22 An Appraisal of the Current Guidelines for the Use of Antifungals in the Treatment of Invasive Candidiasis, Aspergillosis, and Mucormycosis

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Key Points

A suspicion for an invasive fungal infection should be based on host risk factors, a thorough history, and good clinical examination combined with radiologic imaging. It is reasonable to initiate empiric antifungal therapy pending appropriate laboratory investigations if urgent intervention is warranted. Attempts to establish an etiologic diagnosis is crucial, but not always feasible. IDSA guidelines and other guidelines serve as reliable guides but not the final say-so for any patient. Asian setting and in particular, the Indian setting for invasive fungal infection is substantially different from that seen in the Western hemisphere. Local epidemiological data, individual host risk factors and availability of resources should be carefully considered and the guidelines may be appropriately modified for the best outcome.

22.1 Introduction

Invasive fungal infections (IFI) contribute to substantial morbidity and mortality in immunocompromised patients. Although bacterial and viral infections are more frequently encountered relative to fungal infections, the incidence of IFI has steadily

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risen over the last decade. The occurrence of IFIs parallels the extent of immunosuppression; the risk factors associated with IFIs include the type of malignancy, use of vascular catheters, gastrointestinal surgery, solid organ or hematopoietic stem cell transplantation, neutropenia, graft versus host disease, use of steroids and/or other immunosuppressants including the novel biologics. Although a vast majority (>80%) of these infections are caused by *Candida* and *Aspergillus*, emergence of mucormycosis, particularly in countries such as India, has been noted in recent years.

Several reports on the epidemiology and management guidelines of IFI have been published from various countries, mostly from Europe, Australia/New Zealand, and the USA, in the past two decades [1–23], most of them within the last 5 years. Since the publication of our last appraisal in 2013, the field of mycology has witnessed the introduction of yet another second-generation triazole in 2015, isavuconazole which has demonstrated excellent efficacy against aspergillosis and mucormycosis, favorable safety profile with minimal drug interactions [24–30]. Introduction of novel chemotherapeutic regimens, use of antifungal prophylaxis and institution-dependent transplant strategies have resulted in a changing epidemiology of IFI. Most importantly, recent epidemiological studies have reported the emergence of non-*C. albicans* and azole-resistant pathogenic fungi in several cancer centers around the world [31–34]. Epidemiological differences contribute to varied frequency of IFI in different countries. Hence, management guidelines are not universally applicable. Our current appraisal has attempted to accommodate recommendations from most recent guidelines published and includes the ESCMID-ECMM-ERS (European Society of Clinical Microbiology and Infectious Diseases-European Council on Medical Mycology-European Respiratory Society) guidelines from 2018 [7], the ECIL-6 (European Conference on Infection in Leukemia) guidelines from 2017 [3], and the Australian/New Zealand consensus guidelines for management of yeast and mold infections in hematology/oncology setting, 2014 [9–12], with a special focus on the 2016 guidelines for the diagnosis and management of Candidiasis and Aspergillosis published by the Infectious Disease Society of America [1, 2].

We have summarized the clinical practice guidelines for the management of invasive candidiasis and aspergillosis published by the Infectious Disease Society of America (IDSA) [1, 2] and examined their applicability to the Asian setting. We have also included a special section on *Candida auris*, the emerging multi-drug-resistant yeast in various centers around the world. These guidelines serve as valuable tools for the management of patients with IFIs. Although the emphasis of this chapter is on IFIs in India, the epidemiology, clinical presentation, and treatment approaches of IFI in most Asian countries are overlapping; hence, the discussion presented here is largely applicable to IFIs throughout the Asian continent.

Given the wide variation in the risk factors, epidemiology and differential microbial susceptibility, treatment practices and financial constraints in the health care setting, we have attempted to delineate the critical factors that need to be considered for therapy and the modifications needed in the guidelines for the Asian setting.

22.2 Treatment of Candidiasis

We reviewed Indian data on invasive candidiasis from several tertiary care hospitals. The exact incidence and prevalence of invasive candidiasis in different regions within India remain unclear as multicentric studies are scant. From available data, incidence of candidiasis appears to range from 5 to 16%. Importantly, there has been an emergence of azole-resistant, non-albicans *Candida species* over the last decade, particularly *C. tropicalis* [31–34]. Data including a large study from Post Graduate Institute of Medical Education & Research, Chandigarh, indicate that *C. tropicalis* accounted for 35% cases of candidemia while *C. albicans* accounted for only 15% cases [34]. Two studies that evaluated the epidemiology of invasive candidiasis in the critical care setting reported *C. tropicalis* as the predominant pathogen in 85% of cases. The risk factors reported included urinary catheters, central line catheters, mechanical ventilation, peritoneal dialysis, and corticosteroid use [35, 36]. The first largest prospective, nationwide multicentric observational study (2011–2012) of candidemia evaluated the incidence in 27 intensive care units in India, from which 1400 ICU acquired candidemia cases were reported. Overall incidence was 6.51 cases/1000 ICU admissions, 65.2% were adult patients, average time in ICU was 8 days, and predominant species was *C. tropicalis* (41.6%). Azole and multi-drug resistance were seen in 11.8% and 1.9% of isolates, respectively. *Candida auris* was mostly seen in public sector hospitals compared to private institutions (8.2% vs 3.9%). Given that blood cultures detect only 40% of the cases of candidemia, the authors estimated the incidence of candidemia to be ~675–710/year, with an estimated mortality of 50% [37]. Table 22.1 shows the high prevalence of *C. tropicalis* and relatively minor role played by *C. albicans* in India, as compared to other regions [33, 34].

Importantly, in sharp contrast to Western data, frequent fluconazole resistance was noted in *C. albicans* (10–13%) and in non-albicans Candida including *C. tropicalis* (5–19%) and *C. glabrata* (~36%). Incidence of azole resistance in *C. tropicalis* has ranged from 3.9 to 37.5%. A teaching hospital from Vellore, reported that 112 isolates of *Candida species* were isolated from various clinical specimens during the year 2012. Among them 61 (54.3%) were identified as *C. tropicalis*. All *C. tropicalis* isolates were sensitive to amphotericin B (100%) but 23 isolates (37.7%) were

Table 22.1 Percent Candida species causing bloodstream infection, worldwide and in India

Species	USA (n = 4570)	Europe (n = 7659)	L. America (n = 1710)	Asia (n = 5803)	India (n = 2592)
C. albicans	52	61	42	32	16
C. glabrata	20	15	5	8	5
C. parapsilosis	12	12	22	13	4
C. tropicalis	12	7	18	25	37
C. krusei	2	2	3	3	5
C. guilliermondii	0	1	3	5	11
Other Candida species	3	3	7	13	23

References: [33, 34]

resistant to fluconazole [38]. A recent study from Kolkata reported 100% susceptibility of *C. albicans* to fluconazole, but resistance to amphotericin B, 5-flucytosine, voriconazole, and itraconazole was seen in 53.6%, 64.3%, 10.7%, and 21.4% of cases, respectively. For non-*C. albicans*, resistance to amphotericin B, fluconazole, 5FC, voriconazole, and itraconazole was 30.5%, 61.1%, 33.3%, 19.4%, and 38.9%, respectively. All Candida species were susceptible to caspofungin [39]. More recently, Rajalakshmi et al. from South India reported data on candidemia in a tertiary care hospital, from 2010 to 2015. Of 206 isolates, 84% was non-albicans *Candida* (*C. tropicalis, C. parapsilosis, C. haemulonii* sensu *lato* (complex), and *C. glabrata*). Most C. *glabrata* isolates were resistant to fluconazole; among 38 *C. haemulonii* isolates, all were resistant to fluconazole and 37 of 38 were resistant to amphotericin B [40]. Overall, a great variation in both incidence and prevalence of invasive candidiasis has been reported from various centers in India. Exact reasons for the unique epidemiology and high prevalence of azole resistance are unclear although extensive use of fluconazole, improved diagnosis and susceptibility testing may contribute to this finding. Hence, it is essential that hospitals closely monitor their epidemiological shifts in *Candida species* and provide appropriate therapy based on susceptibility, as it impacts clinical outcome.

