Review Article

Invasive candidiasis in non neutropenic critically ill - need for region-specific management guidelines

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Abstract

Use of antifungal agents has increased over past few decades. A number of risk factors such as immunosuppression, broad spectrum antibiotics, dialysis, pancreatitis, surgery, etc., have been linked with the increased risk of invasive candidiasis. Though there are various guidelines available for the use of antifungal therapy, local/regional epidemiology plays an important role in determining the appropriate choice of agent in situations where the offending organism is not known (i.e. empirical, prophylactic or preemptive therapy). Developing countries like India need to generate their own epidemiological data to facilitate appropriate use of antifungal therapy. In this article, the authors have highlighted the need for region-specific policies/guidelines for treatment of invasive candidiasis. Currently available Indian literature on candidemia epidemiology has also been summarized here.

Keywords: Antifungal prescription, candidemia, critically ill, epidemiology

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Introduction

With the ongoing evolution of medical science, evidence-based medicine has become the cornerstone of art of patient management. Ideally, every drug prescription should be backed by hard core scientific evidence generated from randomized controlled trials. Ironically such trials are difficult to conduct, and most of the current literature on antifungal therapy is generated on western population. However, differences in disease burden, health care practices, economic and geographical conditions may require local bodies to format and design region-specific policies and guidelines.

Invasive candidiasis is associated with increased mortality, length of hospital stay and cost of care.[1] Delay in initiation of appropriate antifungal therapy is associated with increased mortality.[2] Blood culture sensitivity for detection of invasive candidiasis ranges from 21% to 71% in studies of autopsy proven cases. Sensitivity is better in patients with candidemia as compared to patients with deep-seated candidiasis.[3] Waiting for positive culture can cause a significant delay in initiation of antifungal therapy and hence increased mortality and morbidity. Identifying the high-risk patients and early initiation of antifungal therapy has become an important strategy for such infections. Factors associated with increased risk of invasive candidiasis include immunosuppression, organ transplant, broad-spectrum antibiotic use, severe sepsis, total parenteral nutrition, surgery, pancreatitis, diabetes mellitus, dialysis, mechanical ventilation, multiple site colonization with *Candida* etc., Various risk factors have been studied and grouped together to design risk prediction models/scores (*Candida* score, Ostrosky's clinical prediction rule, colonization index etc.) for invasive candidiasis.[4] These scores are being used to guide prophylactic, preemptive and empirical antifungal therapies. Broad-spectrum antibiotic use is an important risk factor for invasive candidiasis, and this risk factor is present in a large number of Intensive Care Unit (ICU) patients. Antifungal agents are being frequently used for critically ill patients, but region-specific and cohort-specific epidemiological studies are lacking to support our current prescription practices, especially in developing countries like India. This article is an attempt to study the issues regarding antifungal prescription with respect to geographical variation.

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Recently, a 17 member expert panel from Iran reviewed the currently available international guidelines and gave their consensus statement on management of invasive candidiasis in ICU. They emphasized the need for prompt identification of high-risk patients and institution of prophylactic and empirical therapy.[5]

This is in contrast to the practice recommended by FIRE study group in UK. The FIRE study group from UK studied the epidemiology of the invasive fungal disease (IFD) in nonneutropenic adults admitted to UK critical care units. Of 60,778 admissions, 383 patients (0.6%) were admitted with or developed IFD. About 94% of these infections were due to *Candida* species. The group developed a risk prediction model for identification of high-risk patients for invasive candidiasis. However, the economic model did not find it to be cost effective strategy and, therefore, a strategy of no risk assessment and no antifungal prophylaxis was recommended by the study group.[6]

Differences in Recommendations of International Guidelines

A number of societies have given their guidelines for the management of candidiasis in critically ill, summary of which can be found in Table 1.[7-10] Due to delay in diagnosis and associated high mortality with candidemia, prophylactic (risk factor driven therapy), preemptive (laboratory parameters driven like colonization or beta D glucan [BDG]) and empirical therapy (fever driven therapy) are important strategies in the management of patients at high risk for *Candida* infections. Prophylactic therapy is given to patients who qualify one or more of risk prediction models. Empirical therapy is given to patients who qualify these models and also show features of sepsis and/or septic shock.

