1].

Three major classes of fungi cause infection: yeasts, molds, and dimorphic fungi. The yeasts, which include *Candida* spp., *Cryptococcus* spp., and *Trichosporon* spp., lack true hyphae, and infection is related to invasion through compromised host defenses. The molds, which include *Aspergillus* spp., *Fusarium* spp., and the agents of mucormycosis, are transmitted via inhalation of conidial (spore) forms, and these organisms have true hyphae. The dimorphic fungi, *Blastomycosis*, *Histoplasma*, and *Coccidioides*, have both yeast and hyphal forms and are generally restricted to specific geographic areas. The majority of fungal infections in cancer patients are caused by *Candida* and *Aspergillus*. Over the past two to three decades, there has been an increasing trend and recognition of non-candidal infections, especially those caused by non-*Aspergillus* molds. See Table 1 for a brief description of the various fungal pathogens, typical diseases they cause, and treatments of choice.

This chapter will focus on a general overview of fungal infections. It will offer a review of the epidemiology and risk factors for fungal infections as well as a description of the commonly encountered fungal pathogens and the infections that they cause. A review of the available antifungal agents will also be described.

Table 1 Typical fungal pathogens, type of infection, and treatment of choice

Pathogen	Type of infection	Treatment of choice
***Candida* spp.**		
• *C. albicans* • *C. krusei* • *C. tropicalis* • *C. glabrata* • *C. parapsilosis* • *C. lusitaniae*	Mucocutaneous Blood infections Endocarditis Disseminated (Hepatosplenic) Ocular	**Azoles** • *C. krusei* and *C. glabrata* azole resistant **Echinocandins** • *C. parapsilosis* resistant to echinocandins **Polyenes** • *C. lusitaniae* resistant to polyenes
***Tricosporon* spp.**		
• *T. asahii* • *T. asteroides* • *T. cutaneum* • *T. inkin* • *T. mucoides* • *T. ovoides* • *Geotrichum capitatum*	Cutaneous Pneumonia	Fluconazole
Pneumocystis jirovecii		
	Pneumonia	TMP–SMX Pentamidine Primaquine + clindamycin Atovaquone
***Cryptococcus* spp.**		
• *C. neoformans* • *C. gattii*	Pneumonia Cutaneous CNS (meningoencephalitis)	AMB-D/L-AMB + 5-FC *Disseminated and CNS disease Fluconazole
***Aspergillus* spp.**		
• *A. fumigatus* • *A. terreus* • *A. flavus* • *A. niger*	Pneumonia Sinusitis Cerebral	Voriconazole Polyenes
Mucormycosis		
• *Mucor* spp. • *Rhizopus* spp. • *Rhizomucor* spp. • *Cunninghamella* spp. • *Absidia* spp. • *Basidiobolus* spp. • *Conidiobolus* spp.	Sino-orbital Rhinocerebral Pneumonia	L-AMB AMB-D Posaconazole

(continued)

Table 1 (continued)

Pathogen	Type of infection	Treatment of choice
***Fusarium* spp.**		
• *F. solami* • *F. oxysporum*	Sino-pulmonary Skin and soft tissue Fungemia	Voriconazole Posaconazole
***Scedosporium* spp.**		
• *S. apiospermum* (*Pseudallescheria boydii* asexual state) • *S. prolificans*	Mycetoma Fungemia Disseminated infection (brain abscess, muscle)	Voriconazole ***Optimal therapy unknown** ***Typically resistant to most antifungal agents**
***Paecilomyces* spp.**		
• ***P. variotti*** • ***P. lilacinus***	Pneumonia Cutaneous	Voriconazole Posaconazole
Phaeohyphomycoses (dematiaceous/black molds)		
• *Cladophialophora* spp. • *Wangiella* spp. • *Ramichloridium* spp. • *Chaetomium* spp. • *Alternaria* spp. • *Curvularia* spp.	Sinusitis CNS infection (brain abscess)	Voriconazole Surgical debridement ***Optimal therapy unknown**
Histoplasma capsulatum		
	Pneumonia Lymphadenitis Disseminated (CNS, bone marrow, skin)	AMB-D, L-AMB Itraconazole
Blastomyces dermatitidis		
	Pneumonia Cutaneous Bone and joint	AMB-D, L-AMB Itraconazole
Coccidioides immitis		
	Pneumonia Pleuritis Cutaneous Meningitis Brain abscess	AMB-D, L-AMB Fluconazole

AMB-D amphotericin B deoxycholate; *5-FC* 5-flucytosine; *L-AMB* lipid amphotericin B; *TMP–SMX* trimethoprim–sulfamethoxazole

1 Epidemiology

The epidemiology of IFI in cancer patients is continually changing. In the 1980s, *Candida* species played a significant role in infection in cancer patients, and candidiasis was more prevalent than infections caused by molds. With the introduction of azole antifungals, a shift in fungal pathogens was seen. The azoles offered increased tolerability, compared with polyene antifungals, and their widespread use as prophylaxis led to a decrease in the incidence of candidal infections [2]. Along with this decrease, there has been an increase in infections caused non-*Candida albicans* yeast, *Aspergillus,* and other molds over the last two decades.

A major consequence of azole use has been a shift in the *Candida* species causing infection, with a shift to azole-resistant species such as *Candida krusei* and *C. glabrata*. These azole-resistant species now account for more than half of candidal isolates identified [3–5]. Newer antifungal agents, such as the echinocandins, have a broader spectrum of activity and are useful in treating azole-resistant candidal isolates. As the use of these agents has increased, there has also been a rise in the incidence of echinocandin-resistant organisms such as *C. parapsilosis* [6]. It remains unclear if this shift is secondary to the pressures of the antifungal agents or other host and treatment factors.

