Indian Journal of Medical Microbiology, (2012) 30(3): 270-8

Review Article

A review of *Candida* species causing blood stream infection

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Abstract

The incidence of candidemia has been on a rise worldwide. The epidemiology of invasive fungal infections in general and of candidemia in particular has changed in the past three decades because of a variety of factors like the AIDS epidemic, increased number of patients receiving immunosuppressive therapy for transplantation and the increasing use of antimicrobials in the hospital setups and even in the community. The important risk factors for candidemia include use of broad-spectrum antimicrobials, cancer chemotherapy, mucosal colonization by Candida species, indwelling vascular catheters like central venous catheters, etc. More than 90% of the invasive infections due to Candida species are attributed to five species—*Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei*. However, the list of new species of Candida isolated from clinical specimens continues to grow every year. Early diagnosis and proper treatment is the key for management of candidemia cases.

Key words: *Antifungals, candidemia, echinocandins, immunocompromised*

Introduction

Since the early 1980s, there has been a rise in the incidence and prevalence of fungal infections worldwide. Blood stream infections (BSI) caused by various *Candida* species have been reported from many countries worldwide and are a significant cause of morbidity and mortality in hospitalized patients. Candidemia has been associated with many risk factors like long-term hospitalization, antibiotic therapy, use of intravascular catheters and underlying diseases like diabetes and malignancy. Early and prompt diagnosis, proper treatment and prevention of candidemia pose a major challenge for microbiologists and clinicians worldwide. Added to this is the emerging trend of antifungal drug resistance among the *Candida* species.

Epidemiology of Candidemia

Incidence and prevalence of candidemia

The importance of *Candida* species as a cause of BSI has been highlighted in many studies in the past few years. In a 7-year long study analyzing nosocomial BSI in hospitals in the United States (Surveillance and Control of Pathogens of Epidemiological Importance [SCOPE]), *Candida* species was found to be the fourth most common cause of BSI in a hospital setup.[1] A retrospective study from the United States which was based on the attributable mortality, length of hospital stay and hospital charges related to candidemia found that candidemia was associated with a 14.5% increase in mortality, a mean 10.1 day increase in length of hospital stay thereby leading to a rise in the total expense.[2]

An increase in the incidence rate of candidemia has been reported from other parts of the world as well. Studies from European countries like Norway, Iceland and Denmark have shown a considerable rise in the incidence of candidemia over a period of a decade (2/100,000 population/year in 1991–1994 to 3/100,000/year in 2001–2003).[3] A study in Switzerland over a 10 year period found *Candida* species to be the seventh most common cause of BSI in hospitals.[4] A similar study from Finland reported an increase in the annual incidence rate of candidemia from 1.7 per 100,000 population in 1995 to 2.2 in 1999.[5] A Norwegian study reported candidemia episodes from approximately two episodes in the early 1990s to three episodes during 2001 to 2003.[6] Studies carried out in developing countries have also reflected on similar lines. A nationwide sentinel surveillance of candidemia carried out in Brazil reported an overall incidence of 2.49 cases of candidemia per 1000 admissions.[7]

The Asian scenario regarding incidence of candidemia is, however, not very clear due to lack of multicentric studies. A 13-year long study on candidemia from a tertiary care hospital in Thailand showed a prevalence of 6.14% for

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Received: 09-01-2012
Accepted: 27-03-2012

Access this article online	
Quick Response Code:	Website: www.ijmm.org
	DOI: 10.4103/0255-0857.99484

Candida species among blood culture isolates.[8]

There has been a lot of variation in the prevalence and incidence reports quoted from different parts of India. A study by Verma *et al*. from SGPGI in Lucknow ranked *Candida* species as eighth among all isolates from BSI. This study reported an incidence rate of 1.61 per 1000 hospital admissions for candidemia.[9] A New Delhi-based study gave a prevalence rate of 18% for *Candida* species among blood culture isolates.[10] A study in South India reported an incidence rate of 5.7% for candidemia among children with onco-haematological malignancies.[11] Another study from Rohtak, North India, reported an isolation rate of 8.1% for *Candida* species from cases of neonatal septicaemia.[12] Xess *et al*. from AIIMS, New Delhi, found a prevalence rate of 6% for *Candida* species in a 5-year study (2001–2005).[13] A study by Sahni *et al*. from Maulana Azad Medical College, New Delhi, found an incidence rate of 6.9% for *Candida* species in BSI.[14]

