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Candida Species – Morphology, Medical Aspects And Pathogenic Spectrum.

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ABSTRACT
Emergence of candidal infections are increasing from decades and found to be a leading cause of human disease and mortality. Candida spp. is one of the communal of human body and is known to cause opportunistic superficial and invasive infections. Many of mycoses-related deaths were due to Candida spp. Major shift of Candida infection towards NAC (non-albicans Candida) is matter of concern worldwide. In this study we had given a systemic review about medically important Candidaspp. Along with their morphological features, treatment and drugs. Spectrum of the pathogen is also discussed. Morphology of Different Medically Important Candida Species with their medical aspects along and pathogenic spectrum. Corn meal agar morphology along with anti-candida drugs has been discussed. The study is done after considering various published review's and the mycological studies.

Key words: Candida, Yeast, C.albicans, C. tropicalis, C. parapsilosis, C. glabrata, C. krusei and C. lusitaniae

1. INTRODUCTION

Yeasts are unicellular, sometimes dimorphic fungi. It can give rise to wide range of infections in humans commonly called fungal infections. Yeast infections varies from superficial cutaneous/skin infections, mucosa related infections to multi-organ disseminated infections.(Sardi et al., 2013)Cutaneous and mucosal yeast infections can infect a number of regions in human body including the skin, nails, oral cavity, gastrointestinal tract, female genital tract and esophageal part and lead to chronic nature. Invasive and multi-organ disseminated yeast infections can infects respiratory tract, central nervous system, eye, bronchial region, cardiac region, gall bladder and urinary bladder(Sardi et al., 2013; Vermitsky et al., 2008).Since the late 20th century fungi is found to be the most common cause of human disease and immuno-compromised patients remain most susceptible (M A Pfaller & Diekema, 2007). *Candida* spp. are one of the communal of human body and are known to cause opportunistic superficial and invasive infections. (Marak & Dhanashree, 2018)The alteration of *Candida* spp. from commensal to pathogen is due to its virulent properties as adherence to host tissue, invasive biomedical devices (catheter), biofilm production, Moreover the release of extra cellular hydrolytic enzymes(Savastano et al., 2016). In a study many of mycoses-related deaths were due to *Candida, Aspergilllus, and Cryptococcus* spp. infections (Chandra & Mukherjee, 2015). *Candida albicans* is most commonly isolated from HAI (Hospital Acquired Infections). Other NAC speciesshowed a growing incidence against nosocomial infections in blood stream and ICU.(Awad et al., 2018)

Classification of Candida Species:
As per taxonomical classification
Kingdom: 'Fungi'
Division: 'Ascomycota'
Class: 'Saccharomycetes'
Order: 'Saccharomycetales'
Family: 'Saccharomycetaceae'
Genus: '*Candida'*(Reiss et al., 2011)

Morphology and characteristics of Different Medically Important Candida Species:
Candida albicans
*Cultural characteristics***:** Colony morphology on Sabouraud dextrose agar at 25°C can be from whitish to creamy, soft, from smooth to wrinkle. Variants may be dry and wrinkled. *Candida albicans* can grow at 42°C and on media containing cyclohexiamide.(Chow et al., 2008; Milazzo et al., 2014)
*Microscopic morphology***:** On corn meal agar, after 72 hours incubation at 25°C, two morphological forms are seen: chlamydospores found singly or in clusters and blastoconidia formed in dense clusters at septations with branched and true hyphae. Terminal chlamydoconidia may be formed withextended incubation.(Chi et al., 2011)
Most frequent yeast organism in human disorder. It is seen in both superficial and systemic conditions. It is involved in causing infections in skin, urinary bladder, female genital tract, cornea, nail, ear, endocardium and BSI (Kauffman, 1996). Risk factors for infections with *C. albicans* cover age groups ≥65, "immunosuppression before steroid use", "leukocytosis", intensive care unit (ICU) stay or indwelling of biomedical devices (catheter) (Rex & Pfaller, 2002). *Candida albicans* is difficult to notice on mucosae of humans. Oral cavity, lower intestinal tract, female's genital tract are habitats for *Candida albicans.* It cannot survive well in environment so it's not a part of nourishing smooth skin. Though it can be isolated from skin folding and toes. (Reiss et al., 2011).
Candida glabrata:
Cultural characteristics: Colonies on Sabouraud dextrose agar at 25°C are from whitish, smooth to glossing and glistening. It can grow at 42ºC; addition of cyclohexamide inhibits the growth(Cheng et al., 2005).
Microscopic morphology:
It is the single species that don't form pseudohyphae or hyphae (He et al., 2006). On corn meal agar, after 72 hours incubation at 25°C, only blastoconidia are observed. Cells are tiny; size varies from "2.5-4.0 x 3.0-6.0 μm as compared to *C. albicans* which is 3.5-6.0 x 4.0-8.0 μm" (Koehler et al., 1999).
C. glabrata is occasionally found on the smooth epidermis of immuno-competentpersons and is considered of little importance, but strict normal flora of mucosa in warm-blooded animals like mammal and birds (Procop, 2014).
Candidaparapsilosis
*Cultural characterstics***:**
*C. parapsilosis*colonies are shiny, creamy, moist, wrinkled on Sabouraud dextrose agar. It turns rust color with age. It don't grows on the surface when cultured in Sabouraud broth(Pelletier et al., 2005)
*Microscopic morphology***:** On corn meal agar at 25°C after 72 h, it produces blastospores. Blastoconidia are typically single or in short chains at distal ends of cells, the pseudohyphae are elongated and are called "giant cells". Satellite spider clonies give sage brush appearance. (Koehler et al., 1999)

