ISSN: 2474-3674

Mehta. Int J Crit Care Emerg Med 2024, 10:165
DOI: 10.23937/2474-3674/1510165
Volume 10 | Issue 1
Open Access

International Journal of
Critical Care and Emergency Medicine

REVIEW ARTICLE

Challenges in the Diagnosis and Treatment of Invasive Candidiasis in India

*Yatin Mehta**

Chairman, Institute of Critical Care & Anesthesia, Medanta the Medicity, Gurgaon 122001, Haryana, India

***Corresponding author:** *Dr. Yatin Mehta, Chairman, Institute of Critical Care & Anesthesia, Medanta the Medicity, Sector 38, Gurgaon 122001, Haryana, India, Tel: +91-124-41-41-414, Fax: 91-124-483411*

Abstract

Background: Invasive candidiasis (IC) is a serious candidal infection often associated with high rates of morbidity and mortality. The timely initiation of appropriate antifungal therapy is important to reduce the risk of mortality.

Methods: Intensive care, infectious disease, and haemato-oncology specialists from across India discussed the epidemiology and challenges in management of IC in India. This review summarizes the experts' opinions on early diagnosis of IC and appropriate rational treatment modalities to reduce mortality from IC in Indian clinical practice.

Results: The incidence of IC in India is 4-5% among patients admitted to the ICU, ~2% among hospitalized neonates, and 5%-10% among children with malignancy undergoing transplant or chemotherapy. The common risk factors for IC include chronic kidney disease, total parenteral nutrition, administration of broad-spectrum antibiotics for more than 7 to 10 days, abdominal surgery, underlying respiratory illness, and acute kidney injury. The five most dominant *Candida* species found in Indian ICUs include *C. tropicalis, C. albicans, C. parapsilosis, C. glabrata*, and *C. krusei*. In children, *C. tropicalis, C. parapsilosis, C. albicans, C. auris, C. glabrata,* and *C. krusie* are more common. Experts suggested that in the presence of risk factors, when a patient is not responding to antibacterial treatment, IC should be suspected. Hypotension, hypoglycemia, hyperglycemia, and necrotizing enterocolitis are other clinical manifestations of IC. Biomarkers like β-D-glucan and blood culture are reliable diagnostic tests for IC. Prophylaxis should not be used routinely to prevent IC. Appropriate candidates for prophylactic antifungal therapy in India are high-risk patients, such as those undergoing solid organ or bone marrow transplants and immunocompromised patients. The first line empirical antifungal drug should be echinocandin, except in cases of central nervous system candidiasis and urinary tract infections. The recommended duration of antifungal treatment is to continue treatment for at least 14 days after a negative culture, followed by de-escalation based on clinical judgment. For deep-seated candidemia at least 6 weeks of treatment is necessary.

Conclusion: Echinocandins are the first line empirical antifungal drugs for IC, except in cases of central nervous system candidiasis and urinary tract infections. Treatment de-escalation and discontinuation should be based on clinical judgment, negative biomarkers, and negative cultures as recommended by the guidelines.

Keywords

Critically ill patient, Invasive candidiasis, Antifungal susceptibility testing, Antifungal resistance, β-D-glucan, Echinocandins

Abbreviations

AKI: Acute Kidney Injury; BDG: β-D-Glucan Detection Assays; CKD: Chronic Kidney Disease; CNS: Central Nervous System; CRP: C-Reactive Protein; CRRT: Continuous Renal Replacement Therapy; ECMO: Extracorporeal Membrane Oxygenation; EORTC/MSGERC: European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium; ESCMID: European Society of Clinical Microbiology and Infectious Diseases; EUCANDICU: Candidemia/Intra-Abdominal Candidiasis in European ICU Project; FDA: Food and Drug Administration; HSCT: Hematopoietic Stem Cell Transplant; IC: Invasive Candidiasis; ICUs: Intensive Care Units; IDSA: Infectious Diseases Society of America; NAC: Non-Albicans Candida; PCR: Polymerase Chain Reaction; TPN: Total Parenteral Nutrition

Introduction

Candidiasis is a broad term that encompasses cutaneous, mucosal, and deep-seated organ infections caused by various species of the *Candida* genus [1].

Citation: Mehta Y (2024) Challenges in the Diagnosis and Treatment of Invasive Candidiasis in India. Int J Crit Care Emerg Med 10:165. doi.org/10.23937/2474-3674/1510165

Accepted: August 20, 2024: **Published:** August 22, 2024

Invasive candidiasis (IC) is a serious candida infection, which might involve candidemia (bloodstream infections with *Candida* spp.), deep-seated candidiasis, or deep-seated candidiasis with associated candidemia [2]. The incidence of IC has increased over the past few decades and, on an average, ~700,000 people across the world are affected every year [3]. It is often associated with high rates of morbidity and mortality, as well as prolonged hospitalization. Patients who develop IC are typically those being treated for serious medical conditions; hence, it is difficult to estimate the mortality directly due to IC [4]. Despite improved access to antifungal drugs, an estimated mortality of 40%-55% due to IC has been reported in studies among patients in the intensive care units (ICUs) over the past decade [2]. Risk factors for IC include exposure to broad-spectrum antibiotics, cancer chemotherapy, premature neonates requiring advanced care, major abdominal surgery, organ transplantation, prolonged ICU stay, implanted medical devices such as vascular catheters and prosthetic heart valves, and total parenteral nutrition (TPN) [5]. The timely initiation of appropriate antifungal therapy and controlling the source of infection are associated with decrease in mortality. Further, there is considerable geographic, center-to-center, and even unit-to-unit variability in the prevalence of pathogenic *Candida* species [6]. Although there is sufficient evidence on the burden of candidiasis and its impact on Indian patients, knowledge about management protocols is limited. This could be due to the lack of a national surveillance system and the absence of a law for obligatory reporting of fungal diseases. Knowledge about local epidemiology, rates of antifungal resistance, the organism and susceptibility profile, and treatment outcomes with existing therapies is important for prompt and appropriate therapeutic decisions while awaiting culture and susceptibility data.

Hence, a group of intensive care specialists, infectious disease specialists and hemato-oncologists from across India discussed the epidemiology and challenges of treating IC in India, best practices for early diagnosis of IC, and appropriate treatment to reduce mortality.

Burden of IC in India

There are very few recent or large-scale population-based studies on the burden of IC in India, and most studies conducted over the last 2 decades have reported data from individual centers (Table 1). Only one multicenter study involving 27 centers across India has been conducted, which reported a low incidence of 0.65% with wide regional variations, and a highest reported incidence of 0.9% [7]. The reported incidence of IC varied from 5% to 7% in 3 other single-center studies [8-10] to as low as 0.65% in 2 studies [7,11] and 4.2% in the pediatric population [12]. Findings from a study conducted over 20 years at a tertiary care center from North India revealed a rising trend of candidemia over 20 years from 1999 to 2018 with the majority of cases being reported from pediatric units [13].

