Mycoses in Intensive Care Units

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Key Points

- The incidence of candidemia is 6.5 cases/1000 ICU admission in India.
- Candidemia should always be regarded as pathological warranting treatment.
- The mean age of patients with opportunistic mycoses is relatively younger in the Indian study.
- Candidemia occurs relatively early during the ICU stay.
- Candidemia occurred in less sicker group of patients than the western counterpart.
- *Candida tropicalis* and *Candida albicans* are the most common *Candida* species isolated.
- Fluconazole sensitivity is still high among *C. tropicalis* and *C. albicans*, though resistance is increasing in those species.
- *Candida glabrata* is rare.
- Multidrug resistant *Candida auris* is being increasingly recognized.
- Risk prediction scoring system has a very low positive predictive value.
- Experience with beta-D-glucan is limited but may be used to limit empirical antifungal therapy.
- Source control and removal of invasive lines is of paramount importance in management of candidemia.
- Crude mortality of candidemia can be as high as 40%.

5.1 Introduction

Invasive fungal infections (IFIs) in Intensive Care Units (ICUs) are increasingly being recognized globally in critically ill patients [1, 2]. With increasing growth of ICUs in the developing world, the prevalence of IFI is exponentially increasing in

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this part of the world. The most common IFI encountered in ICU is invasive candidiasis but other severe invasive fungal infections like invasive aspergillosis, mucormycosis, cryptococcal meningitis, and pneumocystis pneumonia are also encountered in specific subset of ICU population [3]. The increased prevalence of IFIs is partly real due to more life sustaining treatments offered to this vulnerable group, but it may be partly artiefactual due to increasing awareness, recognition, and availability of modern diagnostic tools in the developing world. The epidemiology of IFIs in ICU specifically the species of different fungi may be different in Asia Pacific region as compared to Western hemisphere. The reason for this is not entirely clear and may be environmental due to the tropical climate and/or genetic. C*andida auris* for example is being increasingly reported from the South Asia region [3]. New risk factors for developing IFIs are being recognized, with uncontrolled diabetes being one of them. Due to increasing prevalence of diabetes in India, mucormycosis is being increasingly reported. In general, infection control practices are below par in the ICUs of developing world, which facilitates the spread of IFIs within the unit. Antibiotic stewardship practice is not very common in the developing world, which also leads to overuse of broad-spectrum antibiotics in ICUs leading to secondary fungal sepsis. This chapter will highlight recent advances in the epidemiology of IFIs in Asia with emphasis on original research on this aspect from this part of the world.

5.2 Invasive Candidiasis (IC)

Candida growth in the blood culture should always be regarded as pathological warranting treatment and should not be disregarded as a colonizer or contaminant. Two-thirds of patients with IC in ICU will have candidemia and most of the other non-candidemic patients will have deep seated candidiasis like intra-abdominal candidiasis [4, 5]. Although candiduria is detected in 20% of ICU patients, it seldom leads to secondary candidemia [6]. A seminal study was conducted by Chakrabarti et al. in 27 ICUs across India, to observe the epidemiological pattern of candidemia [3]. During the eighteen month study period, 1400 candidemia cases were reported from the ICUs which gave an incidence of 6.51 cases/1000 ICU admission. There was regional variation among the incidence of candidemia and a higher incidence was noted in the public hospital as opposed to private hospital, which is a phenomenon peculiar to the developing world due to the overcrowding of public hospitals and less stringent infection control policies. In a survey of other published research on global epidemiological studies of candidemia maintained by Leading International Fungal Education (LIFE) portal, it was noticed that fifty percent of the global cases of candidemia were reported in Asia followed by Americas and Europe [7]. The highest prevalence of candidemia was reported in Pakistan (21 cases per 100,000) followed by Brazil (14.9 cases per 100,000) and Russia (8.29 cases per 100,000).

In the Indian study, the mean age of patients with ICU acquired candidemia was much lower (49.7 years) than in other countries (mean 59–66.2 years). This may be reflective of the general population census in the developing world. ICU acquired

candidemia was noted to occur significantly earlier (8 days) than in other studies (11–15 days), which may be a reflection of delayed hospital admission of critically ill patients in resource limited setting. Severity of illness scores like APACHE was relatively less in this study. One of the reasons could be the younger age of study population lowering the APACHE score, or it could be due to the excessive noted exposure of broad-spectrum antibiotics and corticosteroids to a relatively less sick ICU population and inadequate infection control practices make them prone to acquire nosocomial candidemia.

Very high prevalence (41.6%) of *Candida tropicalis* was noted in this study which was also observed in studies from other Asian countries. *Candida albicans* and *Candida parapsilosis* affected 20% and 10% of the study population, respectively. This is in contrast to studies in western population where *Candida tropicalis* is less common (5–10%) and *Candida albicans* and *Candida glabrata* are more common [8]. The reason for this change in epidemiology is unclear. In a survey of health care personnel in the study centers, 82% were carrier of yeast on their hands of which 80% were *Candida tropicalis* [9]. Prior azole exposure is not probably an explanation of increased incidence of *Candida tropicalis* as the species was mostly susceptible to fluconazole. On the other hand, low incidence of *Candida glabrata* was noted in spite of prior fluconazole exposure in many patients, a finding contrary to the observation from the West.