*Candida parapsilosis*is found on healthy skin but also lives well in the nature.(Koehler et al., 1999; Sardi et al., 2013)

The specific habitat of *C. parapsilosis*is vast including humans and domestic animals. Moreover it is isolated from marine areas like "off the coast of Florida", "the Bahamas", and the "Indian Ocean" (Procop, 2014).

Candida tropicalis

Cultural Characteristics:

C. tropicalis on Sabouraud dextrose agar are dull, dry semi-white or cream colored with a slightly mycelial border.

*Microscopic morphology***:**

On corn meal agar at 25°C after 72 h, it produces oval blastospores sparsely anywhere along hyphae in small irregular clusters. Chlamydosphores are extremely rare. *C. tropicalis* also can produce true hyphae (Pelletier et al., 2005)

Candida tropicalis is found on the skin and in the healthy gastro intestinal tracts of humans. Naturally *C. tropicalis*isfound in soil nourished with organics and aquatic areas. *C. tropicalis* is used in production of perfumes, esters and amides. Xylitol a sugar alcohol that is alternate of sucrose is made from *C. tropicalis*(Hazen, 1995; Sardi et al., 2013).

Candida krusei

Cultural Characteristics: Colonies on SDA are flat, dry spreading, sometimes ground glass appearance. Some dull and non-spreading variations are shown. It can also grow without vitamin support(Koehler et al., 1999).

Microscopic morphology: On corn meal agar following 72 hours incubation at 25°C, abundant pseudohyphae and elongated blastoconidia is produced. *C. inconspicua* and *C. krusei*are morphologically and biochemically similar and can be differentiated by the cross match stick pseudohyphae production by *C. krusei*(Procop, 2014). This isolate well documented in human disease with known resistance to Fluconazole due to its innate reduced susceptibility. But in a recent case report capsofungin treatment lead disseminated *C.krusei*infection, later treated successfully with Amphotericin B and flucytosine combination (Reiss et al., 2011).

*C. krusei*is normally found in soil, water, plants, and other natural sources (Cheng et al., 2005).

Medical Aspects:

As an opportunistic human pathogen *Candida spp.* causes fungal infection in different parts of body known as candidiasis. Candidaemiais most severe known infection caused by *Candida species.* Major clinical forms of infections are:

1. Cutaneous candidiasis: It is the *Candida* infection of skin and nails. The most common areas are inguinal folds in infants, skin folds and nail folds. The warm and moist areas of skin allow the pathogen to thrive. (Pelletier et al., 2005).
2. Mucosal candidiasis: People who are immuno-compromised, have poor oral hygiene, hyposalivation, dentures, smoking have more risk to have candidiasis of mucosal membrane. Oral thrush is candidiasis of mouth. Esophageal candidiasis is less common than oral candidiasis. Vulvovaginal candidiasis is infection of female genital tract(Pelletier et al., 2005).
3. Disseminated candidiasis: It can also be called as invasive or systemic candidiasis. It is a serious infection that can infect blood, eyes, brain, liver and can cause disseminated disease. Patients who are immuno-compromised are susceptible to these infections (Hazen, 1995).

Pathogen Spectrum*:*

Main members of disease-causing yeasts belong to genera *Candida* and *Cryptococcus*. *Candida* genera include variety of 150 spp. out of which 17 are known to be pathogenic (M A Pfaller & Diekema, 2004). In yeasts infections *Candida* spp. is responsible to cause about 90 percent infection worldwide. It is the most common fungal pathogen leading to nosocomial infections(Nett, 2018). The pathogenic species are *Candida albicans*, *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis* and *Candida krusei*. *C. auris*is new emerging pathogen associated with Multi-drug resistance isolated from hospitals globally(Chowdhary et al., 2017).

The most frequent found species in a study is *C. glabrata* (37.62%), Normally of low virulence and high mortality of *C. albicans*. Simultaneously, *C. parapsilosis*(25.74%), *C.tropicalis* (16.86%) and *C. albicans*(9.90%) isolated from environmental health associates of a Brazilian Hospital (Reiss et al., 2011).