In a recent study conducted at 23 ICUs from 9 European countries as part of the candidemia/intra-abdominal candidiasis in European ICU (EUCANDICU) project, the cumulative incidence of IC was 7.07 episodes per 1000 ICU admissions [14]. Similarly, the overall incidence of IC in another long-term follow-up study from the United States was 90/100,000 patients from 2009 to 2017, which did not change significantly over time [15]. Comparing various studies in terms of the incidence of IC might not be meaningful because denominators used to calculate incidence vary among different studies. Population-based studies report incidence as cases per 100,000 persons, while hospital-based studies often report it as cases per 10,000 patient days or 1000 admissions. Moreover, some diagnostic methods are not standardized across healthcare settings. Furthermore, many studies look at a single disease spectrum, e.g., bloodstream candidemia, and deep-seated candidiasis often gets overlooked [16].

According to the Indian experts, the incidence of IC is 4-5% among patients admitted to the ICU. Among tertiary-care hospitals, the incidence in public hospitals may be higher. The incidence is about 10% to 15% among hospitalized pediatric patients, and it is more commonly seen in those receiving TPN. The incidence of IC is 2% among the hospitalized neonates and 5%-10% among children with malignancy undergoing transplant and chemotherapy. In the opinion of the experts, no major regional variations have been observed in the incidence rates of IC across India.

Risk Factors for IC in ICUs in India

It has been reported that among all admitted patients, those in the ICU have the highest rate of *Candida* infections [17]. A recently published systematic review and meta-analysis of 34 studies reported that the factors associated with the highest risk for IC among critically ill patients were broad-spectrum antibiotics, blood transfusion, *Candida* colonization, central venous catheter, and TPN. Moreover, length of ICU stay was associated with extremely high risk. Results from a meta-analysis also identified renal replacement therapy, mechanical ventilation, blood transfusion, and diabetes as important risk factors [18].

Common medical devices that have been associated with *Candida* infections include central venous catheters, cardiovascular devices, and urinary catheter [19]. *C. albicans* is the predominant fungal species isolated from medical device infections and is known to form biofilms on surfaces of catheters. A *C. albicans* biofilm on an implanted medical device is highly resistant to antimicrobials and the host immune system and can subsequently lead to disseminated bloodstream infections (candidemia) and invasive systemic infections of tissues and organs [20] although echinocandins have

DOI: 10.23937/2474-3674/1510165

Table 1: Incidence of invasive candidiasis in India.

Authors	Year and Set-up	Patients	Incidence of IC	Risk factors	Predominant species	Resistance and key outcomes
Sahni, et al. [8]	2005; teaching hospital in North India	101 in the medical and surgical wards, and ICUs having signs and symptoms of nosocomial bloodstream infection	6.9%; All were patients from ICU	Length of hospitalization, broad-spectrum antibiotics, central venous catheters, mechanical ventilation, and TPN	*Candida albicans* (42.8%)	-
Xess, et al. [9]	2007; tertiary care center in North India	5-year study (2001-2005); 7,297 patients suspected with candidemia	6%	Prior use of antibiotic (71.2%), ventilator and urinary catheter (55.6%), central venous catheter (37.5%), and post-operative care (41.8%)	*C. tropicalis* (35.3%) *C. albicans* (21.5%) *C. parapsilosis* (20%) *C. glabrata* (17.5%) *C. krusei* (3.3%) *C. haemulonii* (1.5%) *C. guilliermondii* (1%)	Dose-dependent susceptibility to fluconazole seen in 5% of strains. Antifungal resistance found in 11.7% (only *C. glabrata*). Death: 71.2% from 2001-2004; 45.5% in 2005
Chander, et al. [10]	2013; tertiary care center in North India	4,651 samples from admitted patients	5.79%	ICU admission (88.9%), use of broad-spectrum antibiotics (91.6%), and central line catheter insertion (83.3%)	*C. tropicalis* (40.8%) *C. albicans* (29.6%) *C. glabrata* (18.5%) Others (11.1%)	Resistance to amphotericin B (18.5%); resistance to fluconazole (77.8%)
Chakrabarti, et al. [7]	2015; nationwide, multicenter, observational study at 27 Indian ICUs	1,400 ICU-acquired candidemia cases	0.65% of all ICU admissions	Admission to ICU, underlying respiratory illness (25%), underlying renal disease (22.9%), central venous catheterization (74%), parenteral nutrition (13.4%), and broad-spectrum antibiotics (93%)	*C. tropicalis* (41.6%) *C. albicans* (20.9%) *C. parapsilosis* (10.9%)	Azole and multidrug resistance were seen in 11.8% and 1.9% of isolates. 30-day crude and attributable mortality rates were 44.7% and 19.6%, respectively
Giri, et al. [11]	2013; tertiary care center in South India	5,976 ICU patients	0.65%	Long term antibiotic therapy (64.1%), use of CVCs (56.4%), urinary catheters (53.9%), steroid therapy (35.9%), diabetes mellitus (33.3%), mechanical ventilation (28.2%), prior surgery (25.6%), TPN (23.1%), preterm babies with low birth weight (17.9%), and malignancy (7.7%)	*C. tropicalis* (74.35%), *C. albicans*, (10.26%) *C. parapsilosis*, (7.69%) *C. krusei* (5.13%) *C. glabrata* (2.56%)	100% isolates were sensitive to amphotericin B; 30.8% were resistant to fluconazole. Mortality 23.8%

ISSN: 2474-3674

DOI: 10.23937/2474-3674/1510165

Bhattacharjee P [47]	2016; tertiary care hospital in east India	70 samples positive for *Candida* spp.			*C. albicans* (48.57%) *C. tropicalis* (24.28%) *C. haemulonii* (8.57%) *C. glabrata* (5.71%) *C. pelliculosa* (2.86%) *C. sake* (4.29%) *C. rugosa* (2.86%) *C. famata* (2.86%)	All *C. albicans* sensitive to fluconazole. Resistance of *C. albicans* to amphotericin B, flucytosine, voriconazole, and itraconazole seen in 44.12%, 52.94%, 8.82%, and 17.65% of isolates, respectively. Non-albicans resistance to amphotericin B, flucytosine, voriconazole, and itraconazole seen in 30.56%, 61.11%, 33.33%, 19.44%, and 38.89% isolates, respectively
Rajni, et al. [43]	2022; tertiary-care hospital in Western India	3,443 blood samples from suspected sepsis cases during 2017-2020	2.8%; prevalence of candidemia significantly higher in the ICU compared to other wards: 79% vs. 21%	Broad-spectrum antibiotic usage (68%), presence of central venous catheter (49%), urinary catheterization (45%), corticosteroid therapy (34%), comorbid diabetes (46%), and comorbid hypertension (37%)	*C. tropicalis* (38%) *C. parapsilosis* (18%) *C. famata* (12%) *C. auris* (11%) *C. albicans* (11%) *C. glabrata* (5%)	Resistance to fluconazole 36%, resistance to voriconazole 20%, resistance to 5-flucytosine 4%, and resistance to amphotericin-B 7%. *C. auris* isolates were more resistant than other NAC spp. No resistance to echinocandins detected. Mortality 25.26% and mortality from *C. albicans* 3.15%
Rajeshwari, et al. [12]	2022; tertiary care center in Southern India	109 children admitted to the pediatric intensive care unit (PICU) with confirmed candidemia	4.2%	Neutropenia, antibiotic duration > 5 days, peritoneal dialysis, amino acid administration, mechanical ventilation, and presence of CVC	*C. albicans* (30%) *C. tropicalis* (50%) *C. glabrata* (5.5%) *C. parapsilosis* (4.5%) *C. krusei* (1%) Other *Candida* species (9%)	Mortality 34%