Risk Factors for Candidemia

In the past two decades, a variety of factors like the Acquired Immuno-Deficiency Syndrome (AIDS) epidemic, increased number of patients receiving immunosuppressive therapy for transplantation, the increasing use of antimicrobials in the hospital setups and even in the community have played a key role in altering the epidemiology of invasive fungal infections in general and of candidemia in particular. The importance of risk factors analysis cannot be over emphasized for infections like candidemia so that preventive measures and prophylactic therapy can be initiated for patients at risk. Many studies have established independent risk factors for candidemia on the basis of multivariate analyses. The important independent risk factors include use of broad-spectrum antimicrobials, cancer chemotherapy, mucosal colonization by *Candida* species, indwelling vascular catheters like central venous catheters (CVCs), etc.

Exposure to long term antibiotic therapy

Long-term antibiotic therapy is one of the most extensively studied risk factors. Exposure to multiple and prolonged use of broad spectrum antimicrobials have been found to be independent risk factors for candidemia.[3] The reason for this being, many of the antibiotics like beta-lactams and vancomycin used in the wards and intensive care unit (ICU) settings lead to the depletion of normal bacterial flora resulting in fungal overgrowth. The increasing use of oral vancomycin in the ICUs results in the depletion of anaerobic bacterial flora of the gut.

Intravascular Catheters and Central Venous Catheters

Intravascular catheters are also one of the important risk factors in the acquisition of candidemia. *Candida* species adhere avidly to materials used in intravascular catheters and provide a potential nidus for infection.[15] Some species like *Candida parapsilosis* are especially implicated in intravascular catheter-related infections in neonates and in the paediatric age group.

The role played by intravascular catheters in perpetuating candidemia has implications for its management. Removal of vascular catheters has been advocated as an adjunctive strategy for treating patients with catheter-related candidemia. However, there is some controversy regarding the benefits and risks of removal of vascular catheters in management of candidemia.[15]

Malignancies and cancer chemotherapy

Malignancies are not independent risk factors for candidemia. However, patients with malignancies are at increased risk of developing candidemia because of a number of factors like cancer chemotherapy, longer duration of hospital stay and treatment with various antimicrobials.

Candida colonization and candidemia

The source of BSI with *Candida* species has been a subject of considerable debate in the last couple of decades. Two major sources of infection have been proposed—the gastrointestinal tract (endogenous infection) and the skin (exogenous infection). In the past few years, however, there has been ample evidence pointing towards an endogenous, gastrointestinal origin for candidemia. For some species of *Candida* like *C. parapsilosis*, however, the skin has been identified as the source of infection. This fact is of clinical importance and *C. parapsilosis* has been found to be increasingly implicated in BSI after placement of intravascular devices.[3]

Candiduria and candidemia

Candiduria has been found to be a risk factor for candidemia and can sometimes be an indicator of impending sepsis with *Candida* species in patients admitted to hospitals, especially those in ICUs. A few studies have suggested that as many as 10% of all candiduria cases may be associated with candidemia.[16] In patients with candiduria, the presence of other risk factors like CVCs, surgical intervention or procedures involving the urinary tract, presence of urinary catheters are significantly associated with development of candidemia.[16]

Prior surgery and risk of candidemia

Surgical procedures in general and gastrointestinal surgeries in particular have been associated with an increased risk of candidemia in patients. Surgical procedures of the gastrointestinal tract might lead to mucosal disruption and cause seeding of the bloodstream by *Candida* species which colonize the gut.[17]

Total parenteral nutrition

Total Parenteral Nutrition (TPN) is life saving in chronically debilitated patients who lack gastrointestinal absorption. That *Candida* species can grow well in available nutritive parenteral solutions has been known for more than three decades now. TPN has been found to be an independent risk factor for invasive candidiasis and candidemia on the basis of many multivariate studies.[3]

Neutropenia

Prior to 1990, the focus of attention was on the increased risk of candidemia in neutropenic patients. In the recent years, however, the focus has shifted to non-neutropenic patients admitted in ICUs.[3]

Diabetes mellitus

Few studies have found a greater degree of colonization with *Candida* species in diabetic patients compared to control subjects.[18] Isolates of *Candida* species colonizing diabetic patients have also been found to show a greater degree of resistance to antifungals than strains isolated from control subjects.