The true incidence of IFIs is difficult to assess as much of the data have come from single centers or regional retrospective studies, with most studies having an incidence ranging from 5 to 30 % in patients with cancer. Over the past two decades, there has been a shift in the causative agents of IFI, with an increase in infections by molds such as *Aspergillus* spp., *Fusarium* spp., and the agents of mucormycosis [7–9]. Autopsy studies from the MD Anderson Cancer Center have evaluated the prevalence of IFI from 1989 to 2003. Over the study period, the overall rate of IFI remained stable at approximately 30 %. The major finding was a rise in the prevalence of invasive mold infections, from 60 to 76 %, and a corresponding decrease in candidal infections, from 40 to 26 %. Major increases were seen in infections caused by *Aspergillus* spp. and endemic fungi and in mucormycosis [8, 10].

Retrospective case series have identified similar trends in the epidemiology of IFI in cancer patients. Auberger et al. reviewed the incidence and outcomes of IFI in a single Austrian center between 1995 and 2004. During the study period, IFIs occurred in 167 of 1,095 (15 %) patients. A significant increase in the incidence of IFI was seen over time, 12.7 % (1995–2000) to 18.1 % (2001–2004). The vast majority of cases were attributed to invasive mold infections (87 %), with *Aspergillus* spp. predominating. Overall mortality from IFI was 35 %, with a significant reduction in mortality between the periods studied, 44 % (1995–2000) versus 28 % (2001–2004) [11]. Similar results have been reported by Hahn-Ast et al. who compared the incidence of IFI from 1995 to 2006 in a German cancer center. In this series, the incidence of IFI was 8.8 %, with an increase in the incidence over time, 7.1 % (1995–2001) to 10.9 % (2001–2006). Most of IFIs

(approximately 63 %) occurred in individuals with acute mylogenous leukemia (AML). The overall mortality from these infections was 41 %; however, there was a decrease in the mortality seen over the two time periods, 56.9 versus 28.6 %. Better survival was observed in those with controlled cancer, age <60 years, infection during 2002–2006 and the use of novel antifungal agents (echinocandin and/or voriconazole) [12]. In an Italian multicenter review, Pagano et al. found that a majority of IFIs were secondary to molds, especially *Aspergillus* spp., and the incidence was greatest in individuals with AML. Mortality from these infections was high, especially for mucormycosis (mortality rate of ~64 %) [13].

There are limited data available on the epidemiology of IFI in pediatric cancer patients. Children with acute leukemia are at the highest risk of IFI, with incidence rates varying between 4.9 and 29 % [14–18]. Neutropenia, diagnosis of acute leukemia, corticosteroid use, and antifungal prophylaxis are associated with the development of IFI in pediatric cancer patients [16–18]. As seen in the adult population, there is a declining incidence of candidal infections with an increase in aspergillosis [14, 16, 17]. Other studies in the pediatric population have confirmed similar rates of fungal infections in children, with a majority of cases occurring in the setting of acute leukemia and with *Candida* spp. and *Aspergillus* spp. the leading causative organisms [14, 16].

2 Risk Factors

Fungal organisms are ubiquitous in the environment, and humans are constantly exposed to fungal spores via the respiratory tract and on skin and mucosal surfaces. Anatomic barriers and an intact immune system are highly efficient at containing these fungal elements in the immune competent host. Systemic fungal infections occur as a result of breaks in the normal host defenses such as those seen in patients with cancer. The first line of defense against these organisms is the anatomic barrier provided by structures such as skin and mucous membranes. These surfaces prevent the entry of microorganisms from entering the body and produce enzymes and other antimicrobial secretions that lead to the removal of fungal organisms. These barriers are compromised in cancer patients through invasive procedures such as indwelling central venous catheters and mucosal damage, resulting from chemotherapy. Compromise of these structures allows for the penetration of fungal organisms into the tissues and accesses the bloodstream [19]. The next line of defense against fungal infection is an intact immune system. The complement cascade, phagocytosis, and cell-mediated immunity all play a critical role in controlling and protecting against IFI. Many of the components of the immune system become compromised in patients with cancer secondary to the malignancy itself, chemotherapy, radiation therapy, and the use of immunosuppressive agents [20, 21]. This breakdown of immune defenses increases the susceptibility of cancer patients to fungal infections.

The major risk factors for IFI in cancer patients are the underlying malignancy, neutropenia, older age, and degree of immunosuppression. Other factors that contribute to the development of IFI are the state of the underlying malignancy, indwelling venous catheters, broad spectrum anti-bacterial therapy, renal insufficiency, intensive care unit admission, total parenteral nutrition, prior IFI, mucosal colonization with *Candida* spp., and innate immune defects [20]. To assess the risk of IFI, Prentice et al. developed a risk stratification that categorizes patients into low-, intermediate-, and high-risk groups. Those individuals at the highest risk of infection have prolonged and severe neutropenia, use of high doses of corticosteroids, treatment with high-dose cytarabine, AML, and colonization with *Candida* spp. [22]. This stratification tool has been validated and may help to provide more effective antifungal prophylaxis and early detection and treatment of IFI in cancer patients [23].

