MODESTUM
OPEN ACCESS

Review Article

Eur J Gen Med 2018;15(2):71-75
ISSN:1304-3889 eISSN:1304-3897
https://doi.org/10.29333/ejgm/82346

# *Candida* species as potential nosocomial pathogens – A review

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**ABSTRACT**

The frequency of nosocomial fungal infections is being increased because of the advent of newer diagnostic and therapeutic techniques. Among various fungal pathogens, *Candida* spp. are the cause of substantial morbidity and mortality in hospitalized patients, especially among critically ill hospitalized patients. The frequency of non-ablicans spp. of *Candida (*NAC) causing nosocomial infections is increasing. The Candida infections are usually endogenous, however, the exogenous infections may also occur. The important predisposing factors leading to nosocomial candidiasis include treatment with broad spectrum antibiotics, immunosuppression, malignancy, surgical intervention, diabetes and prolonged hospitalization. Virulence factors like adherence to biotic and abiotic substances and production of hydrolytic enzymes play important role. Also the biofilm forming ability makes it more noxious. Nosocomial Candida infections are difficult to diagnose clinically and refractory to therapy. Therefore, rapid and accurate laboratory diagnosis is very important to provide appropriate antifungal treatment. This review is structured to know the key factors responsible for emergence of *Candida* spp. as important nosocomial pathogens. The available data suggests that the nosocomial infections caused by *Candida* spp. should be dealt through awareness and constant vigilance.

**Keywords:** *Candida albicans*, non-albicans *Candida* spp., nosocomial infections

## INTRODUCTION

Nosocomial Infections are infections that occur in hospitalized patients which were not present or they were in incubation period at the time of admission. These infections are major problem in any health care set up because they not only increase the cost of treatment and stay in the hospital but also increase the morbidity and mortality. Any microorganisms can cause nosocomial infections including fungi. In the recent past, the frequency of nosocomial fungal infections is increased because of the advent of newer diagnostic and therapeutic techniques. Fungal pathogens, now are responsible for about 10 percent of all nosocomial blood stream infections (BSI) (1). Among various fungal pathogens, *Candida* spp. are important pathogens causing substantial morbidity and mortality in hospitalized patients, especially among critically ill hospitalized patients (2).

*Candida* spp. account for 10 percent of blood stream infections and 25 percent of urinary tract infections in ICU (3). At present, *Candida* spp. are considered as the third or fourth most common cause of nosocomial infections in United States, outnumbering all Gram negative bacilli (4). Nosocomial candidiasis is associated with prolonged hospitalization and increased health care cost (5). Over past few decades, the frequency of non-ablicans spp. of *Candida (*NAC) causing nosocomial infections is increased replacing the *Candida albicans*. Also these NAC spp. have been found resistant to treatment. Hence, continuous monitoring to evaluate their distribution, epidemiology and antifungal resistance is of utmost importance.

Meticulously structured literature is available on the nosocomial infections, but the available literature is mostly focused on bacterial pathogens. Hence, we present the overview of the factors responsible for emergence of *Candida* spp. as an important nosocomial pathogen**.**

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*Received: 22 Sep 2017, Accepted: 24 Dec 2017*

## *CANDIDA* SPP. AND ITS ROLE IN NOSOCOMIAL INFECTIONS

Currently, there are 200 recognized species of genus *Candida*. *Candida albicans* is the most prevalent pathogenic species responsible for various types of candidiasis. However, a drastic increase in incidence of NAC spp. has been reported in last few decades. Among NAC spp., *C. tropicalis, C. krusei, C. parapsilosis,* and *C. lusitaniae* are the most common isolates. The species distribution varies according to geographical area and health care set up. In India, *C. tropicalis* has been reported to be the most common cause of nosocomal candidemia (6).