22.2.1 Candidemia in the Non-neutropenic Patient

Table 22.2 summarizes the recommendations from the IDSA for the management of invasive candidal infections [2]. The table includes suggested options for the Indian/Asian setting.

Table 22.2 Management of candidiasis based on IDSA guidelines and suggested options for the Indian setting

Clinical situation	IDSA guidelines	Suggested options for the Indian setting
Candidemia in non-neutropenic patients	1. Echinocandin 2. Fluconazole (800–400 mg/day)	1. Fluconazole (800 mg/day) 2. AMB-d (0.5–1 mg/kg/day)/ Fungisome (1–3 mg/kg/day)
Candidemia in neutropenic patients	1. Echinocandin 2. Lipid form AMB (3–5 mg/kg/day)	1. AMB-d (0.5 mg/kg/day)/ Fungisome (1–3 mg/kg/day) 2. Step down to fluconazole (800 mg/day)
Empiric therapy for invasive candidiasis in non-neutropenic patients (in ICU)	1. Echinocandin 2. Fluconazole 800 mg/day	1. Fluconazole 800 mg/day → 400 mg/day 2. AMB-d (0.5–1 mg/kg/day)/ Fungisome (1–3 mg/kg/day)
Empiric therapy for invasive candidiasis in neutropenic patients	1. Echinocandin 2. Lipid form AMB (3–5 mg/kg/day) 3. Voriconazole (6 mg/kg/day followed by 4 mg/kg/day)	1. AMB-d (0.5–1 mg/kg/day)/ Fungisome (1–3 mg/kg/day) 2. Step down to fluconazole (800 mg/day)
Asymptomatic cystitis	No treatment, remove, or change urinary catheters	No treatment, remove, or change urinary catheters

Table 22.2 (continued)

Clinical situation	IDSA guidelines	Suggested options for the Indian setting
Symptomatic cystitis	Fluconazole (200 mg/day for 2 weeks)	Fluconazole (200 mg/day for 2 weeks) or for fluconazole-R isolates, AMB-d 0.5–1 mg/day for 1–7 days
Acute pyelonephritis	Fluconazole (200–400 mg/day for 2 weeks)	Fluconazole (200–400 mg/day for 2 weeks) or for fluconazole-R isolates, AMB-d 0.3–0.6 mg/kg/day for 1–7 days with or without oral flucytosine
Fungal balls in bladder	1. Surgical removal 2. Same for cystitis/pyelonephritis	1. Surgical removal 2. Same for cystitis/pyelonephritis
Osteomyelitis	1. Surgical debridement in selected cases 2. Fluconazole 400 mg/day for 6–12 months OR an echinocandin for 2 weeks followed by fluconazole 3. Lipid form AMB for 2 weeks switch to oral fluconazole (400–800 mg/day) for 6–12 months (depending on susceptibility)	1. Surgical debridement 2. Fluconazole 400 mg/day for 6–12 months 3. AMB-d (0.5–1 mg/kg/day)/ Fungisome (1–3 mg/kg/day) for 2 weeks switch to oral fluconazole (400–800 mg/day) for 6–12 months (depending on susceptibility)
Septic arthritis	1. Joint washouts/removal of prosthesis 2. Fluconazole 400 mg/day for 6 weeks OR an echinocandin × 2 weeks, followed by fluconazole × 4 weeks 3. Lipid form AMB for 2 weeks switch to oral fluconazole (400–800 mg/day) for 4 weeks (depending on susceptibility)	1. Joint washouts/removal of prosthesis 2. Fluconazole 400 mg/day for 6 weeks 3. Lipid form AMB for several weeks switch to oral fluconazole (400–800 mg/day) for total 6 weeks (depending on susceptibility)
Central nervous system involvement	1. Removal of shunts/catheters/ prosthetic devices 2. Liposomal AMB ± 5FC for 2 weeks, switch to fluconazole 400–800 mg/day until clinical, CSF, and radiological improvement	1. Removal of shunts/catheters/ prosthetic devices 2. AMB-d (1 mg/kg/day)/ Fungisome (1–3 mg/kg/day) for 2 weeks switch to fluconazole 400–800 mg/day until clinical, CSF, and radiological improvement
Cardiovascular involvement	1. Removal of shunts/catheters/ prosthetic devices 2. Lipid form AMB ± 5FC, OR high dose echinocandin for several weeks switch to fluconazole 400–800 mg/day until clearance of candidemia plus clinical, CSF, and radiological improvement (lifelong suppression, if device cannot be removed)	1. Removal of shunts/catheters/ prosthetic devices 2. AMB-d (1 mg/kg/day)/ Fungisome (1–3 mg/kg/day) for 2 weeks switch to fluconazole 400–800 mg/day until clearance of candidemia plus clinical, CSF, and radiological improvement (lifelong suppression if device cannot be removed)

The three major classes of agents used in the treatment of candidiasis include polyenes, azoles, and echinocandins. The choice of appropriate antifungal agent should be based on the epidemiology, recent history of antifungal exposure, antifungal susceptibility pattern, severity of illness, comorbidities, and tolerability. In general, severe infections (meningeal or endocardial) and hemodynamically unstable patients requiring ICU admission benefit from the use of fungicidal agents such as polyenes and echinocandins. In the USA, *C. albicans* (52%) remains the most common *Candida* species associated with candidemia although there has been an increase in the incidence of non-*C. albicans* reported over the last decade. *C. glabrata*, *C. parapsilosis,* and *C. tropicalis* are the most frequently encountered non-albicans species causing candidemia. Other rare non-albicans pathogenic species include *C. krusei*, *C. guilliermondii* and *C. lusitaniae*.

Based on data from several clinical trials, fluconazole is recommended as first-line therapy for selected patients with candidemia. Such patients are those with mild-to-moderate illness, likely infected with *C. albicans*, have not received azoles in the recent past, have no meningeal or endocardial involvement, and are hemodynamically stable. However, in patients who are severely ill and/or hemodynamically unstable or infected with non-albicans *Candida* species or have had recent azole exposure, or with involvement of meninges or endocardium, the IDSA panel recommends echinocandins (effective against most common species) as first-line agents, and not to rely on fluconazole in view of the possibility of azole-resistant *Candida*. Polyenes, in general, have been replaced by azoles and echinocandins due to severe adverse reactions associated with amphotericin B.