The two most significant risk factors for IFI are the underlying malignancy diagnosis and neutropenia. The risk of IFI is greater for individuals with hematologic malignancy, compared with those of solid tumors, and is greatest among those with acute leukemia (AML and acute lymphocytic leukemia, ALL) [20, 24]. Patients with acute leukemia are also at risk of developing these infections early, even before chemotherapy or during induction chemotherapy. A review of invasive filamentous fungal infections in cancer patients found that 7 % of infections occurred prior to initiation of chemotherapy, mostly in patients with acute leukemia and myelodysplastic syndrome [24]. The study also found that nearly half of the infections occurred during the first-induction chemotherapy [24]. The reason for the high rate of early infection is unclear, but it has been suggested that the bone marrow aplasia as a result of the leukemia may play a role [18].

Neutropenia is the most important risk factor for the development of IFI. Almost all patients undergoing chemotherapy will develop neutropenia during the course of therapy; however, the degree and duration of neutropenia varies. Individuals with solid tumors typically have short-lived neutropenia (usually less than 7 days), and IFI is an infrequent complication [19]. The degree of neutropenia is an important risk factor, and those with an absolute neutrophil count of $<0.1 \times 10^9$ cells/μL have the highest risk of infection [22]. Prolonged neutropenia greater than 10 days confers a much higher risk of IFI than shorter durations of neutropenia [24–26]. It is estimated that there is a 1 % risk of developing an IFI for each day a patient is neutropenic. This risk increases to >4 % per day if the patient remains neutropenic for more than 24 days [25]. Furthermore, short intervals between neutropenic episodes (<14 days) increase the risk of IFI [26].

Many of the chemotherapies used to treat malignancy have also been associated with increased risk of IFI. Studies have demonstrated an increased risk of IFI with the use of high doses of corticosteroids and fludarabine-based regimens [20, 27–29]. Use of monoclonal antibodies has also demonstrated an increase risk of infection, especially with fungi. Alemtuzumab, a humanized anti-CD52 antibody, leads to the depletion of CD4 and CD8 T-cells. This depletion increases the risk of severe infection, especially with *Candida* spp., *Aspergillus* spp., and *Pneumocystis jirovecii* [30, 31].

Genetic immune defects in host recognition and response to fungal organisms may also play a role in the risk of infection. The mannose-binding lectin (MBL) and toll-like receptors (TLR) play a critical role in immune recognition of fungal organisms, and defects in these proteins have been linked to increased risk of fungal infection [32]. MBL is a secreted pattern-recognition receptor of the innate immune system. These proteins bind to conserved carbohydrates found on many microorganisms and promote the initiation of the compliment cascade and phagocytosis [32]. Mutations in the *mbl2* gene led to a non-functional protein that has been linked to an increased risk of fever and serious infection, including fungal infections [33–36]. MBL binds to the mannan-rich outer wall of *Aspergillus* leading to the clearance of the organisms, and MBL-deficient mice are much more susceptible to infection with *Aspergillus* [36]. In immunocompromised humans, MBL deficiency has been significantly linked to the development of invasive *Aspergillus* infection [32]. The TLR is a transmembrane protein that detects specific "microbe-associated molecular patterns," and binding of these receptors leads to cytokine release and immune activation [37]. TLR2 and TLR4 are major components of the initial immune response to fungal pathogens, and defects in these receptors lead to decreased neutrophil recruitment and reduced cytokine production [37, 38]. In humans, genetic polymorphisms within the TLR4 gene have been associated with an increased risk of cavitary aspergillosis [39]. Defects in dectin-1, tumor necrosis factor (TNF), and interleukin-10 (IL10) have also been linked with increased risk of fungal infections [40–44].

The environment, geographic location, and hospital exposure can all play a role in acquisition of fungal pathogens. Fungal spores are ubiquitous in the environment, and humans are constantly exposed to these organisms. Climate can have a profound impact on the burden of fungal spores in the environment, with higher rates of infection seen in warm, dry climates compared with more temperate climates [45, 46]. For example, *Aspergillus* spore counts have been shown to increase during warm and dry months in Seattle, Washington; *Coccidioides* proliferate during periods of high precipitation, and spread of infection has been linked to the warm and dry months in Arizona [46–48]. Nosocomial spread of infection has been linked with fireproofing material, carpets, hospital water supply (especially showers), and food products such as tea, pepper, fruit, and freeze-dried soups [49–56]. Hospital air has also been found to contain fungal spores, especially during building construction, and the use of HEPA filtration in hospital can dramatically reduce the spore load of air [50, 56].

3 Diagnosis of IFI

The diagnosis of fungal infections remains a challenge. Infections with these organisms can present in a myriad of ways, including persistent fever, sepsis, fungemia, and organ invasive disease. Isolation and identification of the causative fungus often require invasive procedures, and many of the molds are difficult to

cultivate in the laboratory. The primary step in identification of an IFI is having a high index of suspicion based on the clinical signs of illness. An aggressive search should be made to identify a causative fungus. This may require cultures performed on tissue specimens, histopathology of these specimens, the use of fungal antigen assays, and molecular tests to identify fungal specific DNA.

