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Review Article

TREATMENT APPROACHES FOR MANAGEMENT OF INVASIVE FUNGAL INFECTION: A REVIEW

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Abstract

Over the past few years the invasive fungal infections (IFIs) incidences has increased as the populations of patients at risk have continued to rise due to current situation in covid. Earlier diagnosis and the subsequent usage of appropriate antifungal therapy become difficult, these leads to a high mortality rate in patients with IFI management. Along with the widespread use of antifungal prophylaxis, the epidemiology of invasive fungal pathogens has also changed. Non-albicans fungus, Non-fumigatus fungus genus, and molds aside from fungus genus became additional common pathogens inflicting invasive diseases, and most of those rising fungi are proof against or less inclined than others to plain antifungal agents. Therefore, invasive infections to these previously rare fungi are tougher to treat. Advances in more potent and less toxic antifungal agents, such as second-generation triazoles and echinocandins, may potentially improve the outcomes of these infections. This reviews shows the different spectrum of invasive fungal infections and the introduction of recent available antifungal agents.

Keywords: invasive fungal infection, amphotericin B, antifungal agents, fungus

INTRODUCTION

Invasive fungal infection (IFIs) poses a significant threat to human health, particularly in the immunocompromised, with an increasing global burden in solid organ and bone marrow transplant recipients, cancer patients, those with HIV, and those being treated with immunomodulators. The most common causes of IFI are Candida spp., followed by Aspergillus spp.; other pathogens such as Cryptococcus spp., the Mucorales, and Pneumocystis accounting for varying frequency of IFDs depending on geographic region and patient population. [1] Despite advances in antifungal therapy, mortality rates from IFI are substantial but vary with infection.

Now we are facing another devastating worldwide pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with to date >24 million individuals infected and a mortality rate >3%. Although superinfections were rarely reported in the beginning of the current pandemic, they are now on the rise, particularly reports about secondary fungal disease. SARS-CoV-2–associated pulmonary aspergillosis (CAPA) has been the predominant fungal disease, adding

insult to injury in coronavirus disease 2019 (COVID-19) patients with acute respiratory distress syndrome (ARDS), and although the pathogenesis is incompletely understood, there are several immunological mechanisms that may contribute to the development of CAPA and other fungal diseases. SARS-CoV-2 invasion results in the release of danger-associated molecular patterns (DAMPs) that act as endogenous signals that exacerbate the immune and inflammatory response leading to lung injury [2, 3]. Importantly, DAMPs are known to play a central role in the pathogenesis offungal diseases [4]. Moreover, collateral effects of host recognition pathways required for the activation of antiviral immunity may, paradoxically, contribute to a highly permissive inflammatory environment that favors fungal pathogenesis [2].

In this article, focus will be on invasive mold infections, (particularly invasive aspergillosis) and invasive candidiasis. Specifically, the following topics will be reviewed: epidemiology, including incidence and mortality rates for invasive fungal infections; emerging resistance patterns; high-risk groups and risk factors; clinical presentation of each type of invasive fungal infection; diagnosis; antifungal treatment options; management; and future developments in the treatment and prevention of invasive fungal infections.

EPIDEMIOLOGY

Candida spp. have become important causes of sepsis in hospitals with incidence constantly growing over the last 20 years. Candida spp. is now the 4th most common isolate of bloodstream infections in many countries (and the most common IFI), mainly due to the increasing complexity of medical care [5]. Candida albicans is still the main cause of candidemia in population-based studies worldwide, but its relative frequency is decreasing, while the frequency of the other species is increasing. Patients' characteristics influence Candida species distribution; C. glabrata infections are more common in the elderly, C. krusei in immunocompromised patients, while C. parapsilosis is most common in children and neonates. Risk factors for candidemia include neutropenia, especially during periods of mucositis, broad spectrum antibiotic therapy, abdominal surgery mainly involving the colon, total parenteral nutrition and combination of such risk factors. Invasive aspergillosis is the second most common IFI, with increasing incidence over the last 20 years along with the advances in the treatment of hematological malignancies.