The duration of therapy recommended is 2 weeks from the time of clearance of candidemia, provided there are no metastatic complications. This recommendation is based on several randomized controlled trials that have shown reduced metastatic complications and relapses with 2 weeks of therapy. However, the exact duration of therapy and the time of switch to an oral azole from intravenous therapy remain somewhat ill defined and must be based on clinical improvement, epidemiological factors, and feasibility. As most cases of Candidemia are central line- or vascular catheter-related, removal of the intravenous catheter is strongly recommended for all non-neutropenic patients with candidemia. In the presence of azole-susceptible *Candida* causing candidemia without any metastatic complication, switching to oral fluconazole (400–800 mg po once daily) after the first several days of parenteral therapy with amphotericin B deoxycholate (AMB-d) (1 mg/kg/day) or Fungisome (1–3 mg/kg/day) is acceptable, provided absorption of fluconazole in the gastrointestinal tract is not impaired. In azole-resistant candidemia, a polyene or an echinocandin would be the optimal choice. Examination of the fundus must be performed in all cases of candidemia; if retinal or vitreal involvement is seen, therapy is prolonged and surgery may be indicated.

22.2.2 Candidemia in the Neutropenic Patient

Candidemia is a serious, life-threatening infection in the neutropenic population. It is associated with an increased risk for dissemination and high mortality. There are several critical factors that need to be considered during treatment of neutropenic

patients with candidemia: (1) wide use of fluconazole for prophylaxis in hematopoietic stem cell transplant patients and patients on chemotherapy, and, as a result, possible selection of azole-resistant Candida, (2) rapid dissemination of infection during neutropenia and (3) adverse drug reactions.

In the setting of neutropenia, echinocandins are recommended as first-line therapy. Echinocandins, like polyenes, are rapidly fungicidal in contrast to azoles that are fungistatic. Echinocandins have excellent anti-candidal activity against *C. glabrata* and *C. krusei*. However, for infections due to *C. parapsilosis*, since echinocandins generally have suboptimal activity in vitro, fluconazole or AMB-d (1 mg/kg/day)/ or Fungisome (1–3 mg/kg/day) may be preferred as initial therapy. Duration of therapy is 2 weeks from the time of clearance of candidemia. The potential source, i.e., intravenous device, must ideally be removed; however in the profoundly neutropenic setting, removal of the device may lead to more complications, and so the guidelines recommend use of clinical judgment regarding device removal.

22.2.3 Empiric Therapy of Candidemia in the Non-neutropenic Patient

Given the relatively common prevalence of azole resistance in Candida, fluconazole may not be a reasonable option for empiric therapy of invasive candidiasis in India (Table 22.2). In a critically ill patient, a polyene or an echinocandin may be more reliable, and both classes appear equally effective, though the former is more toxic. Lipid formulations of amphotericin B (LFAmB) as well as echinocandins are in general, expensive and so, may not be a viable option for prolonged use in resource-limited settings. Although associated with major disadvantages including infusion reactions, electrolyte abnormalities and nephrotoxicity, closely monitored use of conventional amphotericin B deoxycholate (AmB-d) remains a viable potent therapeutic option. The advantages of the lipid forms of amphotericin over conventional amphotericin B deoxycholate are easy tolerability and significantly reduced nephrotoxicity; efficacy wise, the two appear similar and there are no good data to suggest superiority of one over the other.

Amphotericin B deoxycholate (at a dosage of 0.5–1 mg/kg daily) or Fungisome (1–3 mg/kg/day) daily are reasonable options. Once the organism is identified to be fluconazole-susceptible, a switch to therapy with fluconazole is acceptable. With the prevalence of azole resistance, routine susceptibility testing is prudent when managing infections due to *C albicans, C. tropicalis* and other potentially resistant species. Unfortunately, susceptibility testing of *Candida* isolates is not readily available in most hospital laboratories.

22.2.4 Empiric Therapy of Candidemia in the Neutropenic Patient

Neutropenic patients who remain febrile despite broad spectrum antibacterial agents may be suspected to have invasive candidal infections and empirically treated with antifungal drugs. Serum beta-D-glucan test, commonly used biomarker in the USA,

may not be readily available in the Asian setting for an early diagnosis of invasive candidiasis. Since diagnosis of candidiasis is not always easily established, empiric anti-candidal therapy in this setting is acceptable and has been associated with improved outcome.

The IDSA guidelines recommend lipid formulation of AMB, caspofungin, or voriconazole intravenously as primary empiric therapy, and high dose fluconazole or itraconazole as alternative agents. Following options may be suitable for the resource-limited setting: an echinocandin or amphotericin B deoxycholate or Fungisome (1–3 mg/kg/day) or a lipid formulation of AmB. Once the susceptibility is known, transition to fluconazole is acceptable if the isolate is fluconazole-susceptible. Until susceptibility data are known, azoles should not be used for empiric therapy in patients who had received an azole for prophylaxis.

22.2.4.1 Candidal Urinary Tract Infection

IDSA guidelines focus on fluconazole-susceptible *C. albicans* and fluconazole-resistant *C. glabrata* candiduria (Table 22.2). The recommendation is to defer antifungal treatment and eliminate the predisposing factors such as change or removal of indwelling urinary catheters for asymptomatic candiduria. Treatment is indicated in situations where there is a high risk of dissemination such as in neonates and infants with low birth weights, neutropenic patients, and patients prior to urological procedures. Fluconazole at 200 mg daily for 7 days for fluconazole-susceptible *Candida* and AmB-d 0.3–0.6 mg/kg IV daily for 1–7 days for fluconazole-resistant *Candida* are recommended.

Data on the exact incidence of asymptomatic and symptomatic candiduria are not available from India. Few institutions have reported that *C. tropicalis* has replaced *C. albicans* as the most frequently isolated yeast from urine specimens [35, 36]. As fluconazole is highly water soluble, primarily excreted in the urine, and achieves urine concentrations that are 10–20 times higher than serum concentrations, most Candida infections may be treated with fluconazole at 400–800 mg once daily for 2 weeks. This regimen may be effective against selected cases of *C. tropicalis* and *C. glabrata* infections as well. If the isolate is fluconazole-resistant (commonly with *C. glabrata* or *C. krusei*), IV AMB-d at 0.3–0.5 mg/kg daily for 1–7 days may be appropriate. In severely ill patients, continued treatment with IV AMB-d is appropriate until susceptibility data are available. Lipid formulations of AMB and echinocandins achieve low urinary concentrations and are not recommended. Fluconazole may be given orally, thus eliminating the need for IV access. *Candida* prostatitis and epididymo-orchitis are infrequently reported and involve surgical drainage/debridement of the infected site plus antifungal therapy based on the specific pathogen isolated and its antifungal susceptibility.

22.2.4.2 Candidal Osteoarticular Infection

The mainstay of therapy involves surgical debridement in conjunction with antifungal therapy**.** Fluconazole, caspofungin, and AmB-d have been used with success. IDSA recommends the use of AmB-d at 0.5–1 mg/kg daily for 6–10 weeks. Surgical debridement along with AMB-d or Fungisome (1–3 mg/kg/day) for 1–2 weeks

followed by oral fluconazole (400–800 mg daily) for 6–12 months, based on the specific pathogen isolated, is a reasonable strategy. *Candida* prosthetic joint infections necessitate resection arthroplasty in most situations, and if the device cannot be removed, chronic or lifelong suppression with fluconazole is recommended. The data are scarce on fungal osteoarticular infections in India. Few case reports suggest the incidence of primary septic arthritis and osteomyelitis in neonates caused by *Candida* species to be about 7%.