The European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) have developed definitions to classify IFI and aid in the diagnosis of IFI [1]. This classification system assigns levels of probability to the diagnosis of an IFI in individuals with cancer or recipients of an HSCT. The classification system is divided into "proven," "probable," or "possible" IFI based on the patients' underlying condition and clinical factors combined with histopathologic, microbiologic, and radiographic data. "Proven" infection is based on the identification of fungal elements with tissue destruction on biopsy specimens and microbiologic identification of a fungus from a normally sterile site, such as blood, cerebrospinal fluid (CSF), or biopsy specimen. "Probable" infection requires the presence of a host factor (e.g., neutropenia and prolonged use of corticosteroids), a clinical criterion (e.g., symptoms of sinus infection and radiographic findings concerning for a nodular pneumonia), and a mycological criterion (e.g., growth of a mold on culture, positive antigen-detection assay). "Possible" infection is defined as the presence of host and clinical factors in the absence of mycological data. The primary use of this system has been in the development of clinical trials for the treatment of fungal infection and validation of diagnostic assays; however, their implementation into clinical practice has not identified a difference in clinical outcomes between the categories [20]. Given the difficulty in making a "proven" diagnosis, individuals with a "probable/possible" diagnosis should be treated as aggressive as those with "proven" infection while continuing to confirm the diagnosis.

The gold standard for the diagnosis of fungal infection is the histopathologic identification of fungal elements on biopsy specimens and the growth of fungal organisms in culture from blood or other clinical specimens; however, there are limitations to obtaining these specimens. Often patients are not suitable to undergo invasive procedures due to their illness or high risk of complication. Also the sensitivity of fungal culture is limited and may be as low as 35 %, especially for *Aspergillus* spp. and other molds [57]. Currently, there are multiple non-culture-based assays available that can help to aid in the diagnosis of fungal infections and can be performed on serum or urine specimens. These assays include serologic assays and fungal antigen-detection assays. Serology can be helpful in the diagnosis of infections with coccidioidomycosis and paracoccidioidomycosis [1, 58]. Antigen detection has also been useful in the diagnosis of infections caused by cryptococcosis, histoplasmosis, and blastomycosis [59, 60].

Two antigen assays are currently available for the diagnosis of candidiasis and aspergillosis, the (1→3)-B-D-glucan and the galactomannan assays. The (1→3)-B-D-glucan is a cell wall component present in many fungi, limiting the specificity of the assay. The assay identifies (1→3)-B-D-glucan in serum, and the presence of

the antigen can aid in early treatment for fungal infection. The sensitivity to the (1→3)-B-D-glucan is variable, with a range of 61–88 % sensitivity for the diagnosis of aspergillosis [61–63] and 71–97 % for candidiasis [61, 64–67]. Another major issue with the (1→3)-B-D-glucan is the lack of specificity among fungal organisms and the high rate of false positive results in patients on hemodialysis and those with bacteremia [60]. The galactomannan assay offers increased specificity for the diagnosis of aspergillosis. This assay detects specific components of the *Aspergillus* cell wall and for some patients, detection of galactomannan in the serum may precede clinical signs and symptoms of infection [60, 68]. The sensitivity of the galactomannan assay on serum specimens is variable, between 49 and 89 %, with a lower sensitivity seen in those individuals receiving mold active agents as either prophylaxis or treatment [61, 69]. The assay has also been tested on respiratory specimens to increase the sensitivity and diagnostic yield of the assay. Performance of the assay on bronchoalveolar lavage (BAL) specimens has demonstrated an increased sensitivity when compared with serum galactomannan results. Maertens et al. evaluated the performance of BAL galactomannan compared with culture and microscopy of BAL fluid. A greater sensitivity was found on the BAL galactomannan (91 %) compared with that of culture and microscopy (50 and 53 %, respectively) [70]. The galactomannan assay can also be followed serially, usually twice per week, to help provide early diagnosis of IFI [71]. These assays may allow for earlier diagnosis and earlier treatment for individuals suspected of having a fungal infection, especially *Aspergillus* infection.

Polymerase chain reaction (PCR) is a diagnostic technique with the potential to offer an accurate and definitive diagnosis via noninvasive testing. PCR assays demonstrate high specificity, ranging from 92 to 100 % depending on the gene that is amplified [63, 72–74]. White et al. evaluated the utility of monitoring twice weekly the blood PCR assay specific to *Aspergillus*. The negative predictive value for this approach was >99 %, and serial positive results were predictive of proven or probable infection [74]. It has been suggested to combine PCR testing with galactomannan testing; however, the accuracy and practicality of this approach have not been evaluated. The major drawback to PCR assays for the diagnosis of aspergillosis is that they lack standardization, are prone to contamination, and have not been shown to be superior to the galactomannan assay [60]. At this time, PCR assays remain experimental; perhaps with the development of a commercial or standardized assay, this testing method may develop more widespread use and acceptance.

4 Selected Fungal Organisms

4.1 Candidal Infections

Candidal species are part of the normal microbiota of the skin, airways, genitourinary tract, and the gastrointestinal tract. Individuals with malignancies are predisposed to invasion with these organisms secondary to neutropenia, mucositis,

broad spectrum antibacterial therapy, total parenteral nutrition, and invasive central venous catheters [75]. Prior to the use of anti-fungal prophylaxis *Candida* spp. represented 20 % of all blood stream isolates and were the fourth leading cause of death from nosocomial sepsis [76, 77]. Incidence rates for candidal infections have remained stable in recent years despite increased use of antifungal prophylaxis [6]. *Candida albicans* is the most frequently isolated species; however, there has been a shift to azole-resistant non-*C. albicans* yeast, especially *C. krusei* and *C. glabrata* [4, 78]. A recent single center review identified a greater than 50 % reduction in the number of infections caused by *C. albicans* and a 2–3 fold increase in infections caused by *C. krusei* and *C. glabrata*. In patients with hematologic malignancies, 86 % of candidal isolates were non-*C. albicans* species, and the major risk factor for infection with these organisms was the use of fluconazole prophylaxis and neutropenia [79].

