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Use of Fungal Diagnostics and Therapy in Pediatric Cancer Patients in Resource-Limited Settings

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Abstract

Fungal diseases are an important cause of mortality in immunocompromised hosts, and their incidence in pediatric cancer patients in low- to middle-income countries is underestimated. In this review, we present relevant, up-to-date information about the most common opportunistic and endemic fungal diseases among children with cancer, their geographic distribution, and recommended diagnostics and treatment. Efforts to improve the care of children with cancer and fungal disease must address the urgent need for sustainable and cost-effective solutions that improve training, fungal disease testing capability, and the use of available resources. We hope that the collective information presented here will be used to advise healthcare providers, regional and country health leaders, and policymakers of the current challenges in diagnosing and treating fungal infections in children with cancer in low- to middle-income countries.

Keywords

fungus; low- to middle-income countries; pediatric; antifungals; fungal biomarkers; resource-limited settings.

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Compliance with Ethics Guidelines

Conflict of Interest

Sheena Mukkada, Jeannette Kirby, Randall Hayden, and Miguela Caniza declare that they have no conflict of interest. Nopporn Apiwattanakul reports personal fees from Astellas Pharma Co. Ltd. outside the submitted work.

Human and Animal Rights and Informed Consent

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Introduction

Opportunistic and endemic mycoses infect both normal and immunocompromised hosts. The fungal pathogens most frequently affecting immunocompromised hosts include the ubiquitous *Candida*, *Aspergillus, Cryptococcus,* and the Zygomycetes classes, and cause the death of over 1.5 million people every year [1]. Endemic mycoses are constrained by geographic location; these include histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, penicilliosis, and sporotrichosis [2–7]. Although most fungal infections in children are primary, during immunosuppression, dormant infections may be reactivated [8].

Most children with cancer live in low- to middle-income countries (LMICs) [9]. In this population, infectious complications are the most frequent cause of treatment-related morbidity and mortality [10, 11]. Higher-intensity cancer treatments and the use of hematopoietic stem cell transplantation improve cancer survival rates, but place children at risk of infection, including those of fungal etiology, because of longer and more severe periods of immunosuppression [12]. Although fungal disease is frequently reported among children with oncologic disease in high-income countries (HICs) [13, 14], there is limited information on fungal diseases complicating cancer treatment in LMICs. In many resource-limited settings, as access to cancer care, including hematopoietic stem cell transplantation, is improved, more children with cancer will be at risk for fungal infection [15–19]. The capacity to diagnose and treat invasive fungal infection in LMICs is essential for the safety and success of cancer treatments. The purpose of this review is to provide an update on the status of diagnosis and treatment options for fungal infections in LMICs, with particular emphasis on pediatric oncology patients.

FUNGAL DISEASES IN IMMUNOCOMPROMISED HOSTS

Overview

Host susceptibility and fungal pathogen virulence are key determining factors in the incidence of fungal infections [20]. Although the distribution of species varies by location, the risk of exposure to these pathogens is global [1]. Clinical presentations depend on the host immune response, the amount of fungal inoculum, the route of exposure, and properties of the pathogen. Identical fungi can cause a wide range of disease severity in immunocompetent patients [21–23], and fungi with low inherent pathogenicity can cause severe and disseminated disease in patients with deficient immune function [24, 25]. For reference purposes, a breakdown of common fungi and basic morphologic characteristics is provided in Table 1 [26]. Comprehensive reviews of individual fungi can be found in other sources [27], but points relevant to pediatric cancer patients in LMICs are noted here.

Candida

Candida species inhabit the gastrointestinal tract and are part of the resident flora. They can cause localized disease of mucous membranes in immunocompetent hosts and disseminated disease in patients with innate or acquired immunodeficiency [28]. Risk factors for invasive disease include central venous catheter use, total parenteral nutrition, surgery, broad-