Ventricular assist devices

Invasive candidiasis is also common in ventricular assist devices (VADs) and is associated with poor outcomes. In a study from Washington DC, USA, candidemia developed in 6% of the 117 patients undergoing placement of VADs.[19] Another study found *Candida* species to be responsible for 13.6% of all the BSI among VAD recipients and was second only to *Staphylococcus* species as a cause of BSI.[20]

Candidemia in patients with multiple risk factors

The presence of multiple risk factors in a particular patient exponentially increases the chances of getting candidemia. For example, it has been demonstrated that a patient receiving eight different antimicrobials and who is colonized with *Candida* species has 832 times higher risk of developing candidemia when compared to a similar patient without antimicrobial therapy.[21] However, the frequency with which many of these risk factors are found in patients admitted in ICUs make them less useful in accurately predicting which patient in the ICU setting will develop candidemia.[3] Many workers have tried to develop risk assessment strategies and calculate "Candida scores" to predict the true risk of disease in patients admitted in ICUs[22,23] [Table 1].

"Candida risk scores" might aid physicians in ruling out candidemia and in identifying those at high risk of candidemia early in the hospital stay.

Table 1: *Candida* "risk scores" to predict at risk patients for candidemia in ICUs

Reference	Defined risk factors
Leon *et al*.[3]	clinical sepsis (2 points), surgery (1 point), TPN (1 point) and multifocal colonization (1 point)
Wenzel and Gennings[22]	colonization with *Candida* species, number of antibiotics, presence of intravenous catheters and haemodialysis
Shorr *et al*.[23]	age <65 years, temperature ≤98°F or severe altered mental status, cachexia, previous hospitalization within 30 days, admitted from other healthcare facility and need for mechanical ventilation

Risk Factors for Candidemia in Various Groups of Patients

Risk factors for candidemia in paediatric patients

Most of the time paediatricians and neonatologists are reliant on data from adult clinical trials when dealing with candidemia. Not many studies are available which deal with the epidemiology of candidemia in paediatric patients. A few case-control studies have found prolonged parenteral nutrition, use of CVCs, topical antifungals as important risk factors associated with development of candidemia.[24]

Risk factors for candidemia in neonates

Among the various risk factors implicated in the acquisition of candidemia or invasive candidiasis in neonates, the most important factor is low birth weight (LBW) and prematurity. In a study by Lee *et al*., neonates with birth weights less than 1250 g were found to be at a greater risk of getting candidemia or meningitis caused by *Candida*. Such neonates also had a higher chance of developing complications like intraventricular haemorrhage and greater mortality rate than control neonates.[25] A few Indian studies have also evaluated the risk factors in neonates associated with candidemia and found that the isolation of *Candida* species from any other focus of infection and indwelling intravascular catheters to be the most common risk factors associated with this condition.[26] Admission in the ICU is another important risk factor for candidemia in neonates.

Risk factors for candidemia in patients admitted in surgical ICUs

Among patients admitted in ICUs, those admitted in surgical ICUs (SICUs) are considered to be at a greater risk for developing candidemia.[17] According to a large prospective multicentre study to evaluate risk factors for development of candidemia in SICU patients (NEMIS SICU study), there was a wide variation in infection rates between institutions with the highest rates of candidemia in urban hospitals caring for

trauma patients.[17] The risk factors independently associated with development of candidemia in this study were prior surgery, acute renal failure and parenteral nutrition. Many authors have suggested that an elevated APACHE II score can help identify ICU patients who can have a higher risk of developing candidemia, although some studies suggest there is no relationship between the two.[17] Heitner *et al*. compared the risk factors for candidemia in patients admitted in medicine ICUs (MICUs) to those admitted in SICUs and found significant differences between the two.[27] SICU patients had a longer duration of antibiotic therapy and received a larger number of antibiotics than patients admitted in MICU. SICU patients were also more likely to have other risk factors like TPN and CVCs.[27]

Liver transplantation and candidemia

Invasive candidiasis is one of the most important infections to occur after liver transplantation.[28] Use of more than three antibiotics and hyperglycaemia that requires insulin therapy were found to be important risk factors associated with candidemia in liver transplant patients in a study carried out in Pittsburgh, USA.[28]

Indian studies analyzing risk factors for candidemia

A few studies from India have analyzed various risk factors associated with candidemia and invasive candidiasis [Table 2].