Candidal infections range from mucosal infection, such as thrush and esophagitis, to bloodstream and multi-organ-disseminated infection. Breakdown of skin and mucosal barriers allows for the invasion into the blood stream and eventual dissemination of the organisms. The most common source for invasion is the gastrointestinal and genitourinary tracts; however, isolation of *C. parapsilosis* usually indicates contamination of a central venous device. Candidemia is associated with significant morbidity and mortality, with mortality rates ranging from 30 to 75 % [6, 79, 80]. The major factors associated with mortality are hematologic malignancy, neutropenia, and infection with *C. glabrata* [6, 79–81]. Disseminated (hepatosplenic) candidiasis typically arises as a complication of candidemia and is the result of seeding of candidal organisms in various organs, especially the liver and spleen. Often, the only symptom present is persistent fevers. As neutropenia resolves, lesions within the affected organ(s) may become apparent on imaging and with the development of organ dysfunction. Disseminated candidiasis has been reported in about 6 % of individuals with acute leukemia, and remission of the leukemia is associated with recovery from the candidal infection [82].

Mucocutaneous candidiasis can be treated with topical agents, such as nystatin for thrush or clotrimazole for vulvovaginal infection, or with systemic triazoles such as fluconazole for esophagitis [83]. All patients with suspected or documented candidemia require systemic antifungal therapy. The current recommendation for treatment of neutropenic patients with candidemia is to initiate an echinocandin and tailor therapy once the organism has been identified. Typically, *C. albicans* and *C. tropicalis* are susceptible to the triazoles, such as fluconazole and voriconazole. *C. glabrata* and *C. krusei* tend to be resistant to the triazoles; therefore, it is recommended that an echinocandin can be used for treatment. *C. parapsilosis* has in vitro resistance to the echinocandins, and treatment with an azole or polyene (amphotericin B product) is recommended [83]. In addition to antifungal therapy, indwelling catheters should be removed. In non-neutropenic individuals, catheter removal has been associated with earlier sterilization of the blood, which may decrease the likelihood of dissemination. In neutropenic individuals, catheter removal may be problematic since removal of the central line

may lead to access problems. Additionally, there is a lack of association between early catheter removal and improved survival [84, 85]. However, catheter removal should be undertaken in all patients with persistent candidemia or with worsening infection while on appropriate antifungal therapy, and in all other individuals with candidemia, central venous catheter removal is strongly recommended [83].

4.2 Trichosporonosis

Trichosporonosis is an uncommon infection usually seen in immunocompromised hosts, especially those with hematologic malignancies. The major causes of trichosporonosis are the *Trichosporon* spp. (*T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, *T. ovoides*) and *Geothrichum capitatum* [86]. These yeasts are part of the normal skin, gastrointestinal, and pulmonary microbiota and have also been identified in multiple environmental sources [86, 87]. Portal of entry for these organisms is via breaks in mechanical barriers such as skin or mucosa. Fungemia and pneumonia are the primary infections seen with these yeasts. A large Italian review identified 52 cases of trichosporonosis over a 20-year period, with 33 % secondary to *Trichosporon* spp. and 67 % secondary to *G. capitatum*. Fungemia was the most frequent manifestation of infection, and mortality was high (57 % for *G. capitatum*, 65 % *Trichosporon* spp.) [87]. Pulmonary infection resembles classic mycetoma with round lung lesions and a halo sign on imaging [88]. Respiratory tract infection with these fungi is difficult to diagnose since these organisms may colonize the airways.

The azoles, such as fluconazole, are the treatment of choice for these infections based on in vitro susceptibility testing. Despite in vitro susceptibility data, recurrent or breakthrough infections are common [86, 89, 90]. Mortality rates are high, ranging between 55 and 65 % [86, 87]. Factors associated with favorable outcomes are neutrophil recovery, lack of hyperglycemia, and azole therapy [86].

4.3 *Pneumocystis jiroveci* Infection

Pneumocystis jiroveci was initially classified as a protozoan; however, it is now considered a fungus based on gene sequencing and analysis of cell wall constituents. There are multiple species of *Pneumocystis*, each with its own genetic distinctiveness and host specificities. Based on this species uniqueness, the human pathogen has been renamed *P. jiroveci*, formerly known as *P. carinii*. Infection with *Pneumocystis* relies on defective T-cell immunity. This T-cell defect is most commonly seen in individuals with T-cell depletion such as those with acquired immunodeficiency syndrome (AIDS) and is less common in patients with malignancy. The highest risk appears to be individuals with lymphoproliferative conditions [91, 92]. In a series of 55 cases of *P. jiroveci* pneumonia (PJP) over a 10-year period, patients with non-Hodgkin's lymphoma and lymphoid leukemia

had the highest risk of infection [93]. Infection is also seen in patients with solid tumors, especially those treated with long-term steroids [91, 94]. A more recent risk factor for the development of PJP is the use of lymphocyte-depleting antibodies, such as rituximab [95, 96]. It is estimated that 11–14 % of individuals treated with rituximab develop PJP [95, 96]. *P. jiroveci* has a unique tropism for the lung where it resides as an alveolar pathogen, rarely causing disseminated disease. Infection typically presents with the slow onset of dyspnea, cough, and fevers. Examination may reveal tachycardia, crackles, and hypoxia.