ISSN: 2474-3674

DOI: 10.23937/2474-3674/1510165

Ahmad, et al. [42]	2022; tertiary care government institute	125 samples of 120 ICU patients		Sepsis or SIRS (12.50%), TPN (24.17%), Multifocal *Candida* colonization (4.17%), respiratory distress (11.66%), acute renal failure (12.50%), tuberculosis (16.67%), and diabetes mellitus with complications (29.17%)	*C. tropicalis* (49.60%) *C. albicans* (28.00%) *C. parapsilosis* (10.40%) Others (12%)	Majority of *C. albicans* isolates sensitive to voriconazole (71.42%), amphotericin B (62.85%), and fluconazole (57.14%). A significant number of isolates resistant to miconazole (51.42%) and ketoconazole (37.14%) NAC isolates: 80% of isolates were sensitive to voriconazole and two-thirds to amphotericin B and fluconazole. Majority were resistant to miconazole (65.56%) and ketoconazole (46.66%)
Umamaheshwari, et al. [48]	2023; tertiary care hospital in southern India	Retrospective analysis of clinical samples from the hospital database			Candida infection was identified in 751 samples. *C. albicans* (26.36%) *C. tropicalis* (42.88%), *C. glabrata* (11.72%), *C. parapsilosis* (5.06%), *C. krusei* (2.53%), *C. haemulonii* (2.4%), *C. lusitaniae* (2.13%), *C. guillermondii* (2.0%)	741/751 isolates were tested, 182 (24.56%) showed resistance to one or more drugs tested, and 559 (75.44%) were susceptible to all drugs. All samples were susceptible to micafungin. Resistance to Caspofungin: *C. krusei* (31.57%), *C. glabrata* (4.55%), *C. albicans* (3.03%) and *C. tropicalis* (1.55%) Major resistance was exhibited to flucytosine by *C. tropicalis* 77.46% *C. haemulonii* (83.3%) was resistant to amphotericin B

CVC: Central Venous Catheters; ICU: Intensive Care Unit; NAC: Non-Albicans *Candida*; SIRS: Systemic Inflammatory Response Syndrome; TPN: Total Parenteral Nutrition

ISSN: 2474-3674

a good penetration through biofilms. Epidemiological studies from India corroborate these findings. In fact, in most Indian studies, ICU admission and use of broad-spectrum antibiotics were associated with the highest risk of IC, followed by catheterization (Table 1).

According to the experts, common risk factors for IC include chronic kidney disease (CKD), TPN, administration of broad-spectrum antibiotics for more than 7 to 10 days, abdominal surgery, underlying respiratory illness, and acute kidney injury (AKI). Other risk factors include pancreatitis, malnutrition, chronic neutropenia, solid organ transplants, immunosuppressant therapy, and malignancy. Heart disease and history of septic shock were not considered as risk factors for IC by the experts.

Predominant *Candida* Species Associated with IC in India

More than 15 *Candida* species have been described as etiologic agents of IC; however, > 90% of cases were reportedly caused by five species: *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, and C. Krusei* [16]. *Candida albicans* has been the predominant species for a long time; however, in the last 2 decades, there has been a global shift towards non-albicans *Candida* (NAC) species [21]. Among the other species of *Candida*, an emerging strain is *C. auris,* which is multidrug resistant. The incidence of *C. auris* candidemia was reported to be significantly higher in patients who had previous exposure to fluconazole or echinocandin [22]. Results of the global SENTRY Antifungal Surveillance Program conducted from 1997 to 2016 showed a decrease in the isolation of *C. albicans* and an increase in the isolation of *C. glabrata* and *C. parapsilosis* over time. *C. glabrata* was the most common NAC species detected in all geographical regions, except for Latin America, where *C. parapsilosis* and *C. tropicalis* were more common. Data from 2006 to 2016 showed that in Asia, *C. albicans*, *C. glabrata, C. parapsilosis*, and *C. tropicalis* were detected in 46.0%, 17.9%, 12.9%, and 14.1% of isolates, respectively [23]. However, most studies from India show a dominance of *C. tropicalis*, followed by *C. albicans* (Table 1).

The experts agreed that the most common species in recent times is *C. tropicalis* followed by *C. albicans* and the non-albicans species. The 5 most dominant species are *C. tropicalis, C. albicans, C. parapsilosis, C. glabrata*, and *C. krusei*. In children, *C. tropicalis, C. parapsilosis, C. albicans, C. auris, C. glabarata,* and *C. krusei* are the dominant species. The incidence of *C. auris* is largely associated with infection control practices of the hospital. There was an increase in the cases of *C. auris* when COVID-19 was at its peak. Among patients admitted for pancreatitis and long-term surgery, approximately 7% of the bacterial blood culture isolates are found to be *Candida*. The order of prevalence is *C. tropicalis, C. albicans, C. glabrata, and C. auris*.

Signs and Symptoms of IC

No clinical signs or symptoms are specific for IC. IC should be suspected in patients with known risk factors who have unexplained fever that is unresponsive to antibacterial treatment [1]. Other symptoms can develop if the infection spreads to other parts of the body, such as the heart, brain, eyes, bones, or joints. Manifestations range from fever in a hemodynamically stable patient, to sepsis and septic shock [19].

The experts concurred that there are no specific signs and symptoms of fungal infection; however, in the presence of risk factors, when a patient is not responding to antibacterial treatment, IC should be suspected. In children, hypothermia due to IC is more common than fever. Hypotension, hypoglycemia, hyperglycemia, and necrotizing enterocolitis are the other clinical manifestations. Additionally, when vegetation can be seen on intravascular devices and the patient shows no clinical improvement despite antibiotic treatment, IC should be suspected. Sudden hypoglycemia or hyperglycemia in a patient who has been hospitalized for some days indicates clinical deterioration and should raise suspicion for IC. Hypoglycemia in patients on prolonged TPN (for graft vs. host disease or mucositis) might also be an indicator of IC.