Species Distribution among *Candida* Isolates from Blood

The trends in BSI caused by yeasts have been changing in the past few decades and many new species of *Candida* have been isolated from patients with candidemia in the last few years. More than 17 species of *Candida* have been implicated in human infections till date and the list of reported species continues to grow. The emergence of new species of *Candida* as potential pathogens is a reflection of the changing scenario in medicine since the 1960s.

Table 2: Indian studies on risk factors for candidemia

Reference	Place of study	Important risk factors
Kumar *et al*., 2005[11]	Chennai	Neutropenia, cytotoxic chemotherapy, steroid therapy, use of broad spectrum antimicrobials
Goel *et al*., 2009[12]	Rohtak	Low birth weight in neonates, use of broad spectrum antibiotics
Xess *et al*., 2007[13]	New Delhi	Antibiotics, ventilators, urinary catheters, CVCs and TPN
Sahni *et al*., 2005[14]	New Delhi	Prolonged hospital stay, use of broad-spectrum antibiotics, CVCs, mechanical ventilation and TPN
Chowta *et al*. 2007[57]	Mangalore	Intravenous catheters (most common), prolonged use of antimicrobials and HIV infection

More than 90% of the invasive infections due to *Candida* are attributed to five species—*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei.* However, the list of new species of *Candida* isolated from clinical specimens continues to grow every year.[3] This is due to the fact that clinical microbiology laboratories worldwide are using commercially available identification methods to supplement the conventional methods of identification. Besides, the increasing isolation of previously "nonpathogenic" yeasts could also be due to the increased number of immunocompromised patients worldwide in view of the Human Immunodeficiency virus (HIV) epidemic and the increasing number of organ transplantations.

C. albicans has been the most common species of *Candida* isolated from BSI worldwide. A number of surveillance programs in the 1990s gave the percentage prevalence of *C. albicans* as ranging from 50% (in the SENTRY surveillance program 1997-2000) to as much as 71% (Fungal Disease Registry, Canada 1992–1994).[29] However, in the past few years, there is an increasing trend of isolation of non-albicans *Candida* species from BSI. A number of international surveillance programs like the ARTEMIS Antifungal Surveillance program have noted a decreasing trend in the isolation of *C. albicans* although it still remains the most common species overall.[3] The ARTEMIS Surveillance Study which was carried out over a period of 6.5 years (1997–2003) in 127 medical centres in 39 countries has shown an increase in the prevalence of *Candida* species like *C. tropicalis* (4.6% in 1997 to 7.5% in 2003) and *C. parapsilosis* (4.2% in 1997 to 7.3% in 2003).[30] This particular surveillance study showed a 2– to 10-fold increase in the isolation rates of rare species like *C. guillermondii, C. kefyr* and *C. rugosa*.

Among the non-albicans *Candida* species, *C. glabrata* has emerged as an important opportunistic pathogen worldwide. It is the second most common yeast isolated as part of normal flora and its role as a pathogen has only been recognized in the past few decades. Trick *et al*. reported a considerable increase in the isolation rate of *C. glabrata* from BSI in U.S ICUs.[31] In a 8-year long study from Michigan, USA, *C. glabrata* was found to be responsible for 17% of 609 fungemic episodes.[32] *C. glabrata* fungemia is seen more often in older adults and is comparatively uncommon in neonates and in the paediatric age group.[32] Although the risk factors for candidemia due to *C. glabrata* appear to be the same as for candidemia in general, this particular species has emerged prominently among patients with haematological malignancies.

In contrast to the US scenario, in many other countries, *C. tropicalis* and *C. parapsilosis* have become the most common *Candida* species to cause BSI.[3] In India, *C. tropicalis* is now the most common cause of nosocomial candidemia. Epidemiological studies have implicated *C. tropicalis* in as many as 67–90% of cases of

candidemia.[9,10,33] The increased use of fluconazole has been determined to be the major cause of predominance of non-albicans *Candida*, especially *C. tropicalis* over *C. albicans*. The emergence of non-albicans species of *Candida,* mainly *C. tropicalis* has been reported from all over the country. Shivprakasha *et al*. in a study from South India found *C. tropicalis* to be the most prevalent species of *Candida* isolated from cases of candidemia (35.6%).[34] In this particular study, *C. albicans* was isolated in only 3.4% of the cases. Similar reports have also been documented by Adhikary *et al*. (39.7%)[35] and Xess *et al*. from AIIMS, New Delhi.[13]

C. parapsilosis is found commonly on the skin surface and has a better adherence to materials like acrylic in glucose-containing solutions and TPN solutions. It is especially known for causing BSI in infants and neonates.[36] The detection of *C. parapsilosis* in BSI is an indication of exogenous introduction of the pathogen from the environment.

