GUIDELINES

ISCCM Position Statement on the Management of Invasive Fungal Infections in the Intensive Care Unit

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Abstract

Rationale: Invasive fungal infections (IFI) in the intensive care unit (ICU) are an emerging problem owing to the use of broad-spectrum antibiotics, immunosuppressive agents, and frequency of indwelling catheters. Timely diagnosis imperative to improve outcomes can be challenging. This position statement is aimed at understanding risk factors, providing a rational diagnostic approach, and guiding clinicians to optimize anti-fungal therapy.

Objectives: To update evidence on epidemiology, risk factors, diagnostic approach, anti-fungal initiation strategy, therapeutic interventions including site-specific infections and role of therapeutic drug monitoring in IFI in ICU and focus on some practice points relevant to these domains.

Methodology: A committee comprising critical care specialists across the country was formed and specific aspects of fungal infections and anti-fungal treatment were assigned to each member. They extensively reviewed the literature including the electronic databases and the international guidelines and cross-references. The information was shared and discussed over several meetings and position statements were framed to ensure their reliability and relevance in critical practice The draft document was prepared after obtaining inputs and consensus from all the members and was reviewed by an expert in this field.

Results: The existing evidence on the management of IFI was updated and practice points were prepared under each sub-heading to enable critical care practitioners to streamline diagnosis and treatment strategies for patients in the ICU with additional detail on site-specific infections therapeutic drug monitoring.

Conclusions: This position statement attempts to address the management of IFI in immunocompetent and non-neutropenic ICU patients. The practice points should guide to optimization of the management of critically ill patients with suspected or proven fungal infections.

Keywords: Antifungal susceptibility, Antifungal therapy, *Cryptococcus*, Histoplasmosis, Intensive care unit, Invasive aspergillosis, Invasive candidiasis, Invasive fungal infections, Mucormycosis.

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Highlights

Invasive fungal infection is an important contributor to mortality and morbidity in the intensive care unit (ICU). Reports suggest that invasive fungal infections have been found to result in high mortality rates among ICU patients, ranging from 40 to 90%. The high prevalence rate in the ICU is attributed to the increased risk factors and morbidity. Successful management of these patients relies on early recognition, diagnosis, and treatment.

This comprehensive document is a valuable resource for critical care practitioners. It is based on available evidence and provides valuable information on epidemiology, risk factors, diagnostic approaches, and therapeutic interventions for invasive fungal infections in critically ill non-neutropenic patients. It also discusses site-specific infections and the importance of therapeutic drug monitoring for invasive fungal infections.

Introduction

Globally 300 million people suffer from serious fungal infections and about 1.6 million die every year. Invasive candidiasis (IC) accounts for 70%, followed by aspergillosis and mucormycosis.[1–3] Centers for Disease Control and Prevention (CDC) has reported crude mortality of more than 25% in patients with candidemia and 40–90% in patients with invasive aspergillosis (IA) especially in immunocompromised patients.[4–6] Note that 4.1% of the Indian

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population has been estimated to suffer from a serious fungal disease. The reported annual incidence rates range from 188,000 for candidemia, 250,900 IA, and 195,000 for mucormycosis.[7] The 30-day all-cause mortality with fungal infections was reported as 43.4%, whereas the attributable mortality in invasive candidiasis from India has been reported to be 19.6–58.8% for IA, and 28–52% for mucormycosis.[8]

Methodology

This document is an effort to understand the risk factors for invasive fungal infections in critically ill patients, guide diagnostic approach, and guide the clinician to improve the existing anti-fungal treatment strategies in the intensive care unit (ICU) under the aegis of the Indian Society of Critical Care Medicine (ISCCM). The committee was composed of critical care specialists from across the country and the different aspects of fungal infections and anti-fungal treatment were assigned to the members. The team updated the evidence by extensively reviewing the literature through various electronic databases including Pubmed and Embase. They also reviewed all major international guidelines on the subject and cross-references from these articles. The group further exchanged the relevant literature and follow-up meetings with thorough discussions and review, the position statements were framed to ensure their reliability and relevance in clinical practice. The draft document was reviewed by all the committee members and after incorporating comments and suggestions, the final document was prepared, and consensus was achieved from all the members.

Invasive Candidiasis

Most Indian studies have identified candidemia as the most common fungal infection in ICU, with non-albicans candida (NAC) species being the predominant pathogen.[9–11] An Indian multicenter epidemiological study on ICU-acquired candidemia has reported an incidence of 6.51 cases/1000 ICU admissions, with candidemia occurring after a median 8-day stay in ICU. *Candida auris* was identified as an emerging multi-drug resistant fungus and is now the first rank order of isolates in multiple Indian ICUs. During the COVID-19 pandemic, the rates of candidemia doubled with *C. auris* being the dominant species (42%) followed by *Candida tropicalis*.[10,11] Observational studies have reported *C. auris* as being the most common isolate from Indian ICUs, followed by *C. tropicalis* and *C. parapsilosis*. *Candida auris* was associated with a high resistance to Amphotericin B as well as a higher crude mortality as compared to other candida species. The evolving epidemiology emphasizes the need to utilize this data to formulate and execute region and cohort-specific guidelines to optimize therapy.[12–14]

Risk Factors

Urinary catheterization, central venous catheter (CVC) insertion, mechanical ventilation, total parenteral nutrition (TPN), peritoneal dialysis, admission to public sector hospitals, length of ICU stay, renal failure, and steroid therapy.[11,12]

Invasive Aspergillosis

Recent global estimate data shows IA is more frequent in critically ill and chronic obstructive pulmonary disease (COPD) patients than in the immunosuppressed group.[14] It is being increasingly reported from India in patients with COPD, liver failure, and cirrhosis.[1,5] The 30-day all-cause mortality in IA has been reported to be 39.8%.[7]

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In the Indian multicenter ICU study, invasive mold infection was reported at 10.1 cases per 1000 ICU admissions and aspergillosis was detected in 74.8% of these cases. Aspergillus flavus was isolated at an equal frequency to *A. fumigatus*.[15] Since the early phase of the SARS-CoV-2 pandemic, cases of COVID-19-associated pulmonary aspergillosis (CAPA) in critically ill patients have been described, with a reported incidence ranging from 0 to 34.3% in the critically ill.[16] The wide variation of prevalence of CAPA cases is due to difficulty and lack of consensus in diagnosis. Bronchoalveolar lavage (BAL) galactomannan index value above 1 helps in the diagnosis of CAPA.[16]

Risk Factors and Predictors of Death

Lack of high particulate efficiency air (HEPA) facility in ICU, prolonged ICU stay and exposure to corticosteroids, diabetes mellitus, chronic liver disease (CLD), acquired immunodeficiency syndrome (AIDS), coronary artery disease (CAD), trauma, multi-organ failure.

Invasive Mucormycosis

Mucormycosis is considered a rare disease. However, in India, the disease is not so uncommon, with an estimated prevalence of 14 cases per 100,000 individuals, which is nearly 70 times higher than the global data.[17,18] A single-center Indian study has shown nearly a 6-fold rise in mucormycosis cases over a period of 25 years.[19] Further, a multi-center ICU study reported mucormycosis in nearly 24% of patients.[17] The attributable mortality has been reported at 38.2% deaths per year.[17,18]

Risk Factors

Reported from Indian ICUs include high APACHE II Score, mechanical ventilation, dialysis, steroid use, uncontrolled diabetes, hematological malignancy patients, and solid organ transplant recipients.[20–23] Uncontrolled diabetes overshadows all other risk factors in India.