Diagnosis of IC and Challenges in Diagnosis

Blood cultures or culture of samples from other sites have been considered the gold standard for diagnosing IC. Additionally, nonculture diagnostic tests, such as antigen-antibody tests (galactomannan) or β-D-glucan (BDG) detection assays, and polymerase chain reaction (PCR) are used [6]. The 2019 consensus guidelines by the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSGERC) suggested four options for the diagnosis of IC [24]: (1) Histopathologic, cytopathologic, or direct microscopic detection of *Candida* in specimens from normally sterile sites; (2) Positive culture from a sample from a normally sterile site with clinical or radiological abnormality indicative of infection; these include samples from drains placed in the last 24 hours; (3) Detection of *Candida* by PCR with subsequent DNA sequencing; and (4) Positive blood culture for *Candida* species.

Culture-based tests

The sensitivity of blood culture is limited; moreover, the turnaround time is very high. Usually, the incubation time until detection of growth is 24-72 h, followed by an additional 24-48 h for species identification. Further, there is no universally agreed gold standard reference test; hence, its sensitivity remains uncertain and varies with the type of IC (i.e., intravascular or deep-seated with or without secondary candidemia) and the type of *Candida* species (e.g., lower for *C. glabrata*) [25].

The overall sensitivity of blood cultures for diagnosing IC is approximately 50% [6]. The sensitivity can be improved with larger sample volumes and higher testing frequency [26]. However, cultures might be negative in cases of extremely low-level candidemia, deep-seated candidiasis that persists after sterilization of the bloodstream, or direct deep-seated candidiasis without candidemia. Cultures of tissues or fluid recovered from infected sites during deep-seated candidiasis also show poor sensitivity (often < 50%) and have long turnaround times. Moreover, invasive sampling procedures might be required, which could be dangerous or contraindicated due to underlying medical conditions [6,26].

Non-culture-based tests

Challenges with culture-based tests led to the development of non-culture-based and non-histopathological tests for diagnosing IC. Among the antigen-antibody tests, the best-studied test is a combined mannan/anti-mannan antibody assay [6]. However, in a meta-analysis of 14 studies, the sensitivity/specificity of mannan and anti-mannan IgGs individually for the diagnosis of IC were 58%/93% and 59%/83%, respectively. Sensitivity and specificity for the combined assay were 83% and 86%, with best performances for *C. albicans*, *C. glabrata,* and *C. tropicalis* infections [27]. The increase in antibody concentration might be more helpful in the diagnosis of candidiasis. However, the diagnosis might be delayed as a result. Moreover, it is not discriminative in the diagnosis of IC. Currently, neither mannan nor anti-mannan antibody detection has been approved for the diagnosis of IC by the United States Food and Drug Administration (FDA) [26]. The biomarker most commonly used for detecting fungi in critically ill patients is the BDG test [25]. It has been approved by the FDA as an adjunct to cultures for the diagnosis of invasive fungal infections. Nevertheless, results are not specific for IC, but suggest the possibility of an invasive fungal infection [6]. BDG assay has a sensitivity of 92% and specificity of 81% for the diagnosis of IC. The high negative predictive value helps in the exclusion of IC [26]. The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) also recommends the BDG test for ruling out candidemia or IC in adult patients at risk of infection. The specificity of this test can be further increased by using higher cut-off values (≥ 200 pg/mL instead of 80 pg/mL) or by considering two consecutive positive tests as a definitive diagnosis [25].

PCR-based tests are also used for rapid diagnosis of IC. The pooled sensitivity and specificity of PCR for suspected IC in a recent meta-analysis were 95% and 92%, respectively [28]. PCR provides *Candida* spp. identification in 2-4 h and is also useful for monitoring the persistence or resolution of infection [26]. PCR can also detect molecular markers for drug resistance [6]. However, the lack of standardization is a major limitation of this method [25].

The combination of various non-culture tests has a higher negative predictive value than single tests. This strategy is also used to decide discontinuation of unnecessary therapy in cases with suspected IC. The combination of *Candida* antigen detection and procalcitonin is useful in clinical practice for the early differential diagnosis of infection in severely ill patients. Procalcitonin levels in IC do not exceed 2 ng/mL unlike the very high levels in bacterial sepsis. The combination of procalcitonin level < 2 ng/mL and a positive BDG test has a sensitivity of 66% and specificity of 98% for IC [26].

According to the experts, the major challenges in the diagnosis of IC include low sensitivity of the diagnostic tests, high turnaround time of the test results, and lack of adequate laboratories that can conduct specific tests. Nevertheless, the role of biomarkers was considered important by the experts. In a patient with grade III sepsis, low procalcitonin and high C-reactive protein (CRP) can be considered to start pre-emptive treatment instead of empirical treatment while BDG test results are awaited. All the experts agreed that biomarkers and cultures are reliable indicators of IC, while PCR needs to be standardized further. Blood culture remains the gold standard in the diagnosis of IC in children, and the yield is better in newborns than in older children. Among other tests, mannan antigen and anti-mannan antibody detection have limitations because of the challenge of contamination and variations in rates of sensitivity. Sensitivity varies with different *Candida* species; it is better for *C. albicans, C. glabrata,* and *C. tropicalis*. Moreover, specificity decreases in the presence of *Candida* colonization. Further, it has a low positive predictive value, which is further limited by low serum concentrations and rapid bloodstream clearance. Because mannan antigen and anti-mannan antibody detection tests are not species-specific, further tests are required to identify the causative fungal species [29]. Most experts solely depend on the BDG assay. All the experts agreed that combining culture and non-culture-based tests is a useful strategy for early detection of IC in ICU patients. There was a consensus on the following diagnostic tests: Blood culture, histopathology, 1,3-BDG assay (a very high value of BDG is a very good indicator of IC), *Candida* mannan and anti-mannan (serum biomarker), and PCR.

What can be done for early diagnosis of IC?

Timely diagnosis of IC is key to ensure a favorable outcome. In fact, a 1-2-day delay in initiation of effective antifungal therapy has been associated with a doubling of mortality [1].

Goals of early diagnosis: The experts opined that the primary goals of early diagnosis are reducing antifungal toxicity, avoiding the emergence of resistance, and avoiding selection pressure. They suggested that it is important to avoid the inappropriate use of antifungal therapy (especially empirical treatment) to achieve

these goals. There was concurrence that point-of-care diagnosis is the need of the hour. Further, increasing biochemical testing for 1-3 BDG and galactomannan, fungal staining and culture/sensitivity is necessary. Apart from clinical suspicion, sending samples for 2 sets of blood cultures obtained within a few hours of each other via peripheral venipuncture, biomarkers, and procalcitonin levels can help in early diagnosis of IC. Additionally, ultrasound screening can help in locating unexplained hepatic lesions in the absence of fever.