spectrum antibiotic exposure, and severe illness [29], all situations occurring more frequently in cancer patients. In addition, chemotherapeutic agents disrupt mucosal and epithelial barriers in the alimentary tract, increasing the risk of translocation of gastrointestinal flora, including *Candida*, to the blood circulation. Although *Candida albicans* is the single most frequently isolated species, a large multicenter study found that non-*albicans* species occurred more frequently than *C. albicans* in pediatric patients [30, 31]. *Candida parapsilosis* was the second most common isolate in that study and in a study of neonatal intensive care units in the United States [32, 33]. A separate Latin American multinational prospective surveillance study found that malignancy, neutropenia, and previous use of corticosteroids were prominent risk factors for candidemia in patients younger than 18 years [33]. The most frequent species isolated were *C. albicans*, *C. parapsilosis*, and *C. tropicalis* [33], mirroring data collected across all ages in Latin America through the ARTEMIS DISK global surveillance project [34]. Species distribution of *Candida* has implications for treatment, as *C. glabrata*, the second most frequent isolate in this study [34], is often resistant to fluconazole, a frontline therapy for *Candida* [35]. The ARTEMIS project demonstrated a higher incidence of *C. glabrata* in the Asia/Pacific region than in Latin America, and a single prospective study in Indian pediatric cancer patients showed *C. glabrata* isolation in 5% of febrile neutropenic episodes [36]. Nevertheless, other case series in Asia and the Middle East have reported similar findings of *C. tropicalis* and *C. parapsilosis* as primary non-*albicans* pathogens in pediatric cancer patients [37–39].

Molds

Aspergillus and other mold infections such as zygomycosis and fusariosis occur predominantly in patients with deficiencies in innate and adaptive immunity that place them at risk for infection [40]. Patients with prolonged (>10 days) neutropenia (<500 cells/μL) are commonly at the highest risk of mold infections [41], which may affect the lungs, sinuses, and soft tissues [41, 42]. In immunocompetent hosts, *Aspergillus* can cause clinical diseases of chronic aspergillosis and allergic bronchopulmonary aspergillosis, but invasive disease is uncommon [43].

Although *Aspergillus* is a leading cause of invasive mold infection in HICs, patients in LMIC settings may have increased exposure risks not only because of poor environmental control of fungal exposure, including in inpatient units, but also because of the low quality of healthcare delivery, exacerbated by poorly regulated use of steroids and antibacterials. Nevertheless, the reported incidence of invasive aspergillosis in these settings is still low [44]. This may be due to the inherent difficulty of fungal diagnosis in immunocompromised hosts—who are often too sick to undergo procedures to obtain clinical samples to confirm the diagnosis of fungal disease—and to the lack of diagnostic resources (authors' experience). In a retrospective review of 356 Indian children with acute leukemia, 34 patients with diagnosed invasive aspergillosis had pulmonary symptoms and radiologic signs, but only four had disease proven on tissue biopsy [45].

Breakthrough fungal infection occurs when signs and symptoms of invasive fungal infection manifest while the patient is on antifungal therapy [46, 47]. *Candida* spp. infection during antifungal treatment has been reported to occur more frequently with *Candida* non-*albicans*

species, and these are often resistant to fluconazole [48–50]. Mold infection breakthrough has been reported in patients receiving echinocandins [51], voriconazole [52], and posaconazole [53]. Reports of breakthrough fungal infections in LMICs are rare, possibly because at-risk patients receive broad-spectrum antifungal prophylaxis less frequently, and profoundly immunocompromised patients do not live long enough to develop a fungal disease.

Although *Cryptococcus*, particularly *Cryptococcus gattii*, may occur in immunocompetent patients [54], *C. neoformans* var. *neoformans* causes invasive disease almost exclusively in immunocompromised patients. While the bulk of the literature pertaining to *Cryptococcus* in resource-limited countries is about its heavy toll on HIV/AIDS patients, other immunocompromised patients are at risk for this global fungus [55]. This infection is acquired primarily through the pulmonary route, producing pulmonary infection that is often asymptomatic, with reactivation upon suppression of immunity [55]. The most serious manifestation is cryptococcal meningoencephalitis, characterized by prominent neurologic symptoms and increased intracranial pressure [56]. Demonstration of the organism by India ink staining, latex antigen, or lateral flow immunoassay are diagnostic [58].

Endemic mycoses, which occur in both immunocompetent and immunocompromised hosts, are distributed based on their environmental origin [21]. Histoplasmosis, caused by *Histoplasma capsulatum*, is distributed through the Americas, Europe, Asia, and Africa, and has a variety of manifestations, depending on the host's immune status and route of inoculation [8]. Inhalation of heavy fungal inoculum may produce acute pulmonary disease, but primary infection is often asymptomatic in immunocompetent individuals.

The picture is similar for coccidioidomycosis, which is caused by the soil-resident dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*, but the geographic range of the fungi is limited to dry areas of the southwestern United States and limited areas of Mexico and Central and South America [58]. As with histoplasmosis, antifungal therapy is reserved for patients at high risk of progression, including immunocompromised patients and those with extrapulmonary or severe and prolonged (>6 weeks) infection.