Although Candida non-albicans remains the commonest invasive fungal infection in Indian ICUs, mold infections are increasingly being reported from ICUs. The epidemiology of fungal infections has been changing recently with opportunistic infections like Mucorales, Fusarium, Scedosporium, and Trichosporon species being reported more frequently in immunocompromised patients. The increasing emergence of less susceptible non-aspergillus mold infections, multidrug-resistant mold, and azole-resistant Candida non-albicans species is alarming.[8]

Practice Points

- In non-neutropenic ICU patients, Candida non-albicans is the major fungal pathogen. The risk factors include abdominal surgery, urinary catheterization, CVC insertion, mechanical ventilation, TPN, peritoneal dialysis, admission to a public hospital, renal failure, and steroid therapy.
- In neutropenic patients, those with acute myeloid or acute lymphocytic leukemia or hematopoietic stem cell transplant patients, IA is common and has a high mortality. In India, it is being reported more in patients with COPD, liver failure, cirrhosis, and long-term low-dose steroid therapy.

- The burden of mucormycosis in India is significantly higher than rest of the world. The likelihood of mucormycosis infection is higher in patients who are immunocompromised, have a high APACHE score, have uncontrolled diabetes, and have chronic kidney or liver disease. Uncontrolled diabetes overshadows all other risk factors in India.

Antifungal Initiation Strategies

Fungal infections, with their varying clinical presentations and risk factors, demand a multifaceted approach to anti-fungal therapy initiation, in the form of prophylactic, preemptive, empirical, and therapeutic (definitive) strategies.

Prophylactic Approach

Prophylactic anti-fungal therapy involves administering anti-fungal agents in high-risk patient populations to prevent fungal infections.[24,25] Prophylaxis aims to create a protective barrier during this vulnerable period, minimizing the emergence of invasive fungal diseases. A patient undergoing liver transplant or allogeneic stem cell transplantation is considered at high risk for invasive fungal infections, and prophylaxis with azoles such as fluconazole, voriconazole, or posaconazole are administered as prophylactic therapy to prevent potential fungal infections in these high-risk patients.[25,26]

In critically ill non-neutropenic patients, anti-fungal prophylaxis is recommended only in secondary or tertiary peritonitis, repeated gut perforation, and anastomotic leakage. Its role in necrotizing pancreatitis is debatable and depends on local epidemiology. If the incidence of candida infection in necrotizing pancreatitis is more than 10%, it qualifies for prophylaxis.

Preemptive Approach

As delay in initiation of anti-fungal therapy is associated with high mortality, early initiation of treatment in high-risk patients with suspicion of invasive fungal infections is called preemptive anti-fungal therapy. The decision to initiate anti-fungal therapy is based on positive diagnostic biomarkers like β-D- glucan (pan fungal except *Cryptococcus* and Mucorales), galactomannan, and radiological signs in CT scans of the chest in high-risk patients.[24,25] Regular monitoring of these markers two or three times per week, the appearance of radiological signs like small inflammatory clusters or masses or fluffy nodules or halo sign (ground glass opacity surrounding a pulmonary nodule or mass), or air crescent sign (crescent-shaped air space separates mass from the wall of the cavity) guides the decision to initiate anti-fungal therapy in high-risk populations early. While preemptive therapy minimizes unnecessary exposure to anti-fungal drugs, careful patient selection and ongoing monitoring are crucial to strike a balance between early intervention and avoiding overuse.[26,27]

The pre-emptive approach guides the decision to initiate anti-fungal therapy in high-risk populations early before clinical symptoms manifest.[26,27] In patients undergoing hematopoietic stem cell transplant, preemptive anti-fungal therapy is initiated for persistent neutropenia exceeding 10 days, with positive fungal markers or radiological signs.

Empiric Approach

Empirical anti-fungal therapy is initiated based on clinical suspicion without confirmed microbiological evidence.[26,27] This approach is commonly employed in critically ill patients with worsening clinical status like refractory fever despite appropriate antibiotic therapy, increasing respiratory insufficiency, or need for ventilatory support, where prompt intervention is crucial. In patients with septic shock, in addition to empiric broad-spectrum antibiotic therapy, empiric anti-fungal therapy may be added if the patient has risk factors for invasive fungal infections. The knowledge of local epidemiology and risk factors aids in selecting appropriate anti-fungal agents until definitive diagnostic results are available.

In the absence of specific diagnostic evidence, in initiating empirical anti-fungal therapy, the choice of anti-fungal agent is based on clinical signs, patient's risk factors, and use of various scoring systems like candida score, Ostrosky-Zeichner rule and in situations like refractory fever, sepsis unresponsive to appropriate antibacterial therapy in absence of specific diagnostic evidence.[26–29] Empiric anti-fungal therapy in critically ill patients for putative invasive pulmonary aspergillosis may be initiated based on Blot (AspICU) or Modified Blot (MAspICU) criteria.[30,31] Similarly, Bulpa and modified Bulpa criteria have been suggested for initiating anti-fungal therapy for putative aspergillosis in COPD patients admitted to the respiratory ward, or ICU.[32,33]

Targeted

Targeted anti-fungal initiation is the therapy in patients with confirmed fungal infections based on microbiological evidence.[27–29] Targeted anti-fungal initiation involves the presence of a positive blood or tissue culture, using anti-fungal drugs based on susceptibility testing.[28,29] Targeted strategies encompass the use of various anti-fungal classes, with adjustments based on patient response and adverse effects. The duration and intensity of therapy are tailored to the severity and site of infection, ensuring targeted and effective treatment.

Comparative Analysis of Approaches

The high mortality associated with delayed diagnosis of invasive fungal infections has prompted early initiation of antifungal therapy as prophylactic, preemptive, empirical, or targeted in high-risk susceptible patients. Preemptive and empirical strategies address early intervention based on diagnostic radiology, serum biomarkers, and clinical suspicion, while prophylaxis and targeted approaches focus on prevention and targeted treatment, respectively.[28,29]

Practice Points

- Delay in diagnosis and initiation of anti-fungal therapy is associated with a high mortality.
- Use prophylactic anti-fungal therapy in high-risk populations with prevalence of fungal infections more than 10%.
- Biomarkers and radiological signs in high-risk patients help in early initiation of anti-fungal therapy.
- Clinical signs, risk factors for invasive fungal infections, and use of various scoring systems like candida score, and Ostrosky-Zeichner rule help in identifying patients for empirical therapy.

Diagnostic Methods

As mortality associated with delayed diagnosis of invasive fungal infection is very high, the most challenging issue is establishing a confirmatory diagnosis. Clinical findings, radiological findings,

and biomarkers help in establishing a provisional diagnosis and help in initiating empiric or preemptive anti-fungal therapy. However, a definitive diagnosis generally requires a positive tissue (histopathology) or body fluid (blood, cerebrospinal fluid [CSF], etc.) report. There are specific tests available for the diagnosis of different fungal infections (Table 1).

