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Fungal Infections in Children with Hematologic Malignancies and Stem Cell Transplant Recipients

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Summary

Children with hematologic malignancies and hematopoietic stem cell transplant recipients are at high risk for invasive fungal diseases (IFD). There have been an increased number of at-risk children over the past two decades due to improvements in cancer therapies resulting in improved survival of children with high-risk and refractory malignancies. The predominant organisms that cause IFD include *Candida* spp., *Aspergillus* spp., and the *Mucorales* molds. Clinical presentations of IFD vary based on host immune status and the causative organism. Though serum biomarkers such as the galactomannan assay and beta-D-glucan assay have been validated in adults, there are limited data regarding their diagnostic value in children. Thus, the gold standard for IFD diagnosis remains tissue biopsy with histopathological and microbiological evaluation. Treatment of IFD is multimodal and involves anti-fungal drugs, correction of immune dysfunction, and surgical resection when feasible. Pediatric practice regarding IFD is largely extrapolated from data generated in adult patients; in this review we evaluate both primary pediatric studies and guidelines intended for adult patients that are applied to pediatric patients. There remain significant knowledge gaps with respect to the prevention, diagnosis, and treatment of IFD in immunocompromised children, and further research is needed to help guide management decisions.

Keywords

immunocompromised; invasive fungal disease; hematologic malignancies; pediatric; anti-fungal prophylaxis

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Introduction

Children with hematologic malignancies and hematopoietic stem cell transplantation (HSCT) recipients are at high risk for infections with a wide range of pathogens due to their immunocompromised status. Specifically, profound neutropenia and severe T-cell defects predispose pediatric hosts to infections with opportunistic fungi, termed invasive fungal diseases (IFD). The leading causes of IFD in children for the past several decades have been yeasts such as *Candida* species, and molds including *Aspergillus* species and the *Mucorales* family (Pana, et al 2017, Steinbach, et al 2012, Wattier, et al 2015, Zaoutis, et al 2005).

IFD are associated with significant morbidity and mortality (Zaoutis, et al 2005) though epidemiologic quantification of incidence is complex. New advances in cancer therapy and supportive care for children undergoing chemotherapy or HSCT have resulted in an increased number of children at risk for IFD (Hale, et al 2010). The advent of improved fungal diagnostic tests have additionally altered the epidemiology of reported IFD (Pana, et al 2017). Institutional variation in diagnostic and supportive care practices impact the incidence of IFD (Groll, et al 2014, Lehrnbecher, et al 2009). Furthermore, recently revised definitions of invasive fungal disease and inconsistencies in the diagnostic criteria make assessment of IFD prevalence difficult (De Pauw, et al 2008, Groll, et al 2014, Pana, et al 2017). Epidemiologic efforts are additionally complicated by the variety of disease phenotypes that comprise IFD, which are dependent upon both pathogen and host immune dysfunction (King, et al 2017).

Symptoms of IFD are more indolent than those of invasive bacterial or viral infections. Pathogens that cause IFD share the potential for hematogenous dissemination of organism resulting in infection of distant tissues. Widely disseminated IFD is extremely difficult to cure in severely immunocompromised patients. Thus, timely diagnosis and treatment of IFD is essential for limiting morbidity and improving survival. However, fungal organisms can be difficult to culture in microbiology laboratories. Adjunctive radiographic imaging, non-culture assays, and serum biomarkers can amplify diagnostic yield (Groll, et al 2014, Huppler, et al 2017, Katragkou, et al 2017). These diagnostic strategies are used to determine the extent of disease dissemination and monitor IFD throughout treatment. Empiric anti-fungal treatment should be initiated promptly when there is suspicion for IFD in a severely immunocompromised patient. However, not all antifungal agents are approved for use in children, and there are limited data regarding appropriate dosing of newer antifungals for various pediatric age groups. Much of pediatric practice is extrapolated from data generated from adult patients.

In this review article, we discuss the risk factors for IFD in children with hematologic malignancies and allogeneic HSCT recipients. We review the epidemiology and clinical presentation of the most common IFD and assess current diagnostic testing methods and treatment regimens, as well as the use of antifungal prophylaxis and environmental control procedures to prevent these infections. Lastly, we identify future directions in the diagnosis, treatment, and prevention of IFD in pediatric patients that will be important subjects of clinical research.

Children at Risk for Invasive Fungal Disease

Risk of IFD is largely mediated by host immune status, though it is also dependent on infectious exposure. IFD are truly opportunistic infections and therefore are extremely rare in patients without significantly impaired immunity. Phagocyte activity and the development of T-cell responses are critical components of the host immune response to fungal infections. Thus, children with hematologic malignancies and allogeneic HSCT recipients carry a particularly high risk for IFD (Barnes and Marr 2007, Fisher, et al 2018).

Acute Leukemia

The treatment of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) involves recurrent cycles of chemotherapy in order to achieve and maintain disease remission. Acute leukemia is risk-stratified by likelihood of durable remission, and high-risk disease is treated with more intensive chemotherapy. Thus, children with high-risk leukemia undergo periods of profound, prolonged immunosuppression, and specifically myelosuppression, and are therefore at high risk for opportunistic infections (Castagnola, et al 2006, Sung, et al 2009).

Severe neutropenia secondary to intensive chemotherapy has been associated with IFD (Fisher, et al 2018). A multicenter retrospective study of children with AML reported that absolute neutrophil count (ANC) ≤500 cells/ul at the start of a chemotherapy cycle increased the probability of IFD three-fold (Johnston, et al 2013). The exact duration of neutropenia at which risk increases is unknown, but prolonged neutropenia certainly portends an increased risk of IFD (Johnston, et al 2013).

Allogeneic Hematopoietic Stem Cell Transplant

Allogeneic HSCT is the standard of care for many children with hematologic disorders and primary immunodeficiencies. HSCT recipients undergo several phases of immune dysfunction that mediate risk for IFD including pre-engraftment, post-engraftment, and development of graft versus host disease (GVHD). Various host factors and chemotherapeutic agents used during HSCT also impact risk for IFD.

Pre-Engraftment.—Myeloablative conditioning delivered prior to HSCT results in transient bone marrow aplasia. The major IFD risk factor during the pre-engraftment period is prolonged, profound neutropenia. The expected duration of neutropenia following conditioning is dependent upon several factors, including the source and dose of stem cells, but generally lasts several weeks prior to engraftment. During the pre-engraftment period, patients are at significant risk for infectious complications, including IFD (Srinivasan, et al 2013). Similar to patients with leukemia, longer durations of neutropenia increase the risk of IFD.

Post-Engraftment.—After neutrophil engraftment occurs and neutropenia resolves, the risk for IFD is largely mediated by T-cell dysfunction, which persists for months following HSCT. Patients may also receive prophylactic T-cell-suppressive therapy or undergo

allograft T-cell depletion to decrease the risk of graft-versus-host disease (GVHD), which may prolong the duration of T-cell dysfunction.

GVHD.—The risk for IFD is increased in patients with GVHD due to both T-cell dysfunction inherent to the disease and T-cell suppressive therapies used to quell GVHD (Barnes and Marr 2007). Acute GVHD, particularly high-grade GVHD, has been reported as a potential risk factor for IFD in several single-center studies (Hale, et al 2010, Hovi, et al 2000, Srinivasan, et al 2013), as well as one retrospective, multicenter study (Hazar, et al 2019). Similarly, chronic GVHD has been identified as a risk factor for IFD (Castagnola, et al 2018, Hale, et al 2010, Hovi, et al 2000, Kobayashi, et al 2007, Srinivasan, et al 2013). Data are limited with respect to specific therapies for GVHD, however calcineurin inhibitors alone are rarely associated with IFD.