Infectious disease society of America, Canadian and European guidelines recommend prophylaxis as well as empirical therapy in selected group of patients, while American thoracic society guideline has no such recommendations.[7-10] Preemptive therapy in BDG positive patients is recommended only by European guidelines though the level of recommendation is C-II. Fluconazole is the preferred agent for targeted and empirical therapy in hemodynamically stable patients while echinocandins are preferred in hemodynamically unstable patients. Guidelines have emphasized the role of local epidemiology data in appropriate selection of therapy.

Differences in Regional Epidemiology of Candidemia

Species distribution of *Candida* shows geographical variation [Table 2]. SENTRY Antimicrobial Surveillance Program (2008–2009) evaluated a total of 2085 clinical *Candida* isolates collected from 79 different medical centers in Asia, Europe, Latin America and North America. These isolates were either from blood or any other sterile body site, thus representing an infectious event. The most common species isolated from Asia-pacific region was *Candida albicans* (56.9%) followed by *Candida glabrata* (13.7%), *Candida parapsilosis* (13.7%) and *Candida tropicalis* (11.7%). North America had 43.4% of *C. albicans*, 23.5% of *C. glabrata* while Europe had 55% of *C. albicans* and 15.7% of *C. glabrata*.[11]

In a recently published laboratory based multicentric survey from Italy, 462 episodes of candidemia were evaluated. They reported *C. albicans* (49.2%) as the most common isolate, followed by *C. parapsilosis* (26.2%) and *C. glabrata* (10.4%). They also reviewed European literature to study distribution and frequency of *Candida* spp. from 2000 to 2013. *C glabrata* was found to be common in France, UK and North Europe and *C. parapsilosis* in Turkey, Spain and Greece.[12]

Epidemiological data regarding Indian population is scarce. Candidemia has been more extensively studied in Indian pediatric population as compared to adult population. Most of the Indian data have been generated by retrospective analysis of microbiological records and largely comprise of short communication, correspondence and letter to editor. The most common species reported in Asia-Pacific region in SENTRY survey is *C. albicans* that is different from the findings of Indian literature which report *C. tropicalis* as the most common offending species.

Xess *et al*. evaluated 7297 samples blood culture samples, of which 465 were positive for *Candida*.[13] *C. tropicalis* (35.3%) was the most common reported species followed by *C. albicans* (21.5%). Singh *et al*. studied 6519 samples in trauma patients and found 89 to be positive for *Candida*.[14] They reported *C. tropicalis* (39.0%) as the most common species followed by *C. parapsilosis* (22.1%) and *Candida rugosa* (18.4%). Fluconazole resistance was present in 5.9% isolates. This is in contrast to findings of Chander *et al*. who reported 77.8% fluconazole resistance in 27 *Candida* isolates from 4651 blood culture samples.[15]

Although, most of the studies have reported *C. tropicalis* as the most common species in India [Table 3],[13-27] at least

Table 1: Guidelines at a glance for treatment of invasive candidiasis in nonneutropenic adult