The geographic range of *Paracoccidioides brasiliensis*, the causative agent of paracoccidioidomycosis, is extensive in Latin America's tropical and subtropical areas with acidic soils and high humidity [59, 60]. The typical mechanisms initiating the infection are the inhalation of the fungal spore or direct inoculation into the skin or mucous membranes; the manifestations of the primary infection are dependent on the immune response of the host, and reactivation of latent infection can occur during immune suppression [61]. If symptomatic, children are more likely to present with lymphadenopathy or signs of reticuloendothelial system involvement [61].

Blastomyces dermatitidis, another endemic mycosis, is a thermal dimorphic fungus inhabitant of areas with wet soil and decayed matter, with distribution overlapping and extending beyond the northern range of histoplasmosis in North America up to Canada, although it has also been reported in India and Africa [62, 63]. When symptomatic, blastomycosis is usually a pulmonary infection, but its cutaneous manifestations may draw

comparisons to paracoccidioidomycosis [62]. Like the other mycoses, its clinical manifestations may be more severe in immunocompromised patients, so immunocompromised status is an indication for antifungal treatment [64].

In summary, certain endemic mycoses may occur with greater frequency in immunocompromised hosts, whereas others cause more severe disease in these patients.

FUNGAL DIAGNOSTICS

Overview

Expedited diagnosis and treatment of fungal infections can improve outcomes in children with cancer [65]. Definitive diagnosis of mold infections is difficult, because signs and symptoms are nonspecific; in the early stages, persistent or recurrent fever may be the only sign of infection. In advanced infection, organ system involvement may occur. The results of imaging studies may reveal suggestive abnormalities in lungs or sinuses and liver or spleen, but reimaging is often necessary after neutrophil recovery because radiologic abnormalities may not be obvious in neutropenic patients [43]. Except for *Fusarium*, [66] blood culture results are rarely used to diagnose molds. Mold infections are usually confirmed by the study of infected tissue [65]. In LMICs, collecting surgical specimens and radiographs is often too expensive or inaccessible.

In light of the limitations in current methods of fungal detection and the frequent complexity of underlying diseases in the infected patient—especially the immunocompromised host—clinicians may choose to approach the diagnosis and management of potential fungal pathogens from the perspective of a clinical syndrome rather than a definitive diagnosis of a specific pathogen. In fact, empiric rather than diagnosis-directed treatment is frequently used to manage fungal infections in immunocompromised patients. Recognizing this, in 2002, the European Organization for the Research and Treatment of Cancer (EORTC) Cooperative Group and the National Institute for Allergy and Infectious Diseases Mycoses Study Group (MSG) established definitions to facilitate epidemiologic surveillance and clinical research [67]. Probable, possible, and proven fungal disease diagnoses incorporate host-, clinic-, and pathogen-specific laboratory criteria and are intended for use in immunocompromised adult patients. The 2008 revision to the definition adopted the use of fungal antigens, or cell wall biomarkers, as criteria for probable fungal infection [68]. Molecular fungal diagnostics do not appear in the revised version because most of the tests were not validated and standardized at the time [68].

Most of the fungal biomarkers have produced conflicting results or have not yet been fully evaluated within the immunocompromised pediatric population [68]. However, deficiencies in access to and quality of these diagnostics complicate efforts to obtain reliable information about fungal diseases in LMICs [26]. In these settings, although expertise and resources for fungal testing may be available at tertiary referral centers, where most pediatric cancer centers are housed, obtaining diagnostic samples from cancer patients is more challenging, because neutropenia and thrombocytopenia that are commonly seen in pediatric cancer populations may be contraindications to invasive procedures. The ability to perform surgical biopsy and bronchoscopy for tissue diagnosis is further limited by the low availability of

surgeons and equipment. Once a sample is obtained, the appearance of fungal elements may dictate initial treatment; however, definitive diagnosis traditionally requires morphologic and biochemical identification procedures. Furthermore, culture-based methods, while specific, vary in sensitivity depending on the causative organism, the quality of the sample, and the organ system involved.