Steroid exposure.—Though any exposure to steroids increases risk of IFD, high-dose steroid treatment (as is commonly used for GVHD) has been described as a risk factor for the development of IFD in several single-center studies (Dvorak, et al 2005, Hol, et al 2014, Hovi, et al 2000, Kobayashi, et al 2007). Prolonged duration (>10 days) of steroid therapy, was also reported to increase risk of IFD (Dvorak, et al 2005). Similar findings have been noted in patients with leukemia (Johnston, et al 2013). However, variations in prescribing among centers limit conclusive quantifications of either dose or duration of steroid therapy that significantly increases risk for IFD (Fisher, et al 2018).

Autologous Hematopoietic Stem Cell Transplantation

Autologous HSCT is utilized for treatment of pediatric cancers including neuroblastoma, central nervous system tumors, and lymphoma. Autologous HSCT enables administration of high doses of chemotherapy to achieve increased tumor penetration by providing stem-cell rescue. Patients who undergo autologous HSCT experience a period of profound neutropenia following conditioning. However, several factors ensure a decreased risk for IFD in comparison to allogeneic HSCT recipients. First, neutrophil engraftment is relatively rapid, usually less than 14 days. Additionally, autologous HSCT has no risk of GVHD and thus no need for immunosuppression or T cell depletion, resulting in minimal T cell dysfunction.

Epidemiology of IFD in Children with Hematologic Malignancy and HSCT Recipients

Defining the incidence of IFD in immunocompromised children is difficult due to institutional practice variations, including the use of antifungal prophylaxis (Lehrnbecher, et al 2009) and reporting of adverse events (Miller, et al 2016). Much of the available epidemiological data are from single center studies (Georgiadou, et al 2012, Hale, et al 2010, Mor, et al 2011) or those focusing specifically on candidiasis or mold infections (Steinbach, et al 2012, Wattier, et al 2015). Additionally, inconsistent use of standardized diagnostic criteria for IFD (De Pauw, et al 2008) makes comparison between studies difficult (Pana, et al 2017).

While the incidence of IFD is low in ALL cohorts (~1%) (Afzal, et al 2009, Inaba, et al 2017), fungal infections have an outsized contribution to infection-related mortality in children with ALL, up to 20% in some reports (O'Connor, et al 2014). IFD during ALL induction therapy has been reported to account for >70% of infection-related mortality (Rubnitz, et al 2004). Rates of IFD in AML cohorts are consistently higher, with a reported incidence of 12–20% (Johnston, et al 2013, Sung, et al 2007a) and accounting for up to 60% of infection-related deaths (Sung, et al 2007a). However, a recent multi-center study in Germany only identified IFD in 3% of AML patients, possibly reflecting the impact of more contemporary supportive care practices in which a majority of patients received antifungal prophylaxis (Bochennek, et al 2016).

Most studies of allogeneic HSCT have reported IFD in ~12–16% of patients (Dvorak, et al 2005, Gomez, et al 2018, Hol, et al 2014, Hovi, et al 2000, Simms-Waldrip, et al 2015). A majority of cases (42–54%) occur in the first 30 days after transplantation, prior to neutrophil engraftment (Castagnola, et al 2006, Cesaro, et al 2017, Hazar, et al 2019). Another large proportion of IFD episodes occur >100 days post-transplant, during which time patients have developed GVHD and consequent T-cell dysfunction (Castagnola, et al 2006, Cesaro, et al 2017, Hazar, et al 2019, Hovi, et al 2000). Autologous transplants have much lower rates of IFD, with the vast majority of infections occurring in the pre-engraftment period (Cesaro, et al 2017, Hovi, et al 2000). A large, multicenter, retrospective study recently reported a one-year cumulative incidence of proven or probable IFD of 0.7% after autologous HSCT (Cesaro, et al 2017). IFD is associated with a significant increase in all-cause mortality among pediatric HSCT recipients (Dvorak, et al 2005), with multiple studies reporting case fatality rates >60% (Gomez, et al 2018, Hovi, et al 2000, Simms-Waldrip, et al 2015).

The microbiology of IFD in children is incompletely reported and available data are primarily derived from single-center studies. Yeast are the predominate pathogens identified in IFD cases in children with hematologic malignancies and HSCT recipients (Hale, et al 2010). Multicenter, prospective studies of candidemia in all pediatric patients, including immunocompetent children, identified *Candida albicans* is the most commonly reported species isolated (Palazzi, et al 2014, Steinbach, et al 2012). However, non-*albicans Candida* species occurred more frequently overall than *Candida albicans* (Palazzi, et al 2014). This is consistent with studies of children with cancer (Castagnola, et al 2006). The majority of invasive mold infections are caused by *Aspergillus* spp.; (Wattier, et al 2015). The *Mucorales* molds are the next most commonly reported cause of IFD (Pana, et al 2017) (Otto, et al 2019, Zaoutis, et al 2007). The epidemiology of IFD with other yeasts and molds is not well-defined, though Bartlett and colleagues recently identified non-*Candida* yeasts in nearly 5% of cases and non-*Aspergillus,* non-*Mucorales* molds in >20% of cases (Bartlett, et al 2018).

Clinical Presentation

Invasive fungal disease should be considered in any immunocompromised child with prolonged fever (Mor, et al 2011, Musial, et al 1988). Frequently, patients with IFD present with persistent fever despite broad-spectrum antibacterial treatment. The clinical

manifestations of IFD are varied and depend on both the causative organism (Table 1) and the mode of acquisition of infection (Figure 1).

Invasive Candidiasis

Invasive candidiasis should be included on the differential diagnosis for any immunocompromised child with fever or concern for sepsis (King, et al 2017). Generally, invasive candidiasis is conceptualized as one of three conditions: candidemia, fungemia with dissemination, or hepatosplenic candidiasis. Invasive candidiasis is most commonly identified after growth of yeast on blood cultures (Steinbach, et al 2012). Yeast enters the bloodstream after disruption of the gastrointestinal mucosa in neutropenic patients (Nucci and Anaissie 2001). However, acquisition of a bloodstream infection can also occur via a central venous catheter. In contrast to angioinvasive molds, *Candida* spp. do not infect the respiratory tract after inhalation. *Candida* spp. colonizes the upper respiratory tract and is often identified in sputum or deep lung cultures, but this represents colonization rather than invasive infection.

Dissemination to almost any organ can occur, including the brain, eyes, lung, liver, spleen, or kidneys. *Candida* spp. can cause central nervous system (CNS) disease in the form of meningitis, meningoencephalitis, or abscesses – presenting signs may include headache, altered mental status, or seizure (McCarthy, et al 2017). Ocular candidiasis can present as chorioretinitis or endophthalmitis and may result in vision loss (Fierro, et al 2013). Current guidelines from the Infectious Diseases Society of America (IDSA) recommend an ophthalmologic exam for all patients with candidemia (Pappas, et al 2016). Given the higher risk of dissemination, assessment for metastatic foci of candida should occur in all severely immunocompromised patients with candidemia, and disseminated infections require a longer course of treatment than candidemia alone (Pappas, et al 2016).