C. krusei accounts for about 2% to 4% of all BSI caused by *Candida* species and is especially important in patients with haematological malignancies and bone marrow transplants.[3] One of the major reasons for the emergence of this pathogen is the increasing use of fluconazole worldwide, especially in patients admitted to ICUs.

C. guilliermondii is a relatively rare species which is being isolated with increasing frequency from blood and has been found to be isolated more frequently in patients with prior cardiovascular or gastrointestinal surgery. *C. rugosa* is a cause of catheter-related BSI reported from a few countries.[3]

Among the other uncommon species of *Candida* isolated from blood, *C. inconspicua* and *C. norvegensis* are phenotypically similar to *C. krusei* and also show resistance to fluconazole. These two species are mostly isolated from respiratory tract samples.[3]

C. dubliniensis is commonly misidentified as *C. albicans* because of similar phenotypic characteristics like production of chlamydospores. This species has been isolated from a few cases of candidemia in the recent years. Baradkar *et al*. from Mumbai reported a case of neonatal septicaemia caused by *C. dubliniensis* in a preterm baby.[37]

C. pelliculosa is another rare species which was reported from five cases of candidemia in a tertiary care hospital in South India.[34] Agarwal *et al*. from IGMC, Shimla, have reported a case of catheter-related candidemia caused by *C. lipolytica*.[38].

A particular species of *Candida* isolated from a case of candidemia seems to be an important determinant of the outcome as has been evidenced by many studies. In a patient population extracted from the Prospective Antifungal Therapy (PATH) Alliance database, the highest mortality was found among patients with *C. krusei* infection (crude mortality rate of 52.9%) while those infected with *C.parapsilosis* had the lowest mortality rate of 23.7%.[39] The SCOPE surveillance study also reported similar trends for various *Candida* species.[1]

Trends in Antifungal Susceptibility in Isolates of *Candida* Species from Blood

Fluconazole resistance in candidemia isolates

C. krusei and many strains of other rare species which closely resemble it like *C. inconspicua* and *C. norvegensis* are intrinsically resistant to fluconazole.[40] About 10% of strains of *C. glabrata* from BSI may also be highly resistant to fluconazole.[41]

C. glabrata is the predominant species of *Candida* isolated from BSI in many countries like the United States and remains the subject of concern when it comes to fluconazole resistance. The frequency of fluconazole resistance in *C. glabrata* shows geographical variation, much in the same way as the isolation of this species from cases of candidemia. In regions like the Asia-Pacific and Latin America where the isolation of *C. glabrata* is less frequent, resistance to fluconazole has been found to be low (10–13%). On the other hand, countries like the United States where *C. glabrata* predominates as the cause of candidemia have fluconazole resistance rates which are much higher (18%).[3]

Fluconazole resistance in india

In India, there is a lack of multicentric studies regarding antifungal susceptibility pattern. However, there are few studies from different parts of the country which give some idea regarding the epidemiology of antifungal resistance among candidemia isolates [Table 3].

Table 3: Indian studies on fluconazole resistance

Reference	Place of study	Percentage resistance to azoles
Kothari *et al*., 2008[10]	New Delhi	Fluconazole (36), Itraconazole (24), Voriconazole (56)
Kumar *et al*., 2005[11]	Chennai	Fluconazole (17.2)
Goel *et al*., 2009[12]	Rohtak	Fluconazole (4.5)
Xess *et al*., 2007[13]	New Delhi	Fluconazole (11.7)
Gupta *et al*. 2001[26]	New Delhi	Fluconazole (37.5)
Adhikary *et al*. 2011[35]	Bangalore	Fluconazole (25)
Capoor *et al*. 2005[58]	New Delhi	Fluconazole (4.9), Itraconazole (3.9)