Candida auris, a rapidly emerging multidrug resistant Candida comprised 5.2% of all *Candida* isolates [10]. This organism which is difficult to detect and treat is increasingly being reported from intensive care units worldwide and more so from the developing world. In a recent study from a neurosurgical unit, axillary temperature probe contaminated with *Candida auris* was reported as a cause of outbreak of these fungi in the unit, which emphasizes the need for strict infection control as a measure to control the spread of these dreaded fungi. Many of the current fungal identification systems misidentify *Candida auris* and a close collaboration with the reference microbiology laboratory is required to properly identify this fungi.

Various scoring systems which include risk prediction models have been derived for predicting IC in ICU population. These models have a very low positive predictive value and cannot be relied upon solely to start empiric antifungal therapy. In an observational study to externally validate the various candida scoring system in a medical/surgical ICU in India, it was observed that more than 90% of patients get colonized during their stay in the ICU and many of the risk factors for candidemia are present in these patients, but the overall incidence of candidemia is low and relying on the predictive model was subjecting a majority of patients to an unnecessary antifungal exposure [11].

Biomarkers like beta-D-glucan (BDG) has been increasingly used for empiric/preemptive therapy for IC in ICU. In general, the availability of this biomarker is low in the developing world. In a cost effective analysis from India, BDG levels were significantly higher in septic patients with IC than in non-septic patients, but the values overlapped with bacterial septic patients. Discontinuation of empiric antifungal therapy based on a value <80 resulted in cost savings of 14,000 INR per day per patient [12].

Appropriate antifungal choice is imperative for a successful outcome of this lethal disease. Although species can predict drug susceptibility, local epidemiological patterns vary and affect the value of species prediction. Overall, more than 95% of *C. albicans* and *C. parapsilosis* isolates remain azole-susceptible. In the Indian study, fluconazole resistant was noted in 2–9% of *C. albicans, C. tropicalis,* and *C. parapsilosis*. In a similar study from China, 10% of *C. albicans* isolates and 19% of *C. parapsilosis* isolates were azole-resistant [13]. *C. glabrata*, *C. krusei*, and *C .auris* are less susceptible than other species to fluconazole. Resistance to echinocandins among *Candida* species like *C. auris* and *C. parapsilosis* is increasingly being reported.

Candiduria should only be treated if symptomatic in ICU patients and the drug of choice is fluconazole as it attains high levels in the urinary tract. For azole-resistant urinary tract infection, high dose fluconazole, amphotericin deoxycholate (not liposomal amphotericin B as they have poor penetration in the urinary tract), micafungin, flucytosine, and local amphotericin bladder wash have been tried [14]. An attempt should be made to remove indwelling urinary catheters, nephrostomy tubes, and stents. Echinocandins are the preferred first line of agent in ICU patients with IC, though this can be de-escalated rapidly for azole sensitive strains. The reason for superiority of echinocandins over azoles is their rapid fungicidal action, safety profile, less drug interaction, and ability to penetrate biofilms, as indwelling catheters are one of main sources of IC in ICU patients. Lipid amphotericin B formulations should be considered in patients with CNS involvement and endocarditis, whereas azoles are the preferred choice for endophthalmitis as echinocandins do not penetrate vitreous well. Repeated blood cultures should be performed and antifungal therapy should be continued for two weeks after the last negative culture. In culture negative patient, shortening the antifungal use by following biomarkers and stopping rules have been successfully tried in recent studies. This approach substantially reduces antifungal burden in ICU [15].

The volume of distribution is high in many ICU patients due to aggressive volume resuscitation in sepsis; moreover, some of these patients have augmented renal clearance which leads to reduced therapeutic drug levels for fluconazole and echinocandins. This in combination with higher minimum inhibitory concentration of many *Candida* species for these antifungals has led to an optimization of pharmacokinetic and pharmacodynamics parameters by advocating higher doses of these dugs which have a high safety margin. (e.g., 12 mg/kg of fluconazole loading followed by 4 mg/kg of maintenance, double the loading dose of caspofungin) resulting in a better therapeutic level leads to a satisfactory therapeutic drug level [16].

Empirical antifungal therapy in symptomatic patients at risk of developing IC is a common practice in ICUs, though effectiveness of this strategy has not been proven in recent studies. This may be due to overall low incidence of IC in general medical/surgical ICUs and number needed to treat will be very high to show a decrease in mortality [17].

Source control is a key factor in managing candidemia in ICU and removal of central venous lines has been recommended in such cases. In the study from India, it was clearly demonstrated that removal of central line was clearly associated with

decreased mortality, but this was performed in only one-third of cases. This highlights the need for protocolized care and proper implementation of guidelines and infectious disease physician involvement which is unfortunately lacking in many developing countries.