22.2.4.3 Candidal Central Nervous System (CNS) Infection

Data on CNS candidiasis are sparse. Sundaram et al. reported six patients with multiple intracerebral abscesses, none had any identifiable immunocompromise [41]. A study from Indore, examining the causes of fungal meningitis in HIV-positive and negative subjects, found *Candida* to be the most common cause of fungal meningitis in both patient groups, after cryptococcal meningitis. In the HIV-negative group, diabetes, renal transplantation, and prematurity were recognized as risk factors. CNS candidiasis has been seen as a co-infection with *A. fumigatus* and *Mucorales*. *C. albicans* and *C. tropicalis* were the common *Candida* species involved [42].

Fluconazole achieves excellent levels in the CSF and brain parenchyma. Guidelines recommend the combination of liposomal AmB at 3–5 mg/kg daily with or without flucytosine at 25 mg/kg four times daily for several weeks, followed by maintenance therapy with oral fluconazole at 400–800 mg daily until there is complete resolution of clinical, CSF, and radiological abnormalities. Removal of all prosthetic devices related to CNS infection is strongly recommended.

Most of these recommendations were not based on randomized controlled trials, but were based on case series, case reports, and clinical expertise. Surgical debridement in selected cases of brain abscess, especially if solitary, and removal of all CNS devices appear prudent. Initial therapy with intravenous AMB-d (1 mg/kg/day) or Fungisome (1–3 mg/kg/day) until clinical stability, and then therapy with fluconazole 800 mg daily for long-term maintenance is a reasonable alternative. Obviously, susceptibility data play an important role. It needs to be remembered that echinocandins do not achieve high concentrations across the blood–brain barrier and are not recommended in the treatment of CNS candidiasis.

22.2.5 Candidal Endophthalmitis

IDSA recommendations are based on published case reports and suggest a combination of conventional AmB-d at a dose of 0.7–1 mg/kg daily with flucytosine at 25 mg/kg four times daily as first-line therapy for candidal endophthalmitis. High dose fluconazole (400–800 mg daily) may be used as monotherapy for less severe cases. Lipid form of AmB and voriconazole are useful alternative agents in case of intolerance to conventional amphotericin B deoxycholate. Endophthalmitis may be due to an endogenous source (such as during candidemia) or due to an exogenous cause (such as following surgery or trauma); the latter is common in non-neutropenic patients. In a single center study (14-year case series) from Chandigarh, fungal

endophthalmitis was reported in 113 patients and the distribution of cases was: post-cataract surgery (53 patients), post-trauma (48 patients), and acquisition via endogenous route (12 patients). *Aspergillus* species was the most common (54.4%) mold isolated, followed by yeasts (24.6%), and melanized fungi (10.5%). Among aspergilli, *Aspergillus flavus* was the most common (24.6%) species, whereas *Candida tropicalis* (8.8%) was the most common yeast isolated [43].

A diagnostic and therapeutic vitreal aspirate with vitrectomy and intravitreal antifungal therapy with conventional IV AmB deoxycholate (AMB-d) is recommended in all patients with severe endophthalmitis and vitritis. Fluconazole may be substituted for amphotericin B after clinical stability has been achieved. Again, susceptibility of the pathogen needs to be known prior to the treatment switch.

22.2.6 Candidal Cardiovascular Infection

Cardiovascular fungal infections are associated with a high rate of relapse and mortality. Removal of shunts, catheters, prosthetic devices, and valve replacement are an integral part of management and if not feasible, patients will need lifelong suppressive antifungal therapy. AMB-d (1 mg/kg/day), Fungisome (1–3 mg/kg/day) or, if available, liposomal AMB (3–5 mg/kg/day) for 2 weeks followed by a switch to fluconazole 400–800 mg/day until documented clearance of candidemia plus clinical, CSF, and radiological improvement may be reasonable.

Evidence for the use of isavuconazole as primary therapy for invasive candidiasis is lacking. Clinical studies do not show adequate comparative efficacy; hence, none of the guidelines have approved the use of isavuconazole for invasive candidiasis [44].

22.2.6.1 *Candida auris*: A Therapeutic Challenge

Since the first report of an ear canal infection with *C. auris* in 2009, this multi-drug-resistant pathogen has been reported from various centers around the world. A significant number of cases have been reported from India. Genotyping revealed that the Indian strains were clonally different from their counterparts in Japan and South Korea [45]. Four clades have been isolated from South Asia, South Africa, South America, and East Asia [46]. Most isolates are resistant to fluconazole and had variable susceptibilities to other azoles, polyenes, and echinocandins. Isolates that were initially identified as *C. haemulonii* were later confirmed to be *C. auris* by gene sequencing [47]. A report by Rudramurthy et al. that performed a subgroup analysis of all cases of candidemia (n = 1400) from 27 intensive care units in India showed that the incidence of *C. auris* was 5.3% and the majority of strains were clonal although hospitals were far apart, and resistance rates to fluconazole, amphotericin B, and caspofungin were 58.1%, 13.5%, and 9.5%, respectively [48]. Majority of cases were reported from public sector hospitals and a few trauma centers in northern parts of India. Major risk factors are a long stay in ICU, diabetes mellitus, malignancy, underlying respiratory illness, vascular surgery, medical interventions (central venous catheters, urinary catheters, post-operative drains, TPN), and prior antifungal exposure [49]. An outbreak of *C. auris* (50 cases) was reported from a cardiothoracic surgery hospital in London, further emphasizing the need for stringent infection control and preventive measures [50]. The overall crude mortality is

30–60%. Given the intrinsic resistance to fluconazole (MIC ≥32 μg/mL), *C. auris* infections remain a diagnostic and therapeutic challenge, with no consensus currently available for optimal treatment. Based on available data, resistance to fluconazole and voriconazole resistance are ~90% and ~50%, respectively. However, posaconazole (MIC 0.06–1 μg/mL) and isavuconazole (0.015–0.5 μg/mL) have shown excellent in vitro activity against *C. auris* and may be potential therapeutic options. Given the relatively low incidence of resistance (2–8%), echinocandins are the first-line therapy for *C. auris* infections. As echinocandins do not achieve optimal concentrations in urine, flucytosine (MIC 50 0.125–1 μg/mL) is preferred for management of urinary tract infections [51]. The global emergence of *C. auris* infections over the last few years has prompted the Center for Disease Control (CDC) to issue health alerts and publish guidelines on appropriate surveillance for prevention and management of these infections.

22.3 Epidemiology of Invasive Aspergillosis

Table 22.3 describes unique features/characteristics of invasive mold infections in the Indian setting [52, 53].

Table 22.3 Invasive mold infections in the Indian setting (aspergillosis, mucormycosis)

Likely factors contributing to increased frequency
1. Agricultural activities
• Poor protective equipment
• Contact with soil
• Exposure to high fungal spore burden
2. High frequency of trauma
• Eye/skin/soft tissue infection
3. Construction activities
• High exposure to fungal burden/poor protective equipment
4. Poor hygiene/suboptimal sanitary conditions
5. Hospital settings
• Suboptimal protection of compromised hosts
– No HEPA filters
– Open windows
• Poor hygienic conditions
6. High prevalence of poorly controlled diabetes mellitus
7. Liberal use of corticosteroids/antimicrobials—over-the-counter availability
Frequent features in India
1. Immunocompetent host: Not uncommon
2. Aspergillosis
• *A. flavus* most common
• Rhinosinusitis/endophthalmitis/CNS infections
3. Mucormycosis
• Linked to diabetes/trauma
• Renal mucormycosis—well described

In Western reports, *A. fumigatus* is the most common cause of invasive aspergillosis (IA) followed by *A. flavus, A. terreus, A. niger, A. ustus, and A. lentulus*. Several cancer centers have reported the emergence of *A. niger, A. flavus,* and *A. terreus* over recent years. Non-fumigatus Aspergillus species have a variable susceptibility pattern to the available antifungal agents. *Aspergillus flavus, A. ustus,* and *A. lentulus* are known to have higher MICs to voriconazole while *A. terreus* is intrinsically resistant to amphotericin B. Antifungal susceptibility of aspergillus is not performed in most clinical settings and until recently was not warranted in the routine management of invasive aspergillosis [1].