	IDSA 2009[7]*	Canadian 2010[8]	American Thoracic Society 2011[9]	ESCMID 2012[10]**
Prophylaxis therapy	Fluconazole prophylaxis to be given in high-risk patients admitted in units with high incidence of IC (B-I)	Routine prophylaxis to all ICU patients is not recommended (B-III). Fluconazole prophylaxis may be given patients with recurrent gastrointestinal perforations (A-I) or in units where there is 10% or greater baseline risk of fungal infection if anticipated stay is more than 3 days (A-I)	Not recommended	Fluconazole prophylaxis to be given in patients with recent abdominal surgery and recurrent gastrointestinal perforations or leaks (B-I)
Preemptive therapy	Not recommended	Not recommended	Not recommended	Any antifungal can be used for (1, 3)-beta - D glucan positive patients (C-II). *Candida* in respiratory secretions should be taken as colonization
Empirical therapy	Similar to that for proven candidiasis. Fluconazole or echinocandins to be given as initial therapy. Amphotericin B can be used as alternative therapy (B-III)	May be beneficial in patients who qualify specific criteria of clinical prediction rules (B-II). Fluconazole efficacious in hemodynamically stable patients (B-II). Echinocandins may be in hemodynamically unstable patients (C-III)	Not recommended	No specific recommendation for fever driven therapy. Choice of agent to be guided by local epidemiological data and patient profile
Targeted therapy	Fluconazole or echinocandins to be given as initial therapy (A-I). Echinocandins preferred by experts in more sick patients and patients with azole exposure (A-III). Amphotericin B can be used as alternative therapy (A-I). *C. glabrata* to be treated with echinocandins preferably (B-III). De-escalation to azole should not be done till sensitivity is available (B-III). *C. parapsilosis* to be treated with fluconazole (B-III)	Fluconazole or echinocandin can be used for hemodynamically stable patients with no previous azole use (A-I). Amphotericin B is an alternative (B-I). Hemodynamically unstable patients with infection other than *C. parapsilosis* to be treated with echinocandin preferably (B-III). For *C. parapsilosis* infection Fluconazole is preferred irrespective of hemodynamic status (B-II). Amphotericin B is an alternative (C-II). *C. glabrata* infections to be treated with fluconazole only if sensitivity is documented	Any one of the following agent can be used: Fluconazole, amphotericin B, an echinocandin, combination regimen with fluconazole and amphotericin B (B-II). Choice depends upon the clinical status, antifungal susceptibility, prior use of antifungal agent and species identification (B-III). Voriconazole can be used as first-line therapy for candidemia (A-I). Local epidemiological data should be taken into consideration	Echinocandins are strongly recommended (A-I). Amphotericin B and voriconazole are alternatives (B-I). Fluconazole to be used for *Candida parapsilosis*. Local epidemiology to be considered

*IDSA: Infectious Diseases Society of America; **ESCMID: European Society of Clinical Microbiology and Infectious Diseases. Grade A: A recommendation is strongly supported by evidence; Grade B: A recommendation is moderately supported by evidence; Grade C: A recommendation is marginally supported by evidence. Level I: Evidence from one or more properly designed randomized, controlled trial; Level II: Evidence from one or more well-designed clinical trial, without randomization, from cohort or case-controlled analytical studies (preferably from >1 center); from multiple time series or from dramatic results of uncontrolled experiments. Level III: Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies or reports of expert committees. ICU: Intensive Care Unit

Table 2: Commonest species causing candidemia as per SENTRY survey (2008-2009)[11]

Region (*n*=number tested)	Commonest species (%)	Second commonest (%)
Asia Pacific (*n*=51)	*C. albicans* 56.4*	*C. glabrata* 13.7 and *C. parapsilosis* 13.7
Latin America (*n*=348)	*C. albicans* 43.2	*C. parapsilosis* 25.6
Europe (*n*=750)	*C. albicans* 55.2	*C. glabrata* 15.7
North America (*n*=936)	*C. albicans* 43.4	*C. glabrata* 23.5

*Note that the most common species reported in Asia Pacific region is *C. albicans* that is in contrast to findings of most Indian epidemiological studies which report *C. tropicalis* as the most common species as shown in Table 3. *C. albicans*: *Candida albicans*; *C. glabrata*: *Candida glabrata*; *C. parapsilosis*: *Candida parapsilosis*; *C. tropicalis*: *Candida tropicalis*

two studies on neonatal sepsis have reported *C. glabrata* as the commonest species.[17,23] These findings are important because *C. glabrata* may show resistance to amphotericin B and fluconazole, and this may represent beginning of epidemiological shift toward more resistant species.

Differences in Diagnostic Techniques

Most of the epidemiological studies in Indian set up have used conventional methods for species identification. Conventional methods include germ tube test, sporulation on cornmeal Tween 80 agar, tetrazolium reduction test, urease production test, and carbohydrate fermentation and assimilation test. These conventional tests have been replaced by automated systems (Vitek-2, matrix-assisted laser desorption/ionization time of flight mass spectrometry [MALDI-TOF MS]) in developed countries.