Fungemia has been estimated to occur in one-third of patients with invasive candidiasis [69] and most of those with disseminated *Fusarium* [66], but occurs more rarely with molds, such as *Aspergillus* [70], which may require tissue specimens. The use of automated systems and even rapid identification systems (e.g., peptide nucleic acid fluorescence in situ hybridization/matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [PNA-FISH/MALDI-TOF]) to identify bloodstream yeasts is becoming more widespread [71]; however, traditional characterization by morphologic and biochemical characteristics is still commonly used in LMICs [65, 72–74]. The clinical validity of susceptibility testing is better established for yeast than for mold; accordingly, the literature from resource-limited countries reflects greater use of such testing for yeast [33].

Fungal antibody testing can be used to determine prior or current infection in immunocompetent hosts, but its use is limited in immunocompromised patients because of their impaired capacity to produce antibodies. Serologic detection of histoplasmosis, blastomycosis, coccidioidomycosis, and chronic or allergic aspergillosis can indicate exposure to the fungal disease, but interpretation of the acuity or activity of infection requires clinical assessment of the host [75]. The presence of fungal-specific antibodies may help in identifying patients at risk for reactivation of the disease during immunosuppression [26, 76].

Antigenic testing for fungal cell wall components can be used in combination with other testing modalities and clinical manifestations to manage fungal disease. Antigen detection alerts clinicians to the presence of invasive infection and can be used to determine the need for preemptive therapy in at-risk patients and the response to antifungal treatment [77–80]. Fungal antigens such as (1,3)-beta-D-glucan and *Aspergillus* galactomannan can detect multiple types of fungi. The presence of (1,3)-beta-D-glucan can be detected in *Candida*, *Pneumocystis jirovecii*, and certain molds, such as *Aspergillus*, *Fusarium*, and *Acremonium* [81–83]. False-positive results have occurred in the setting of gram-positive bacteremia, hemodialysis, and products containing glucans, which are common events in oncologic patients [84]. Additionally, sample collection, handling, and testing methodology are all critical components, and opportunities for specimen contamination exist during each step of the process. The assay is not useful for detection of Mucorales species or *Cryptococcus* spp., which produce little or no beta-D-glucan [57]. Very limited data are available on the performance characteristics of this marker in special populations, such as in pediatric patients, and results must therefore be interpreted with additional caution.

Galactomannan is produced by *Aspergillus*, and has been reported to cross react with *Penicillium*, *Paecilomyces*, and *Histoplasma* [86]. The galactomannan assay can be used to supplement clinical and host criteria for delineating probable or possible aspergillosis, and can be performed in blood and bronchoalveolar lavage fluid. Cutoff levels and utility in

pediatric oncology patients have been disputed; however, detection in bronchoalveolar lavage fluid has been shown to predict pulmonary aspergillosis [86]. Its positive predictive value has been challenged by reports of false-positive results in patients receiving certain beta-lactam antibiotics, depending on the cutoffs used [57], and sensitivity is markedly reduced in settings where mold-active antifungal agents are used prophylactically [78, 87]. A retrospective study in pediatric patients at three hospitals in Brazil also found that serum galactomannan was positive in 15 of 18 patients with invasive *Fusarium* infection [88].

Other fungal antigens are specific to certain fungi, such as dimorphic fungi (*Histoplasma*, *Blastomyces*, and *Coccidioides*) [89–91] and *Cryptococcus* [92]. The detection of these antigens in blood, cerebrospinal fluid, urine, and respiratory secretions is clinically useful for diagnosis and for monitoring response to treatment. The detection of cryptococcal antigen in CSF confirms infection by EORTC/MSG criteria [68]. *Histoplasma* antigenic testing is normally performed using urine, but the antigen can be found in the blood in disseminated infection in immunocompromised patients. Cross-reactivity of the *Histoplasma* antigen with *Coccidioides* spp. and in cases of blastomycosis has been cited as a limitation to its use [89]. *Candida*/mannan antigens have been explored as a proxy marker of *Candida* infection that could be useful in the immunocompromised host, but there is limited evidence for use in pediatric populations [14, 93]. In adult populations, most studies found that sensitivity and specificity were improved by performing anti-mannan antibody and mannan antigen tests in combination [94].

Lateral flow assay (LFA) is an attractive diagnostic technology that uses a format similar to that of home pregnancy tests, requiring minimal infrastructure and useful for testing at the point of care. In a recent meta-analysis and systematic review [95], a new cryptococcal antigen LFA demonstrated high accuracy in serum and CSF for the diagnosis of cryptococcosis. LFA may eventually be extended to other fungal antigens, since the technology is inexpensive and requires little expertise, but produces accurate results.