Table 1: Diagnostic methods

Test	*Description*	*Advantages*	*Limitations*	*Practice statement*
Conventional direct microscopy, culture, and histopathology of samples like blood, respiratory specimens, and biopsy[28]	Blood culture and culture of sample from apparent sterile site is the gold standard diagnostic test. Around 8–10 mL of blood per bottle, two bottles per set should be take. For diagnosis of intra-abdominal candidiasis, per-operative sample is more desirable, peritoneal fluid aspirated in spontaneous peritonitis should be tested for both bacteria and fungi isolation; drain fluid for drain installed > 24 hours should be discarded Sputum and broncho-alveolar are better samples than tracheal aspirate Though collection of biopsy sample is difficult in critically ill patient, bronchoscopy, EBUS, imaging guided biopsy/ aspiration improve diagnosis especially mold infection	It identifies the specific causative organism and can provide antifungal susceptibility testing results	Turnaround time is longer Conventional species identification method requires a further 1–2 days. For 50% time, culture may miss the causative fungus. Blood culture is rarely positive in aspergillosis. Presence of mold in respiratory specimen (sputum and BAL) may represent colonization	Blood culture should be obtained for all patients with suspicion of IFI Aspirated samples from sterile sites help in the diagnosis For suspected respiratory fungal infections, sputum, BAL samples processed Bronchoscopy and EBUS technique improve diagnosis Image-guided biopsy/ aspiration should be attempted if infection site can be localized Biopsies should be sent for culture and histopathology to confirm fungal infection
T2 Candida[34,35]	The assay breaks yeast cells apart, releasing deoxyribonucleic acid (DNA), copies the target DNA, and detects the amplified DNA using magnetic resonance technology. This technology enhances the early detection of Candidemia	Detects as low as 1 colony forming unit (CFU)/mL Turnaround time <5 hours Detects five species including *C. Albicans, C. Tropicalis, C. Parapsilosis, C. Krusei, C. Glabrata*	Can detect only the mentioned five Candida species Expensive and not available in Indian market	T2 Candida may be used when available in India along with blood culture in patients with high clinical probability of invasive Candidiasis
MALDI-TOF-MS[36,37]	Species identification is done from culture. identification of fungi is also possible from broth of blood culture when there is positive signal.	Can detect most of the yeast and Mycelial species Faster turnaround time	Expensive equipment, though consumable cost is minimal	MALDI-TOF-MS should be used for early identification of Candida species
Serological tests—They can diagnose IFI before the symptoms develop. The sensitivity and specificity of these tests are better than the conventional tests.				
B-d-glucan (BDG)[38,39]	It detects 1,3-β-d-glucan which is a component of fungal cell wall. It is used as a screening test for presuming the diagnosis of invasive fungal infections. A cut-off value of 80 Pg/mL and greater in a single test and 60 Pg/mL in two consecutive tests are considered positive (Fungitell). Cut-off values depend on the platform used for testing	Non-specific pan-fungal biomarker Detects all species of fungal infections including *candida, aspergillus* except *Cryptococcus* and Mucorales[40] Negative predictive value is around 80% Also useful in diagnosis of intra-abdominal Candidiasis [41] Rapid turnaround time of 2–4 hours. May vary according to the frequency at which the test is performed.	False positive result due to: Recent administration of β-Lactam antibiotics Infusion of immunoglobulin, albumin Contamination with cellulose filter, gauze Patients on Hemodialysis or after abdominal surgery Gram Positive bacteria Septicemia, *Alcaligenes faecalis*	1,3-β-d-glucan may be used as a guide to stop empirical anti-fungal therapy due to its high negative predictive value

(Contd...)

Table 1: *(Contd...)*

Test	*Description*	*Advantages*	*Limitations*	*Practice statement*
Mannan antigen and anti-mannan antibodies[42]	Mannan is component of fungal cell wall and is specific to *Candida* spp. Tested by latex agglutination or enzyme immunoassay	More specific and less sensitive than BDG Turnaround time same as BDG	Only detects presence of Candida species. Most sensitive to *Candida albicans* and least to *Candida parapsilosis*. Sensitivity 54–65%, specificity 79–97%	It can be used along with BDG to detect Candidemia
Candida albicans germ tube antibody (CAGTA)	Detects response against a hyphal protein (hwp1) expressed during tissue invasion and biofilm	Sensitivity—42–96% Specificity—54–100%[43] Good test when local epidemiology shows higher percentage of *C. albicans* infection	In India, the test may not be suitable where non-*C. albicans* species are prevalent	Can combine with other biomarker tests for diagnosis of invasive candidiasis
Galactomannan (GM)[44–46]	A specific test for *aspergillus* spp. The principle is testing of heteropolysaccharide which is present in Aspergillus cell wall. The cut-off value above 0.5 is considered positive for serum and 1.0 for bronchoalveolar lavage (BAL). GM can be found in serum, urine, cerebrospinal fluid, and BAL (urine and CSF are not yet FDA approved)	Combined testing of serum and BAL gm increases the sensitivity	False negative may be found in non-neutropenic patients due to slow progression. False negative in patients on anti-fungal prophylaxis. False positive in patients receiving piperacillin-tazobactam, plasmalyte fluid, and sodium gluconate; bacterial infection by bifidobacterium, presence of non-aspergillus fungi including penicillium, alternaria, paecilomyces, histoplasma, geotrichum; food intake like pasta, yoghurt.[44]	GM should be performed in neutropenic patients who have lung infiltrates. GM testing in non-neutropenic patients should be combined with BAL GM. Serum GM has better sensitivity (65%) in influenza-associated aspergillosis (IPA) as compared to COVID-19-associated aspergillosis (CAPA) (20%).[47]
Lateral flow device assay (LFA)	This is a point-of-care (POC) testing Separate LFA tests have been developed for cryptococcosis, aspergillosis, and histoplasmosis diagnosis Crag can be found in blood and body fluids including cerebrospinal fluid.[48,49]	The sensitivity is 99%. POC testing so can be used in resource-limited settings.	The test is well standardized in cryptococcosis, need further standardization in Indian context for routine use in aspergillosis and histoplasmosis	LFA *Cryptococcus* may be used when suspecting cryptococcosis Other two LFA tests will be utilized in routine practice

(Contd...)

Table 1: *(Contd...)*

Test	*Description*	*Advantages*	*Limitations*	*Practice statement*
Molecular methods—Though these methods provide rapid results, require standardization in ICU patients				
Polymerase chain reaction (PCR) test[50–52]	Detects fungal nucleic acid. Standardized for *aspergillus*	Highly sensitive (96.3%) compared with culture-based techniques. Faster turnaround time. Various body fluids can be tested. Can be used when culture fails to isolate the fungus. At least two positive tests are needed for diagnosis. PCR for aspergillus species has shown good sensitivity and specificity.[53,54] BAL aspergillus PCR has high diagnostic performance and only single BAL PCR is recommended.[55]	Not validated in large randomized controlled trials.	PCR test can be used for diagnosis of aspergillosis. PCR for candidiasis requires more standardization Commercial tests are preferred rather than in-house test, as standardization is difficult for in-house test
Radiology—They are non-diagnostic and require co-relation with clinical history				
Chest X-ray	Non-diagnostic	No major advantage	Very low sensitivity and plain chest radiograph should not be used to diagnose invasive fungal infections	It may be helpful in chronic pulmonary *aspergillosis*
Computed Tomography (CT)	Chest CT may reveal nodules, areas of consolidation, cavitatory lesion, localized bronchiectasis, tree-in-bud lesions, or nodules in immunocompetent host Immunocompromised (neutropenic) patients may have halo sign (nodule surrounded by ground glass shadows) or air crescent sign[56,57] In invasive mold infection, sinus and brain CT may be used to screen mucormycosis or invasive aspergillosis	Helps to identify the site and extent of infection Helps to plan further investigations like bronchoscopy or biopsy	Radiation hazard	Chest CT should be done for all patients with suspicion of invasive aspergillosis or mucormycosis