Prolonged neutropenia is the main risk factor. Patients with acute myeloid leukaemia (AML) and those who undergo allogeneic hematopoietic stem cell transplantation (HSCT) have prolonged durations (more than 10 days) of neutropenia and are at highest risk. In the highest risk group, invasive aspergillosis rates can reach 25% [6]. An optimal risk score for invasive aspergillosis would have to include fine details on the underlying malignancy and its predicted response to chemotherapy, chemotherapy regimens, allogeneic transplantation and the presence of GVHD. However, the incidence of invasive aspergillosis is very much dependent on local epidemiology and the quality of air control in hemato-oncological units. Thus, in some settings, invasive aspergillosis is more frequent than invasive candidiasis [6].

Mucormycosis is the second most common invasive mould infection and its incidence increased from 0.7 per million in 1997 to 1.2 per million in 2006 [7]. In addition to immunosuppression, there are some unique host risk factors for mucormycosis such as diabetes keto-acidosis, burns, iron overload and, on the other hand, deferoxamine therapy. The specific clinical syndrome of mucormycosis is associated with host risk factors; thus, pulmonary mucormycosis is more common in patients with hematological malignancies, while rhino-cerebral mucormycosis is more common in

diabetic patients [8]. The aetiologic agents involved in the disease have been reclassified in recent years, based on molecular methods establishing taxonomy [8]. Thus, “zygomycosis” was reclassified to either “mucormycosis” or “entomophthoromycosis”. It appears that genera that belong to the subphylum mucormycotina are ubiquitous worldwide and cause severe life-threatening infections in immunocompromised patients, while entomophthoromycotina are found in tropical regions and cause chronic subcutaneous infections in otherwise healthy patients. Early identification of mucor spp. to the species level and advances in epidemiological data will perhaps allow in the future better prediction of patients’ prognosis and tailoring of treatment.

OTHER INVASIVE FUNGAL INFECTIONS

Other invasive fungal infections in the transplant population occur less frequently than invasive aspergillosis, invasive candidiasis, and zygomycosis. In the hematopoietic cell transplantation population, the incidences for non-*Aspergillus* and unspecified mold were approximately 0.3% and 0.2%, respectively.The proportion of invasive fungal infections caused by *Fusarium* species was 3%. *Acremonium*, *Alternaria*, and *Scedosporium* species accounted for 7%. Unspecified molds accounted for 6% of invasive fungal infections.

The majority of these infections occurred after day 100 posthematopoietic cell transplantation. In the solid organ transplantation population, the incidences were 0.1%–0.2% for other molds and endemic invasive fungal infections. *Cryptococcus* infections comprised 8% of all invasive fungal infections, and other molds comprised 6.5%. Endemic fungal infections comprised 5.3% of all invasive fungal infections. [9] In intensive care patients, infections caused by other fungi occurred at a rate of 2.2%, representing 10% of all invasive fungal infections. [10]

Mortality rates for molds other than *Aspergillus* species and Zygomycetes vary according to pathogen. The highest mortality rate is seen with fusariosis in hematopoietic cell transplantation (93.7%). The 12-month mortality among solid organ transplant recipients was 39% for other molds, and 27% for Cryptococcus. Other studies have reported3-month mortality rates of 80% in hematopoietic cell transplantation from infections due to *Fusarium* and *Scedosporium* species. [11]

RISK FACTORS

There are risk factors for invasive aspergillosis include graft versus host disease, corticosteroids, neutropenia, cytomegalovirus infection, and prior lung disease. Risk factors for invasive candidiasis include neutropenia, central venous catheter, total parental nutrition, corticosteroids, gastrointestinal surgery, prolonged intensive care stay, and broad spectrum antibiotics. These risk factors relate to impairment of the host immune system, genetic predisposition, and environmental exposure.

Host/immune system

It has long been observed that the longer and more profound the neutropenia, the more at risk the patient will be for invasive fungal infections. Circulating neutrophils have been demonstrated to have an inverse relationship with prevalence of infections. The duration of neutropenia was found to be the most important factor, especially when persisting for 3 weeks or more. In addition to risk for invasive fungal infections, recovery of neutrophil count is important in patient outcomes.