Molecular diagnostics

Although recent studies have evaluated the use of molecular diagnostics, these tests are currently used more in the research domain than for clinical care, particularly in LMICs. Rapid diagnostic tests for *Candida* based on both nucleic acid probe and hybridization technology have been approved for clinical use in both the United States and Europe [96]. There are no validated in vitro diagnostic tests for molds in the United States, and the limited options approved in Europe primarily target *Aspergillus* [97].The performance of in-house PCR assays of both blood and bronchoalveolar lavage fluid has been promising; however, the lack of standardized targets, primers, and methods means that further validation is required prior to introducing these tests into routine practice [31, 77, 98, 99]. Moreover, the laboratory infrastructure in many LMICs would require substantial modification to enable molecular testing capability.

ANTIFUNGALS

Access to effective antifungals is essential for supportive care during intensive chemotherapy. A full review of the spectrum of activity, pharmacology, and clinical

indications is described in a recent publication [100]. Three major categories of antifungals are regularly used in children with cancer and fungal complications: polyenes, triazoles, and echinocandins. Amphotericin B (AmB) and fluconazole are the two antifungals listed by the Working Group on Essential Medicines of the Pediatric Oncology in Developing Countries committee of the International Society of Paediatric Oncology (SIOP) [101]. However, in up to one-third of countries in low-resource areas, these medications are not included in the national essential medicines list [102].

Polyene group

AmB deoxycholate, liposomal AmB, and AmB lipid complex belong to this group. They exhibit broad antifungal activity, including activity against most *Candida*, endemic fungi, most *Aspergillus* species, most dematiaceous fungi, and Zygomycetes [100]), but they are not effective against *Candida lusitaniae* [100], *Trichosporon* spp. [103], *Aspergillus terreus* [104], *Scedosporium* spp. [100], or *Fusarium* spp. [100]. They have good tissue penetration in the kidney, liver, and bone, and acceptable lung penetration [105]. Though their penetration into cerebrospinal fluid is mediocre, they are the frontline drugs for the induction treatment of cryptococcal meningitis [92]. AmBs are used for severe or disseminated histoplasmosis [89]; severe, pulmonary or disseminated coccidioidomycosis [106]; mucormycosis [107]; and most situations of candidiasis, including *Candida* endocarditis and neonatal infection, central nervous system (CNS) infection, and hepatosplenic candidiasis, and candidemia in neutropenic and non-neutropenic hosts [69]. They are alternative drugs for aspergillosis [43].

AmB deoxycholate is the standard antifungal agent for the treatment of most fungal diseases in LMICs because of its affordability and availability through hospital formularies; however, the low cost of the drug is offset by negative effects, including acute reactions, renal toxicity, and electrolyte imbalance (especially hypokalemia). Acute reactions to AmB infusion (fever, shaking chills, hypotension, nausea, vomiting, headache, and tachypnea) are more severe with the initial infusions. These can be minimized with antipyretics (e.g., acetaminophen), antihistamines, or antiemetics, and the administration of meperidine, a narcotic and analgesic, can reduce the duration of shaking chills. Premedication before AmB infusion is a common practice in pediatric cancer patients. Hydration prior to administration of AmB reduces its renal toxicity [108]. Electrolyte levels should be closely monitored [109], and prompt replacement of dangerously low electrolytes (e.g., potassium) is lifesaving. Also, because patients with fungal infection might receive other antimicrobials, the use of other nephrotoxic medications (e.g., aminoglycosides, vancomycin) should be minimized. AmB is available only in its parenteral formulation, and administration requires vascular access and the use of hospital resources. Lipidic formulations are less nephrotoxic, and their dose can be escalated to overcome borderline high minimum inhibitory concentration (MIC) of some molds [100]; but these formulations are prohibitively expensive for use in LMICs.

Triazole group

Triazoles are frequently used as prophylaxis and treatment in immunocompromised patients. Members of the triazole group include fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole [100]. Fluconazole is widely used to treat mucosa

candidiasis, although *C. glabrata* and *C. krusei* [69] have become somewhat resistant to it. Fluconazole is still frequently used for prophylaxis during malignancy. Other clinical indications for the use of fluconazole are treatment of cryptococcosis during the maintenance phase [92], step-down therapy for invasive candidiasis after initial therapy with echinocandins [69], and *Candida* prophylaxis in low-risk oncologic or hematologic stem cell transplant patients [110]. Fluconazole lacks activity against molds, including *Aspergillus* spp. It is widely available in LMICs, is inexpensive, and has few side effects. Important considerations with the use of fluconazole include providing the appropriate dosage, being cognizant of fungi with higher MIC, being aware of drug interactions, and avoiding medications that might reduce fluconazole concentrations (e.g., rifampin) and induce liver toxicity.