Practice Points

- Culture of Blood, and fluid from sterile sites or tissue are the gold standard for fungal infections.
- All biopsy specimens should be tested for both histopathology and microbiological culture.
- The MALDI-TOF technique should be performed for species identification.
- β-d glucan should be used to stop empiric anti-fungal therapy.
- BAL GM is more sensitive than serum GM in diagnosing Aspergillus infections.
- In most settings, positive predictive values (PPVs) of biomarker tests are low and negative predictive values (NPVs) are high.
- The threshold PPVs and NPVs that justify anti-fungal treatment in critically ill patients is not well established.
- In many instances, test performance has not been validated for different types of candida sepsis or in different patient populations.
- Clinicians must understand the pretest likelihood of invasive candidiasis or aspergillosis and test performance for the most common disease manifestation in a given patient.
- NPV of ≥–85% may justify withholding treatment.
- In suspected patients suspected to have invasive fungal infection, if biomarker tests are negative, suspect mucormycosis.
- None of the tests is likely to have value if ordered indiscriminately each time a blood culture is collected, especially in the group of patients where the baseline rate of invasive candidiasis is low.
- Caution should be maintained for false positivity and negativity of biomarker tests

Antifungal Agents for Appropriate Fungal Infections

The principal classes of anti-fungal agents based on their inhibition targets are:[58–60]

- Leakage in the cell wall by the development of cell membrane pores after adherence to ergosterol—Polyenes.

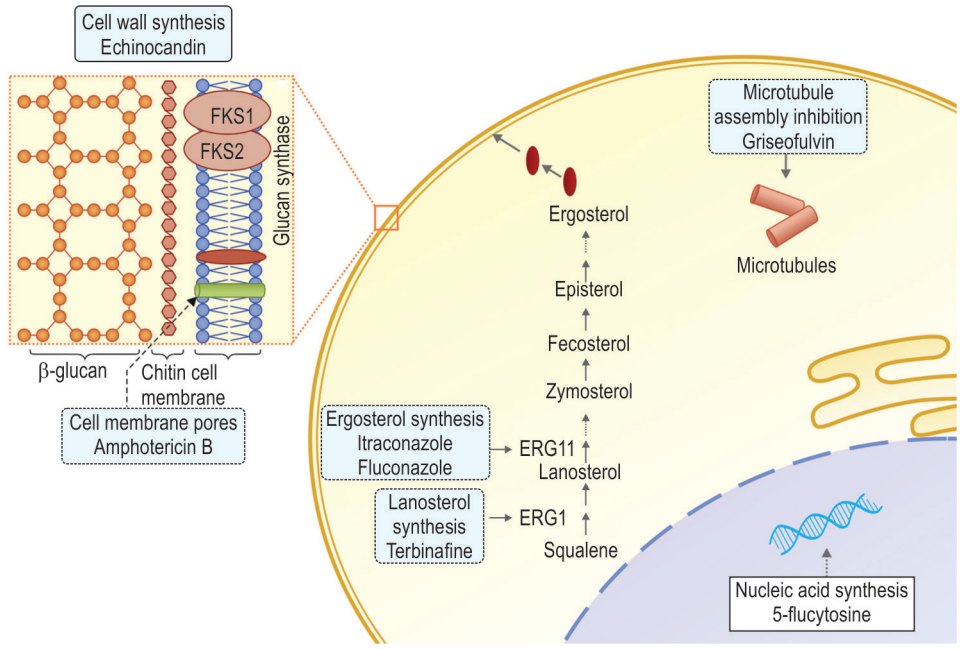

Fig. 1: Mechanism of action of anti-fungal drugs

Table 2A: Echinocandins[61–67]

Drug	*Dose*	*Duration*	*Comments*
Caspofungin	70 mg loading dose followed by 50 mg once daily IV	14 days from last negative blood culture. However, shorter course (9 days) vs longer course (14 days) did not affect mortality or BSI recurrence in uncomplicated candidemia. More studies required. Till that follow 14 days from last negative blood culture	In moderate to severe hepatic impairment (Child-Pugh B and C) —70 mg on day 1 followed by 35 mg once daily Echinocandins should be avoided when central nervous system is involved, fungal endophthalmitis, intra-abdominal candidiasis, non-*Candida* fungemia
Micafungin	100 mg once daily IV	Same as above	No loading dose is required
Anidulafungin	200 mg loading dose followed by 100 mg once daily IV	Same as above	Can be administered without dose adjustments to patients with any degree of renal/hepatic insufficiency, and also does not require dose adjustments with any concomitant drug
Rezafungin	400 mg on day 1 followed by 200 mg once a week from day 8	Up to 4 doses	To be used when other options are limited or unavailable

- Ergosterol inhibitors: Azoles
- 1,3 β-d-glucan synthase component (GS) FKS1 inhibitors: Echinocandins and Ibrexafungerp which have recently been approved.
- Flucytosine: Interferes with DNA and RNA metabolism [commonly used in combination with polyenes (Fig. 1)].

Candidemia/Invasive Candidiasis

Management includes prompt initiation of appropriate anti-fungal, source control, and invasive device removal which needs to be individualized.

Initial Therapy (Tables 2A and B)

Candida Auris

It is desirable to perform antifungal susceptibility testing when *C. auris* is isolated, as Indian isolates are under clade I, which is fluconazole resistant, 50% voriconazole resistant, and 35% polyene resistant. The initial treatment for *C. auris* should be with an Echinocandin. Because *C. auris* can develop resistance quickly, patients receiving antifungal therapy should be monitored carefully with follow-up surveillance blood cultures. If the clinical response to treatment with an Echinocandin is inadequate or candidemia persists for several days, treatment can be switched to a lipid formulation of Amphotericin B 5 mg/kg IV daily. Azoles are usually not effective for the treatment of *C. auris* clade I isolated in India.[62,63]

The following table may serve as a guide till susceptibility results are available. Echinocandin monotherapy is as effective as other anti-fungal and hence there is no indication of routine combination therapy in most cases (Table 3).[64–66]

Invasive Aspergillosis

Treatment includes early definitive diagnosis and appropriate therapy combined with a reduction in immune suppression and surgery where feasible. The choice of agent depends upon immune

Table 2B: Other drugs for Invasive candidiasis

Drug	*Dose*	*Duration*	*Comments*
Fluconazole	800 mg (12 mg/kg) IV on day 1 followed by 400 mg (6 mg/kg)	14 days from last negative blood culture	In patients who are not critically ill, not infected with an azole resistant *Candida* (*glabrata, krusei*) or where the prevalence of azole resistance is low. It can be used as a step-down therapy once the patient is stable and the organism is susceptible.
Liposomal Amphotericin B	3–5 mg/kg IV	14 days from last negative blood culture	Intolerance, limited availability, CNS involvement or in case of *Candida parapsilosis*. In case of renal infections, Amphotericin B deoxycholate should be used.