Amphotericin B resistance in candidemia isolates

Amphotericin B is a polyene and the mechanism of resistance to polyenes has been found to be a reduction in the ergosterol content of the plasma membrane. This leads to a lower affinity of amphotericin B to the plasma membrane. Reports of resistance to amphotericin B among isolates of *Candida* are limited. However, some species like *C. lusitaniae, C. lipolytica* and *C. guilliermondii* can show intrinsic resistance to amphotericin B. There have been a few reports of strains of *C. albicans* showing resistance to amphotericin B.[42] Species like *C. rugosa* have been seen to have elevated levels of MIC for amphotericin B especially in the setting of nystatin prophylaxis and breakthrough fungemia in patients already on amphotericin B.[3]

Echinocandin resistance in candidemia isolates

Echinocandins are lipopeptides with a broad spectrum of antifungal activity and include agents like caspofungin, anidulafungin and micafungin. These agents act by inhibition of the synthesis of 1,3-β-D-glucan in the fungal cell wall. Echinocandins have favourable fungicidal activity against *Candida* isolates irrespective of their resistance or susceptibility to azoles or amphotericin B. Results of a global surveillance which dealt with trends in the susceptibility of *Candida* species to caspofungin since the clinical availability of the drug found no evidence for a shift in the caspofungin MIC distribution.[43] However, few reports of clinical and *in vitro* resistance to echinocandins in patients with candidemia do exist.[44] In many of these studies, the strains showing resistance to echinocandins like caspofungin have been found to have co-resistance to azoles as well. A recent study by Lee *et al*. in BALB/c mice has found that the efficacy of caspofungin against *C. albicans* was reduced *in vivo* due to either elevation of chitin levels in the cell wall or acquisition of FKS1 point mutations.[45]

Management of Candidemia

Antifungal agents for treatment of disseminated candidiasis and candidemia

Azoles

This group of antifungal agents is most commonly used for treatment of candidemia. Fluconazole is the most common azole to be used for invasive candidiasis and its efficacy in non-neutropenic patients is comparable to that of amphotericin B, notwithstanding the fact that amphotericin B has greater *in vitro* activity against *Candida* species. Other advantages of fluconazole are that it is available in both intravenous and oral formulations with high bioavailability and is significantly less expensive than other antifungal agents. Fluconazole and the other triazoles have less activity against species of *Candida* like *C. krusei* and some strains of *C. glabrata*. Fluconazole is the only antifungal agent for which considerable information regarding antifungal resistance trends and well-standardized guidelines for susceptibility testing are available.

Itraconazole is a triazole available in intravenous formulations with very good bioavailability. However, this agent has mostly been used for treatment of mucosal candidiasis and not many studies are available regarding its role in the treatment of invasive candidiasis and candidemia.

Voriconazole is also available in both oral and parenteral formulations and seems to be active against isolates of *Candida* which are resistant to fluconazole. The *in vitro* activity of posaconazole has been found to be comparable to that of other triazoles. However, this drug has not been frequently used in the treatment of candidemia. One of the major reasons is that this particular drug is available only in the form of oral formulations.[46]

Polyenes (Amphotericin B)

Amphotericin B in various formulations has been used for the treatment of disseminated candidiasis and candidemia. Although amphotericin B has a rapid cidal action against most strains of *Candida* species (especially *C.albicans*), it is not the first choice for treatment of cases of candidemia because of the nephrotoxicity associated with it. Amphotericin has been reformulated into various lipid-based formulations which have comparatively superior side-effect profiles. Such formulations include liposomal amphotericin B and amphotericin B lipid complex and their effectiveness has been demonstrated by many trials and studies.[47] Amphotericin B has an optimal molecular structure for liposomal incorporation. Entrapment of amphotericin B into liposomes increases its therapeutic index through selective transfer of amphotericin B into fungal cells, with reduced uptake into human cells.[48] A major advantage of these lipid-based formulations is that because of their better side-effect profiles, these agents can be used at increased doses for treating serious infections like candidemia. However, since these lipid formulations are very expensive, these are not very widely used, especially in resource poor settings. Amphotericin B also has delayed killing kinetics *in vitro* against *C. glabrata* and *C. krusei* compared to the killing kinetics against other species like *C. albicans*. This clinically translates to using higher doses of amphotericin B when dealing with infections caused by *C. krusei* or *C. glabrata* despite the increased toxicity associated with higher doses of amphotericin B.[49]