Invasive aspergillosis

One study found that risk factors varied slightly depending on when infection occurred, ie, within 40 days or after 40 days posthematopoietic cell transplantation.46 Risk factors related to the host that were similar for both early and later onset of

infection were underlying disease, donor type (autologous, matched-related , matched-unrelated , mismatch-related), and graft versus host disease. There were additional host immune factors found for infection risk 40 days posttransplant,ie, neutropenia and corticosteroid use. However, it is often difficult to determine if the risk of invasive aspergillosis is due to graft versus host disease itself or due to the corticosteroids used to treat the graft versus host disease. Compared with patients who did not have invasive aspergillosis, patients with hematologic malignancy in “non-first remission” were 8.9 times more at risk for onset of infection within 40 days posthematopoietic cell transplantation, and 3.06 times more at risk 40 days posttransplant. Mismatched-related donor hematopoietic cell transplantation has a significantly higher risk in the early posttransplant period, whereas after 40 days, the risk is higher with unrelated donor transplants. [12]

Other studies have reported similar findings with regard to risk factors for invasive fungal infection. T cell-depleting therapies (antithymocyte globulin or alemtuzumab) delay immune recovery and also increase the risk of invasive aspergillosis. Chronic treatment for graft versus host disease with corticosteroids places hematopoietic cell transplantation recipients at increased risk of infection. Risk was found to be associated with the duration and intensity of the corticosteroid regimen.

Cytomegalovirus infection has been associated with risk for invasive fungal infection. The virus itself is marrow-suppressive, as is the drug therapy commonly used to treat cytomegalovirus, ie, ganciclovir. Cytomegalovirus suppresses cellular and humoral immunity, causes abnormalities in lymphocytes and monocytes, and suppresses antigenspecific cytotoxic T lymphocytes. Ganciclovir (an antiviral agent with marrow-suppressive effects) has been associated with a significant risk for invasive aspergillosis, with a hazard ratio of 13.5, even higher than the use of high-dose corticosteroids, graft versus host disease, or neutropenia.

Genetic predisposition

The study of genetic risk factors as they relate to development of invasive fungal infection is becoming increasingly important to evaluate. This is not only to select those patients who are at high risk for invasive fungal infection for prophylaxis, but to illuminate the immunology and pathophysiology of invasive fungal infections. Invasive aspergillosis has beenstudied the most in this regard. Polymorphisms in toll-like receptors (TLRs) and tumor necrosis factor (TNF)-α are considered to be one of the more significant genetic factors associated with infection.

TLRs are immune cell surface proteins that recognize fungal pathogens. TLR polymorphisms have been associated with different types of infections. [13]

Environmental factors

Environmental factors can play a role in the risk of invasive fungal infection in high-risk patients. In regards to hematopoietic cell transplantation, it was found that transplants that occurred outside laminar air flow rooms had an increased risk of invasive aspergillosis during the early posthematopoietic cell transplantation period, within 40 days after transplant.46 The risk for infection was 5.6 times higher than for transplants occurring within a laminar air flow room.

For infections occurring beyond 40 days post-transplant, environmental factors were also found to be significant.

This is important because most hematopoietic cell transplant recipients are discharged from the hospital (and their HEPA [Health Enhancing Physical Activity]-filtered environment) by day 40 when they are at high risk for invasive mold infection.

Invasive candidiasis

Another high-risk group for fungal infections is critically ill patients. These patients are mainly at increased risk of invasive candidiasis. There are multiple risk factors that have been associated with invasive candidiasis, ie, colonization, presence of a central venous catheter, hemodialysis, and surgery, particularly complicated and repeated abdominal surgery. Patients who are clinically unstable are at increased risk for invasive candidiasis, ie, those with acute renal failure, shock, and disseminated intravascular coagulation. Certain medications have been associated with increased risk for candidemia. These include antianerobic antibiotics (2.2 relative risk) such as carbapenems, metronidazole, clindamycin, and piperacillin/tazobactam. However, there was no increased risk with individual antibiotics, such as aminoglycosides, cephalosporins, and quinolones. Of those patients who did not receive an antibacterial antibiotic, none developed candidemia.

This is likely related to replacement of the normal gastrointestinal flora with *Candida* species. Other agents associated with invasive candidiasis are parenteral nutrition and intralipid agents.

CLINICAL PRESENTATION OF INVASIVE FUNGAL INFECTIONS

Manifestations of invasive fungal infection may range from fever of unknown etiology to symptoms and signs referable to a specific organ system affected by the fungal pathogen. At the other end of the spectrum are patients with no symptoms or signs, primarily due to the underlying immunosuppression, steroid use, andneutropenia. [14]

Candidemia and visceral (chronic disseminated) candidiasis

Fever persisting despite appropriate empiric antibacterial therapy during neutropenia is one of the most common manifestations of candidemia in immunocompromised patients; up to 88% of episodes in one series and 99% in another.