Non, neutropenic

Table 3: Susceptibility of *Candida* species

	Azoles			*Echinocandins*	*Polyenes*	*Others*
Organism	*Fluconazole*	*Itraconazole*	*Voriconazole*	*Anidulafungin*	*Liposomal Amphotericin B*	*Flucytosine*
Yeast						
Candida albicans	S	S	S	S	S	S
Candida glabrata	SDD, high dose required	R	S	S	S	S
Candida krusei	R	R	S	S	Check susceptibility data	Check susceptibility data
Candida lusitaniae	S	S	S	S	R	S
Candida parapsilosis	S	S	S	I, high dose required	S	S
Candida tropicalis	S	S	S	S	S	S
Candida neoformans	S	Variable	S	R	S	S
Candida auris	R	R	Variable	S	S	S

I, intermediate; R, resistant; S, susceptible; SDD, susceptible dose dependent

Table 4: Treatment for invasive *aspergillosis*

Drug	*Dose*	*Comments*
Voriconazole	6 mg/kg twice daily IV on day 1 followed by 4 mg/kg twice daily IV for at least 7 days—may be changed to 200 mg orally twice daily	IV preparation—contains cyclodextrin which may be nephrotoxic in case of renal impairment. Drug-drug interactions, hepatotoxicity, hallucination and dark skin, QT prolongation
Posaconazole	IV/Delayed release tablets—300 mg twice daily for 2 doses then 300 mg once daily	Non-inferior to voriconazole with comparatively less drug interaction. If liquid preparation is used, fatty meal should be provided to improve absorption
Isavuconazole	IV/Oral—372 mg (Isavuconazole-200mg) every 8 hours for 6 doses then 200 mg once daily	Noninferior to Voriconazole with fewer adverse effects and drug-drug interactions
Liposomal Amphotericin B (L-Amb)	3–5 mg/kg/day	May have an advantage in case of suspected mold infection without confirmation of IA. Nephrotoxicity is a concern
Amphotericin B lipid complex	5 mg/kg/day	Same as Liposomal Amphotericin B

status, organ function (liver, kidney), prior azole exposure, and the likelihood of resistance.

Initial Therapy

Voriconazole and Isavuconazole are the primary drugs of choice unless resistance is suspected. In case of intolerance or side effects, Posaconazole or Liposomal Amphotericin B can be used as alternatives. Posaconazole is included in both first choice and alternative. For Liposomal Amphotericin B or Amphotericin B lipid complex nephrotoxicity and IV administration are the limitations (Table 4).[68–71]

Combination Therapy

Voriconazole with Echinocandins may be considered in case of severe disease both as initial and salvage therapy with the strongest evidence in hematological malignancies and HCT.[72]

However, the toxicity cost of therapy and feasibility of prolonged IV administration need to be considered.

Duration of Therapy

Till resolution of all signs and symptoms which is usually for a minimum of 6–12 weeks may need to be individualized based on site of infection, response to therapy, immunosuppression, and underlying disease. Monitoring by imaging and galactomannan measurement can also help in the termination of therapy. In cases such as endocarditis or brain abscess, lifelong therapy may need to be continued in the therapeutic dosage.

Mucormycosis

Treatment of mucormycosis includes aggressive surgical debridement with early appropriate anti-fungal therapy, and reducing immunosuppression and blood sugar control.

Initial Therapy

Liposomal Amphotericin B[73,74]

Dose

5 mg/kg/day may need to be increased to 10 mg/kg/day (CNS disease—start with 10 mg/kg/day)

Duration

Till clinical improvement and radiological resolution which may take several weeks to months and sometimes patients may need lifelong treatment if immunosuppression cannot be reversed.

Step Down

Posaconazole[75] (IV or delayed released tablets) or Isavuconazole[75,76] may be used as step-down therapy after 2–6 weeks of Amphotericin B therapy.

Salvage Therapy

If unable to tolerate Amphotericin B or no response, Isavuconazole or Posaconazole IV can be used as salvage therapy and switched over to oral formulations once the patient stabilizes.[77,78]

Cryptococcosis

Treatment should be tailored according to immune status, site of infection, and availability of drugs. Amphotericin B, Flucytosine, and Azoles are effective agents. Newer agents like Fosmanogepix and Opelconazole are under development and have efficacy against *Cryptococcus* and may provide novel options in the future.[78–82] A combination of Amphotericin B with flucytosine is preferred.

Duration

Induction phase (2 weeks), consolidation phase (8 weeks), and maintenance therapy to prevent recurrence in selected patients.

Histoplasmosis[83–87]

Treatment depends on severity of disease and presence of CNS involvement.

Lipid formulation of Amphotericin B for 2 weeks (CNS involvement–6 weeks) followed by Itraconazole 200 mg twice daily for at least 12 months. Alternative agents to Itraconazole are Fluconazole Voriconazole, Posaconazole and Isavuconazole.

Pneumocystis Jirovecii (PCP)

Trimethoprim-sulfamethoxazole (TMP-SMX) is the treatment of choice for PCP of any severity without HIV with adjunctive glucocorticoids for 21 days.[88]

Dose

5–20 mg/kg (based upon the TMP component) intravenously or orally daily in three or four divided doses. The dose should be adjusted as per creatinine clearance (Tables 5 and 6).

Site-specific Fungal Infections

Table 5: Candida

Site	*Treatment options*
Invasive candidiasis—Empiric treatment[89–94]	For critically ill patients who have a high risk of getting a fungal infection, have signs that suggest a fungal infection, and further not responding to antibacterial therapy, empiric antifungal therapy is advisable For suspected candidiasis in non-neutropenic ICU patients, Echinocandins (Caspofungin: 70 mg loading dose, then 50 mg daily; Micafungin: 100 mg daily; Anidulafungin: 200 mg loading dose, then 100 mg daily) should be used as empiric therapy Fluconazole, 800-mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, is an acceptable alternative where Echinocandin could not be instituted for any reason Lipid formulation Amphotericin B, 3–5 mg/kg daily, is recommended when other antifungals are intolerable Duration—Empiric therapy can be given for 2 weeks. In case of no response to therapy after 1 week, no invasive candidiasis, negative non-culture-based diagnostic assay treatment should be stopped. Negative β-d-glucan is an ideal marker to stop empiric therapy
Should prophylaxis be used to prevent invasive candidiasis in the ICU setting?[95–99]	In high-risk patients in adult ICUs with a high rate of invasive candidiasis (in cohorts where prevalence of invasive candidiasis is more than 10%), Fluconazole 400 mg (6 mg/kg) daily can be used. Alternatively Caspofungin: 70-mg loading dose, then 50 mg daily; Anidulafungin: 200-mg loading dose and then 100 mg daily; or Micafungin: 100 mg daily can be considered. Chlorhexidine body bath can be used to decrease *Candida* colonization, especially required in *C. auris* colonization

(Contd...)