Hepatosplenic candidiasis, also called chronic disseminated candidiasis, is a distinct entity characterized by focal lesions in the liver and spleen (Rammaert, et al 2012). Typical presentations include prolonged fever despite recovery of neutrophil count (Rammaert, et al 2012). Patients usually present with negative blood cultures and no signs of acute disease, and the diagnosis is frequently made radiographically. Diagnostic imaging will reveal focal changes in the liver and spleen, characteristic of hepatosplenic candidiasis (Katragkou, et al 2017). Occasionally, involvement of other abdominal organs or skin occurs. Though the pathogenesis is not well understood, disruption of the mucosal barrier in the gastrointestinal tract is hypothesized to allow for invasion of local vasculature leading to infection of the portal circulation by *Candida* spp. With the exception of fever, symptoms of hepatosplenic candidiasis often do not occur until immune reconstitution (King, et al 2017), and it is thought that dysfunctional immune responses contribute to symptoms (Rammaert, et al 2012). Fever may be prolonged well beyond immune reconstitution despite resolution of radiographic findings and other symptoms.

Invasive Aspergillosis

The most common site of infection for invasive aspergillosis is the respiratory tract. The primary mode of transmission is inhalation of aerosolized conidia from the environment

(Musial, et al 1988). *Aspergillus* infection can occur in upper and lower respiratory tracts. Pulmonary disease may present with nonspecific symptoms such as cough, dyspnea, and/or chest pain (Müller, et al 2002), although many patients are asymptomatic and diagnoses are made based on incidental finding of pulmonary nodules or other radiographic results (Burgos, et al 2008, King, et al 2017). Rhinosinusitis may present with facial pain, numbness, soft tissue swelling, or eye pain similar to periorbital cellulitis.

Another common site of primary infection is the skin, where fungal spores may be directly inoculated. A history of occlusive dressing or trauma at the site of infection is common (Smith, et al 2018). Cutaneous aspergillosis often presents as a solitary hemorrhagic or necrotic ulcer, though a variety of skin manifestations can occur.

Aspergillus spp. are notable for their ability to cause angioinvasion and subsequently disseminated disease. Dissemination to the brain occurs in immunocompromised children (Müller, et al 2002), resulting in abscesses, meningoencephalitis, or vasculitis. Disseminated aspergillosis may involve the eye, gastrointestinal tract, heart valves, liver, kidneys, or bones (Müller, et al 2002). Cutaneous disease may also be a sign of dissemination, which can manifest as diffuse skin lesions.

Mucormycosis

The clinical features of mucormycosis are similar to aspergillosis, and clinical distinction is rarely possible (Groll, et al 2014). Pulmonary disease and rhinosinusitis are the most common clinical manifestations, but cutaneous disease also occurs. Gastrointestinal mucormycosis can present as an intra-abdominal mass. The clinical presentation of disseminated disease varies based on involved organs.

Diagnostic Testing

Early recognition and diagnosis is paramount in the treatment and control of IFD in immunocompromised hosts. Diagnosis may be challenging, as patients can present with symptoms that are attributed to co-morbidities. Consensus definitions for proven, probable, and possible IFD can guide diagnostic evaluation (Table 2). The approach to diagnosis of IFD relies on histopathology and culture, but is multi-faceted and includes the use of blood cultures, diagnostic imaging, serum biomarkers, and ophthalmologic examination (Table 1). Blood cultures may be useful in yeasts such as *Candida* spp. or *Trichosporon* spp. though are of low utility in the diagnosis of invasive mold infections besides those caused by *Fusarium* spp. (Campigotto, et al 2016).

Diagnostic Imaging

The diagnostic process for IFD often begins with radiographic imaging, and the initial imaging modality should be guided by symptoms or clinical manifestations. Diagnostic imaging helps to establish the diagnosis, guide tissue biopsy, and determine extent and site(s) of dissemination (Katragkou, et al 2017).

Candidiasis.—Diagnostic imaging is useful for evaluating dissemination of *Candida* infection. CNS lesions are best seen by Magnetic resonance imaging (MRI), and the most

common findings are nodular enhancing lesions or multiple abscesses (Katragkou, et al 2017). Computed tomography (CT) of the chest is preferred for evaluation of hematogenously disseminated lung disease, which frequently appear as pulmonary nodules.

MRI is superior to CT or ultrasound in the evaluation of hepatosplenic candidiasis (Rammaert, et al 2012). However lesions may not be detected radiographically prior to immune reconstitution (Katragkou, et al 2017). Ultrasound or CT may be useful for surveillance imaging of hepatosplenic candidiasis.

Mold Infections.—Imaging for suspected invasive mold infection should be guided by clinical presentation. However, for patients with prolonged fever and no apparent target organ, imaging should focus on the most common sites of disease – the sinuses and lungs. Diagnostic imaging of fungal rhinosinusitis is difficult to interpret in isolation as there are no imaging findings specific to fungal sinus disease. Imaging may be normal and should not be used as the sole diagnostic tool. Bony erosion on CT is consistent with sinusitis, but is a late finding in fungal disease and is often absent on diagnostic imaging (Katragkou, et al 2017). Fungal sinusitis may appear as an absence of enhancement on MRI due to the devascularization of infected tissues (Groppo, et al 2011). MRI has been reported to be more sensitive for detecting early changes seen in fungal rhinosinusitis, though the specificity of CT and MRI are similar (Groppo, et al 2011).

In pulmonary mold infections, CT imaging may reveal pulmonary lesions, including consolidation, cavitation, abscess, or nodules (Katragkou, et al 2017). Imaging does not distinguish between aspergillus and mucormycosis, despite reported association of certain imaging findings with specific organisms. Importantly, classical imaging findings of aspergillosis that are seen in adults (cavitation or air crescent lesions) are not always present in children (Burgos, et al 2008).

Serum biomarkers

Biomarkers are used in conjunction with traditional histopathologic and microbiologic diagnostics in order to improve surveillance and detection of IFD (Huppler, et al 2017). The most frequently used fungal biomarkers are the galactomannan and beta-D-glucan assays. The diagnostic value of these tests differs between adults and children, and data in pediatric populations are relatively limited (Lehrnbecher, et al 2016).

Beta-D-glucan.—The beta-D-glucan assay detects (1–3)-beta-D-glucan, a polysaccharide found within the fungal cell wall (Figure 2) of *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Trichosporon* spp., and some endemic. Data from adult patients with hematologic malignancies found that the beta-D-glucan assay has high specificity and positive predictive value as a diagnostic assay, especially when two consecutive test results were positive (Lamoth, et al 2012). There have been few studies to address the utility of the beta-D-glucan assay in children, and the optimal cut-off for a positive test result has not been established (Huppler, et al 2017). Additionally, several medications and blood products can cause false positive results. Of note, the use of the beta-D-glucan assay as a screening tool for IFD in children with fever and neutropenia is not recommended (Groll, et al 2014, Lehrnbecher, et al 2017).

Galactomannan.—The *Aspergillus* galactomannan assay detects the galactomannan polysaccharide component of *Aspergillus* spp cell wall. The assay is used both for screening and for diagnostic testing. The sensitivity and specificity depend greatly on the population tested, with the highest sensitivity in patients with hematologic malignancies or HSCT recipients (Arvanitis, et al 2014). A recent meta-analysis of studies evaluating the use of galactomannan detection in pediatric oncology and HSCT revealed variable sensitivity and specificity when the galactomannan assay was used for screening (specificity 50–100%, sensitivity 0–100%) or diagnostic testing (specificity 35–100%, sensitivity 14–100%) (Lehrnbecher, et al 2016). Furthermore, the use of antifungal therapy can decrease the sensitivity of the test and data from adult patients show that the low pretest probability makes it an unreliable surveillance test (Arvanitis, et al 2014, Groll, et al 2014). Expert opinion on the use of galactomannan detection in children is varied: ECIL-4 guidelines recommend consideration of galactomannan assay use for surveillance of children at risk for invasive aspergillosis (Groll, et al 2014), however the international pediatric febrile neutropenia guidelines recommend against routine use (Lehrnbecher, et al 2017).