Sepsis syndrome/septic shock can be an initial presentation of candidemia with multiorgan dysfunction. Skin and soft tissue involvement usually manifests as a rash that may have a variable presentation, ranging from maculopapular erythematous to nodular lesions, and may be painful. The lesions may appear similar to ecthyma gangrenosum. Muscle pain/ myositis may be present. Candida endophthalmitis may be asymptomatic (depending on location of lesions), but may manifest with blurred vision, creamy white retinal lesions that may evolve to retinal necrosis evident on funduscopic examination. Vitritis and uveitis can be seen. Cardiac involvement can be in the form of infective endocarditis of a native or prosthetic valve, pericarditis, and septic thrombophlebitis, usually in the setting of indwelling central venous catheters. Candidemia can be associated with dissemination todeep organs causing visceral (chronic disseminated) candidiasis, identified most commonly in the setting of resolving neutropenia after cytotoxic chemotherapy in acute leukemia and hematopoietic cell transplantation. This syndrome is associated with a low yield of fungal isolates on blood culture. With resolution of neutropenia, the patient may present with fever, right upper quadrant pain, palpable tender hepatomegaly, and elevated serum alkaline phosphatase.

Diagnosis is often pursued based on a prior episode of documented candidemia. Other organs that are affected include the spleen and kidneys. In a prospective study, 2019 episodes of candidemia were identified. Distribution of the organs involved in those determined to have disseminated disease were abdomen in (53%), lungs in (9.5%), skin and soft tissue in (7.8%), eyes in nine (5%), heart in seven (3.9%), tracheobronchial tree in seven (3.9%), skeleton in three (1.7%), and central nervous system in two (1.1%). [15] Lung involvement is rare, but is manifested as

innumerable nodules on imaging, usually in conjunction with dissemination to other sites, and is mostly asymptomatic. Skeletal involvement can manifest as vertebral osteomyelitis/ discitis, and commonly manifests with progressive back pain and a relative lack of constitutional symptoms. Central nervous system involvement can be in the form of meningitis or brain abscess.

Invasive mold infections

The most common clinical presentation of invasive mold infection is pneumonia, with *Aspergillus* species being the leading cause in patients with hematologic malignancy, hematopoietic cell transplantation (especially in association with graft versus host disease and corticosteroid therapy), and solid organ transplantation. The classic symptoms include fever, cough, pleuritic chest pain, and, at times, hemoptysis, and on examination there may be a pleural rub. All of these symptoms are rarely present simultaneously. Aspergillus tracheobronchitis is seen more frequently in lung transplant recipients. Non-*Aspergillus* septated mold infections (*Scedosporium*, *Fusarium*, and *Acremonium* species), and Zygomycetes may also present in a similar manner. Invasive sinusitis can manifest as headache/sinus pain, nasal stuffiness with or without discharge, fever, ptosis, proptosis, and cranial nerve deficits. Rapidly progressive disease may be suggestive of zygomycosis. The nasal examination may reveal a grayish discoloration of the mucosa early on, and necrotic turbinates or eschar later on. Intracranial extension of invasive sinusitis can result in central nervous system infection, manifesting as brain abscess, cavernous sinus thrombosis, and meningitis. Central nervous system infection may result from hematogenous dissemination with vascular thrombosis and infarction. The angioinvasive molds have a propensity to cause brain abscesses. The sudden appearance of mental status changes and/or focal neurologic deficits should alert one to central nervous system involvement. Other manifestations include skin lesions in the setting of disseminated infection (such as *Fusarium* species, *Acremonium* species, *Aspergillus* species, and Zygomycetes), ocular involvement (endophthalmitis with blindness), osteoarticular infections, and uncommonly, gastrointestinal involvement. [16]

DIAGNOSTIC EVALUATION

The safe and early diagnosis of invasive fungal infections is the central challenge in routine clinical practice and forms the crucial basis for targeted treatment. The diagnosis of an invasive fungal infection is based on three elements: the clinical examination, imaging, and confirmation/proof of the causative agent. [17]

The clinical diagnostic criteria for invasive fungal infections were defined by an international working group (the (EORTC/MSG Study Group). These criteria selectively apply to immunosuppressed patients and were conceived primarily for clinical studies. In addition to congenital immunodeficiencies, the relevant clinical risk factors include:

- Prolonged (>10 days) deep granulocytopenia ($<0.55 \times 10^9$/L)
- Allogeneic stem cell transplantation
- Medication-induced immunosuppression, or
- Treatment with prednisone (the equivalent of at least 0.3 mg/kg/d for a minimum of 3 weeks).