Table 5: *(Contd...)*

Site	*Treatment options*
Bloodstream infections[100–108]	• The first treatment option is Caspofungin (70 mg loading dose, followed by 50 mg daily), Micafungin (100 mg daily), or Anidulafungin (200 mg loading dose, followed by 100 mg daily). • For non-critically ill patients and patients unlikely to have resistance against Fluconazole, Fluconazole IV/Oral can be used as an alternative to Echinocandins. The recommended dosage is an 800-mg loading dose (or 12 mg/kg) followed by a daily dose of 400 mg (or 6 mg/kg). • In stable patients and Isolates that are susceptible to Fluconazole and those where there is negative blood culture after initiation of antifungal therapy switching from Echinocandin to Fluconazole should be done typically within 5–7 days of Echinocandin therapy. • *C. glabrata*, where within susceptible dose-dependent range against fluconazole, should be treated with higher doses of Fluconazole (800 mg or 12 mg/kg) on a daily basis, or Voriconazole (200–300 mg or 3–4 mg/kg) twice daily. • When other antifungal drugs are not tolerated, or resistance is found, a lipid-based formulation of Amphotericin B (AmB) at a dosage of 3–5 mg/kg per day is a good option. • Switching from AmB to Fluconazole should be done after 5–7 days for patients who have isolates that are susceptible to Fluconazole, where the patient is clinically stable. • Azole and Echinocandin-resistant cases can be treated with lipid formulation AmB at a daily dosage of 3–5 mg/kg. • Voriconazole at a dose of 400 mg (6 mg/kg) taken twice daily for 2 doses, followed by a dose of 200 mg (3 mg/kg) taken twice daily, may be used to treat Candidemia. • In *C. krusei* infection, fluconazole and Amphotericin B should be avoided, treated with Echinocandin • In *C. auris* infection, Echinocandins should be used and antifungal susceptibility testing should be performed for the isolate • Better to remove CVC when possible; Otherwise, Echinocandin or polyene • Inadequate antifungal exposure has been documented in these patients due to third spacing (movement of fluid from intra-vascular to interstitial space), hypoalbuminemia, renal failure, hepatic failure, RRT, and ECMO (Echinocandin is extracted by ECMO circuit); should adopt PK/PD-based dosing as part of routine clinical practice • Due to the high toxicity of azoles and the high probability of drug-drug interactions, TDM should be considered when using itraconazole, Posaconazole, or voriconazole as antifungal therapy • Echinocandin exposure suboptimal exposure in critically ill patients and also in overweight patients, reasons that favor TDM • PK parameters are not well elucidated for Amphotericin B so routine TDM is not desirable, except when toxicity is a major concern • Routine TDM for flucytosine is recommended due to the high variability in serum concentrations following administration and severe adverse effects • Fundoscopy examination after 1 week of diagnosis of candidemia after neutrophil counts recover
Urinary tract infections[109–116]	Asymptomatic Candiduria • Eliminate predisposing factors like catheters • Treatment is only advisable for neutropenic patients, low birth weight infants or those undergoing urologic interventions • Neutropenic patients and very-low-birth-weight infants should be treated for candidemia with Echinocandins Patients undergoing urologic procedures should be treated with oral fluconazole, 400 mg (6 mg/kg) daily, OR AmB deoxycholate, 0.3–0.6 mg/kg daily, for several days before and after the procedure **Treatment** *Candida cystitis* • Oral Fluconazole, 200 mg (3 mg/kg) daily for 2 weeks should be used for Fluconazole-susceptible organisms • AmB deoxycholate, 0.3–0.6 mg/kg daily for 1–7 days, or oral Flucytosine, 25 mg/kg 4 times daily for 7–10 days should be used for Fluconazole-resistant *C. glabrata* • Deoxycholate bladder irrigation, 50 mg/L in sterile water daily for 5 days, may be used to treat Fluconazole-resistant cystitis in *C. glabrata* and *C. Krusei* **Ascending *candida* pyelonephritis** • Oral Fluconazole 200–400 mg (3–6 mg/kg) daily for 2 weeks should be used for Fluconazole-susceptible organisms • AmB deoxycholate, 0.3–0.6 mg/kg daily with or without oral Flucytosine, 25 mg/kg 4 times daily for 1–7 days should be used for Fluconazole-resistant *C. glabrata* Tubes and any associated obstructions should be removed immediately. **Candida urinary tract infection associated with fungus balls** • Adults should undergo surgical intervention • Antifungal therapy is the same as for cystitis or pyelonephritis • Irrigation should be done with 25–50 mg AmB deoxycholate in 200–500 mL sterile water if nephrostomy tubes are present.

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Table 5: *(Contd...)*

Site	*Treatment options*
Intra abdominal infections [117–121]	Patients with recent abdominal surgery, anastomotic leaks, necrotizing pancreatitis, intra-abdominal infection, and risk factors for Candidiasis should receive • Echinocandins (Caspofungin: 70 mg loading dose, then 50 mg daily; Micafungin: 100 mg daily; Anidulafungin: 200 mg loading dose, then 100 mg daily). • Fluconazole, 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily, is an acceptable alternative where azoles are restricted • Lipid formulation AmB, 3–5 mg/kg daily, is recommended when other antifungals are intolerable • Therapy can be given for 2 weeks. In case of no response to therapy after 1 week, no invasive candidiasis, negative non-culture-based diagnostic assay, the treatment should be stopped. Negative β-d-glucan can also be used to stop therapy Source control, drainage and/or debridement, should be implemented at the earliest. Adequacy of source control and clinical response should determine the duration of therapy.
Device associated infections	**Infected central nervous system devices**[122–124] Infected device should be removed if at all possible. For patients in whom device cannot be removed, AmB deoxycholate can be administered through the device into at a dosage ranging from 0.01 to 0.5 mg in 2 mL 5% dextrose in water. After device removal, patients should be monitored for response to treatment based on clinical parameters; monitoring of CSF cultures is recommended to ensure that they become negative. CSF Candida mannan antigen and anti-mannan antibodies may be useful additional tests in patients with suspected Candida meningitis in whom cultures are negative ***Candida* infection of implantable cardiac devices and native valve endocarditis**[125–142] Infected devices should be removed if at all possible. • Lipid formulation Amphotericin B, 3–5 mg/kg daily, with or without Flucytosine, 25 mg/kg 4 times daily, OR high-dose Echinocandin (Caspofungin 150 mg daily, Micafungin 150 mg daily, or Anidulafungin 200 mg daily) is recommended for initial therapy. • Switch over to Fluconazole, 400–800 mg (6–12 mg/kg) daily, who have susceptible *Candida* isolates, have cleared *Candida* from the bloodstream and are clinically stable, • Oral Voriconazole, 200–300 mg (3–4 mg/kg) two times daily, or Posaconazole tablets, 300 mg daily, where Fluconazole resistance is there. For infections that are only in generator pockets, 4 weeks of antifungal therapy should be given after removal of the device. Regarding infections that affect the wires, at least 6 weeks of antifungal therapy after wire removal should be given. **Native valve endocarditis** • Lipid formulation Amphotericin B, 3–5 mg/kg daily, with or without Flucytosine, 25 mg/kg 4 times daily, OR high-dose Echinocandin (Caspofungin 150 mg daily, Micafungin 150 mg daily, or Anidulafungin 200 mg daily) should be used as initial therapy. • .In endocarditis, Azole should be avoided as primary therapy due to biofilm issues. • Valve replacement should be done after 1–2 weeks antifungal therapy unless contraindicated • Drug therapy should continue for at least 6 weeks after surgery and for a longer duration in patients with perivalvular abscesses or other complications. • For patients who cannot undergo valve replacement, long-term suppression with Fluconazole, 400–800 mg (6–12 mg/ kg) daily, should be used for susceptible isolates. **Prosthetic valve endocarditis** The same antifungal regimens that are suggested for native valve endocarditis should be used. Valve should be replaced after 1–2 weeks of antifungal therapy. Chronic suppressive anti-fungal therapy with Fluconazole 400–800 mg (6–12 mg/kg) daily should be used to prevent recurrence. **Ventricular assist devices** If it is not possible to remove the device, the anti-fungal regimen is the same as that for native valve endocarditis. For devices that cannot be removed: Lipid formulation AmB, 3–5 mg/kg daily with or without Flucytosine 25mg/kg 4 times daily, OR high dose Echinocandin (Caspofungin150 mg daily, Micafungin 150 mg daily or Anidulafungin 200 mg daily is recommended for initial therapy. Switch over to Fluconazole 400–800 mg (6–12 mg/kg) daily, for those who have susceptible *Candida* isolates, have cleared *Candida* from the bloodstream, and are clinically stable. Oral Voriconazole, 200–300 mg (3–4 mg/kg) two times daily, or Posaconazole tablets, 300 mg daily, if Fluconazole resistance is present.
Septic arthritis[143–146]	Where prosthetic device has been used, it should be removed. If it cannot be removed, and if the isolate is susceptible, chronic suppressive therapy with Fluconazole, 400 mg (6 mg/kg) daily should be used.
Endophthalmitis[147–154]	Dilated retinal examination by ophthalmologist should be done to exclude endophthalmitis Infectious disease physician and ophthalmologist will jointly decide regarding type and duration of antifungal therapy.