Histopathology and Culture

Histopathologic analysis and culture of tissue samples are essential for the diagnosis of IFD, and tissue biopsy should be pursued whenever possible. Histopathology enables visualization of fungal elements within tissue and can guide initiation of antifungal therapy or changes to empiric antifungal therapy (Dekio, et al 2015). Histopathology may offer preliminary identification of an invasive mold – for example, *Aspergillus* spp. are known to have septate hyphae, whereas molds of the *Mucorales* family are broad and pauci-septate or aseptate. However, a change to more narrow spectrum antifungal treatment should be reserved until definitive identification of pathogen is done by culture or molecular testing.

Molecular diagnostics

Culture of tissue specimens is the gold standard for identification of fungal pathogens, although contemporary molecular techniques enhance pathogen identification efforts (Larone 2011). Molecular testing allows for the identification of organisms that do not grow in culture and should offer higher sensitivity than other diagnostic techniques (Huppler, et al 2017, Larone 2011). Molecular testing is particularly helpful for more rapid identification of organisms than traditional microbiologic methods, as well as identification of organisms seen on histopathology that do not grow in culture (Chang, et al 2019). One study of invasive mold infection reported increased diagnostic yield from 63% to 96% when PCR testing was utilized (Rickerts, et al 2007). Molecular testing also offers enhanced accuracy; in a recent single-center study fungal sequencing yielded sensitivity of 96.6% and specificity of 98.2% in tissue specimens (Gomez, et al 2017).

However, the utility of molecular assays as screening tests for IFD is unclear. When used as a screening test, serum polymerase chain reaction (PCR) resulted in specificity ranging from 43–85% and sensitivity of 11–80% (Lehrnbecher, et al 2016). When used as a diagnostic test, the specificity was 36–83% and sensitivity was 0–100% (Lehrnbecher, et al 2016). Current guidelines do not recommend routine use of serum PCR for screening or diagnosis of IFD in children (Groll, et al 2014, Lehrnbecher, et al 2017).

Treatment of IFD

The optimal management of IFD includes three factors: antifungal agents, surgical removal when feasible, and an intact immune system. The nature of the underlying diseases in children with hematologic malignancies and HSCT recipients makes the latter very difficult, though every attempt at immune reconstitution should be made in patients with suspected IFD. Appropriate antifungal therapy is the backbone of any therapeutic regimen. However, antifungal therapy is often inadequate for invasive infection as tissue necrosis results in poor penetration of antifungal drugs to the site of infection. Consultation with an infectious diseases specialist with experience treating infections in immunocompromised children is recommended.

Antifungal Therapy

The prompt initiation of empiric antifungal therapy is key in the treatment of children with suspected IFD. The commonly used antifungal agents, including the triazoles, echinocandins, and amphotericin B formulations have varied mechanisms and action and spectrum of activity, as shown in Figure 2 and Table 3, respectively. Empiric therapy can be tailored once a causative pathogen is identified, although specific pathogens are often not defined in IFD. Antifungal susceptibility testing can help guide therapy, though is only routinely performed for *Candida* spp. (Arendrup, et al 2013). As resistance to antifungal drugs is increasingly recognized, antifungal susceptibility testing has become increasingly important in planning therapy for IFD.

Invasive Candidiasis.—With respect to antifungal treatment for invasive candidiasis, the management principles for pediatric patients are similar to those for adults. There have been few comparative trials evaluating the performance of different antifungal agents in children, and recommendations in children have been extrapolated from adult data. The choice of antifungal agent as well as the duration of therapy is determined by the infecting organism, the extent of dissemination, and the patient's immune status.

For candidemia, IDSA guidelines recommend initial therapy with an echinocandin (Pappas, et al 2016). One study comparing an echinocandin to fluconazole showed non-inferiority, however there was a trend towards more favorable outcomes with the echinocandin (Reboli, et al 2007). Sub-group analysis of patients with *C. albicans* demonstrated that echinocandin therapy was more effective than fluconazole, leading to more rapid clearance of positive blood cultures (Reboli, et al 2011). After patients have stabilized and blood cultures are sterilized, many clinicians transition to azole therapy; an international open-label comparative trial of patients treated with echinocandin therapy for 5 days before transitioning to enteral azole therapy did not find a difference in outcomes compared to those treated entirely with echinocandins (Vazquez, et al 2014). Patients should be treated with an antifungal agent for a minimum 14 days after blood cultures have sterilized (Groll, et al 2014, Pappas, et al 2016). In the neutropenic patient, the gastrointestinal tract is the predominant source of infection rather than seeding of a central venous catheter. However, seeding of central catheters is possible as either an initiating or secondary event in neutropenic patients, therefore catheter removal should be considered (Pappas, et al 2016).

Antifungal therapy for disseminated candidiasis is dependent upon the site of dissemination. For hematogenous spread to lungs or abdominal organs (not including hepatosplenic candidiasis), echinocandin therapy is sufficient. However, echinocandins have poor penetration into the vitreous of the eye or the CNS, thus disseminated infections involving the eye or CNS require treatment with amphotericin B or the triazole antifungals (Pappas, et al 2016). The duration of treatment is dependent upon the site of infection, the resolution of symptoms, and correction of predisposing disorders (Groll, et al 2014). In pediatric oncology patients, resolution of neutropenia is essential prior to discontinuation of antifungals.

Initial therapy for hepatosplenic candidiasis should consist of liposomal AmB (LAmB) or an echinocandin, though there are no comparative trials to guide therapy (Pappas, et al 2016). Step-down to oral azole therapy can be done after improvement in symptoms. Patients should be treated until radiographic resolution of lesions, as premature discontinuation of therapy may result in relapse of infection. Given the likely contribution of immune reconstitution or immune dysfunction to symptoms, some have advocated for the use of corticosteroids as adjunctive therapy in those patients for whom fever persists beyond radiographic improvement (Rammaert, et al 2012). However, there have been no systematic analyses of corticosteroid treatment and its role in the treatment of hepatosplenic candidiasis.

Invasive Aspergillosis.—Treatment for aspergillosis should commence once there is suspicion for invasive disease, and voriconazole is the drug of choice for primary treatment (Patterson, et al 2016). Voriconazole is associated with improved survival and fewer side effects when compared to amphotericin B deoxycholate for treatment of aspergillosis (Herbrecht, et al 2002). LAmB and the other lipid formulations have also been used successfully for the treatment of invasive aspergillosis (Cornely, et al 2007a). Caspofungin can also be used as an alternative agent, though comparative trials are lacking (Patterson, et al 2016).