Tomography imaging yields crucial clues. Infections of the respiratory tract require computed tomography (CT), neurological infections require magnetic resonance imaging (MRI), and abdominal infections require CT or MRI scanning in order to identify abscesses that are characteristic for the special variety of hepatolienal candidiasis. Abdominal infections can also be visualized by using sonography. [18]

Where a diagnosis is suspected, the next step will be confirmation of the pathogen. Bloodstream infections with Candida spp. are almost exclusively confirmed by blood

cultures. The identification of Candida in specimens taken from the respiratory tract does not indicate an invasive infection; for other, non-sterile specimens, a decision always has to be made on the basis of the individual clinical situation as to whether it is a case of colonization or a clinically relevant situation. Because of their wide environmental spread, the confirmation of molds from physiologically non-sterile material should be interpreted with caution; this is also the case for all specimens from the respiratory tract. [19]

For serological diagnostic evaluation, Candida antigen/antibody confirmation is not recommended in current guidelines because of the lack of pertinent studies. Beta D-glucan (BDG) is not specific for Candida, but it does indicate an invasive fungal infection. A patient's risk profile, symptoms, and imaging results will narrow down this differential diagnosis, however. The sensitivity and specificity of this marker vary substantially between different patient populations and depend on the test system used. To confirm A. fumigatus, galactomannan ("aspergillus antigen") is available—in addition to BDG—which can be determined from serum and bronchial secretions (and, if applicable, cerebrospinal fluid). The sensitivity for serum is about 78%, the specificity is 85%, depending on the cut-off value and the patient population. To confirm invasive aspergillosis, furthermore, reference protocols for molecular diagnostics have been developed that function as examples for molecular diagnostic evaluation of infections and, in combination with other methods, contribute to improved diagnostics. [20]

RESISTANCE

Moreover, the problem of antifungal resistance is on the rise: both that which has evolved in formerly sensitive species, as well as the prevalence of intrinsically-resistant species of fungi. To date, resistance exists to all of the currently available classes of antifungal agent. Candida species have a high prevalence of azole resistance, largely attributed to the cytostatic nature of these drugs. Similarly, Aspergillus and Cryptococcus strains have recently also demonstrated azole resistance. Only a few years ago, echinocandins were considered effective therapy for most clinically-relevant Candida isolates. However, with increased use of these antifungal agents, echinocandin resistance in Candida species has also become more prevalent. Additionally, the intrinsically drug-resistant fungi, such as Scedosporium species, continue to cause a background of infections in highly immunosuppressed patients, especially those who are heavily treated with antifungals. These infections are often associated with poor patient outcomes. Due to these limitations, there is an urgent need for new antifungal agents. Research goals for novel antifungal agents have emphasized a few major points. First, potency is a key characteristic of a novel drug. New drugs must be able to effectively control fungal growth in the context of the patient, at compound levels that are readily achievable at infection sites. Additionally, ideal novel antifungal agents should possess little to no host toxicity. Selectivity is also crucial, as the differences between the fungal pathogen and the human host are evolutionarily much smaller than those between bacterial pathogens and humans. Ideally, novel agents would be broad spectrum and able to treat multiple species of fungi. However, many antifungal compounds that are in development have potent, but very specialized, activity. [21]

ANTI –FUNGAL AGENTS FOR IFIs

Currently, there are four major classes of antifungal drugs that are indicated for the treatment of invasive fungal infections. When used as indicated, these drugs can be highly effective at treating IFIs, with significant beneficial effects on patient mortality. A short summary of these drugs and their primary indications and usages can be found in Table 1.