Candida from respiratory isolates—Candida is often detected in respiratory specimens from humans with and without lung disease; its significance remains uncertain.

Anti-fungal therapy may be given to those who are immunodeficient, not improving with antibiotics, with positive biomarkers (BDG), and without an alternative etiology.

Mucormycosis

Early diagnosis and prompt therapy remain the cornerstone of mucormycosis management. Treatment of mucormycosis involves surgical debridement, anti-fungal therapy, and modifying underlying immunosuppression or co-morbidities. Since it is

Table 6: Aspergillosis[68,69,155–166]

Site	*Treatment*
Invasive aspergillosis/ invasive pulmonary aspergillosis (IPA)	**Primary treatment** Voriconazole (6 mg/kg IV every 12 hours for 1 day, followed by 4 mg/kg IV every 12 hours/oral therapy can be used at 200–300 mg every 12 hours OR Isavuconazole IV/ Oral—372 mg (Isavuconazole 200 mg) every 8 hours for 6 doses then 200 mg once daily OR Posaconazole IV/Delayed release tablets 300 mg twice daily for 2 doses then 300 mg once daily **Alternative treatment** **Primary:** Liposomal AmB (3–5 mg/kg/day IV) **Salvage:** ABLC (5 mg/kg/day IV), Caspofungin (70 mg/day IV × 1, then 50 mg/day IV thereafter), Micafungin (100–150 mg/day IV), Posaconazole (oral suspension: 200 mg TID; tablet: 300 mg BID on day 1, then 300 mg daily, IV: 300 mg BID on day 1, then 300 mg daily, Itraconazole suspension (200 mg PO every 12 hours) Amphotericin B (AmB) deoxycholate and its lipid derivatives can be used when Voriconazole cannot be administered. Lipid formulations of AmB should be considered in settings in which Azoles are contraindicated or not tolerated. **Empiric and pre-emptive therapy** Liposomal AmB (3 mg/kg/day IV), Caspofungin (70 mg day 1 IV then 50 mg/day IV thereafter), Micafungin (100 mg/day), Voriconazole (6 mg/kg IV every 12 hours for 1 day, followed by 4 mg/kg IV every 12 hours, Oral therapy can be used at 200–300 mg every 12 hours or 3–4 mg /kg every 12 hours) **Indications of empiric/pre-emptive therapy** When broad-spectrum antibiotic therapy fails to relieve persistent febrile symptoms in high-risk patients with prolonged neutropenia, empiric anti-aspergillus therapy should be initiated. When patients are expected to experience short-term neutropenia, (less than 10 days), empirical anti-aspergillus therapy should not be administered unless additional findings point to a possible IFI. Anti-aspergillus therapy can be guided by serum or BAL biomarkers like GM or 1-3-β-d-glucan in asymptomatic or febrile high-risk patients, reducing unnecessary treatment. The pre-emptive approach can document more IPA cases without compromising survival and replace empiric antifungal therapy. In patients having a high suspicion of IPA, antifungal therapy should be started as soon as possible while a diagnostic assessment is being completed. Breakthrough infection—Treatment should be individualized depending on possible etiological agent, severity of infection, and local epidemiology. Aggressive attempts at establishing diagnosis and therapeutic drug monitoring should be considered. Switching therapy to alternate drug class with anti-Aspergillus activity should be done. **Prophylaxis** Posaconazole: Oral suspension: 200 mg TID; Tablet: 300mg BID on day 1, then 300 mg daily Intravenous therapy: 300 mg BID on day 1, then 300 mg daily. Voriconazole: 200 mg PO BID Itraconazole suspension: 200 mg PO every 12 hours Micafungin: 50–100 mg/day Caspofungin: 50 mg/day **Indications for prophylaxis against Aspergillus** • Allogeneic HSCT recipients with GVHD throughout duration of immunosuppression • Lung transplant —for 3–4 months post-transplant • Select patients post cardiac and liver transplant based on individual risk factors and institutional epidemiology of infection (duration unclear). **Invasive pulmonary aspergillosis (IPA) treatment** Early initiation of antifungals therapy in patients with strongly suspected IPA is warranted. Voriconazole/Isavuconazole/Posaconazole should be used for primary treatment. Liposomal Amphotericin B or Isavuconazole should be used as an alternative therapy when required. Other lipid formulations of Amphotericin B may also be considered. Combination antifungals therapy with Voriconazole and an Echinocandin may be considered in select patients. Echinocandins (Micafungin or Caspofungin) can be used where Azoles and Polyenes are contraindicated. Treatment of IPA should be continued for a minimum of 6–12 weeks. For localized disease that can be easily debrided, such as invasive fungal sinusitis or localized cutaneous disease, surgery is advisable. The patient's immune system, other health issues, single focus of infection and surgical risks must be considered when interpreting the unclear indications.

challenging to establish a definitive diagnosis, many patients need to be offered empirical treatment for mucormycosis if they have risk factors for infection and positive cultures and/or compatible clinical syndromes (Table 7).

Cryptococcosis (Table 8)

Treatment is recommended for pulmonary disease or disseminated disease (the latter could be in HIV- infected or non-HIV-infected).

Table 7: Mucormycosis[167–177]

Site	*Treatment*
Mucormycosis—any site	Amphotericin B, liposomal, 5–10 mg/kg per day for initial 4–6 weeks Alternative—Amphotericin B, lipid complex, 5 mg/kg/day
	Assess response (weekly imaging) Stable disease or partial response Continuation of 1st line treatment or change to oral treatment Isavuconazole PO 3 × 200 mg day 1–2 1 × 200 mg per day from day 3 or Posaconazole DR tablets 2 × 300 mg day 1 1 × 300 mg per day from day 2 Progressive disease or toxicity Isavuconazole IV 3 × 200 mg day 1–2 1 × 200 mg/day 2 from day 3 or Posaconazole IV or DR tablets 2 × 300 mg day 1 1 × 300 mg per day from day 2 Posaconazole oral suspension 4 × 200 mg per day
CNS involvement	Amphotericin B, liposomal, 10 mg/kg per day, initial 28 days (up to 6–12 weeks)
Orbital Mucormycosis	Retrobulbar injection of Amphotericin B deoxycholate in addition to systemic therapy

Table 8: Cryptococcosis[78,178–179]