Combination therapies including AmB or mold-active azoles with echinocandins have been reported to be beneficial for treatment of invasive aspergillosis. A recent international randomized trial of adult patients with hematologic malignancies and HSCT recipients with aspergillosis compared voriconazole monotherapy versus combination therapy of voriconazole and anidulafungin (Marr, et al 2015). Treatment with combination therapy was associated with a decrease in mortality after 6 weeks of treatment (19.3% versus 27.5%, p= 0.087). Though the decrease in mortality was not statistically significant, the authors concluded that it was clinically significant. Therapeutic drug monitoring was not performed in this study, thus it is possible that patients randomized to voriconazole alone may have had sub-therapeutic drug levels. Current guidelines suggest that combination therapy of voriconazole and an echinocandin can be utilized for severe disease (Patterson, et al 2016). Our practice is to utilize combination therapy initially with step-down to voriconazole monotherapy after clinical improvement, immune reconstitution, and achievement of appropriate serum voriconazole levels.

Importantly, triazole-resistant *Aspergillus* is an emerging threat especially in Western European countries. Multi- and pan-azole resistant isolates of *A. fumigatus*, the most common cause of invasive aspergillosis, have been detected on nearly every continent (Verweij, et al 2015). Resistance appears to be environmentally-acquired since resistant isolates have been cultured from azole-naïve patients. Outcomes associated with invasive azole-resistant *Aspergillus* are poor; a recent retrospective cohort study found an excess mortality of 25% in patients with voriconazole-resistant isolates (Lestrade, et al 2019). Recommendations from an international expert panel include empiric treatment with LAmB or combination therapy with a triazole and an echinocandin in regions with >10% triazole resistance (Verweij, et al 2015).

Treatment for invasive aspergillosis should be continued for a minimum of 6–12 weeks, with the final duration of therapy determined by the resolution of infection and underlying immune deficit (Groll, et al 2014). Serial radiographic imaging is necessary to document resolution of pulmonary findings or other visceral involvement.

Mucormycosis.—There have been few randomized controlled trials comparing the effectiveness of antifungal agents in the treatment of mucormycosis, and most published data is derived from case series or case reports. This is in part because few antifungals have activity against the *Mucorales* fungi (Table 3). LAmB remains the cornerstone medical treatment for mucormycosis.

Early initiation of AmB is associated with improved survival in cases of mucormycosis (Chamilos, et al 2008). The lipid formulations of AmB had been shown to be safe in children, and higher doses can be given with minimal toxicity (Wiley, et al 2005). Pediatric dosing is largely extrapolated from adult trials. The European Society for Clinical Microbiology and Infectious Diseases and European Confederation of Medical Mycology joint clinical guidelines recommend LAmB dosing of ≥5 mg/kg/day for most cases of mucormycosis, and up to 10 mg/kg/day for CNS involvement (Cornely, et al 2014b).

Posaconazole, a broad-spectrum triazole, also has activity against most *Mucorales* fungi and is generally better tolerated than LAmB. Posaconazole is safe and well tolerated in children (Doring, et al 2012), though dosing data for children ≤ 13 years of age are limited. The successful use of posaconazole as salvage therapy has been documented in both adult and pediatric patients with mucormycosis (Greenberg, et al 2006, van Burik, et al 2006).

The triazole drug isavuconazole has activity against *Mucorales* molds, and a recent single-arm, open label trial in adults showed that isavuconazole had similar all-cause mortality to LAmB (Marty, et al 2016). The safety and efficacy of isavuconazole in pediatric patients have not been established, but isavuconazole has been used successfully to treat mucormycosis in children (Barg, et al 2018). A clinical trial is ongoing to determine the optimal delivery of isavuconazole in pediatric patients (ClinicalTrials.gov: NCT 03241550).

There have been limited published data regarding the efficacy of combination therapy for treatment of mucormycosis in children. A recent retrospective analysis comparing combination therapy versus monotherapy for the initial treatment of mucormycosis in adults

with hematologic malignancies found no significant differences in 6-week mortality (Kyvernitakis, et al 2016). Regardless, reviews of published cases of pediatric mucormycosis show that combination therapy is frequently used (Otto, et al 2019, Zaoutis, et al 2007). As with invasive aspergillosis, the duration of therapy is guided by resolution of infection and correction of immune dysfunction.

Therapeutic Drug Monitoring.—Patients with IFD often have comorbid conditions that affect the pharmacokinetics and pharmacodynamics of antifungal medications (Ullmann, et al 2018). Therapeutic drug monitoring (TDM) has been shown to improve the efficacy of treatment with voriconazole while decreasing the drug discontinuation due to adverse outcomes (Park, et al 2012). Similar findings have been reported with the use of TDM with posaconazole, particularly for patients receiving the posaconzaole suspension (Groll, et al 2014). Pediatric guidelines recommend the use of TDM with triazole antifungals, with a target trough level of 1.0–5.0 mg/L for voriconazole and ≥0.5 mg/L for posaconazole (Groll, et al 2014).

Surgical Resection

The odds of therapeutic success and resolution of infection are maximized when surgical resection is combined with medical management (Cornely, et al 2014b). A significant reduction in mortality has been noted when aggressive surgical resection is performed in cases of pulmonary and sinus disease (Cesaro, et al 2014). Therefore, surgical intervention should be considered for accessible lesions that can be resected with clean margins. However, for infections that are widely disseminated or will require radical resections, reduction of fungal burden must be weighed with the potential for surgical morbidity.

Correction of Immune Dysfunction

Correction of a patient's immune dysfunction is critical to successful treatment of IFD . When possible, immunosuppressive therapy (including corticosteroids) should be minimized.

Neutrophil recovery has been linked with improved outcomes in IFD, and the use of granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) as adjunctive therapy is hypothesized to be beneficial by hastening neutrophil recovery (Cornely, et al 2014a). A large meta-analysis evaluating the use of prophylactic colony stimulating factors in adults and children receiving chemotherapy or undergoing HSCT did not show a mortality benefit but reported a decreased rate of infection due to all causes, including IFD (Sung, et al 2007b).

High-dose granulocyte transfusions are also hypothesized to have benefit by ameliorating the severity and duration of neutropenia, though efficacy data has been inconclusive. A systematic review of randomized controlled trials for granulocyte transfusions concluded that there is insufficient evidence to determine whether granulocyte transfusions impact all-cause mortality, largely due to high risk of bias and ambiguous outcome measurements (Estcourt, et al 2016). However, granulocyte transfusions should be considered for transient supportive therapy for patients in whom neutrophil recovery is expected (West, et al 2017).

Prevention of Invasive Fungal Disease

Given the morbidity and mortality associated with IFD, significant emphasis has been placed on infection prevention. A multi-faceted approach is needed and involves both limiting exposure through environmental control as well as prophylaxis with antifungal drugs.

Environmental Control Measures

Environmental exposure to aerosolized fungal spores or plants and soil can occur both outdoors and in the hospital setting, and is associated with IFD (Pagano, et al 2017). The development of a protective environment and the utilization of high-efficiency particulate air (HEPA) filtration or laminar air-flow reduce nosocomial exposure to fungal spores (Hahn, et al 2002).

Hospital construction or renovation causes significant dust contamination and dispersal of spores (Kanamori, et al 2015). Infection prevention efforts should focus on decreasing airborne fungal spores and maintaining an active surveillance system for construction-related IFD (Kanamori, et al 2015).

Primary Antifungal Prophylaxis

Antifungal prophylaxis should be considered in patients at high risk for developing IFD. While institutional practices vary, patients that should receive antifungal prophylaxis include those with AML, relapsed leukemia, and allogeneic HSCT recipients (Groll, et al 2014, Science, et al 2014). Data are limited regarding the use of primary antifungal prophylaxis in other populations, though some advocate for consideration of antifungal prophylaxis in all patients with high-risk leukemias (Groll, et al 2014).