Table 1 Treatment approaches for Invasive Fungal Infections

Drug	Indication
Polyenes	
Amphotericin B	Life-threatening fungal infections, including cryptococcal meningitis, aspergillosis, blastomycosis and mucormycosis
Azoles	
Fluconazole	Invasive infections due to susceptible *Candida* species; cryptococcosis
Itraconazole	Blastomycosis, histoplasmosis, aspergillosis in patients refractory to Amphotericin B
Voriconazole	Invasive aspergillosis; non-neutropenic candidiasis; serious *Scedosporium* or *Fusarium* infections refractory to other agents
Posaconazole	Prevention of invasive fungal infections in neutropenic or HSC [1] transplant recipients
Isavuconazole	Invasive yeast and mold infections, including aspergillosis and mucormycosis
Echinocandins	
Caspofungin	Candidemia; refractory aspergillosis
Micafungin	Candidiasis
Anidulafungin	Candidiasis (adjunctive therapy with voriconazole for aspergillosis)
Anti-metabolites	
Flucytosine	Adjunctive therapy in *Cryptococcus neoformans* meningitis and *Candida* septicemia and endocarditis (in combination with amphotericin B)

Polyenes

Amphotericin B and Its derivatives Amphotericin B and its newer lipid formulations are polyene antifungals that target the fungal plasma membrane. Recent models posit that these drugs act as "sponges" that bind to and remove ergosterol from the plasma membrane, reducing membrane integrity. Due to its mechanism of action, amphotericin B is broad spectrum and indicated for the treatment of severe infections caused by Candida species, Cryptococcus species, Zygomycetes and as an alternative therapy for aspergillosis. Amphotericin B is also used to treat many life-threatening IFIs due to other filamentous molds, as well as the thermally-dimorphic fungi, such as Histoplasma, Coccidioides and Blastomyces. Amphotericin B is cytocidal for most fungi. As amphotericin B is not highly bioavailable when administered orally, only intravenous (IV) formulations are used clinically. However, amphotericin B can have severe side effects, such as nephrotoxicity due to off-target binding of host membranes, limiting its usage to patients with life-threatening infections. Newer formulations of this drug, such as the lipid-associated and liposomal formulations, demonstrate more selective fungal targeting and less host toxicity.

Azoles and Triazoles

Antifungal agents in the azole class target the fungal plasma membrane through inhibition of the biosynthesis of ergosterol, a fungal plasma membrane component that is similar to cholesterol found in mammalian cell membranes. This occurs through the inhibition of the sterol 14α-demethylase (cytochrome P450 51 or CYP51), which catalyzes the final step in ergosterol biosynthesis. The inhibition of this enzyme leads to defects in fungal plasma membrane integrity and cellular integrity. The most commonly-used azoles

for treating IFIs can be functionally divided between agents with primary activity against yeast-like fungi (yeast-active azoles), and those with expanded activity against fungi that often grow as molds (mold-active azoles). Fluconazole is the most widely-used yeast-active azole, and it is often very effective for treating infections caused by Cryptococcus and Candida species. Importantly, fluconazole resistance can present a significant clinical issue in systemic candidiasis: some Candida species, such as C. krusei, are intrinsically resistant to this drug, and other Candida isolates are often susceptible to this drug at high concentrations. Therefore, precise species identification and targeted antifungal susceptibility testing for clinically-relevant isolates are very important components of the care of patients with Candida IFIs. The mold-active azoles include itraconazole, voriconazole, posaconazole and isavuconazole. In addition to retaining activity against Candida and Cryptococcus yeasts, these agents also inhibit many filamentous fungi. Itraconazole was the first available azole with significant activity against molds, such as Aspergillus fumigatus. However, issues with bioavailability and toxicity limit its current use for IFIs. Two newer agents, voriconazole and posaconazole, are more widely used for these infections, especially in highly immunocompromised patients. Voriconazole has become the first-line antifungal drug for treatment of invasive aspergillosis due to Aspergillus fumigatus. Comparative trials indicate that voriconazole is superior to many other antifungal agents for this infection. Posaconazole is indicated for the prevention of IFIs, especially in the setting of prolonged neutropenia after high dose cancer chemotherapy. The use of these drugs has likely greatly improved outcomes in patients with invasive mold infections. However, both drugs have the potential to interact with other medications due to their inhibition of hepatic cytochrome P-450-dependent metabolism. Moreover, many azoles can result in cardiac conduction changes, and the QT interval should be monitored during therapy. Isavuconazole is the most recently approved triazole antifungal drug. It differs from other approved azoles in several clinically-relevant ways. First, it has expanded in vitro activity that includes the Mucorales molds (Zygomycetes), such as Rhizopus, Mucor and Cunninghamella species, and it may, therefore, be an effective component of the complex, medical-surgical treatment of mucormycosis. Additionally, the intravenous (IV) formulation of isavuconazole lacks cyclodextrin, a solubilizing agent used with other triazoles that is associated with nephrotoxicity in patients with renal insufficiency. Additionally, unlike other azole drugs isavuconazole does not appear to exacerbate QT prolongation, and it may actually shorten the QT interval in some patients.