Site	*Treatment*
Pulmonary	**Mild to moderate disease** (no diffuse pulmonary infiltrates/disseminated disease) Fluconazole—400 mg (6 mg/kg) per day for 6–12 months
	Alternative agents Itraconazole—200mg three times daily x 3 days followed by 200 mg twice a day Voriconazole—400 mg (6 mg/kg) twice a day for 1 day then 200 mg twice a day Posaconazole (delayed-release tablets)—300 mg orally twice daily on day 1 followed by 300 mg once daily Isavuconazole—200 mg three times daily for 2 days followed by 200 mg once daily
	Severe disease (diffuse pulmonary infiltrates/disseminated disease) **Induction therapy (2–6 weeks)** Lipid formulation Amphotericin B + Flucytosine Liposomal Amphotericin B—3–4 mg/kg/day OR Amphotericin B lipid complex—5 mg/kg/ day Flucytosine—100 mg/kg/day (adjusted according to renal function) in 4 divided doses
	Consolidation therapy (8 weeks) Fluconazole—800 mg (12 mg/kg in children) per day—8 weeks **Maintenance therapy** (1 year from diagnosis) Fluconazole—200–400 mg/ day
Meningitis	**Lipid formulation Amphotericin B + Flucytosine—**for 2–4 weeks and then Fluconazole for 8 weeks Patients with neurological complications Induction therapy—extend to at least 6 weeks (or 4 weeks after culture negative) **Alternative in resource limited** Amphotericin B deoxycholate—0.7 mg/kg/day + Flucytosine (100 mg/kg/day in 4 divided doses)

Histoplasmosis

Pulmonary infection—Most pulmonary infections in the community are self-limited and do not require any treatment. However, Histoplasmosis can cause severe disease if the inoculum is large or in an immunocompromised subject. Treatment should be based on clinical syndromes (Table 9).

Pneumocystis Infection (Table 10)

Therapeutic Drug Monitoring (TDM) in Invasive Fungal Infections

Sub-therapeutic serum concentration can promote resistance to antifungals. The physiological changes causing increased permeability of vascular endothelium and altered drug metabolism

Table 9: Histoplasmosis [82,84,85,180,181]

Site	*Infection*
Pulmonary	**Moderately severe to severe disease** Amphotericin B (Liposomal Amphotericin B 3 mg/kg/day or Amphotericin B deoxycholate 0.7–1 mg/kg/day) IV for 1–2 weeks followed by Itraconazole (200 mg thrice daily for 3 days followed by 200 mg twice daily) for 3–6 months
	Mild to moderate disease Less than 4 weeks—no treatment More than 4 weeks—Itraconazole-loading + maintenance dose for 6–12 weeks **Chronic pulmonary histoplasmosis—**treatment is always indicated
Progressive disseminated histoplasmosis	Treatment depends on severity of disease and presence of CNS involvement
HIV (non-infected)	**Moderate to severe** Liposomal Amphotericin B (3 mg/kg/day) IV followed by Itraconazole (200 mg) for 6–12 months
	Mild to moderate Itraconazole 200 mg twice daily for at least 12 months
	CNS involvement Liposomal Amphotericin B (5 mg/kg/day) IV for 4–6 weeks followed by Itraconazole (200 mg) 2–3 times a day for at least 12 months
HIV (infected)	**Moderate to severe (non-meningeal)** Liposomal Amphotericin B (3 mg/kg/day) IV followed by Itraconazole PO (200 mg) three times a day for 3 days followed by twice a day for at least 6–12 months
	Mild to moderate (non-meningeal) Itraconazole 200 mg thrice daily for 3 days followed by twice daily for at least 12 months
	Meningeal disease Liposomal Amphotericin B (5 mg/kg/day) IV for 4–6 weeks(total 175mg/kg) followed by Itraconazole 200 mg 2–3 times a day for at least 12 months

Table 10: Pneumocystis infection [182–198]

Site	*Treatment*
Pulmonary	Prophylaxis
HIV +VE	First line: Trimethoprim/sulfamethoxazole one single-strength (80 mg TMP/400 mg SMX) daily or one double-strength tablet (160 mg TMP/800 mg SMX)/daily Second line: One single strength tablet daily if patient does not require prophylaxis for toxoplasmosis One double strength tablet daily to patients who require prophylaxis against toxoplasmosis
	Treatment
	First line: Trimethoprim/sulfamethoxazole (15–20 mg/kg TMP; 75–100 mg/kg SMX per day) For moderate to severe disease (i.e., hypoxemia) adjunctive corticosteroids should be used Second line for severe disease Primaquine and clindamycin [30 mg/(600 mg × 3)] per day Pentamidine IV (4 mg/kg/day)/Second line for mild to moderate disease: Dapsone (100 mg daily) + trimethoprim (15 mg daily) Atovaquone (750 mg BID)

Table 11: Therapeutic drug monitoring (TDM)

Drug	*Comment*	*Reference*
Voriconazole	Routine TDM—trough levels should be considered for ICU patients especially non-responders Voriconazole level of 0.5 mg/L (recommended target concentration between 0.5 and 3 mg/L) should be considered as lower threshold for efficacy, and trough levels more than 3.0 and 4.0 mg/L are associated with increased risks of hepatotoxicity and neurotoxicity respectively	199–201
Itraconazole	Itraconazole level should be measured between 5th and 7th day targeting a concentration of >0.5mg/L for both prophylactic and therapeutic indications,	202–204
Posaconazole	Measure level within 7 days of starting therapy. Target plasma concentration of >0.7 mg/L in prophylaxis and >1–1.25 mg/L of steady-state plasma level measured within 7 days of starting the therapy lead to better outcomes	205–208
Isavuconazole	TDM not routinely required May be considered in pre-existing liver disease, hepatic injury, obesity, solid organ transplant, and patients below 18 years of age	209,210
Fluconazole	TDM not routinely required May be considered in pediatric patients and patients on RRT	211
Echinocandins	Routine TDM not required. Echinocandins—suboptimal exposure in critically ill patients and also in overweight patients, with documented high inter-individual variability. Hypoalbuminemia and body weight >75 kg may have suboptimal levels.	212–218
Amphotericin B	Routine TDM not required May consider in narrow therapeutic index and major concern regarding toxicity	219
Flucytosine	TDM should be done— measure serum concentration within 72 hours and not later than 120 hours, Target serum concentration 25–100 mg/L	78,220

resulting from hepatic and/or renal dysfunction lead to PK/PD disturbances. The increased endothelial permeability in sepsis, and the low albumin in the critically ill results in an increased volume of distribution of water-soluble drugs in the former, and of protein-bound drugs (e.g., Echinocandins) in the latter.

The challenges in therapeutic drug monitoring of anti-fungal agents include the lack of universal availability and the variations in recommended drug levels by various societies based on varying studies (Table 11).

Summary

The aforementioned position statement has been drafted for the management of critically ill patients who fall into the non-neutropenic category and are not immunosuppressed due to malignancy or post-transplant condition, The text extensively addresses infections caused by various fungal species that are accountable for invasive fungal infections in ICUs. Additionally, it explores diverse methods for initiating anti-fungal therapy, fundamental and advanced diagnostic techniques that are valuable in diagnosing invasive fungal infections, approaches for monitoring therapeutic response to treatment, and available anti-fungal agents that are beneficial for site-specific management in light of distinct fungal pathogens. However, it provides only a limited overview of special populations. The entirety of this document has been compiled usingcurrently available literature. It will undoubtedly assist readers in promptly identifying suitable recommendations when necessary.

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