## EPIDEMIOLOGY OF NOSOCOMIAL CANDIDIASIS

*Candida* spp. are the most important cause of mycoses worldwide. Surgical and Intensive Care Unit (ICU) patients are at higher risk of developing nosocomial fungal infections. In ICU, common type of infections are bloodstream infections, catheter related infections, intra-abdominal infections and UTI (7). In critically ill patients, the disseminated Candida infections are the leading causes of morbidity and mortality both in immunocompetent and immunocompromised patients (4). There is dearth of information on nosocomial candidiasis from developing countries like India (8, 9).

The Candida infections are usually endogenous, as *Candida* spp. are commensal in GIT and other body sites. However, the exogenous infections may also occur (10). In recent years, there has been an emergence of NAC spp. as most predominant *Candida* spp. than *C. albicans* causing nosocomial candidiasis. One of the reasons for this shift is increased use of azole group of antifungal agents (4). The mortality rate varies according to species. *C. glabrata* and *C. krusei* are associated with high mortality as compared to other NAC spp. (7).

## RISK FACTORS FOR NOSOCOMIAL CANDIDIASIS

Multiple risk factors are responsible for candida infections. The important predisposing factors include treatment with broad spectrum antibiotics, immunosuppression, malignancy, surgical intervention, diabetes and prolonged hospitalization. *Candida* spp. can be transmitted from hand to hand and can survive upto 45 minutes on hands after inoculation (11). *Candida* spp. can grow on a variety of habitats (12). They can survive for up to 4 months in hospital environment (10). Use of azole group of antifungal agents is important risk factor for infection with NAC spp. NAC spp. are more commonly isolated from hematology patients with prolonged neutropenia than in non-neutropenic patients in surgical ICU (10). Candida colonization, umbilical vessel catheterization, prolonged hospitalization and very low birth rate are important risk factors for nosocomial neonatal candidemia (13).

## PATHOGENECITY OF *CANDIDA* SPP.

Certain virulence factors like adherence to biotic and abiotic substances and production of hydrolytic enzymes play important role in pathogenesis of *Candida* spp. (14). The primary event in Candida colonization and infection is adherence to host cells (15). Adherence prevents or at least reduces the clearance of yeast cells by host defense mechanisms and also ensures the delivery of toxins and enzymes to the host cells.

Nearly half of the cases of nosocomial infections are associated with medical devices (16). *Candida* spp. can form biofilm on most of the medical devices such as stents, shunts, endotracheal tubes, catheters, implants and pacemakers. Biofilm forming ability is one of the important virulence factors in candidiasis (17). Biofilm production provides protection against host defense mechanism and also responsible for drug resistance. Production of hydrolytic enzymes is one of the important virulance factors contributing to pathogenesis of *Candida* spp. *Candida* secrets hydrolytic enzymes like lipase, phospholipase, phosphomonoestrase, hemolysins, hexosaminidase, and aspartic proteinase (18). Extra cellular hydrolytic enzymes facilitate adherence, tissue penetration, invasion and the destruction of host tissue.

## LABORATORY DIAGNOSIS OF NOSOCOMIAL CANDIDA INFECTIONS

Nosocomial Candida infections are often severe, rapidly progressive, difficult to diagnose clinically and refractory to therapy (19). Therefore, rapid and accurate laboratory diagnosis is very important to provide appropriate antifungal treatment. The laboratory diagnosis of Candida infection remains problematic as no single laboratory test provides satisfactory and rapid results (10, 15).

Although blood culture is considered as gold standard for diagnosis of disseminated candidiasis, it lacks sensitivity. New culture media, lysis centrifugation and automated blood culture monitoring systems have decreased the assay time required for isolation of etiological agent. However, these techniques have moderate sensitivity. Automated blood

culture systems like BACTEC 9240 and ALERT 3D have demonstrated appreciable sensitivity and specificity for diagnosis of disseminated candidiasis.