Risk prediction models: Several studies have looked at prediction models to identify patients at highest risk of IC. These studies are characterized by high specificity, but low sensitivity; therefore, many patients with candidiasis are missed [6]. The commonly known risk prediction models for IC are scores based on clinical risk factors, i.e., clinical prediction rules e.g., Ostrosky-Zeichner clinical prediction rule, scores based on microbiological parameters (*Candida* colonization), and combined clinical and microbiological *Candida* scores [30]. The components of *Candida* score are severe sepsis, TPN, multifocal colonization, and surgery. Each component is assigned 1 point, except for severe sepsis, which is assigned 2 points [31]. *Candida* colonization index is calculated as non-blood distinct body sites colonized by *Candida* divided by total number of sites tested [32]. The Ostrosky-Zeichner clinical prediction score includes intensive care admission for 72 h with mechanical ventilation for at least 48 h, antibiotic use for 3 days, central line use for 3 days with at least any one of the following criteria: Any surgery (day -7 to day 0), immunosuppressive use (day -7 to day 0), pancreatitis (day -7 to day 0), TPN (day 1 to day 3), any dialysis (day 1 to day 3), and steroid use (day -7 to day 0) [33]. A recent systematic review of major risk prediction models for IC reported that due to major limitations, including lack of model generalizability, inconvenience of use, and inadequate validation, risk prediction models are currently impractical for clinical use. Moreover, when they were created, they had several inclusion and exclusion criteria, which can significantly restrict the patient population in which they can be reliably used [34].

However, none of the experts believed in using risk prediction models for IC in daily clinical practice. According to them, the risk prediction scores are not practical or significantly beneficial in terms of positive patient outcomes. Some experts suggested that risk prediction models can be used for research purposes but not for initiation of therapy.

Management of IC

There are three main groups of antifungal agents: the azoles, the polyenes, and the echinocandins. The selection of an antifungal regimen is based on multiple factors, including patient characteristics, epidemiological data, hospital setting, fungal strain, patient comorbidities, site of infection, and safety profiles of the antifungal agents [35]. International guidelines for the treatment of IC published by ESICM/ESCMID and by the Infectious Diseases Society of America (IDSA) are widely known and followed [6,25]. The four widely understood treatment strategies for IC are (1) Prophylactic therapies, which are administered to critically ill patients with a high risk of developing IC because of intrinsic or patient-specific risk factors (such as immunosuppression); (2) Pre-emptive therapies, which are administered to patients at risk of IC with a diagnosis based on fungal biomarkers. (The ESCMID guidelines define pre-emptive therapy as therapy triggered by microbiological evidence without proof of invasive infection due to *Candida* species [25]. However, the IDSA guidelines no longer use this term nor have any recommendations related to it [6]); (3) Empirical therapy, which refers to the administration of antifungal agents in patients with signs and symptoms of infection along with specific risk factors for IC, irrespective of biomarkers; and (4) Directed/targeted therapies, which are treatments based on microbiological confirmation of an invasive infection due to *Candida* species (e.g., a positive blood culture for *Candida* species) [25].

The key recommendations of IDSA and ESICM/ESCMID guidelines are shown in Table 2. The IDSA guidelines are more detailed [6]. Echinocandins (micafungin, anidulafungin, caspofungin) are usually the recommended first-line drugs with transition from an echinocandin to fluconazole (usually within 5-7 days) in patients who are clinically stable, have isolates that are susceptible to fluconazole, and have negative repeat blood cultures. In various clinical trials, micafungin has shown favorable efficacy against IC with response rates ranging from 71% to 90% [36-39]. Micafungin has also been shown to be useful as a preventive measure (prophylaxis) against fungal infections in patients with neutropenia [40].

The experts in the panel follow the IDSA guidelines in general [6]. Though the ESCMID guidelines do not recommend amphotericin B for IC, experts agreed that the drug may have to be considered in Indian practice for patients with limited economic resources [25].

Prophylaxis

According to the experts, colonization scores cannot be used to guide prophylactic treatment and infection control. Further, prophylaxis should not be used routinely and universally to prevent IC. Appropriate candidates for prophylactic antifungal therapy in India are high-risk patients, such as those undergoing solid organ or bone marrow transplants and immunocompromised patients. Among unstable patients with multifocal *Candida* colonization and/or clinical risk factors for infection, pre-emptive therapy may also be considered.

Empirical therapy

According to the experts, in hospitalized patients

DOI: 10.23937/2474-3674/1510165

Table 2: Key recommendations by international guidelines for the treatment of invasive candidiasis.

		Infectious Diseases Society of America 2016 [6]	European Society of Clinical Microbiology and Infectious Diseases 2019 [25]
IC in non-neutropenic patients	Initial therapy	Echinocandin recommended as initial therapy. Fluconazole acceptable as alternative to echinocandin in patients who not critically ill and considered unlikely to have a fluconazole-resistant *Candida* species. AmB 3-5 mg/kg daily is a reasonable alternative if there is intolerance, limited availability, or resistance to other antifungal agents.	AmB-d should not be used as a first-line treatment in critically ill patients with documented or suspected IC because of its significant nephrotoxicity
	Transition (Switch)	Transition from an echinocandin to fluconazole (usually within 5-7 days) for patients who are clinically stable, have isolates that are susceptible to fluconazole (e.g., *C. albicans*), and negative repeat blood cultures. Transition from AmB to fluconazole after 5-7 days in patients with isolates susceptible to fluconazole, who are clinically stable, and in whom repeat cultures on antifungal therapy are negative. Voriconazole is recommended as step-down oral therapy for selected cases of candidemia due to *C. krusei.*	De-escalation from echinocandin to fluconazole when the patient is clinically stable, and the isolate is susceptible to fluconazole. Echinocandins should not be de-escalated if central venous catheter or any other foreign material has not been removed or if an intravascular device (e.g., pacemaker) must be left in place because echinocandins have enhanced activity against biofilm.
	Resistance	Among patients with suspected azole- and echinocandin-resistant *Candida* infections, lipid formulation AmB (3-5 mg/kg daily) is recommended.	
	Treatment duration and follow-up	Follow-up blood cultures should be performed every day or every other day to establish the time point at which candidemia has been cleared. Recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of symptoms attributable to candidemia	IC should be treated for at least 14 days after the first negative blood culture. IC without positive blood cultures should be treated for 10-14 days.
Neutropenic patients	Initial therapy	Echinocandin is recommended as initial therapy. Lipid formulation AmB, 3-5 mg/kg daily, is an effective but less attractive alternative because of the potential for toxicity. Fluconazole 800 mg (12 mg/kg) loading dose then 400 mg (6 mg/kg) daily, is an alternative for patients who are not critically ill and have had no prior azole exposure. For infections due to *C. krusei*, an echinocandin, lipid formulation AmB, or voriconazole is recommended.	