Clinical syndromes associated with aspergillosis in patients with preexisting lung disease include allergic pulmonary aspergillosis, chronic necrotizing aspergillosis, and aspergilloma. The most common forms reported in immunocompromised cancer patients are invasive pulmonary aspergillosis, cerebral aspergillosis, and disseminated infection.

A recent study reviewed invasive aspergillosis from 1970 to 2010 in developing countries including India. Authors report that suboptimal hospital practices, construction or renovation work in the vicinity, inappropriate use of steroids and broad-spectrum antibiotics, contaminated infusion fluids, and intravenous drug use were identified as important risk factors for IA. In addition to classical risk factors, liver failure, chronic obstructive pulmonary disease, diabetes, and tuberculosis have been identified as diseases associated with IA [53]. There is a geographic variation in the distribution of species, with *A. flavus* being reported as the predominant pathogen in South East Asia, the Middle East, and arid regions of Africa. A recent large-scale 1-year multicentric retrospective study assessed the incidence and clinical determinants of invasive mold infections in five countries (Thailand, Taiwan, Singapore, China, and India). Among patients without classic risk factors such as neutropenia and steroid use, diabetes and rheumatological diseases were frequently associated with IA. Aspergillosis (*A. fumigatus and A. flavus*) was the most common mold (71%), with a 90-day mortality rate of 32.9% [54]. Several studies are available regarding the incidence and prevalence of *Aspergillus* species from India. *A. flavus* is the second most common mold and is frequently associated with fungal rhinosinusitis, keratitis, and cerebral infections [55]. In a retrospective study performed over a 4-year period (2001–2004), Xess et al. reported that *A. flavus* (46.9%) was most frequently isolated from sinuses whereas *A. fumigatus* (37.7%) was the most common pathogen isolated from respiratory specimens followed by *A. niger* (15.1%) from nail samples [56]. Cases of invasive pulmonary aspergillosis have also been reported from patients with pulmonary tuberculosis [57]. Most Indian isolates of *A. fumigatus* remain susceptible to voriconazole, itraconazole, posaconazole, and echinocandins in vitro. However, azole resistance in *A. fumigatus*, as seen in the West, has been reported in India as well [58, 59].

Triazole resistance in *Aspergillus* is an increasing problem in both clinical and environmental isolates. Prevalence of resistance and its clinical impact in different countries are unclear. This phenomenon is well recognized in several European countries, likely related to widespread use of azole containing

agricultural pesticides, and complicates diagnosis and treatment of aspergillosis. Patients with azole-resistant aspergillosis have a higher mortality compared to those with triazole susceptible infection. Recent ESCMID-ECMM-ERS aspergillus guideline recommends susceptibility testing in *A. fumigatus* and local resistance surveillance in regions of >10% azole resistance in aspergillus isolates. Moreover, many suggest that in regions where resistance rates exceed 10%, liposomal amphotericin B or a combination of triazole plus echinocandin should be considered as first-line therapy [60]. Based on scant resistance prevalence data, within Asia, it does not appear necessary to change current practice of management. However, regular local surveillance of resistance is prudent. Also, appropriate attention needs to be drawn to the inclusion of azoles in agricultural pesticides.

In comparison to the occurrence of IA in immunocompromised hosts in the western hemisphere, there are multiple Indian reports of chronic pulmonary aspergillosis [61, 62] and sino-orbital Aspergillosis in immunocompetent individuals. Reasons for the infections in immunocompetent host may be: (1) increased exposure with agriculture being a major factor in most rural and semi-urban areas, (2) environmental conditions resulting in several annual monsoons creating a favorable medium for fungal growth, (3) availability of systemic corticosteroids over the counter with widespread misuse by untrained health care professionals in rural and urban locations (4) intravenous drug use with products contaminated with fungal spores. Hence, the threshold for suspecting invasive mold infections needs to be much lower and needs to be strongly considered in the appropriate clinical setting regardless of the immune status of the patient.

22.4 Treatment of Invasive Aspergillosis

IDSA guideline recommends initiation of empiric therapy in patients at high risk with suggestive clinical and radiological findings [1]. Parenteral or oral voriconazole is generally preferred as empiric therapy. The latest addition to the anti-aspergillus armamentarium is isavuconazole. It was FDA (Food and Drug Administration) approved for treatment of invasive aspergillosis in 2015, based on compelling clinical efficacy established based on a randomized double-blind clinical comparative phase III trial (SECURE study), of patients who received either isavuconazole or voriconazole for invasive aspergillosis. ECIL-6 guidelines published in 2017 have included isavuconazole as first-line therapy for patients with IA, but not for salvage therapy. However, the IDSA guidelines have included isavuconazole as only alternative therapy in patients with invasive aspergillosis. It is recommended when drug interactions and/or toxicity preclude the use of voriconazole. It may also be considered in select clinical situations where broad empiric coverage for molds (including mucormycosis) is considered. Also, liposomal AMB may be used as alternative therapy, particularly in patients who are intolerant of or refractory to voriconazole. The recommendation for salvage therapy includes amphotericin B lipid complex (ABLC), posaconazole, itraconazole, or

Table 22.4 Treatment of Aspergillosis (IDSA, 2016—guidelines)

	Primary/alternative	Comment
Pulmonary[a]	Voriconazole; liposomal AmB or isavuconazole	No routine combination therapy
Endophthalmitis	IV/PO voriconazole + intravitreal AmB/voriconazole	Partial vitrectomy
Empiric/pre-emptive therapy	Liposomal AmB/voriconazole/ micafungin/caspofungin	
Prophylaxis	Posaconazole: Suspension/tablet/IV Altern: Vorizonazole/Itraconazole suspension/caspofungin/micafungin	
Other syndromes		
Aspergilloma	No surgery/ no drug Rx Alternative: Itraconazole/voriconazole	
Chronic Cavitary Pulmonary aspergillosis	Similar to invasive pulmonary aspergillosis	Consider long-term Rx; avoid surgery
Allergic syndromes		
Bronchopulmonary aspergillosis	Corticosteroids: Main Rx	Itraconazole Altern: Voriconazole/ posaconazole
Rhinosinusitis	Polypectomy/steroid washouts	If refractory, antifungal use

[a]Therapy similar in sinus/trachea-bronchial aspergillosis, CNS/cardiac/osteoarticular aspergillosis, cutaneous/peritoneal aspergillosis. Surgery in appropriate cases

micafungin/caspofungin. Guidelines do not support the use of combination therapy (antimold azole + echinocandin) for all patients with invasive aspergillosis. Duration of therapy is for 6–12 weeks or through the period of immunosuppression. Table 22.4 summarizes the IDSA recommendations for various syndromes of aspergillosis.