Conventional methods are manual, labor intensive, time-consuming and dependent upon the efficiency of the laboratory. Automated systems have better quality control but more costly. In spite of the development of commercial automated systems, *correct* and *rapid* identification of fungal species remains an evolving domain. Iriart *et al*. compared Vitek MS with conventional laboratory identification and Vitek 2.[28] Correct identification was reported as 93.2% by Vitek MS, compared to 94.1% by the conventional method and 88.0% by Vitek-2. Castanheira *et al*. reported that

Table 3: Epidemiology of candidemia in India from 2007 onward

Year	Cohort/number of samples processed	Study period	Candidemia (incidence) (%)	Method used for *Candida* species identification	Results	
					Commonest species (%)	Reported resistance
Xess *et al.*[13] 2007 New Delhi	7297 blood culture samples from patients suspected of candidemia	5 years	439 (6) samples were positive	Conventional* method	*C. tropicalis* (35.3) *C. albicans* (21.5) *C. parapsilosis* (20) *C. glabrata* (17.5)	Fluconazole resistance in *C. glabrata* (11.5%) isolates. Resistance not reported in other species
Singhi *et al.*[16] 2008 Chandigarh	186 pediatric critically ill patients with severe sepsis and septic shock	9 months	20 patients (11)	Conventional method	*C. tropicalis* (40) *C. guilliermondii* (20), *C. pelliculosa* (15)	Not reported
Baradkar *et al.*[17] 2008 Mumbai	266 neonates with suspected sepsis	1-year	49 patients (19.4)	Conventional method	*C. glabrata* (61.22) *C. parapsilosis* (20.40) *C. albicans* (12.24) *C. krusei* (4.08), *C. tropicalis* (2.04)	Not reported
Saha *et al.*[18] 2008 New Delhi	140 blood cultures samples from pediatric patients suspected of candidemia	2 years	80 samples (57)	Conventional method	*C. tropicalis* (35) *C. albicans* (20) *C. glabrata* (17.5) *C. krusei* (15) *C. gullermondi* (7.5)	96% of all the *Candida* species isolated were sensitive to fluconazole
Goel *et al.*[19] 2009, Rohtak	825 clinically suspected cases of neonatal sepsis	6 months	8.1	Conventional method	*C. tropicalis* (61.19) *C. albicans* (19.40) *C. glabrata* (11.94) *C. parapsilosis* (5.97) *C. guillermondii* (1.49)	95.53% of the *Candida* isolates were sensitive to fluconazole
Kothari et al.[20] 2009 New Delhi	53 episodes of candidemia in 48 patients	17 months		API ID32C	*C. tropicalis* (45) *C. albicans* (23) Other *Candida* spp. (32)	92% isolates sensitive to amphotericin B, 56% to voriconazole and 36% to fluconazole *C. albicans* 100% sensitive to amphotericin B, 58% to fluconazole. *C. tropicalis* 87.5% sensitive to amphotericin B and 17% to fluconazole
Adhikary et al.[21] 2011,Manipal	68 episodes of candidemia from 55 patients	2 years	-	Vitek-2	*C. tropicalis* (39.7) *C. albicans* (26.4) *C. lipolytica* (5.8)	Overall isolates showed 100% sensitivity to voriconazole, 92% to amphotericin B, 75% to fluconazole. *C. tropicalis* showed 100% sensitive to amphotericin B and voriconazole, 81% sensitive to fluconazole
Singh *et al.* 2011[14] New Delhi	6519 blood culture samples from trauma patients	21 months	89 episodes of candidemia	Vitek-2 system and chromagar	*C. tropicalis* (39.0) *C. parapsilosis* (22.1) *C. albicans* (14.7) *C. rugosa* (18.4) *C. glabrata* (5.9)	5.9% of the isolates resistant to fluconazole. None of the isolates showed resistance to voriconazole or amphotericin B
Oberoi *et al.*** 2012[22] New Delhi	69,010 blood culture samples	9 years	1206 (1.74)	Vitek-2	*C. tropicalis* (29.2) *C. albicans* (16.8) *C. haemulonii* (15.5) *C. parapsilosis* (12.5) *C. glabrata* (8.5)	Overall isolates showed 89.6% sensitivity to amphotericin B 88.6% to voriconazole 68.8% to fluconazole
Sardana *et al.* 2012[23] Meerut	527 blood culture samples from septicemic neonates	1-year	110 (20.87)	Conventional method	*C. glabrata* (39) *C. tropicalis* (26.4) *C. parapsilosis* (14.5) *C. guilliermondii* (2.7) *C. krusei* (1.8)	Not done
Chander *et al.* 2013[15] Chandigarh	4651 blood culture samples	6 months	27 (0.5)	Conventional method	*C. tropicalis* (40.8) *C. albicans* (29.6) C.glabrata (18.5)	Amphotericin B resistance in 18.5% isolates. Fluconazole resistance in 77.8% isolates
Juyal *et al.* 2013[24]	132 neonates who were culture positive for candidemia	1-year	-	Conventional method	*C. parapsilosis* (25.0) *C. tropicalis* (21.97) *C. albicans* (19.70) *C. glabrata* (14.39) *C. krusei* (10.61)	65.91% isolates sensitive to fluconazole, and 96.21% sensitive to amphotericin B