Unlike other fungal infections, antifungal agents have little to no effect in the treatment of PJP. The treatment of choice is trimethoprim–sulfamethoxazole (TMP/SMX). Acute therapeutic alternatives are intravenous pentamidine, primaquine combined with clindamycin, or atovaquone. Given the high risk of infection with *P. jiroveci* in patients treated with steroids or rituximab, primary prophylaxis should be considered. As with treatment, TMP/SMX is the preferred agent for prophylaxis and is administered daily or thrice per week. Alternatives are monthly inhaled pentamidine, daily oral atovaquone, or dapsone.

4.4 Cryptococcosis

Infection with *Cryptococcus* results in a wide spectrum of illness, ranging from asymptomatic disease to life-threatening meningoencephalitis [97]. *Cryptococcus* is ubiquitous environmental yeast, with the *C. neoformans* species complex causing most human infection. Cryptococcosis is an infrequent complication in patients with malignancy, and underlying hematologic malignancy accounts for the majority of cases [98]. The major risk factors for cryptococcosis are steroid use, chemotherapy with fludarabine, and lymphopenia [98]. Pulmonary infection occurs in >60 % of cases with patients presenting with nonspecific symptoms, such as fever (37 %), dyspnea (37 %), cough (37 %), chest pain (16 %), and ARDS (11 %). Asymptomatic disease is seen in more than 30 % of cases pulmonary cryptococcosis [98]. Only 10 % of cryptococcal infections involve the central nervous system (CNS) in patients with malignancy, much less frequent when compared with other patient populations. The signs and symptoms of CNS infection are similar to other patient populations and include altered mental status, headaches, and fevers [98] (see Chapter Central Nervous System Infectionsin Cancer Patients and Hematopoietic Stem Cell Transplant Recipients).

4.5 Aspergillosis

Infection with *Aspergillus* is the most common invasive mold infection encountered in individuals with malignancy. There are more than 200 species of *Aspergillus*, but only a few cause disease in humans, namely *Aspergillus fumigatus*, *A. terreus*, *A. flavus,* and *A. niger* [8].

Infection may occur in the lung, sinuses, skin, mucosal surfaces, eye, and CNS. The most common sites of acquisition are the lungs and sinuses. Clinical manifestations of invasive pulmonary aspergillosis (IPA) may be varied and range from cough and fever to hemoptysis and respiratory failure. The most frequent manifestations of disease in neutropenic individuals are fever, cough, and dyspnea [99]. The earliest indications of IPA are radiographic findings, especially with computerized tomography (CT) scanning of the lung. CT scan of the lung may identify micronodules, macronodules, diffuse interstitial infiltrates, the "halo sign" or the "air-crescent sign" [100, 101]. These findings can allow for early recognition of IPA, and appropriate testing can be obtained to make an early diagnosis.

Cerebral aspergillosis is a rare condition with an incidence of approximately 7 % but a mortality rate greater than 90 % [13, 102]. The clinical presentation is nonspecific with fevers, altered mental status, focal neurologic deficits, and seizures [103, 104]. These nonspecific findings can be found in other infectious and non-infectious conditions of the CNS. Diagnosis of CNS aspergillosis relies on neuroimaging. The typical findings associated with aspergillosis on CT or magnetic resonance (MR) imaging are multiple, complex ring-enhancing lesions within the brain parenchyma [105, 106]. Those with sinus disease may have dural enhancement adjacent to the involved sinuses [105, 106]. Evaluation of the cerebral spinal fluid (CSF) is of limited use, and culture positivity is rare. However, in a small series of patients, levels of galactomannan in CSF were significantly higher in patients with CNS aspergillosis versus controls [107]. This assay may provide a means to establish an early diagnosis and allow for early directed therapy against CNS aspergillosis.

Sinus infection with *Aspergillus* is most often symptomatic with facial swelling, periorbital swelling, and sinus drainage that is bloody or black [108]. It is often difficult to distinguish sinus infection with *Aspergillus* from other causes, including bacteria and other molds. Diagnosis is most often made by sinus endoscopy. Endoscopic findings include crusting of the nasal mucosa, nasal ulceration, and necrotic, or dusky nasal mucosa [109]. Therapy involves a combination of surgical debridement and anti-fungal medications (either voriconazole of amphotericin B-based therapy) [108].

Evaluation of biopsy specimens reveals tissue invasion of the fungus, with invasion into blood vessels. The fungus appears as 45° angle branching, septated hyphae; this is not a unique feature of *Aspergillus* and may be seen with other invasive molds such as *Fusarium* and the agents of mucormycosis. Given the similarity of the various molds on pathologic specimens, culture is required to make a definitive diagnosis. *Aspergillus* can be grown easily on routine fungal culture media, and large white or black colonies are seen on the media plates [110]. Microscopically, the mold consists of hyphal stalks and a conidial head. Newer PCR techniques can be performed directly on tissue specimens, but identification may only be to the genus level and susceptibility information cannot be obtained.

4.6 Mucormycosis

Over the last few decades, there has been a steady increase in cases of mucormycosis with a stable mortality rate between 40 and 50 % [111]. The increase in these infections may be related to newer chemotherapies, increased longevity of individuals with malignancy, and increased awareness of this infection in this population [111]. Infections with the Zygomycetes class of fungi belong to two orders, Mucorales and Entomophthorales. Multiple genera within these two orders can lead to infection, but the most frequently encountered genera are *Rhizopus*, *Mucor,* and *Rhizomucor* [111]. These molds are ubiquitous in the soil and decaying organic material. Infection occurs through inhalation of fungal spores in a susceptible host; however, infection can also occur via direct cutaneous inoculation or ingestion of contaminated foods [112]. Infection in patients with malignancy is uncommon, and the vast majority of infections occur in individuals with hematologic malignancies, especially those with acute leukemias [13]. The major sites of infection are the lung and sinuses, with infection of the skin, throat, and gastrointestinal tract seen less frequently. The major findings with respiratory tract infection are fever, cough, thoracic pain, and dyspnea. Patients with sinus infection may develop orbital cellulitis, paresis of the extraocular muscles, or proptosis. These molds can result in vascular invasion and destruction of bone that may lead to direct invasion of the brain in sinus infections [13, 111].