Serological tests to detect antigen or antibody in serum or other body fluids are useful for presumptive diagnosis and initiation of antifungal therapy but not for identification of species (20). Common antigens detected are galactomannan and (1, 3) – β – d- glucan. Other antigens that can be seen circulating in the blood are D-arabinitol, enolase and SAP. Due to low levels of circulating antibodies, in immunosuppresed individuals, immunoglobulin detection test lacks sensitivity.

Molecular diagnostic techniques are gaining importance in recent years because they are highly accurate, sensitive and specific for identification of *Candida* spp. (21). However, these are expensive and require expertise technical support (22). Molecular techniques are based on either Polymerase Chain Reaction (PCR) or non-PCR based techniques (21). Various PCR based techniques include conventional, semi-nested and nested-PCR, PCR- enzyme immunoassay, real time PCR and multiplex PCR. However, the non PCR based techniques include The Yeast Traffic Light peptide nucleic acid fluorescence in situ hybridization assay (PNA-FISH) and pyrolysis and matrix- assisted laser desorption ionization – time of fight mass spectrometry (MALDI-TOFMS) (21).

## TREATMENT OF NOSOCOMIAL CANDIDA INFECTIONS

The antifungal agents for treating disseminated candidiasis differ in mode of action, pharmacokinetics, pharmacodynamics, route of administration, indication, cost and safety. These differences are to be considered while treating particular patient for particular purpose (22). The purpose for initiation of antifungal treatment may be prophylaxis, initial therapy (empiric, pre-emptive or targeted) or salvage therapy.

The prophylactic therapy is given to avoid infections by *Candida* spp. in high risk immunosuppressed individuals. But this involves risk of overuse and development of resistance. The pre-emptive therapy is started to avoid disseminated candidiasis in patients. The empiric therapy is started on the basis of presenting clinical signs and symptoms and local epidemiology (23). However, the role of empirical therapy remains controversial because it leads to overuse and drug resistance. For prophylaxis and treatment of candidiasis, four principal classes of antifungals are available i.e. polynes, pyrimidines, azoles and echinocandins (24).

The polynes are broad spectrum antifungal agents, which bind with the ergosterol in cell membrane of fungal cell and alters permeability. This finally causes leakage of cellular contents and cell death (25). Amphotericin B is the only polyne that can be administered systemically.

The pyrimidine analogues affect fungal pyrimidine metabolism by inhibiting RNA and protein synthesis (24). Flucytocine (5FC) is example of pyrimidine analogues used in combination with Amphotericin B in treating life threatening candida infections like endocarditis, meningitis and hepatosplenic disease (26).

Widely used azole group of antifungals acts by blocking synthesis of ergosterol of cell membrane by inhibiting P450 dependent enzyme sterol 14-α-demethylase. The inhibition of this enzyme leads to increased cell membrane permeability, cessation of cell growth and reproduction (10, 27). There are two classes in azole group of antifungals i.e. triazoles (flucanozole, itraconazole, posaconazole) and imidazole (ketoconazole, miconazole and clotrimazole). Fluconazole is extensively used for prophylaxis and treatment of superficial and disseminated candidiasis (27).

Echinocandins are newer antifungal agents, which target the cell wall and inhibit 1,3- and 1,6,β-D-glucan synthesis. The examples of echinocandins approved by FDA are capsofungin, micafugin and anidulafungin. All these three compounds have fungicidal (action both in vivo and in vitro) against most *Candida* species irrespective of their resistance or susceptibility to azole or Amphotericin B (6). Recently echinocandins are used increasingly. Echinocandins (especially capsofungin) are now considered as first line drugs for treatment of disseminated candidiasis or azole resistant candida infection.

## CONCLUSION

The review of literature shows that there is an alarming increase in the rate of nosocomial candida infection that leads to increased morbidity, extended hospital stay, expenses and mortality. Also there has been change in pattern of infection from *Candida albicans* to treatment resistant NAC spp. making the management of infections more and more difficult. The review of literature further suggests that these nosocomial infections caused by *Candida* spp. should be dealt through awareness, constant vigilance and change in practice.

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