ISSN: 2474-3674

DOI: 10.23937/2474-3674/1510165

	Transition (Switch)	Fluconazole, 400 mg (6 mg/kg) daily, can be used for step-down therapy during persistent neutropenia in clinically stable patients who have susceptible isolates and documented bloodstream clearance. Voriconazole can also be used as step-down therapy during neutropenia in clinically stable patients who have had documented bloodstream clearance and isolates that are susceptible to voriconazole.	
	Treatment duration and follow-up	Recommended minimum duration of therapy for candidemia without metastatic complications is 2 weeks after documented clearance of *Candida* from the bloodstream, provided neutropenia and symptoms attributable to candidemia have resolved.	
Prophylaxis in ICU settings		Fluconazole could be used in high-risk patients in adult ICUs with a high rate (> 5%) of IC. An alternative is to give an echinocandin.	The panel recommends against the routine and universal administration of antifungal pre-emptive therapy or prophylaxis in critically ill patients.
Empirical therapy in non-neutropenic patients in the ICU		Should be considered in critically ill patients with risk factors for IC and no other known cause of fever. It should be based on clinical assessment of risk factors, surrogate markers for IC, and/or culture report from nonsterile sites. Preferred empirical therapy is echinocandin. Fluconazole is an acceptable alternative for patients with no recent azole exposure and without azole-resistant *Candida* species colonization. Lipid formulation AmB, 3-5 mg/kg daily, can be used if there is intolerance to other antifungal agents. Recommended duration of empirical therapy is the same as for treatment of documented candidemia. For patients with no clinical response to empirical antifungal therapy at 4-5 days and no subsequent evidence of IC after the start of empirical therapy or a negative non-culture-based diagnostic assay with a high negative predictive value, stopping antifungal therapy should be considered.	Might be considered only in patients with septic shock and MOF with more than 1 extra-digestive site (i.e., urine, mouth, throat, upper and lower respiratory tracts, skin folds, drains, or operative site) with proven *Candida* species colonization. Not recommended in patients without septic shock and MOF. Echinocandins should be used as the first-line treatment in critically ill patients with septic shock and MOF with IC. Fluconazole should be considered as first-line treatment for critically ill patients with low severity of disease (i.e., without septic shock and/or MOF) in settings with low fluconazole resistance. Liposomal AmB should be preferred over other lipid formulations when previous treatment with echinocandins and azoles has failed. Antifungal treatment should be stopped in patients with suspected (but not proven) IC with negative blood cultures and/or other negative culture specimens taken from suspected infectious foci before starting antifungal therapy.

ISSN: 2474-3674

DOI: 10.23937/2474-3674/1510165

Neonatal candidiasis		AmB deoxycholate, 1 mg/kg daily, is recommended. Fluconazole, 12 mg/kg intravenous or oral daily, is a reasonable alternative in patients who have not been on fluconazole prophylaxis. Echinocandins should be used with caution and limited to salvage therapy or situations in which resistance or toxicity preclude the use of AmB deoxycholate or fluconazole. The recommended duration of therapy for candidemia without obvious metastatic complications is 2 weeks after documented clearance of *Candida* species from the bloodstream and resolution of signs attributable to candidemia	
Central nervous system candidiasis		For initial treatment, liposomal AmB, 5 mg/kg daily, with or without oral flucytosine, 25 mg/kg 4 times daily is recommended. For step-down therapy after the patient has responded to initial treatment, fluconazole, 400-800 mg (6-12 mg/kg) daily, is recommended	

AmB: Amphotericin B; IC: Invasive Candidiasis; ICU: Intensive Care Unit; MOF: Multi Organ Failure

ISSN: 2474-3674

with refractory fever despite 4/5 days of broad-spectrum antibacterial therapy, empiric antifungal therapy is reasonable where local incidence rates are high. In such cases, antifungals are started empirically, and samples are sent to assess biomarker levels. This helps in early detection of candidiasis, especially if the BDG level is very high. Empirical antifungal therapy may also be administered to an ICU patient who exhibits signs of new-onset sepsis of unknown origin or persisting signs of infection following 4 to 7 days in the ICU with adequate antibiotic therapy. The first-line antifungal drug in such cases should be echinocandin, except in cases of central nervous system (CNS) candidiasis and urinary tract infections. For urinary tract infections, fluconazole is the first drug of choice. Echinocandins are not used for treating CNS infections as they cannot pass through the blood-brain barrier. Hence, amphotericin B alone or combined with voriconazole is preferred. Treatment discontinuation should be based on clinical judgment, negative biomarkers, and negative cultures.

Some experts suggested that fluconazole can be a good drug of choice for patients in a low-resource setting like public sector setups, who have not been exposed to an azole. However, some experts disagreed with this strategy considering that public sector setups have high rates of resistance.

Duration of treatment and dose adjustment

All experts agreed to switching to fluconazole from echinocandin once the patient is clinically stable, repeat blood cultures are negative, and the *Candida* isolate is found to be sensitive to fluconazole. If a patient has no clinical response to empirical antifungal therapy by 4 to 5 days with no subsequent evidence of IC after the initiation of empirical therapy, investigations should be repeated to confirm the diagnosis of IC. Some experts recommended looking for seeding while others suggested 2 to 3 cultures to rule out the absence of candidiasis. Furthermore, close monitoring for any complications like endocarditis is necessary. The recommended duration of antifungal treatment in patients with uncomplicated candidemia and IC depends on the extent of infection, organ involvement, and source control. It should be continued for at least 14 days after a negative culture and then de-escalated based on clinical judgment. For deep-seated candidemia, at least 6 weeks of treatment is necessary. Blood cultures should be performed on alternate days till 3 negative cultures. De-escalation from echinocandins is not recommended in cases where intravascular catheter or any other foreign device cannot be removed. Among echinocandins, both caspofungin and anidulafungin require a loading dose, while micafungin does not [41].

Resistance

The ESICM/ESCMID and the IDSA guidelines have not discussed resistance in detail [6,25]. Azole and multidrug resistance were seen in 11.8% and 1.9% of isolates in a multicenter Indian study [7]. Among two recent studies from India, *Candida* species showed good sensitivity to voriconazole (80%), fluconazole (67.78%), and amphotericin B (62.22%) in a tertiary care center from North India [42]. In the other study from North-West India, resistance to fluconazole, voriconazole, 5-flucytosine, and amphotericin-B was 36%, 20%, 4%, and 7%, respectively. There was no resistance to echinocandins [43]. However, various studies from different centers in India have reported varying rates of resistance (Table 1). Nevertheless, all experts agreed that *Candida* species are highly susceptible to echinocandins. According to them, *C. tropicalis*, *C. albicans*, and *C. parapsilosis* are sensitive to echinocandins. Some experts opined that high minimum inhibitory concentration (MIC) for some echinocandins like anidulafungin has been observed in cases of *C. parapsilosis*. Micafungin and caspofungin can also be administered for *C. parapsilosis* infections. *C. auris* has a high MIC for echinocandins, but it is sensitive to all 3 types of echinocandins, namely, caspofungin, micafungin, and anidulafungin. However, some experts contended that *C. auris* is sensitive to both echinocandins and amphotericin B though most isolates of *C. auris* are resistant to azoles. Hence, they recommended starting with echinocandins and then switching to amphotericin B if required in cases with *C. auris* infection.