Diagnosis is often based on the combination of clinical signs and symptoms along with radiographic imaging. Infection results in vascular invasion with resultant vascular occlusion and infarction and necrosis of infected tissue. Radiographic imaging may identify hemorrhage, abscess or consolidation of inflammation within the lungs [113]. Rhinocerebral or sino-orbital infection may demonstrate inflammation of the sinuses with destruction of boney structures and direct invasion into the orbit or brain [113]. Biopsy specimens will identify the characteristic right angle branching, pseudoseptate, and ribbon-like hyphae [114]. Fungal cultures can help to identify the genera and species of the mold; however, they are positive in less than 50 % of cases [111].

Treatment of mucormycosis involves surgical debridement, reduction or correction of immunosuppression, and antifungal medications. Surgical resection of necrotic, infected tissue can help to enhance antifungal activity and decrease the fungal burden [112]. Antifungal therapy is limited to the polyenes and posaconazole. The polyenes remain the initial treatment of choice (amphotericin B deoxycholate, liposomal amphotericin B, and lipid complex amphotericin B). The lipid formulations of amphotericin (AmB-L) offer the advantage of higher doses of amphotericin and a decrease in nephrotoxicty [111, 115]. Retrospective data demonstrate response rates of 52–69 % and improved survival with AmB-L compared with amphotericin B deoxycholate [115]. A newer extended spectrum azole, posaconazole, has in vitro and in vivo activity against Mucorales. Posaconazole has been evaluated as salvage therapy for treatment of mucormycosis [116, 117]. In 91 patients treated with posaconazole as salvage therapy for mucormycosis, successful treatment was seen in

60 % of patients at 12 weeks, complete response was seen in 14 %, and partial or clinical response was seen in 46 % of patients [117]. The major disadvantage to posaconazole is that it is only available as an oral formulation and requires a high fat meal to enhance absorption, making it difficult to administer to all patients. Other therapies have been investigated for the treatment of mucormycosis such as colony stimulating factor, interferon therapy, iron chelation, and combination antifungal therapy, all with varying results, and are not recommended for use at this time [118]. Currently, it is recommended that therapy begin with a polyene and any surgical debridement, if possible, followed by a change to posaconazole once a response to therapy has been identified [118].

4.7 Other Mold Infections (Fusarium, Alternaria, Phaeohyphomycosis, Endemic Fungi)

Over the past few decades, there has been an increase in infections with exotic, environmental molds. The genera most commonly identified are *Fusarium* spp., *Scedosporium* spp., and the dematiaceous molds. These molds are ubiquitous in the environment and have been identified in water, soil, and on vegetation worldwide, and it is believed that acquisition of these infections primarily occurs outside the hospital [112, 119]. A variety of infections, from cutaneous infection to disseminated disease with fungemia, may be caused by these molds. *Fusarium* spp. is a common mold of plants and decaying matter. A majority of reported infections with these molds have occurred in patients with hematologic malignancy and neutropenia [120]. The major syndrome related to *Fusarium* is disseminated disease with fungemia and multiple organ involvement; however, this mold may also cause skin, sinus, and pulmonary infection [120–122]. Most patients are treated with a combination of antifungals, and, despite therapy, mortality rates are >50 %, especially for patients with fungemia and disseminated disease [120]. The two major *Scedosporium* spp., *Scedosporium apiospermum* and *S. prolificans*, are found worldwide and are the major causative agents of mycetoma (*S. apiospermum*) and localized bone infection (*S. prolificans*) [123]. Infection typically involves the lungs with dissemination of the mold to secondary sites of infection including muscle, brain, and fungemia [124–126]. Resistance to the polyenes and echinocandins occurs in both species of *Scedosporium,* and the most active agent in vitro is voriconazole; however, mortality rates remain very high for this infection [126, 127]. Phaeohypohomycosis results from infection with the pigmented molds. These infections remain extremely rare in patients with malignancy, but can lead to brain abscess, pneumonia, and fungemia [128].

Histoplasma, *Blastomyces,* and *Coccidioides* all can cause endemic mycoses. These fungi are dimorphic and have a yeast phase seen at human body temperatures and a mold phase seen on culture or in the environment. These infections are rare in patients with malignancy and are often restricted to the geographic location of the fungus. Disease results from newly acquired infection related to

environmental exposure or reactivation of latent infection. Most individuals will develop pneumonia from these molds, but cutaneous, CNS, and disseminated disease can occur [129–131]. The key to diagnosis is early recognition of a potential endemic mycoses and identification of the yeast forms on histopathologic specimens and early institution of therapy [131].

5 Antifungal Therapy

Multiple antifungal agents are currently available with diverse mechanisms of action, spectrum of activity, and tolerability. The major classes of antifungals are the polyenes, echinocandins, and the azoles. Table 2 lists the common antifungal agents, their route of administration, spectrum of activity, and common adverse effects. Specific treatment varies based on the fungal pathogen, the site of infection, drug tolerability, and toxicity profile of the chosen agent.