Allogeneic HSCT transplant recipients should receive antifungal prophylaxis during the neutropenic phase pre-engraftment (Groll, et al 2014, Science, et al 2014). Fluconazole is commonly utilized for this indication. In two randomized controlled trials enrolling patients ≥12 years old, fluconazole prophylaxis reduced the rate of IFD in HSCT recipients (Goodman, et al 1992, Slavin, et al 1995). A meta-analysis of the use of mold-active prophylaxis compared to fluconazole showed decreased mortality related to IFD, but had no effect on overall mortality and was associated with increased adverse effects (Ethier, et al 2012). Therefore, fluconazole is currently the recommended agent (Science, et al 2014). A trial in adult HSCT recipients, which also enrolled a small number of children, showed that micafungin prophylaxis was superior to fluconazole (van Burik, et al 2004). Echinocandins are well-tolerated and can be utilized as alternative antifungal prophylactic agents in HSCT recipients pre-engraftment.

Given the higher risk for IFD in the setting of GVHD and related immunosuppressive therapies used to treat GVHD (in particular corticosteroids), prophylaxis against both yeast and mold is recommended (Groll, et al 2014, Science, et al 2014). Specific drug recommendations vary based on patient age. Echinocandins can be utilized in infants and children (van Burik, et al 2004). Voriconazole has been utilized successfully as antifungal prophylaxis in HSCT recipients ≥2 years of age (Marks, et al 2011). For children ≥13 years of age, posaconazole can be utilized as antifungal prophylaxis. An international randomized,

double-blind trial comparing posaconazole to fluconazole prophylaxis for HSCT recipients with GVHD showed that use of oral posaconazole suspension (with TDM) was as effective as fluconazole in the prevention of all fungal infections but was superior to fluconazole in preventing invasive aspergillosis and in reducing the rate of death attributable to IFD (Ullmann, et al 2007). However, the role of posaconazole as anti-fungal prophylaxis in children with GVHD has yet to be comprehensively studied.

With respect to pediatric patients with AML and relapsed ALL, fluconazole is currently the recommended agent for antifungal prophylaxis (Science, et al 2014). A meta-analysis of adult oncology patients revealed that fluconazole prophylaxis resulted in decreased IFD in populations with a high incidence of IFD (Kanda, et al 2000). A subsequent randomized, controlled trial of posaconazole prophylaxis resulted in lower rates of proven or probable IFD along with reduced fungal-related and overall mortality when compared to fluconazole or itraconazole prophylaxis (Cornely, et al 2007b). An open-label randomized trial comparing caspofungin to fluconazole for prevention of IFD in children with AML (Children's Oncology Group ACCL0933) recently completed enrollment and results of this trial may influence future recommendations regarding antifungal prophylaxis for pediatric patients. Additionally, as dosing strategies for triazoles in young children become better defined, the opportunity to provide prophylaxis against mold infection in all high-risk pediatric patients will likely prompt a review of current recommendations. Certainly for older pediatric patients with leukemia who are at risk for IFD, prophylaxis with posaconazole should be considered.

Secondary Antifungal Prophylaxis—Secondary antifungal prophylaxis occurs after a patient has resolution of IFD but is entering a subsequent high-risk period. Antifungal prophylaxis after treatment of IFD has been used successfully in HSCT to reduce the risk of developing new or recurrent IFD (Cordonnier, et al 2011),(Maziarz, et al 2017). Secondary prophylaxis has been shown to be safe and effective in children, and has resulted in greatly decreased fungal-related mortality (Azik, et al 2015, Dvorak, et al 2005). The choice of antifungal agent for secondary prophylaxis should be tailored to a patient's underlying disease, prior IFD, and clinical status. History of previously treated IFD should not be considered an absolute contraindication to proceeding with further chemotherapy or HSCT.

Rare and Emerging Fungal Pathogens

Widespread use of antifungal prophylaxis has improved outcomes for immunocompromised patients, but has resulted in shifting epidemiology of IFD. Improved diagnostic methods additionally have enabled identification of rare human pathogens, many of which are resistant to the antifungal agents used routinely as prophylaxis. A full discussion of rare and emerging fungal pathogens is outside the scope of this review, but clinicians should be aware of hyaline molds, such as *Fusarium* spp. and *Scedosporium* spp., which may present similarly to aspergillosis or mucormycosis, though tend to be highly resistant to most anti-fungal agents (Nucci and Anaissie 2007). Dematiaceous molds, called phaeohyphomycosis, and opportunistic yeasts such as *Cryptococcus* spp. and *Trichosporon* spp. may also cause infections in children with hematologic malignancies or following HSCT. Of note, fungal species that are not exclusively opportunistic may cause more severe or disseminated disease

in immunocompromised patients. These include endemic mycoses caused by dimorphic fungi, such as *Histoplasma* spp. and *Blastomyces* spp.

Future Directions

Much remains to be learned about IFD in children. Development of risk stratification algorithms for high-risk populations will help guide decision-making for diagnostic testing and empiric treatment. Further epidemiological research is needed to better understand the incidence of IFD given the increased use of antifungal prophylaxis.

A better understanding of the validity and usefulness of serum biomarkers and molecular testing for IFD in children is needed. Two active studies, Fungal Biomarkers for Diagnosis and Response to Therapy for Pediatric Candidemia (BIOPIC, ClinicalTrials.gov: NCT 2220790) and Non-Invasive Diagnosis of Pediatric Pulmonary Invasive Mold Infections (DOMINIC, ClinicalTrials.gov: NCT 03827694), will provide insight into non-culture assays for the diagnosis of IFD in children. Additional testing platforms, including the T2Candida assay (T2 Biosystems), metabolomic breath analysis, and next-generation sequencing need to be evaluated in pediatric patients (de Heer, et al 2016, Hamula, et al 2016, Hong, et al 2018).

While many pediatric treatment recommendations are extrapolated from adult data, several ongoing clinical trials are aimed at identifying effective antifungal agents for various manifestations of IFD in children. The Pediatric Antifungal Comparative Effectiveness (PEACE) trial (ClinicalTrials.gov: NCT 01869829) will compare the efficacy of echinocandin versus amphotericin B or triazole antifungal therapy for pediatric invasive candidiasis. Additionally, there are active Phase 1 studies examining pharmacokinetic/pharmacodynamic properties of posaconazole and isavuconazole (ClinicalTrials.gov: NCT 02452034 and 03241550) in children. The role of antifungal prophylaxis requires better definition for nuanced immunocompromised pediatric populations, particularly regarding the choice of antifungal agent and appropriate dosing.

Finally, there is great variability in antifungal prescribing across institutions and geographic regions, and investigation into antifungal stewardship is also needed (Hamdy, et al 2017). The impact of antifungal use on clinical management and costs is not well defined, and further research is needed to identify the best metrics and methods for antifungal stewardship.