Managing IC in specific settings

According to the experts, fluconazole should be the first choice for urinary tract infections due to *Candida*. Because echinocandins do not penetrate CNS, amphotericin B should be the drug of choice for *Candida* infection in the CNS. In such cases, voriconazole must be administered in combination with amphotericin B because posaconazole cannot penetrate the blood brain barrier.

For patients with AKI, those on extracorporeal membrane oxygenation (ECMO), or those with acute/chronic liver failure, echinocandins are the preferred antifungal therapy for IC. There is insufficient literature on the dosage of echinocandins in patients on ECMO [44]. Some experts suggested that ECMO should be treated as continuous renal replacement therapy and the initial dose should be high as there is a possibility of hemodilution. For *C. auris* infection in the urinary tract, some studies suggest one and a half times the usual dose of micafungin [45]. The preferred choice of therapy for IC in critically ill pediatric patients is echinocandins because of azole resistance and higher presence of non-albicans species. For patients undergoing hematopoietic stem cell transplant, echinocandins should be mainly used. Micafungin probably has the lowest drug interactions with tacrolimus, cyclosporine or any other drugs, among the antifungals [46]. In IC due to non-albicans species, a combination of echinocandins + azole (voriconazole)

as targeted therapy should be used. Voriconazole probably has an erratic absorption profile, and its use is challenging without therapeutic drug monitoring. The dose should be 8 to 10 mg/kg in neonates and 2 mg/kg in the pediatric population. In case there is persistent *C. auris* and the culture is positive despite antifungal therapy, the micafungin dose can be increased to 15 mg/kg. Flucytosine can be used for resistant *C. auris*; however, it is nephrotoxic and not easily available. In the pediatric population, micafungin and caspofungin are A-I recommendation for therapy while anidulafungin is B-II [25].

Conclusion

Prolonged ICU stay with use of broad-spectrum antibiotics and catheterization are associated with the highest risk of IC. The 5 most dominant *Candida* species associated with IC are *C. tropicalis, C. albicans, C. parapsilosis, C. glabrata*, and *C. krusei*. Combining culture and non-culture-based tests such as BDG, *Candida* antigen, procalcitonin, and CRP is a useful strategy for early detection of IC. It is important to avoid unnecessary use of empirical antifungal therapy to prevent the emergence of resistance. Appropriate candidates for prophylactic antifungal therapy in India are high-risk patients, while empirical therapy can be initiated in patients with refractory fever or persisting signs of infection despite 4-5 days of broad-spectrum antibacterial therapy. Echinocandins can be considered as first-line therapy for IC except in cases of CNS candidiasis and urinary tract infections. The efficacy of micafungin for the treatment of candidemia and other forms of invasive candidiasis is well-supported by published literature and standard practice guidelines. Treatment de-escalation and discontinuation should be based on clinical judgment, negative biomarkers, and negative cultures in concordance with the guidelines.

Disclosures

The author received speaker's honorarium from Abbott for participation in the focus group discussion.

Funding Support

The expert group discussion was conducted in association with Abbott India Ltd. This article is based on the views expressed during the expert group discussion. The views expressed and discussed in the meetings and stated in this article are the independent views of the authors and not of Abbott.

Acknowledgement

We are grateful to the following doctors for participating in the advisory board meeting and contributing to the concept and recommendations of the present document: Dr. Rajesh Chawla, Dr. Shririsha Rani, Dr. Haripriya Reddy Challa, Dr. Chandrashish Chakravarty, Dr. Rajkumar, Dr. Vishnu Rao, Dr. Asif Iqbal, Dr. Nitin Shinde, Dr. Ashutosh Bhardwaj, Dr. B K Malpani, and Dr. Punit Jain. Medical writing assistance was provided by Dr. Sangeeta Dhanuka and Dr. Sujatha Vijayakumar from Hashtag Medical Writing Solutions Pvt. Ltd., Chennai.

Statement of Authors' Contribution

YM has contributed to the concept, design, critical review, and revision of this document. The author has read and approved the final draft of the manuscript for publication.

References

1. Pappas PG, Lionakis MS, Arendrup MC, Ostrosky-Zeichner L, Kullberg BJ (2018) Invasive candidiasis. Nat Rev Dis Primers 4: 18026.
2. Logan C, Martin-Loeches I, Bicanic T (2020) Invasive candidiasis in critical care: Challenges and future directions. Intensive Care Med 46: 2001-2014.
3. Bongomin F, Gago S, Oladele RO, Denning DW (2017) Global and multi-national prevalence of fungal diseases-estimate precision. J Fungi (Basel) 3: 57.
4. Center for Disease Control and Prevention (2023) Invasive Candidiasis Statistics.
5. Ben-Ami R (2018) Treatment of invasive candidiasis: A narrative review. J Fungi (Basel) 4: 97.
6. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, et al. (2016) Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 62: e1-50.
7. Chakrabarti A, Sood P, Rudramurthy SM, Chen S, Kaur H, et al. (2015) Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med 41: 285-295.
8. Sahni V, Agarwal SK, Singh NP, Anuradha S, Sikdar S, et al. (2005) Candidemia-an under-recognized nosocomial infection in Indian hospitals. J Assoc Physicians India 53: 607-611.
9. Xess I, Jain N, Hasan F, Mandal P, Banerjee U (2007) Epidemiology of candidemia in a tertiary care centre of North India: 5-year study. Infection 35: 256-259.
10. Chander J, Singla N, Sidhu SK, Gombar S (2013) Epidemiology of *Candida* blood stream infections: Experience of a tertiary care centre in North India. J Infect Dev Ctries 7: 670-675.
11. Giri S, Kindo AJ, Kalyani J (2013) Candidemia in intensive care unit patients: A one year study from a tertiary care center in South India. J Postgrad Med. 59: 190-195.
12. Rajeshwari R, Vyasam S, Chandran J, Porwal S, Ebenezer K, et al. (2022) Risk factors for Candida infection among children admitted to a pediatric intensive care unit in a tertiary care centre in Southern India. Indian J Crit Care Med 26: 717-722.
13. Kaur H, Singh S, Rudramurthy SM, Ghosh AK, Jayashree M, et al. (2020) *Candidaemia* in a tertiary care centre of developing country: Monitoring possible change in spectrum of agents and antifungal susceptibility. Indian J Med Microbiol 38: 110-116.
14. Bassetti M, Giacobbe DR, Vena A, Trucchi C, Ansaldi F, et al. (2019) Incidence and outcome of invasive candidiasis in intensive care units (icus) in Europe: results of the EUCANDICU project. Crit Care 23: 219.