5.1 Polyenes

The polyenes, amphotericin B deoxycholate, and the lipid-associated amphotericin preparations bind to ergosterol in the fungal cell membrane. This binding leads to the formation of ion channels in the cell membrane and the physical disruption of the membrane. The polyenes have a broad spectrum of activity and are reactive against most fungi. The greatest limitation to the use of amphotericin B deoxycholate is nephrotoxicity, which can lead to renal failure and the need for dialysis [132, 133]. The lipid formulations of amphotericin B have the advantage of less nephrotoxicity and allow for infusion of higher doses of amphotericin.

5.2 Echinocandins

The echinocandins (caspofungin, micafungin, anidulafungin) are lipopeptides that inhibit the synthesis of 1,3-β-glucan, a polysaccharide involved in strengthening the cell wall. The inhibition results in changes in the osmotic integrity of the fungal cell leading to cell destruction. Activity of these agents is restricted to those fungi that possess the 1,3-β-glucan in their cell membrane; in particular *Candida* spp. and *Aspergillus* spp. The utility of the echinocandins has been demonstrated in the treatment of candidal infections, refractory invasive aspergillosis, and as empiric therapy for neutropenic fever [134–137]. These agents have also demonstrated efficacy in the treatment of refractory aspergillosis when combined with voriconazole [138, 139]. Major adverse effects of the echinocandins include elevations in liver aminotransferases (especially caspofungin), gastrointestinal upset, and headaches. Serum levels of the echinocandins may be increased by cyclosporine, and conversely they may increase the serum levels of tacrolimus [140].

Table 2 Antifungal agents

Antifungal agent	Route	Dose	Toxicity	Spectrum of activity
Polyenes				
Amphotericin B	IV	0.5–1.0 mg/kg	Nephrotoxicity Hypokalemia Hemolysis Infusion related	Broad spectrum of activity: *Candida* *Aspergillus* Mucormycosis *Blastomyces* *Coccidioides* *Histoplasma* *Cryptococcus*
ABCD	IV	2.5–5 mg/kg	As above, Less nephrotoxicity	
ABLC	IV	2.5–7.5 mg/kg		
L-AMB	IV	2.5–10 mg/kg		
Echinocandins				
Caspofungin	IV	70 mg load then, 50 mg	Hepatic	*Candida* spp. *Aspergillus* spp.
Micafungin	IV	50–100 mg	Hepatic GI upset Phlebitis Headache	
Anidulafungin	IV	100 mg load then, 50 mg	GI upset Hepatic	
Azoles				
Fluconazole	PO/IV	200–1,200 mg	Hepatic	*Candida* *Coccidioides* *Cryptococcus*
Itraconazole	PO/IV	100–400 mg	Hepatic Hypokalemia Edema Cardiac Poor absorption	*Candida* *Aspergillus* *Blastomyces* *Histoplasma*
Voriconazole	PO/IV	6 mg/kg load then 4 mg/kg BID	Hepatic Neurologic Vision changes	*Candida* *Aspergillus* *Fusarium* *Scedosporium*
Posaconazole	PO	200–300 mg TID 100–200 mg BID	Hepatic Poor absorption	*Candida* *Aspergillus* *Coccidioides* Mucormycosis *Fusarium* *Scedosporium* *Cryptococcus*

ABCD amphotericin B colloidal complex; *ABLC* amphotericin B lipid complex; BID twice daily; IV, intravenous; *L-AMB* liposomal amphotericin B; *PO* per mouth; *TID* thrice a day

5.3 Azoles

The azoles constitute a group of antifungals with a similar mechanism of action, but varying spectrum of activity. The azoles inhibit the production of ergosterol biosynthesis by inhibiting lanosterol 14-α demethylase, which results in an altered fungal cell membrane. Currently, there are four widely used azole antifungal compounds used in patients with malignancy, fluconazole, itraconazole, voriconazole, and posaconazole. Fluconazole is a narrow spectrum azole that is primarily used to treat candidal infections. This agent has good tolerability and is available in an oral and intravenous formulation. Itraconazole is a broader spectrum azole with activity against *Candida* spp., *Aspergillus* spp., and the endemic fungi. There are both oral and intravenous formulations; however, the capsular formulation of this agent has erratic GI absorption and may lead to GI upset.

Newer azoles such as voriconazole and posaconazole offer broader spectrum of activity and better tolerability. Voriconazole is structurally similar to fluconazole; but has a spectrum of activity that includes *Aspergillus*. Based on available data, voriconazole is considered the drug of choice for the treatment of proven or suspected invasive aspergillosis [141, 142]. Individual variability of voriconazole metabolism may lead to altered serum drug concentrations. This variability may lead to sub-therapeutic levels or toxic levels of the agent that can lead to decreased efficacy or increased toxicity [143]. The major toxicities of voriconazole are visual disturbances, hepatotoxicity, and renal toxicity (intravenous formulation only). The newest azole available in the United States, posaconazole, has been shown to have enhanced activity against a wide variety of fungi, including the Mucorales [144–146]. Clinical data have demonstrated the efficacy of posaconazole as salvage therapy for aspergillosis, mucormycosis, fusariosis, and coccidioidomycosis [116, 117, 147–150].

6 Discussion

IFI are a growing cause of morbidity and mortality in cancer patients. Studies from single, large cancer centers have identified the growing burden of these infections. Strategies to enhance the diagnosis along with the growing armamentarium to treat these infections offer promise at improved survival from these infections. With the use of these newer, broad spectrum agents, the emergence of rare and more resistant fungal pathogens cannot be overlooked.

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