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Table 3: Contd...

Year	Cohort/number of samples processed	Study period	Candidemia (incidence) (%)	Method used for *Candida* species identification	Results	
					Commonest species (%)	Reported resistance
Giri *et al.* 2013 Chennai[25]	Blood culture samples from 5976 ICU patients	1-year	39 (0.67) candidemia	Conventional method + candifast kit	*C. tropicalis* (74.36) *C. albicans* (10.26) *C. parapsilosis* (7.69) *C. krusei* (5.13) *C. glabrata* (2.56)	30.8% Candida isolates resistant to Fluconazole. 100% sensitive to amphotericin B
Kaur *et al.* 2014[26] New Delhi	125 patients admitted to ICU	2 years	10 cases	Conventional method	*C. albicans* (50) *C. tropicalis* (40) *C. glabrata* (10)	-
Pahwa *et al.**** 2014[27] Indore	237 *Candida* isolates from different clinical specimens. 58 isolates from blood	2 years		Vitek-2	*C. tropicalis* (20.69) *C. parapsilosis* (18.97) *C. albicans* (17.2) *C. glabrata* (3.4)	Resistance rates for amphotericin B was 2.9% Fluconazole 5.9% Voriconazole 2.5%

*Conventional methods stands for germ tube test, sporulation on cornmeal Tween 80 agar, tetrazolium reduction test, urease production test, and carbohydrate fermentation and assimilation test; **Oberoi *et al.* studied the trend over 9 years (1999-2008). The species distribution reported is from 2006 to 2008, ***Pahwa *et al.* studied different clinical isolates. Species distribution given here represents only candidemia cases. *C. albicans*: *Candida albicans*; *C. glabrata*: *Candida glabrata*; *C. parapsilosis*: *Candida parapsilosis*; *C. tropicalis*: *Candida tropicalis*; ICU: Intensive Care Unit; *C. krusei*: *Candida krusei*; *C. guilliermondii*: *Candida guilliermondii*

53 strains were wrongly identified as *Candida famata* by various commercial systems (Vitek, Microspan, etc.) during the SENTRY and ARTEMIS surveillance programs.[29] The authors concluded that commercial systems lack accuracy in identification of fungal species except for MALDI-TOF instruments. MALDI-TOF instruments are cost effective, but they require 1 time huge investment though the recurring cost is minimal.

Differences in Antifungal Sensitivity of Various *Candida* Species

Various *Candida* species vary in their susceptibility for different antifungal agents [Table 4].[30-33] As the number of antifungal agents is limited, their irrational use can lead to epidemiological shift toward resistant organisms. During past two decades, there is a rising trend in non albicans Candida (NAC) species all over the world. Many of the NAC species show primary resistance for various antifungal agents. For example, *C. glabrata* shows primary resistance for azoles and polyenes. *C. parapsilosis* and *Candida guilliermondii* exhibit inherently reduced sensitivity to echinocandins while *C. rugosa* and *Candida krusei* show resistance for azoles and polyenes. *Candida lusitaniae* is resistant to amphotericin B and should be treated with fluconazole.

The above insights emphasize that prophylactic or empirical therapies require smart guess based on knowledge of risk factors, epidemiological data and resistance patterns of common species.