15. Ricotta EE, Lai YL, Babiker A, Strich JR, Kadri SS, et al. (2021) Invasive candidiasis species distribution and rends, United States, 2009-2017. J Infect Dis 223: 1295-1302.
16. Parslow BY, Thornton CR (2022) Continuing shifts in epidemiology and antifungal susceptibility highlight the need for improved disease management of invasive candidiasis. Microorganisms 10: 1208.
17. Cortés JA, Corrales IF (2018) Invasive candidiasis: Epidemiology and risk factors. Fungal Infection.
18. Thomas-Rüddel DO, Schlattmann P, Pletz M, Kurzai O, Bloos F (2022) Risk factors for invasive *Candida* infection in critically ill patients: A systematic review and meta-analysis. Chest 161: 345-355.
19. Smith C, Hanna MC (2019) Clinical manifestations of candidiasis: Beyond *Candida albicans*. Virol Immunol J 3: 000219.
20. Gulati M, Nobile CJ (2016) *Candida albicans* biofilms: development, regulation, and molecular mechanisms. Microbes Infect 18: 310-321.
21. Seelbinder B, Chen J, Brunke S, Vazquez-Uribe R, Santhaman R, et al. (2020) Antibiotics create a shift from mutualism to competition in human gut communities with a longer-lasting impact on fungi than bacteria. Microbiome 8: 133.
22. Rudramurthy SM, Chakrabarti A, Paul RA, Sood P, Kaur H, et al. (2017) *Candida auris* candidaemia in Indian icus: analysis of risk factors. J Antimicrob Chemother 72: 1794-1801.
23. Pfaller MA, Diekema DJ, Turnidge JD, Castanheira M, Jones RN (2019) Twenty years of the SENTRY antifungal surveillance program: Results for *Candida* species from 1997-2016. Open Forum Infect Dis 6: S79-S94.
24. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, et al. (2020) Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and Mycoses Study Group Education and Research Consortium. Clin Infect Dis 71: 1367-1376.
25. Martin-Loeches I, Antonelli M, Cuenca-Estrella M, Dimopoulos G, Einav S, et al. (2019) ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. Intensive Care Med 45: 789-805.
26. Barantsevich N, Barantsevich E (2022) Diagnosis and treatment of Invasive candidiasis. Antibiotics (Basel) 11: 718.
27. Mikulska M, Calandra T, Sanguinetti M, Poulain D, Viscoli C (2010) The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: Recommendations from the third European conference on infections in leukemia. Crit Care 14: R222.
28. Avni T, Leibovici L, Paul M (2011) PCR diagnosis of invasive candidiasis: systematic review and meta-analysis. J Clin Microbiol 49: 665-670.
29. Soriano A, Honore PM, Puerta-Alcalde P, Garcia-Vidal C, Pagotto A, et al. (2023) Invasive candidiasis: Current clinical challenges and unmet needs in adult populations. J Antimicrob Chemother 78: 1569-1585.
30. Ahmed A, Baronia AK, Azim A, Marak RSK, Yadav R, et al. (2017) External validation of risk prediction scores for invasive candidiasis in a medical/surgical intensive care unit: An observational study. Indian J Crit Care Med 21: 514-520.
31. León C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, et al. (2006) A bedside scoring system ("*Candida* score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. Crit Care Med 34: 730-737.
32. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R (1994) *Candida* colonization and subsequent infections in critically ill surgical patients. Ann Surg 220: 751-758.
33. Ostrosky-Zeichner L, Pappas PG, Shoham S, Reboli A, Barron MA, et al. (2011) Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. Mycoses 54: 46-51.
34. Rauseo AM, Aljorayid A, Olsen MA, Larson L, Lipsey KL, et al. (2021) Clinical predictive models of invasive *Candida* infection: A systematic literature review. Med Mycol 59: 1053-1067.
35. Shastri P, Nangia V, Sathe P, Pande R, Abraham A, et al. (2019) Consensus statement on the management of invasive candidiasis in Indian scenario. Int J Res Med Sci 7: 4410-4415.
36. Kuse ER, Chetchotisakd P, da Cunha CA, Ruhnke M, Barrios C, Raghunadharao D, et al. (2007) Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. Lancet 369: 1519-1527.
37. Ostrosky-Zeichner L, Kontoyiannis D, Raffalli J, Mullane KM, Vazquez J, et al. (2005) International, open-label, noncomparative, clinical trial of micafungin alone and in combination for treatment of newly diagnosed and refractory candidemia. Eur J Clin Microbiol Infect Dis 24: 654-661.
38. Pappas PG, Rotstein CMF, Betts RF, Nucci M, Talwar D, et al. (2007) Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. Clin Infect Dis 45: 883-893.
39. Queiroz-Telles F, Berezin E, Leverger G, Freire A, van der Vyver A, et al. (2008) Micafungin versus liposomal amphotericin B for pediatric patients with invasive candidiasis: substudy of a randomized double-blind trial. Pediatr Infect Dis J 27: 820-826.
40. Park S, Kim K, Jang JH, Kim SJ, Kim WS, et al. (2016) Randomized trial of micafungin versus fluconazole as prophylaxis against invasive fungal infections in hematopoietic stem cell transplant recipients. J Infect 73: 496-505.
41. Kofla G, Ruhnke M (2011) Pharmacology and metabolism of anidulafungin, caspofungin and micafungin in the treatment of invasive candidiasis: review of the literature. Eur J Med Res 16: 159-166.
42. Ahmad S, Kumar S, Rajpal K, Sinha R, Kumar R, et al. (2022) *Candidemia* among ICU patients: Species characterisation, resistance pattern and association with *Candida* score: A prospective study. Cureus 14: e24612.
43. Rajni E, Chaudhary P, Garg VK, Sharma R, Malik M (2022) A complete clinico-epidemiological and microbiological profile of candidemia cases in a tertiary-care hospital in Western India. Antimicrob Steward Healthc Epidemiol 2: e37.
44. Lyster H, Shekar K, Watt K, Reed A, Roberts JA, et al. (2023) Antifungal dosing in critically ill patients on extracorporeal membrane oxygenation. Clin Pharmacokinet 62: 931-942.
45. Grau S, Luque S, Echeverría-Esnal D, Sorlí L, Campillo N, et al. (2016) Urinary micafungin levels are sufficient to treat urinary tract infections caused by *Candida* spp. Int J Antimicrob Agents 48: 212-214.
46. Wiederhold NP, Cota JM, Frei CR (2008) Micafungin in the treatment of invasive candidiasis and invasive aspergillosis. Infect Drug Resist 1: 63-77.
47. Bhattacharjee P (2016) Epidemiology and antifungal susceptibility of *Candida* species in a tertiary care hospital, Kolkata, India. Curr Med Mycol 2: 20-27.
48. Umamaheshwari S, Sumana MN (2023) Retrospective analysis on distribution and antifungal susceptibility profile of Candida in clinical samples: A study from Southern India. Front Public Health 11: 1160841.