Most IDSA recommendations are applicable to the Asian setting. For chronic necrotizing aspergillosis, oral itraconazole may be suitable. As an alternative to voriconazole, for acute aspergillosis, AMB-d (1 mg/kg/day), or Fungisome (1–3 mg/kg/day) as initial therapy for 1–2 weeks followed by maintenance with oral itraconazole may be employed. With AMB-d use, close monitoring of electrolytes and renal function is important. Itraconazole has poor bio-availability and has not been examined as rigorously as voriconazole for the treatment of acute aspergillosis. Special situations include cardiac involvement where surgical removal of involved valves is the main stay of management followed by medical therapy with AMB-Dd (or Fungisome) for a minimum of 6 weeks, with subsequent lifelong suppression with itraconazole. Aspergillus endophthalmitis and keratitis may occur either as a result of direct contamination from agriculture-related activities, contaminated ophthalmic solutions, or due to poor sanitary conditions, and post-cataract surgery. Immediate vitreal aspiration with pars plana vitrectomy with parenteral and intravitreal AMB-Dd is indicated as a sight saving measure in these patients. High cost and limited availability may restrict the use of lipid form amphotericin B and the newer azole, isavuconazole.

22.5 Fungisome

The Indian preparation of liposomal amphotericin B, namely Fungisome TM, has demonstrated excellent efficacy, better tolerability and has two to four-fold lower MICs as compared to conventional AMB against aspergillus [63, 64]. In a post-marketing analysis, Fungisome demonstrated 74% complete response and 18% partial response, with significant cost savings. Recently, a multicentric, randomized, controlled clinical trial was conducted to compare low (1 mg/kg/day) vs. high dose (3 mg/kg/day) of Fungisome with conventional AMB (1 mg/kg/day) as empirical antifungal therapy for febrile neutropenia [65]. Although it was a small sample, Fungisome was equally effective but safer than conventional AMB, and low dose was as effective and well tolerated as the high dose. As Fungisome may be less expensive than the commercially available liposomal preparation of AMB, it may serve as an alternative therapy in the appropriate clinical setting. From the available literature, the product appears effective both in vitro and in vivo. More extensive clinical data against infections due to different fungi are urgently needed.

22.6 Treatment of Mucormycosis

Excellent reviews on mucormycosis in India have been published [66–70]. The emergence of mucormycosis in the USA and Europe has been noted in patients with hematological malignancies and transplant recipients, whereas cases in India are overwhelmingly associated with uncontrolled diabetes mellitus with or without ketoacidosis. The authors describe several unique features of mucormycosis from India including isolated renal mucormycosis in immunocompetent individuals. New risk factors such as renal failure and chronic liver disease have been reported [67]. The high incidence in India is likely related to the environmental factors such as the warm climate conducive for a high concentration of spores in the soil. A recent review of epidemiology of mucormycosis in India from 1960 to 2012, brought out some contrasting features of mucormycosis in India as compared to data from the USA or Europe. Most infections are rhino-cerebral (58%) followed by cutaneous involvement (14%) [68]. Another recent 10-year study from a teaching hospital in south India reported the emergence of *R. microsporus* (15.7%) and *Apophysomyces elegans* (10.8%) as important pathogens in addition to *R. arrhizus*. Paranasal sinuses (73.9%) followed by musculoskeletal system (15.2%) were frequently involved. *R. microsporus* was more common in patients with hematological conditions (25% vs 15.7%) and was less frequently a cause for sinusitis than *R. arrhizus* (27.58% vs 10.9%). The overall mortality was 30.97%. *Apophysomyces elegans* sensu lata typically produced skin and musculoskeletal disease in immunecompetent individuals, was secondary to trauma, and was associated with a lower mortality [70]. It is important to have a low threshold to include mucormycosis in the differential diagnosis of cutaneous, pulmonary, cerebral, or disseminated infections, particularly in those related to trauma.

The occurrence of renal mucormycosis in Indian patients with no underlying risk factors is unique. This entity carries a 50% mortality, route of entry is unknown, and has not been reported from other regions. Preferred treatment is nephrectomy along with IV AMB-d. Most frequent pathogens are *Rhizopus* species (*R. arrhizus*) followed by *Absidia*, *Rhizomucor*, and *Mucor*; there are emerging case reports of *Apophysomyces elegans* [68, 70] infections.

Isavuconazole was approved for treatment of mucormycosis in 2015, based on clinical efficacy established with data from the VITAL study, an open-label non-comparative study that comprised of a subgroup of 37 patients with proven or probable mucormycosis and results were evaluated by an independent data review committee. The 42-day all-cause mortality was 38% and a matched case control analysis with patient data from the Fungiscope Registry demonstrated comparable efficacy to amphotericin B [71]. With limited data, currently in the USA, the drug is more commonly used, not as primary therapy, but as step-down strategy once the acute infection is controlled with liposomal amphotericin B.

Guidelines for the management of mucormycosis are scant. The ECIL-6 (European Council on Infections in Leukemia) guidelines did not include isavuconazole for the treatment for mucormycosis, pointing out the scarcity of specific data in patients with leukemia [3]. Echinocandins and voriconazole have no reliable clinical activity against mucor infection. Oral posaconazole may be used in suspension or tablet form for salvage or step-down therapy.

The Italian guidelines suggest extensive debridement of all necrotic tissue, control of predisposing metabolic conditions, correction of neutropenia, reduction in immunosuppression, in conjunction with liposomal AMB at 5 mg/kg/day increased up to 12.5 mg/kg/day as tolerated, followed by a step-down to oral posaconazole. Conventional amphotericin B deoxycholate may be equally effective at 1–1.5 mg/kg/day, but its sustained use almost always will lead to unacceptably high nephrotoxicity. Fungisome may be an effective, less expensive and safer alternative, however more data are needed. In the Asian setting, a high index of suspicion needs to be maintained for early diagnosis. With cost considerations, amphotericin B deoxycholate is likely to remain as the main therapeutic agent for this infection.

22.7 Therapeutic Drug Monitoring

Ample data are published regarding serum level monitoring of itraconazole, voriconazole, and posaconazole. Clinical responses with isavuconazole occur across the observed range of MICs (minimum inhibitory concentration), thus monitoring serum levels is not currently recommended. Although data appear to support routine use of therapeutic drug monitoring of other triazoles to avoid toxicity and for optimal outcome, test for measuring drug levels is not readily available in most centers. For echinocandin or polyene use, measurements of serum levels are not recommended.

There are several treatment guidelines for the management of IFI that continue to be published from different regions of the world. Most offer evidence-based guidelines, learned from clinical trials, appropriate for a particular region. Such

guidelines are immensely helpful in choosing appropriate therapy for a given patient in a given scenario. However, there are several factors that need to be considered prior to applying the recommendations from any guideline. Such factors include: (1) local epidemiology of the infection, (2) change in incidence of the infection over time, (3) etiologic pathogen and its susceptibility pattern, (4) specific risk factors in the host, (5) pharmacogenomics and drug toxicities, (6) patient care resources and financial limitations, and (7) availability of antifungal drugs. In the Indian setting, emergence of non-albicans Candida particularly *C. tropicalis, C. auris* and change in susceptibility to azoles among *C albicans* and non-albicans Candida are strikingly unique. As a soil fungus, not uncommonly, aspergillus infection is seen in the immunocompetent host setting, particularly with farm/agricultural environment. Also, a very high incidence of mucormycosis and unique presentations of infections due to aspergillus and mucor are noteworthy. Other critical factors to consider during the management of IFI include excessive empiric use of antimicrobial drugs with consequent emergence of multi-drug-resistant pathogens, poor quality control of drugs, and limited diagnostic capabilities for IFI.