Itraconazole has nearly the same antifungal spectrum as fluconazole, and it is used primarily for the treatment of dimorphic and endemic fungi [100]. It can be used as a second-line agent for aspergillosis [43], and its availability and affordability make it an attractive candidate for treatment of non-severe aspergillosis in LMICs. This antifungal has also been proposed as an alternative agent for fungal prophylaxis in high-risk oncologic or HSCT patients [110]. However, it has major limitations including low CNS penetration [105], adverse effects on liver function and electrolytes, and oral absorption dependent on low gastric pH and dietary lipid levels [43].

Voriconazole has nearly the same antifungal activity as itraconazole but is more potent against *C. glabrata* and *C. krusei.* It is now the recommended drug for treating invasive aspergillosis, including infection of the CNS [43]. It is also a drug of choice for infections caused by *Scedosporium apiospermum* (but not for *S. prolificans*) [111], most dematiaceous molds [112], some *Fusarium* species [66], and *Trichosporon asahii* [113]. Voriconazole is not active against Zygomycetes [52].

Posaconazole has an antifungal spectrum similar to that of voriconazole, but its activity against *Scedosporium apiospermum* may be inferior to that of voriconazole [114]. It is currently recommended for fungal prophylaxis in high-risk oncologic and HSCT settings [110] and is an alternative drug for mucormycosis [107]. Posaconazole's oral suspension formulation should be taken with fatty food, and the drug's level in the blood should be monitored [100]. Isavuconazole, the newest triazole, has antifungal activity similar to that of posaconazole, but the absorption of its oral formulation is not affected by food or gastric acidity [115].

The appropriate use of triazoles, with the exception of fluconazole, requires obtaining therapeutic levels to ensure adequate drug exposure at the site of the infection and to improve efficacy while reducing toxicity [105, 116]. Therapeutic drug monitoring for itraconazole, voriconazole, and posaconazole is expensive, with a lengthy turnaround time [117]. Despite the fact that monitoring of these drugs is strongly recommended [117, 118], it is rarely done in LMICs. Dosages for pediatric use are extrapolated from those of adults; however, the pharmacokinetics of drugs varies with age, and there are few pharmacokinetic data in children with cancer [119]. Drug interactions can increase or decrease the concentration of triazoles. Drugs commonly used that reduce antifungal concentration

include antacids, antibiotics (rifampin, isoniazid), antiepileptics, selected antiretrovirals, H2 blockers, and proton pump inhibitors. Conversely, macrolides, selected antiretrovirals, antiarrhythmics, antiepileptics, calcium channel blockers, and vinca alkaloids increase antifungal concentrations. [100, 120].

Echinocandin group

Like AmB, the echinocandins—anidulafungin, micafungin, and caspofungin—are available only in parenteral form [121]. Echinocandins inhibit the synthesis of (1,3)-beta-D-glucan, disrupting the fungal cell wall. The group is fungicidal for *Candida* spp. and fungistatic for *Aspergillus* spp. [100]. They are recommended for initial treatment of candidemia in neutropenic patients [69] and as the second-line agent or as part of a combination regimen to treat invasive aspergillosis [43]. These drugs are not active against *Cryptococcus, Fusarium, Scedosporium*, other dimorphic fungi, or the Zygomycetes [100].

Echinocandins should be avoided if yeasts are unlikely to be *Candida* spp. or if the CNS is involved (poor drug penetration into CSF). It is important to be aware of drug–drug interaction of caspofungin and rifampicin [122] (which might increase clearance of caspofungin), cyclosporine [123] (which inhibits caspofungin uptake by the hepatocytes), and tacrolimus [124] (caspofungin reduces tacrolimus concentrations) [125]. The expense of echinocandins prohibits their use in resource-limited settings.