Echinocandins

The echinocandins represent the newest class of antifungals. Currently, three drugs from this class are approved for clinical usage: caspofungin, micafungin and anidulafungin. Echinocandins affect cell wall biosynthesis through the noncompetitive inhibition of β-1, 3-glucan synthase. This enzyme is involved in the biosynthesis of one of the most abundant fungal cell wall components. Therefore, treatment with echinocandins leads to defects in fungal cell integrity. These drugs are primarily used for the treatment of invasive candidiasis and as an alternative therapy for treatment of aspergillosis. Echinocandins have low host toxicity and few drug interactions. However, they have no activity against Cryptococcus species, and they are decidedly poor agents for treatment of the endemic mycoses. Additionally, they are not orally bioavailable, likely due to their large molecular size, and so, are only available in IV formulations.

5-Fluorocytosine

5-fluorocytosine (flucytosine) is a fluoridated pyrimidine analog, which inhibits DNA and RNA synthesis by incorporating into the growing nucleic acid chain, preventing further extension. This nucleic acid damage eventually leads to cellular defects in protein biosynthesis and cell division. This antifungal agent has been attributed with cytostatic effects and high rates of resistance developing during monotherapy. Therefore, flucytosine is rarely used as a single agent for the treatment of fungal infections. However, it has been shown in multiple clinical trials to be highly effective in combination with amphotericin B for the treatment of cryptococcal meningitis. Indeed, amphotericin B plus flucytosine is the first-line treatment for Cryptococcus central nervous system (CNS) infections. Flucytosine can also be used in combination with other antifungals to treat Candida infections, though this is a less common practice. Adverse effects for flucytosine include bone marrow toxicity, especially in the presence of renal impairment. However, one of the truly limiting factors of this drug is its limited availability in countries with the highest incidence of cryptococcosis. [22] This, unfortunately, limits the effectiveness of cryptococcal meningitis therapy in those regions of the world in which it is most prevalent, likely increasing rates of mortality in this disease.

PROMISING MOLECULAR APPROACHES TO ANTIFUNGAL DRUG DISCOVERY:

Moving beyond Screening of Natural Products In recent years, as seen above, there has been a push toward repurposing off-patent or FDA-approved drugs as antifungal agents. Researchers have also been working toward the identification of compounds that potentiate currently approved antifungal agents. Additionally, the concept of applying chemical genomics and large, high-throughput screening toward the goal of antifungal drug discovery has opened up promising avenues of study. Multiple groups have been using small molecule libraries to screen for antifungal activity in a high-throughput manner. The Krysan group has developed an in vitro assay for rapidly assessing loss of cellular integrity, which measures the extracellular activity of the cytoplasmic enzyme, adenylate kinase, as a simple marker of cell lysis and fungal cell killing. This assay has been used in multiple contexts to identify novel agents that disrupt cellular integrity in C. neoformans, some of which have been discussed above. Through a different approach, the Wright laboratory performed a screen for the potentiation of fluconazole activity against C. neoformans, C. gattii, C. albicans and S. cerevisiae, identifying several FDA-approved compounds that have synergy with fluconazole and potent activity against the fungi tested. More recently, this group has developed an Antifungal Combination Matrix, which arose from a screen of 3600 small molecules tested in combination with six approved antifungal compounds against four species of fungi: a dataset consisting of nearly 230,000 data points and around 86,000 chemical interactions. This massive dataset can be leveraged toward identifying new agents that can increase the potency of existing antifungal agents. [23]

CONCLUSIONS

Invasive fungal infections represent a pressing global health problem. Although effective therapies exist for treatment of these diseases, resistance is common, and the mortality rates for IFIs are still unacceptably high. However, promising advances are being made in antifungal drug development, both through the development of novel compounds with potent antifungal activity and through the repurposing of previously described compounds for new uses as antifungal agents. Moreover, our expanding insight into the cellular processes required for fungal survival is now being translated to the specific identification of new therapeutic targets. Together, these efforts will greatly expand the currently limited number of drugs that we have to treat patients with life-threatening fungal infections.

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