References

1. Patterson TF, Thompson GR III, Denning DW, et al. Executive summary: practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:433–42.
2. Pappas PJ, Kauffman C, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:e1–e50.
3. Tissot F, Agrawal S, Pagano L, et al. ECIL-6 guidelines for the treatment of invasive candidiasis, aspergillosis and mucormycosis in leukemia and hematopoietic stem cell transplant patients. Haematologica. 2017:102433–44.
4. Schelenz S, Barnes RA, Barton RC, et al. British Society for Medical Mycology best practice recommendations for the diagnosis of serious fungal diseases. Lancet Infect Dis. 2015;15:461–74.
5. Bongomin F, Gago S, Oladele RO. Global and multi-national prevalence of fungal diseases—estimate precision. J Fungi. 2017;3(57):1–29.
6. Rotjanapan P, Chen YC, Chakrabarti A, et al. Epidemiology and clinical characteristics of invasive mould infections: a multicenter, retrospective analysis in five Asian countries. Med Mycol. 2018;56:186–96.
7. Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24(Suppl 1):e1–e38.
8. Singh T, Kashyap AK, Ahluwalia G, et al. Epidemiology of fungal infections in critical care setting of a tertiary care teaching hospital in North India: a prospective surveillance study. J Clin Sci Res. 2014;3:14–25.
9. Slavin MA, Thursky KA, Worth LJ, et al. Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2014. Intern Med J. 2014;44:1267–76.
10. Morrissey CO, Gilroy NM, Macesic N, et al. Consensus guidelines for the use of empiric and diagnostic-driven antifungal treatment strategies in haematological malignancy, 2014. Intern Med J. 2014;44:1298–314.

11. Fleming S, Yannakou CK, Haeusler GM, et al. Consensus guidelines for antifungal prophylaxis in haematological malignancy and haemopoietic stem cell transplantation, 2014. Intern Med J. 2014;44:1283–97.
12. Blyth CC, Gilroy NM, Guy SD, et al. Consensus guidelines for the treatment of invasive mould infections in haematological malignancy and haemopoietic stem cell transplantation, 2014. Intern Med J. 2014;44:1333–49.
13. Cornely OA, Arikan-Akdagli S, Dannaoui E, et al. European Society of Clinical Microbiology and Infectious Diseases Fungal Infection Study Group; European Confederation of Medical Mycology. ESCMID and ECMM joint clinical guidelines for the diagnosis and management of mucormycosis 2013. Clin Microbiol Infect. 2014;20 Suppl 3:5–26.
14. Girmenia C, Aversa F, Busca A, et al. Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer. A hematology consensus agreement on antifungal strategies for neutropenic patients with hematological malignancies and stem cell transplant recipients. Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer. Hematol Oncol. 2013;31:117–26.
15. Leroux S, Ullmann AJ. Management and diagnostic guidelines for fungal diseases in infectious diseases and clinical microbiology: critical appraisal. Clin Microbiol Infect. 2013;19:1115–21.
16. Chen SC, Sorrell TC, Chang CC, et al. Consensus guidelines for the treatment of yeast infections in the haematology, oncology and intensive care setting, 2014. Intern Med J. 2014;44:1315–32.
17. Ullmann AJ, Akova M, Herbrecht R, et al. ESCMID Fungal Infection Study Group. ESCMID guideline for the diagnosis and management of Candida diseases 2012: adults with haematological malignancies and after haematopoietic stem cell transplantation (HCT). Clin Microbiol Infect. 2012;18 Suppl 7:53–67.
18. Maertens J, Marchetti O, Herbrecht R, et al. Third European Conference on Infections in Leukemia. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 update. Bone Marrow Transplant. 2011;46:709–18.
19. Kullberg BJ, Verweij PE, Akova M, et al. European expert opinion on the management of invasive candidiasis in adults. Clin Microbiol Infect. 2011;17(Suppl 5):1–12.
20. Grossi PA, Gasperina DD, Barchiesi F, et al. Italian guidelines for diagnosis, prevention, and treatment of invasive fungal infections in solid organ transplant recipients. Transplant Proc. 2011;43:2463–71.
21. Prentice AG, Glasmacher A, Hobson RP, et al. Guidelines on the management of invasive fungal infection during therapy for haematological malignancy. British Committee for Standards in Haematology. March 2010. Electronic online version only. www.mycology.adelaide.edu.
22. Flückiger U, Marchetti O, Bille J, et al. Fungal Infection Network of Switzerland (FUNGINOS). Treatment options of invasive fungal infections in adults. Swiss Med Wkly. 2006;136:447–63.
23. Ruhnke M, Rickerts V, Cornely OA, et al. German Speaking Mycological Society, Paul-Ehrlich-Society for Chemotherapy. Diagnosis and therapy of Candida infections: joint recommendations of the German Speaking Mycological Society and the Paul-Ehrlich-Society for Chemotherapy. Mycoses. 2011;54:279–310.
24. Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet. 2016;387:760–9.
25. Jenks JD, Salzer HJ, Prattes J, et al. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. Drug Des Devel Ther. 2018;30(12):1033–44.
26. Pfaller MA, Rhomberg PR, Wiederhold NP, et al. In vitro activity of isavuconazole against opportunistic fungal pathogens from two mycology reference laboratories. Antimicrob Agents Chemother. 2018;62:e01230–18.
27. Herbrecht R, Kuessner D, Pooley N, et al. Systematic review and network meta-analysis of clinical outcomes associated with isavuconazole versus relevant comparators for patients with invasive aspergillosis. Curr Med Res Opin. 2018;17:1–9.