Differences in Economic Conditions

Economic factor is a crucial determinant of diagnostic and therapeutic approach for IFD.

Nonculture based techniques like BDG assay and polymerase chain reaction are used in many developed countries as adjuncts to blood culture. However, high cost limits their role in areas of poor resources.

Similarly, economic factor also plays role in deciding the choice of antifungal therapy. By and large echinocandins are preferred drugs for hemodynamically unstable patients but the cost of the therapy is high. Amphotericin B deoxycholate remains a reasonable option in such patients. Therefore, local bodies should look into all such considerations before formulating policies in their areas.

Differences in Prescription Practices

Despite the complexity in diagnosis and treatment of fungal infections, there is limited awareness among the clinicians. For example, central line removal within 48 h of diagnosis of candidemia and eye examination by a skilled physician are standard recommendations for all candidemia patients but not always practiced. Disseminated candidiasis may manifest only with ocular findings and may result in blindness.

An electronic survey conducted on antifungal prescription practice in United Kingdom published in 2011 showed that 57.7% of ICU units had no documented policy on the use of antifungal agents. About 85% units used empirical antifungal therapy. Presence of multiple risk factors in combination was the most common trigger for starting antifungal therapy. Multifocal colonization triggered antifungal therapy even when present alone. Fluconazole was the most commonly used antifungal agent for empirical therapy, as well as proven candidemia. Central line removal was practiced

Table 4: Antifungal resistance pattern among various *Candida* isolates

Species	Azoles	Amphotericin B	Echinocandins	Comments
C. glabrata[30]	Shows moderate primary* azole resistance. Also acquires (secondary) resistance easily during prolonged azole therapy	Shows decreased susceptibility	Considered first-line agent for invasive infection. Reports of therapeutic failure due to acquired resistance emerging	Biofilm formation plays important role in virulence
C. parapsilosis[31]	0-4% resistance reported to fluconazole	2-3% resistance reported	Shows moderate primary resistance	Infection can occur without colonization via horizontal transmission
C. krusei[32]	Shows strong primary resistance	Shows decreased susceptibility	Most active agent	
C. lusitaniae[33]	1-7% resistance to fluconazole	Notorious for developing strong secondary** resistance during treatment	Paucity of literature. One study reports greater killing rates with anidulafungin and micafungin than caspofungin	Do repeat sensitivity testing for patients with persistent infection while being treated with amphotericin B
C. rugosa[32]	Shows strong primary resistance	Shows decreased susceptibility	First-line therapy	
C. albicans[32]	Usually sensitive to all antifungals. 0.5-2% resistance to fluconazole reported in various studies Reports of ergosterol deficient species isolated from South Africa show primary resistance to amphotericin B and fluconazole			
C. tropicalis[32]	Usually sensitive to all antifungals, but reports of resistance to fluconazole in Asia-Pacific region emerging			

*Primary resistance means intrinsic resistance; **Secondary resistance means acquired resistance. *C. glabrata*: *Candida glabrata*; *C. parapsilosis*: *Candida parapsilosis*; *C. krusei*: *Candida krusei*; *C. lusitaniae*: *Candida lusitaniae*; *C. rugosa*: *Candida rugosa*; *C. albicans*: *Candida albicans*; *C. tropicalis*: *Candida tropicalis*

by 73.5% and ophthalmology consultation was taken by 15.1% practitioners.[34]

Swoboda *et al*. showed that implementation of standard practice antifungal guidelines was associated with 50% reduction in cost and a significant decrease in antifungal prescription.[35]

To the best of our knowledge, there is no published literature on antifungal prescription practice in Indian set up. In India, with limited resources and limited patient finances it is extremely important to justify the use of antifungal prescription.

Conclusion

Antifungal prescription practice needs to be streamlined, more so in developing countries like India. Epidemiological studies on colonization and candidemia with automated method of species detection are urgently needed. We need to formulate and execute region-specific and cohort-specific guidelines after collection of epidemiological data. Bed side risk prediction models/ scores should be used for choosing the right patient for prophylaxis or empirical therapy. This practice will help to bring down indiscriminate use of antifungal agents.

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