USE OF DIAGNOSTICS AND ANTIFUNGALS IN LOW-RESOURCE SETTINGS

We recently conducted a survey of perceptions regarding access and availability to diagnostics and antifungals for pediatric cancer services in multiple St. Jude partner sites (www.stjude.org), mainly in LMICs. The participants acknowledged the existence of gaps in the availability of diagnostics and confirmed published information [102, 126] regarding access to few antifungals, mainly AmB and fluconazole and, inconsistently, voriconazole and caspofungin (unpublished results). Until access to therapeutics can be improved, use of current resources must be optimized with appropriate and early identification of patients requiring antifungal therapy. Potential solutions include maximizing the use of samples obtained and using low-cost microscopy studies, cultures, and histopathology staining. Training existing key personnel in performing these laboratory studies and expeditiously communicating the results to care providers could also help improve fungal diagnostic capabilities in these settings.

The training of care providers in LMICs, especially pediatric residents, is essential to providing good care to pediatric oncology patients with suspected fungal disease. This training must address when to suspect fungal disease, risk factors among children with cancer, basic knowledge of endemic mycosis, and the main opportunistic fungal diseases. Subspecialty providers should be trained in obtaining quality clinical samples for fungal diagnosis and should be acquainted with the availability of resources for ancillary microbiology and histopathology testing for their patients. Care providers must also be aware of drug–drug interactions—not only those between antifungals, but those between antifungals and anticancer medications and other support medications as well [127]. Basic training in the pharmacology of available antifungals, especially the use of AmB,

fluconazole, voriconazole, and caspofungin, will also enable optimal use of these life-saving medications.

CONCLUSIONS

Literature regarding the diagnosis and management of fungal infections in pediatric cancer patients in resource-constrained settings is limited. This is the product of limited knowledge about the burden of both pediatric cancer and fungal infections in LMICs. Pediatric cancer registries in these settings are incomplete to nonexistent. In the context of inadequate financial resources and competing disease priorities, pediatric cancer treatment and auxiliary care, including that for fungal disease, remains suboptimal in many settings. However, fungal disease is frequently treated without a proven diagnosis even in HICs. Although biomarkers can guide clinical decision-making to start or stop an antifungal, empirical treatment paradigms persist. Until rapid and reliable diagnostics are validated for care in pediatric immunocompromised patients, the emphasis in resource-limited countries should remain on ensuring the availability of basic antifungal medications—at a minimum, a derivative of amphotericin B and fluconazole [101]. We hope that healthcare providers, regional and national health leaders, and policymakers will use the collective information presented here to address current challenges in diagnosing and treating fungal infections in children with cancer in LMICs.

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Table 1

Frequent fungal pathogens in pediatric cancer (adapted from Ref. [128])

Identifier Structure				Fungus
Yeast	Pseudohyphae			*Candida albicans*
				Candida tropicalis
				Candida parapsilosis
				Candida krusei
				Candida lusitaniae
				Candida guilliermondii
	No pseudohyphae			*Candida glabrata*
	Usually no hyphae, or pseudohyphae, yeast with thick capsule			*Cryptococcus neoformans* *Cryptococcus gattii*
	Arthroconidia			*Trichosporon* spp.
Mold	Septate	Hyaline	Banana-shaped, multicellular macroconidia	*Fusarium* spp.
			Conidiophores with terminal vesicles and chains of conidia	*Aspergillus flavus*
				Aspergillus fumigatus
				Aspergillus niger
				Aspergillus terreus
			Single conidia	*Scedosporium apiospermum*
			Branching conidiophores	*Paecilomyces* spp.
			Conidia aggregated at the apex of phialides	*Acremonium* spp.
			Dermatophytes	*Microsporum* spp.
				Trichophyton spp.
				Epidermophyton spp.
			Thermally dimorphic	*Blastomyces dermatitidis*
				Histoplasma capsulatum
				Coccidioides spp.
				Paracoccidioides spp.
				Sporothrix schenckii
				Penicillium marneffei
		Dematiaceous	Acropetal, multi-celled conidia in chains	*Alternaria* spp.
			Fusiform pseudoseptate conidia, bipolar germination	*Bipolaris* spp.
			Septate conidia with 4 cells the central being larger	*Curvularia* spp.
			Conidia cylindrical, septate, smooth wall	*Drechslera* sp.
	Aseptate	Zygomycetes	Big, terminal, globose multispored sporangia; no rhizoid	*Mucor* sp.
			Stolons and pigmented rhizoids	*Rhizopus* spp.
			Swollen terminal vesicle and emerging single cell spores	*Cunninghamella* sp.

* ***Pseudallescheria boydii* is the sexual state of *Scedosporium***