28. Bagshaw E, Enoch DA, Blackney M, et al. Economic impact of treating invasive mold disease with isavuconazole compared with liposomal amphotericin B in the UK. Future Microbiol. 2018;13:1283–93.
29. Ledoux MP, Toussaint E, Denis J, et al. New pharmacological opportunities for the treatment of invasive mould diseases. J Antimicrob Chemother. 2017;72(Suppl 1):i48–58.
30. Groll AH, Townsend R, Desai A, et al. Drug-drug interactions between triazole antifungal agents used to treat invasive aspergillosis and immunosuppressants metabolized by cytochrome P450 3A4. Transpl Infect Dis. 2017;19:e12751.
31. Giri S, Kindo AJ. A review of *Candida* species causing blood stream infection. Indian Rev Med Microbiol. 2012;30:270–8.
32. Prasad RR, Shree V, Sagar S, et al. Prevalence and antifungal susceptibility of *Candida albicans* in Patna, India. Int J Curr Microbiol App Sci. 2016;5:957–61.
33. Falagas ME, Roussos N, Vardakas KZ. Relative frequency of albicans and the various non-albicans Candida spp among candidemia isolates from inpatients in various parts of the world: a systematic review. Int J Infect Dis. 2010;14:e954–66.
34. Chakrabarti A, Chatterjee SS, Rao KL, Zameer MM, Shivaprakash MR, Singhi S, Singh R, Varma SC. Recent experience with fungaemia: change in species distribution and azole resistance. Scand J Infect Dis. 2009;41:275–84.
35. Singla N, Gulati N, Kaistha N, et al. Candida colonization in urine samples of ICU patients: determination of etiology, antifungal susceptibility testing and evaluation of associated risk factors. Mycopathologia. 2012;174:149–55.
36. Jain M, Dogra V, Mishra B, et al. Candiduria in catheterized intensive care unit patients: emerging microbiological trends. Indian J Pathol Microbiol. 2011;54:552–5.
37. Chakrabarti A, Sood P, Rudramurthy SM, et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med. 2015;41:285–95.
38. Yesudhason BL, Mohanram K. Candida tropicalis as a predominant isolate from clinical specimens and its antifungal susceptibility pattern in a Tertiary Care Hospital in Southern India. J Clin Diagn Res. 2015;9:DC14–6.
39. Bhattacharjee P. Epidemiology and antifungal susceptibility of Candida species in a tertiary care hospital, Kolkata, India. Curr Med Mycol. 2016;2:20–7.
40. Rajalakshmi A, Shareek PS, Sureshkumar D, et al. Candidemia species distribution and emergence of Candida haemulonii complex isolates resistant to fluconazole in South India. J Contemp Clin Pract. 2018;4:47–52.
41. Sundaram C, Umabala P, Laxmi V, et al. Pathology of fungal infections in the central nervous system: 17 years' experience from Southern India. Histopathology. 2006;49:396–405.
42. Shankar SK, Mahadevan A, Sundaram C, Sarkar C, et al. Pathobiology of fungal infections of the central nervous system with special reference to Indian scenario. Neurol India. 2007;55:198–215.
43. Chakrabarti A, Shivaprakash MR, Singh R, Tarai B, et al. Fungal endophthalmitis: fourteen years' experience from a center in India. Retina. 2008;28:1400–7.
44. Kullberg BJ, Viscoli C, Pappas PG, et al. Treatment of candidemia and other invasive candida infections: the ACTIVE trial. Clin Infect Dis. 2018;68:1981–9. https://doi.org/10.1093/cid/ciy827.
45. Chowdhary A, Sharma C, Duggal S, et al. New clonal strain of Candida auris, Delhi, India. Emerg Infect Dis. 2013;19:1670–3.
46. Lockhart SR, Etienne KA, Vallabhaneni S, et al. Simultaneous emergence of multidrug-resistant *Candida auris* on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. Clin Infect Dis. 2017;64:134–40.
47. Vallabhaneni S, Kallen A, Tsay S, et al. Investigation of the first seven reported cases of *Candida auris*, a globally emerging invasive, multidrug-resistant fungus-United States, May 2013-August 2016. MMWR Morb Mortal Wkly Rep. 2016;65:1234–7.
48. Rudramurthy SM, Chakrabarti A, Paul RA, et al. *Candida auris* candidaemia in Indian ICUs: analysis of risk factors. J Antimicrob Chemother. 2017;72:1794–801.

49. Mathur P, Hasan F, Singh PK, Malhotra R, Walia K, Chowdhary A. Five-year profile of candidaemia at an Indian trauma centre: high rates of *Candida auris* blood stream infections. Mycoses. 2018;61:674–80. https://doi.org/10.1111/myc.12790.
50. Schelenz S, Hagen F, Rhodes JL, et al. First hospital outbreak of the globally emerging *Candida auris* in a European hospital. Antimicrob Resist Infect Control. 2016;5: 2–7.
51. Chowdhary A, Sharma C, Meis JF. *Candida auris*: a rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. PLoS Pathog. 2017;13:e1006290.
52. Chakrabarti A, Singh R. The emerging epidemiology of mould infections in developing countries. Curr Opin Infect Dis. 2011;24:521–6.
53. Chakrabarti A, Chatterjee SS, Das A, et al. Invasive aspergillosis in developing countries. Med Mycol. 2011;49(Suppl 1):S35–47.
54. Rotjanapan P, Chen YC, Chakrabarti A, Li RY, Rudramurthy SM, Yu J, Kung HC, Watcharananan S, Tan AL, Saffari SE, Tan BH. Epidemiology and clinical characteristics of invasive mould infections: a multicenter, retrospective analysis in five Asian countries. Med Mycol. 2018;56(2):186–96.
55. Rudramurthy SM, de Valk HA, Chakrabarti A, et al. High resolution genotyping of clinical Aspergillus flavus isolates from India using microsatellites. PLoS One. 2011;6:e16086.
56. Xess I, Mohanty S, Jain N, Banerjee U. Prevalence of *Aspergillus* species in clinical samples isolated in an Indian tertiary care hospital. Indian J Med Sci. 2004;58:513–9.
57. Sivsankari S, Senthamarai S, Anitha C, et al. Prevalence of invasive aspergillosis among (PTB) patients in Kanchipuram, India. J Clin Diagn Res. 2014;8:22–3.
58. Chowdhary A, Kathuria S, Randhawa HS, et al. Isolation of multiple-triazole-resistant *Aspergillus fumigatus* strain carrying the TR/L98H mutations in the *cyp*51A gene in India. J Antimicrob Chemother. 2012;67:362–6.
59. Dabas Y, Xess I, Bakshi S, et al. Emergence of azole-resistant *Aspergillus fumigatus* from immunocompromised hosts in India. Antimicrob Agents Chemother. 2018;62: e02264–17.
60. Lestrade PPA, Meis JF, Melchers WJG, et al. Triazole resistance in *Aspergillus fumigatus*: recent insights and challenges for patient management. Clin Microbiol Infect. 2019;25(7):799–806. pii: S1198-743X(18)30780-8. https://doi.org/10.1016/j.cmi.2018.11.027.
61. Agarwal R, Denning DW, Chakrabarti A. Estimation of the burden of chronic and allergic pulmonary aspergillosis in India. PLoS One. 2014;9:e114745.
62. Maturu VN, Agarwal R. Itraconazole in chronic pulmonary aspergillosis: in whom, for how long, and at what dose? Lung India. 2015;32:309–12.
63. Sanath SS, Gogtay NJ, Kshirsagar NA. Post marketing study to assess the safety, tolerability and effectiveness of Fungisome: and Indian liposomal amphotericin B preparation. J Postgrad Med. 2005;51(Suppl 1):S58–63.
64. Rudramuthy SM, Jatana M, Singh R, et al. In *vitro* antifungal activity of Indian liposomal amphotericin B against clinical isolates of emerging species of yeast and moulds, and its comparison with amphotericin B deoxycholate, voriconazole, itraconazole and fluconazole. Mycoses. 2013;56:39–46.
65. Jadhav MP, Shinde VM, Chandrakala S, et al. A randomized comparative trial evaluating the safety and efficacy of liposomal amphotericin B (Fungisome) versus conventional amphotericin B in the empirical treatment of febrile neutropenia in India. Indian J Cancer. 2012;49: 107–13.
66. Bala K, Chander J, Handa U, et al. A prospective study of mucormycosis in North India: experience from a tertiary care hospital. Med Mycol. 2015;53:248–57.
67. Chakrabarti A, Singh R. Mucormycosis in India: unique features. Mycoses. 2014;57(Suppl 3):85–90.
68. Chakrabarti A, Dhaliwal M. Epidemiology of Mucormycosis in India. Curr Fungal Infect Rep. 2013;7:287–92.

69. Prakash H, Ghosh AK, Rudramurthy SM, et al. A prospective multicenter study on mucormycosis in India: epidemiology, diagnosis, and treatment. Med Mycol. 2019;57(4):395–402. https://doi.org/10.1093/mmy/myy060.
70. Manesh A, Rupali P, Sullivan MO, Raj PM, Rupa V, George B, Michael JS. Mucormycosis—a clinicoepidemiological review of cases over 10 years. Mycoses. 2019;62(4):391–8. https://doi.org/10.1111/myc.12897.
71. Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. VITAL and FungiScope Mucormycosis Investigators. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16:828–37.