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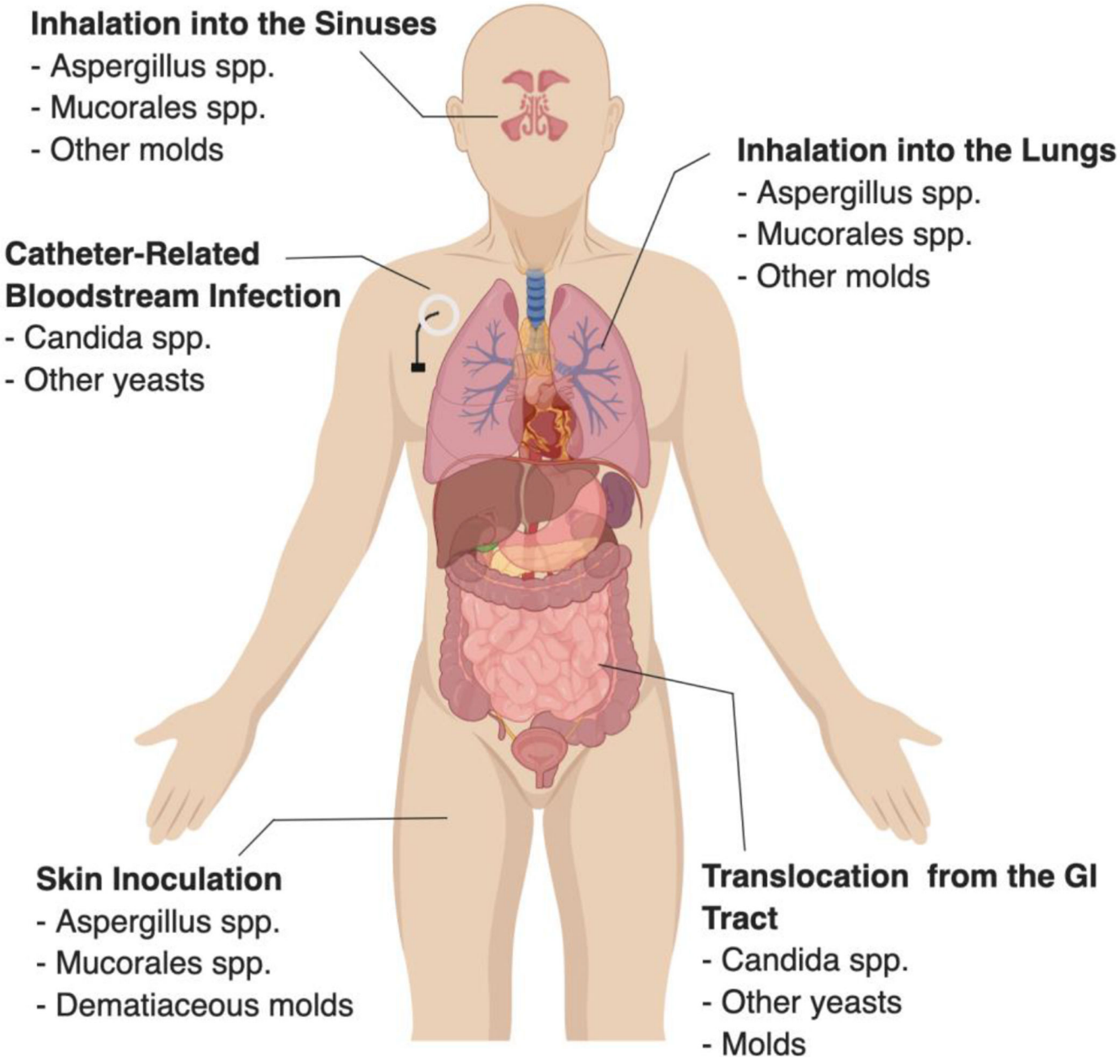

Figure 1.
Common modes of entry for common pathogens seen in invasive fungal disease.

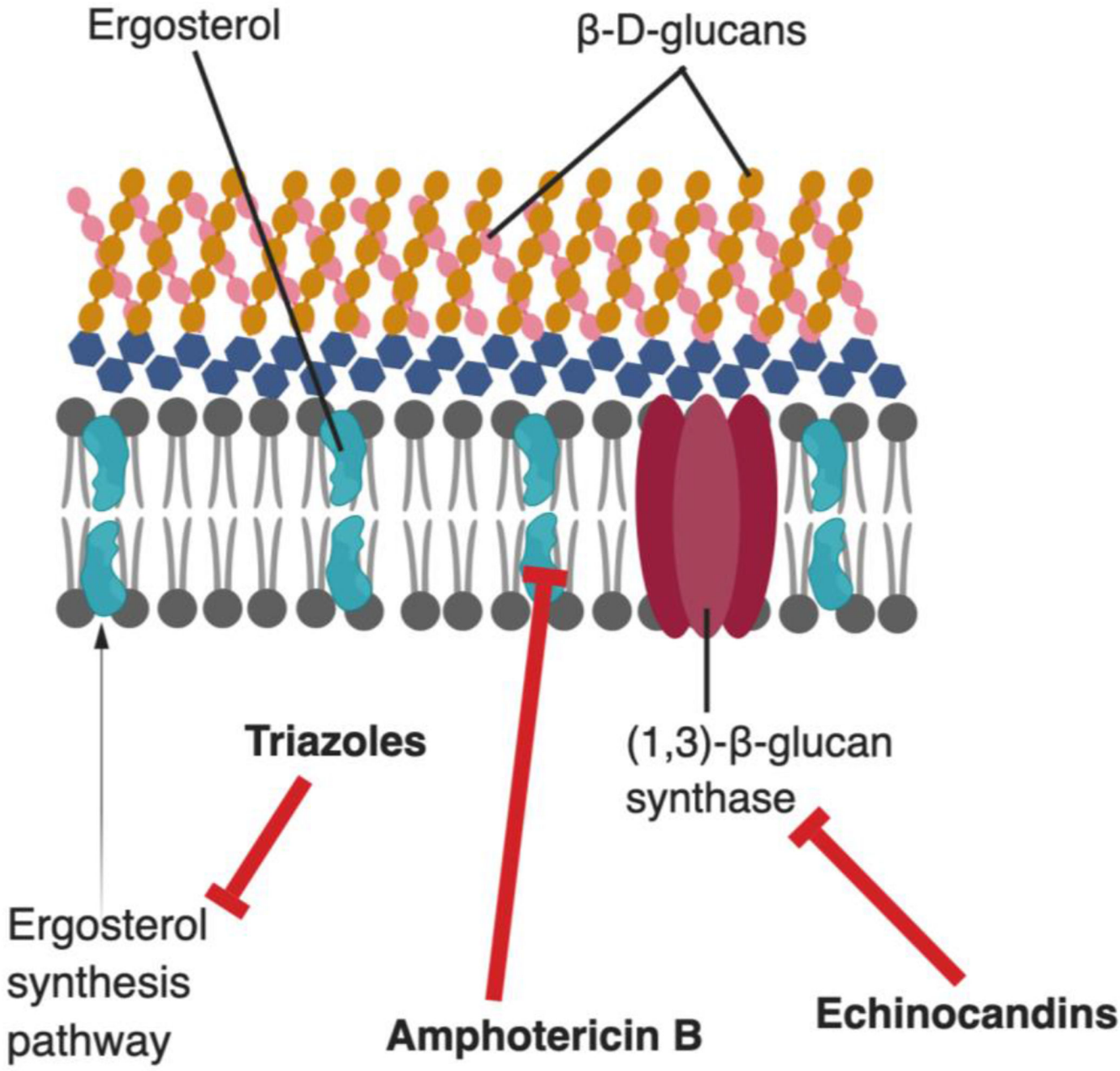

Figure 2.

The fungal cell wall and membrane and the sites of action of common antifungals. Triazole antifungals inhibit the synthesis of ergosterol, a key cell membrane component. Polyene antifungals (such as amphotericin B) act directly on ergosterol and disrupts membrane integrity. Echinocandins prevent the synthesis of (1,3)-β-D-glucan, a key component of the fungal cell wall.