A decreased incidence of *C. albicans*is seen with predominance of *C. glabrata* and *C. parapsilosis* with few emergence of *C. auris* in a study from 1997-2016(Lockhart et al., 2016).

C. albicans is found to be frequently isolated species in vulvovaginal candidiasis and candiduriafollowed by *C. glabrata* and *C. parapsilosis*, globally, studied in 2010's review(Achkar & Fries, 2010).

In retrospective one year and three month study on candidemia in north India *C. tropicalis* (50%)is most commonisolate after *C. glabrata* and *C. parapsilosis*(15%), *C. albicans* (15%) . Study showed showed the increased trend of antifungal resistance to azoles (Thomas et al., 2016).

Candida albicans(76%) found most frequent isolate and *non-albicans Candida* (24%) in retrospective a study and the most commonly isolated NAC was*Candida glabrata*, representing 14% of total *Candida* species and 59% of NAC spp,*C. famata* (9% of NAC), *C. parapsilosis* (3.6% of NAC) and *Candida krusei* (3% of NAC) were recovered unequally from the different departments(Chowdhary et al., 2017).

In a clinical study, people with age group ≥60 years were most frequently diagnosed for *Candida* infection. Majority of patients were females (56%) and were kept in intensive care units (ICUs) (50.2%). Likelihood of Senior citizens at higher outcome of fungal infections found to be high due to exposure of reduced immunity and increased incidence of chronic diseases comes with rising age. Of the 221 *Candida* isolates in two different health care facilities, 35.3% were *C. albicans* and 64.7% were NAC, including 35.4% *C. albicans* and 64.6% NAC species from 1st and 35.1% *C. albicans* and 64.9%. NAC in 2nd facility. In both health care facilities *Candida* spp. were isolated from 11 different clinical specimens, mainly urine (71%), blood samples (9.1%), and tracheal aspirate (9.1%) (Lockhart et al., 2016).

From a study the progressive drug resitance towards Ketoconazole, Fluconazole, miconazole, and Clotrimazole is shown by *C. albicans* (89.3%), *C. glabrata* (42.9%), *C. krusei*(20%) and *C. glabrata* (14.2%) respectively (Michael A Pfaller et al., 2019).

In recent studies there is massive rise in fungal infections due to *Candida* spp., but recently the cause of candidiasis is moving towards the *non-albicans Candida* spp. This shift is probably due use of broad spectrum antibiotics and antifungal drugs(M A Pfaller & Diekema, 2007; Sardi et al., 2013; Vermitsky et al., 2008). Antifungal resistance is matter of concern raised due to increased use of antibacterial therapies and long-term use of azoles. Drug resistant candidiasis is difficult to treat(Milazzo et al., 2014). So, it is important to do early identification and provide antifungal susceptibility pattern. The treatment of candidiasis should be relied on *Candida* spp. and kind of infection. *Candida* spp. can cause severe nosocomial infection. Since no vaccines currently licensed for eradicating yeast infections, the only clinical resource to counter yeast infections is the use of antifungal agents.

(Kauffman, 1996)Many investigations done to study the prevalence of yeast infections and their etiological agents but the studies correlating the predisposing risk factors with clinical diagnosis are very less in India. Prior antifungal susceptibility testing in *in vitro* conditions give drug of choice and efficient to kill specific organism and provide beneficial therapy to the patient under treatment (Rex & Pfaller, 2002). Antifungal susceptibility testing allows us to know coming multi drug resistance in epidemiological studies and it helps researchers for studying and developing new drugs. Many of clinical microbiology laboratoriesare efficient to provide a range of bacteriological services but their services in mycology are restricted to direct microscopic examination of clinical specimens, Moreover very less database on superficial and Invasive fungal infections is available while searching extensive literature. As a result very less information regarding mycoses are available. (Reiss et al., 2011).
According to "CDC" "(Centers for Disease control and Prevention)" they found over 20 species of *Candida* yeast which infects humans. *Candidaalbicans* is most commonly isolated species from disease, probably because of communal in humans. (Wadhwa, R., et al. 2019) The other species can have internal and/or external origin in human body, lying on skin and environmental areas. Four most frequent pathogens are *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. Candida krusei is included however its ubiquity in invasive conditions was low (<3%)(Lockhart et al., 2016).

2. CONCLUSION:

Drug resistant candidiasis is difficult to treat, so the species level identification should be performed and antifungal should be designed as per the species and level of illness**.** A shift towards isolating NAC and emerging resistant towards azoles is a matter of concern worldwide. Predisposing risk factor should be in concern to avoid having nosocomial candidiasis. Clinical correlation helps in obtaining reliable interpretations.
Conflict of Interest: The authors declare no conflict of interest.

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