Candidemia is a lethal disease with crude mortality of up to 50% in some studies. As most of the ICU patients with candidemia have underlying significant comorbidity, attributable mortality is difficult to compute and varies between 5 and 49% in various studies. In the study from India, crude and attributable mortality from candidemia was noted to be 44% and 20%, respectively. In other studies, intra-abdominal candidiasis was associated with high attributable mortality of 26–60% in cases of secondary or tertiary peritonitis [18].

5.2.1 Invasive Mold Infection (IMI)

Invasive infections by filamentous fungi are increasingly being reported from ICUs worldwide. Due to the increasing use of Candida prophylaxis, infections with molds are being increasingly reported from transplant patients [19]. The epidemiology of IMIs is not well studied in developing countries in spite of the fact that risk factors for developing these infections like diabetes are prevalent in this part of the world. Moreover it has been shown that the spore count of aspergillus was found to be high (average of 82 CFU/m^3) [20] in an ICU from India. Newer risk factors for developing IMIs like chronic obstructive pulmonary disease, chronic liver and kidney failure and use of corticosteroids is common in ICUs; moreover, the diagnostic criteria for IMIs is not well defined as opposed to that of hemato/oncology and classical immunosuppressed patients. In ICU patients, classical radiological signs like halo or crescent sign are not seen most of the time and nonspecific infiltrates and nodules are more common. Presence of aspergillus in the respiratory tract cannot be taken as a feature of invasive aspergillosis as this may be mere colonization [21, 22]. Commonly used biomarkers like galactomannan may be falsely high and nonspecific in this patient population. Obtaining a tissue sample which is the gold standard for IMI diagnosis is difficult in ICU patients due to many contraindications like coagulopathy and thrombocytopenia. Moreover, lack of availability and experienced personnel, inertia on the part of physicians, cost involved, and difficulty in obtaining informed consent for biopsy compound to the problem.

In a global epidemiological survey, it was found that 50% of invasive aspergillosis cases are reported from Asia (excluding India and China) [7]. Approximately 95% of invasive aspergillosis is due to the *Aspergillus fumigatus* complex. In a recently published multicentric prospective, observational study conducted by Fungal Infection Study Forum (FISF) from India, risk factors, epidemiology, and outcome of IMIs in Indian ICUs were studied [23]. Over a eighteen months period, eleven tertiary care centers participated in the study. EORTC/MSG criteria was applied for diagnosis of IMI in classical immunocompromised patient, Bulpa et al. criteria applied for COPD patients and Blot et al. criteria for general medical/surgical ICU patients. Patients with "Proven" or "Probable/Putative" IMIs were only included for the study purpose.

During the study period, 398 cases (proven 96, probable 302) of IMI were diagnosed with a prevalence of 9.5 cases per 1000 ICU admissions. Similar to candidemia study conducted in India cases, the severity of illness was low (APACHE mean of 14), younger age at presentation (average age 45 years) and early presentation (average 4 days since ICU admission) as compared to the western counterpart. Nonclassical groups consisting of diabetes, COPD, and H1N1 influenza constituted majority of IMIs (63.6%). Though *Aspergillus* species were the commonest (82.1%) mold isolated, Mucorales were isolated from a considerable number (14.4%) of subjects. The most common radiological finding on CT chest was consolidation followed by nodule and pleural effusion. Majority (80%) of patients had pulmonary disease. The IMI patients were treated with various antifungals both empiric and targeted. Majority (n = 321, 80.7%) of the subjects had pulmonary disease. The crude mortality was 64%, despite the fact that majority of patients received targeted therapy. This may reflect severity of underlying disease, suboptimal or delayed medical therapy, and underutilization of surgical debridement.

5.2.2 *Pneumocystis jirovecii Pneumonia (PCP)* [7]

PCP occurs mainly in patients with HIV/AIDS infection. Global prevalence is thought to be higher than 400,000 annually cases reported worldwide. Though the incidence has come down with highly active antiretroviral therapy (HAART), it still remains high in patients with inadequately treated HIV or noncompliance with HAART therapy. Mortality of PCP ranges from 10 to 30% and can be even higher if the diagnosis is delayed. Increasing incidence of PCP is noticed in non-HIV patients with classical immunocompromised states. Achieving early diagnosis remains the main challenge in treating PCP. A low index of suspicion, CT scan of chest, early bronchoalveolar lavage with proper staining, polymerase chain reaction (PCR) and judicious interpretation of serum galactomannan are the mainstay of early diagnosis of this infection. As per LIFE program, 77% of the cases were reported in Africa, followed by America (10%), Europe (7%), and Asia (6%). Differences in the estimations across countries can be associated to differences in the HIV prevalence in the different countries and the accessibility to highly active antiretroviral therapy. Moreover diagnosis may depend on experience and competence of the laboratory.

5.3 Conclusion

High index of suspicion for opportunistic invasive fungal infection should be maintained in ICU patients. Persistent sepsis in spite of broad-spectrum antibiotics should prompt rapid diagnostic tests to rule out IFI should be done. Empiric treatment against invasive candidiasis though not proven to decrease mortality in ICU patient is still practiced widely. Judicious use of biomarker, and targeted therapy where appropriate should be practiced. Rapid de-escalation and shortening the duration of antifungal based on biomarkers will reduce the antifungal burden in the ICU.

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