Table 1.

Clinical Manifestations, Diagnosis, and Initial Treatment of Invasive Fungal Disease

	Organism	Invasive fungal disease	Diagnostic testing	Treatment[a,b]	Common species
Yeast	*Candida* spp.	Bloodstream infection	• Blood culture • Diagnostic imaging to assess for dissemination • Ophthalmologic exam[c]	• Echinocandin for total of 14 days after clearance of candidemia[d] • Removal of central venous catheter should be considered	*C. albicans* *C. parapsilosis* *C. tropicalis* *C. glabrata*[f]
		Disseminated disease	• Blood culture • Diagnostic imaging • Ophthalmologic exam[c] • Tissue biopsy for culture and histopathology	• Choice of therapy depends on the site of infection • Duration of treatment dependent on treatment of underlying condition • Ocular infections: triazoles[e] • CNS infections: liposomal AmB	
		Hepatosplenic candidiasis	• Blood culture, • Liver/spleen imaging (US and/or CT) • Tissue biopsy for culture and histopathology	• Echinocandin or liposomal AmB • Consider corticosteroid therapy[g]	
	Trichosporon spp.	Disseminated disease	• Blood culture • Tissue biopsy for culture and histopathology	• Voriconazole +/− liposomal AmB • Removal of central venous catheter should be considered	*T. asahii* *T. mucoides*
	Cryptococcus spp.	Pulmonary disease Bloodstream infection Meningoencephalitis	• Blood culture • Lumbar puncture for CSF analysis and culture • Cryptococcal antigen in serum and CSF • Tissue biopsy for culture and histopathology	• CNS infections: liposomal AmB plus flucytosine used for induction, then maintenance therapy with fluconazole • Extraneural infections: fluconazole	*C. neoformans* *C. gattii*
Molds	*Aspergillus* spp.	Isolated cutaneous nodule	• Serum galactomannan • Serum β-D-glucan • Diagnostic imaging • Tissue biopsy for culture, histopathology, and molecular testing	• Voriconazole • Surgical resection	*A. fumigatus* *A. flavus* *A. terreus* *A. niger*[f] *A. lentulusf*
		Disseminated or organ-invasive disease	• Serum galactomannan • Serum β-D-glucan • Diagnostic imaging • Tissue biopsy for culture, histopathology, and molecular testing • Bronchoalveolar lavage for culture and galactomannan testing	• Voriconazole • Surgical resection, if localized disease • Consider G-CSF and/or granulocyte transfusions[h]	
	• *Fusarium spp.*	• Cutaneous disease • Pulmonary disease • Diseminated disease	• Tissue biopsy for culture, histopathology, and molecular testing • Diagnostic imaging	Voriconazole • Surgical resection, if localized disease	*F. solani* species complex

Organism	Invasive fungal disease	Diagnostic testing	Treatment[a,b]	Common species
Mucorales order	Disseminated or organ-invasive disease	• Similar to diagnostic workup for invasive aspergillosis[i]	• Liposomal AmB • Surgical resection, if localized disease • Consider G-CSF and/or granulocyte transfusions[h]	*Rhizopus* spp. *Mucor* spp. *Lichthiemia* spp. *Cunninghamella* spp.

[a] Definitive therapy should be tailored based upon final organism identification and susceptibility testing

[b] In addition to antifungal therapy, every attempt at immune reconstitution should be made

[c] For neutropenic patients, eye examination should be done after recovery from neutropenia

[d] Step-down therapy using a triazole antifungal can be performed for clinically stable patients with susceptible isolates and clearance of candidemia

[e] For ocular candidiasis, intravitreal injection of AmB deoxycholate or voriconazole is recommended

[f] Possess intrinsic resistance to triazole antifungals

[g] Short-term treatment with corticosteroids can be considered for patients with persistent high fevers

[h] For patients with potential for neutrophil recovery

[i] Galactomannan and 1,3-β-D-glucan assays are not useful for detecting *Mucorales* molds

Table 2.

Criteria for proven and probable invasive fungal disease, excluding endemic mycoses[a]

Proven IFD	Mold • Histopathological, cytopathological or microscopic examination of a sterile specimen in which hyphae are seen with associated tissue damage • Recovery of a mold or "black yeast" by culture of a sterile specimen • Blood culture that yields a mold (e.g., *Fusarium* spp.)[c] Yeast • Histopathological, cytopathological or microscopic examination of a sterile specimen showing yeast cells • Recovery of a yeast by culture of a sterile specimen obtained from a site with clinical or radiographic findings consistent with an infectious disease • Blood culture that yields yeast or a yeast-like fungi (e.g. *Candida* spp., *Cryptococcus* spp., or *Trichosporon* spp.) • Presence of cryptococcal antigen in the CSF

Probable or Possible IFD[b]	• Presence of host factors[d]
	  • Prolonged, profound neutropenia
	  • Receipt of an allogeneic HSCT
	  • Prolonged use of corticosteroids
	  • Treatment with T-cell immunosuppressants
	  • Presence of a severe inherited immunodeficiency
	• Presence of clinical criteria consistent with IFD
	  • Radiographic findings of lower respiratory tract fungal disease
	  • Evidence of tracheobronchitis on bronchoscopy
	  • Radiographic evidence of sinonasal disease
	  • Signs of CNS infection on imaging
	  • Evidence of disseminated candidiasis on imaging or examination
	• Mycological evidence of infection
	  • Presence of mold in sputum, bronchoalveolar lavage fluid, or sinus aspirate sample, either through histopathological analysis or culture
	  • Positive indirect testing for IFD, including positive galactomannan antigen testing for aspergillosis or beta-D-glucan detected in the serum for other IFD

[a] Adapted from De Pauw, et al 2008

[b] Probable IFD requires the presence of a host factor, a clinical criterion, and a mycological criterion. Cases that meet the criteria for a host factor and a clinical criterion but for which mycological criteria are absent are considered possible IFD.

[c] Blood cultures are rarely positive for molds other than *Fusarium* spp.

[d] Characteristics by which individuals predisposed to invasive fungal diseases can be recognized

Table 3.

Common antifungal agents, their mechanism, spectrum of activity, and toxicities

Class	Drugs	Yeast Activity	Mold Activity	Formulations	Toxicity
Triazoles[a]	Fluconazole	+++	None	IV/PO	Voriconazole and Posaconazole: hepatotoxicity, QT prolongation[d] Voriconazole: photosensitivity, skin cancer, fluorosis, CNS symptoms (delirium, hallucinations)
	Itraconazole	+++	+	PO	
	Voriconazole[b]	+++	+++[c]	IV/PO	
	Posaconazole[b]	+++	+++	IV/PO	
	Isavuconazole	+++	+++	IV/PO	
Echinocandins[e]	Micafungin Caspofungin	+++	++[c]	IV	Hepatotoxicity
Polyenes	Amphotericin B deoxycholate	+++	+++	IV	Nephrotoxicity[f] Infusion reactions
	Liposomal amphotericin B	+++	+++	IV	

[a] Voriconazole is approved for patients aged ≥2 years and posaconazole is approved for patients ≥13 years. Phase 1 trials for isavuconazole are ongoing (ClinicalTrials.gov: NCT 03241550)

[b] Therapeutic drug monitoring is recommended for voriconazole and posaconazole

[c] No activity against *Mucorales*

[d] Isavuconazole is associated with shortening of the QT interval

[e] For children, there are no relevant pharmacological differences between the echinocandins

[f] Lessened with liposomal formulation