Fluconazole and Amphotericin B combination

A few studies have demonstrated that fluconazole and amphotericin B can be used as a combination therapy.[50] This is unexpected considering that fluconazole which belongs to the azole group of drugs, inhibits the

synthesis of ergosterol, the normal fungal membrane sterol. This therefore removes the very target on which amphotericin B is supposed to act. However, it has been seen that fluconazole and amphotericin B do not show antagonistic effects in animal models of disseminated candidiasis using animals like guinea pigs and rabbits. Studies done on two groups of human subjects by Rex *et al*., one group previously treated with fluconazole and the other without any previous exposure to fluconazole, showed comparable rates of treatment failure in both the groups.[50]

Echinocandins

Echinocandins like caspofungin and micafungin have shown considerable *in vitro* and *in vivo* efficacy in the treatment of invasive candidiasis and candidemia. Caspofungin got the FDA approval for treatment of candidemia in 2003. The emerging trend of resistance to fluconazole and other triazoles among *Candida* isolates from BSI has made the echinocandins very important. People at risk for triazole resistance (prior triazole treatment, prolonged hospitalization or severe immunosuppression) are increasingly being treated empirically with echinocandins while awaiting antifungal susceptibility testing results. Echinocandins have less drug-related toxicity compared to amphotericin B. But the use of echinocandins is limited in developing countries like India due to its high cost and limited availability.

Factors responsible for antifungal treatment failure

Apart from resistance to antifungal agents which is one of the most important causes of antifungal treatment failure, many other factors also play important roles in this. Host factors like severity of the illness or immunosuppression can lead to treatment failure. Decreased bioavailability and decreased concentration of the drug at the target site due to various pharmacokinetic and pharmacodynamic variables also lead to antifungal treatment failure.[51]

Vascular catheters as prognostic factors of candidemia

The presence of vascular catheters, whether peripheral venous catheters or CVCs, has been associated with candidemia, both as a risk factor and prognostic factor. Removal of vascular catheters from patients of candidemia has therefore been advocated as standard practice for quite some time.[52] However, this is not always practical , especially in very sick patients where their very survival depends on the vascular catheters. Moreover, it has been pointed out by many authors that removal of vascular catheters might not have a beneficial effect in all cases of candidemia and that a thoughtful and systematic approach to considering the ratio of risks of catheter removal to its benefits is warranted.[53]

Prevention and prophylaxis for candidemia

Given the high mortality rate and the difficulties encountered in administering early and effective antifungal therapy, better methods of prevention will decrease candidemia-associated mortality more effectively than will advances in therapy. Three strategies – improved hand hygiene, optimal catheter placement and care, and prudent antimicrobial use – should be primary in the approach to prevention of morbidity and mortality resulting from nosocomial candidemia.[3] For hand washing, both alcohol and chlorhexidine have been found to be effective in killing *Candida* species on the hands of health care workers.

Antifungal prophylaxis is commonly used in patients with specific risk factors like malignancies, transplant patients and patients with neutropenia. Whereas guidelines for the treatment of candidemia are available, the role of prophylactic or empirical therapy in preventing candidemia or decreasing the mortality rate associated with it is not very clear. Empirical therapy is instituted before the diagnosis of candidemia. Because of the high mortality associated with delayed therapy in candidemia especially in neutropenic patients, empirical therapy with anti-fungal drugs is usually advocated for such patients.[54]

Prophylactic antifungal therapy is used in patients who have not yet been diagnosed with candidemia and do not have the suggestive symptoms but are at a high risk of acquiring candidal infections. The groups of patients for whom antifungal prophylaxis is indicated include neutropenic patients, recipients of stem cell or organ transplants, especially liver transplant recipients and patients with haematological malignancies. The beneficial effects of such prophylactic therapy have been demonstrated in many randomized clinical trials.[55] Prophylaxis with fluconazole has been shown to be beneficial in low birth weight infants and post-operative patients at high risk of candidemia. Fluconazole is the antifungal agent which is most commonly used for prophylaxis as it can be orally administered and is comparatively cheaper than other antifungal agents. Newer agents like posaconazole and micafungin have also been administered as prophylactic agents and have given promising results.[56] However, the exact role of prophylaxis in certain groups of patients like post-operative patients and patients in ICU is still uncertain and requires further studies.

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How to cite this article: Giri S, Kindo AJ. A review of Candida species causing blood stream infection. Indian J Med Microbiol 2012;30:270-8.

Source of Support: Nil, **Conflict of Interest:** None declared.