Candida Albicans and Non Albicans Species as a Pathogen Causing Oral Candidiasis.

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ABSTRACT

A part of the normal microbial flora of mucosal surfaces in humans forms by a small number of Candida species which may give rise to opportunistic infections when host defences are impaired. Among all Candida species, Candida albicans is the most prevalent commensal and pathogenic. Now a day the reported incidence of fungal infections associated with non-albicans species from the Candida genus is increasing presently. Most of these infections occur in Patients with weak immune system especially those infected with HIV. These emerging species of Candida are favored by the increase of immune compromised patients and new medical practices, and most oropharyngeal candidiasis is observed in HIV-infected patients. Candida non albican species such as Candida glabrata, Candida tropicalis, Candida parapsilosis and Candida dubliniensis are also emerging as a pathogen causing infection in humans increasing the severity of Candidal species. Candida dubliniensis is a recently described opportunistic pathogen that is closely related to C.albicanss but differs from it with respect to epidemiology, certain virulence characteristics, and the ability to develop fluconazole resistance. Most strains of C. dubliniensis are susceptible to antifungal agents, fluconazole-resistant strains have been detected while C.albicans, C.parapsilosis, and C.tropicalis remain...
susceptible to polyenes, azoles, and echinocandins. However, *C. glabrata* and *C. krusei* show reduced triazole susceptibility. In addition, the majority of isolates of *C. albicans* are less susceptible to flucytosine.

**KEYWORDS:** *Candida albicans*, *C. albicans*, *C. parapsilosis*, *C. glabrata*.

**INTRODUCTION**

Oral candidiasis is a common local infection seen in infants, elder adults, and persons with cellular immune deficiency states, such as acquired immunodeficiency syndrome. The most common form of oral candidiasis is the pseudo membranous type seen on buccal mucosa, palate, tongue, or oropharynx, which has the appearance of white plaques that can be rubbed off. The nodular type is a rare form of oral candidiasis, and constitutes one clinical presentation of chronic hyperplastic candidiasis (CHC). Although CHC appears to be a malignant tumor in humans, Candida species, harmless eukaryotic commensal yeasts, belongs to members of the phylum Ascomycota. In mammals, Candida species mostly inhabit on mucosal surfaces of the gastrointestinal and genitourinary tracts\(^1\) as part of the commensal microbial flora, in healthy individuals and cause infection only when host immunity becomes compromised. Peoples with disease like diabetes, old age or weak immune system or those who are receiving antibiotic or corticosteroid treatment, show higher prevalence to Candidal infection and these are predisposing factors for Candida infection.\(^2,3\) Candida species including Candida *albicans*, Candida *glabrata*, Candida *tropicalis*, Candida *parapsilosis* and Candida *dubliniensis* show clinical importance in humans beings. *C. albicans*, most prevalent, pathogenic of the Candida species, and is responsible for the majority of oral and systemic candidiasis cases\(^4,5,6\) as well as community-onset and nosocomial candidaemias.\(^7\) *C. albicans* is a significantly more successful pathogen than Candida non *albicans*.\(^8\) Candida species colonize the mucosal surfaces of all humans soon after birth and the risk of endogenous infection is ever-present. AIDS which led to a parallel increase in the incidence of candida infection in general and the less pathogenic non Candida *albicans* spp. in particular. Oropharyngeal candidiasis (OPC) occurs primarily in individuals with HIV. In general most date to date data suggest that CD4+T Helper cells are critical for host defence against infections. The major pathogen worldwide is *Candida albicans*. This fungus is detected in the body microbiota of healthy humans and accounts for 75% of the organisms residing in the oral cavity. It is diploid and has a largely clonal mode of reproduction. However, it can undergo considerable genetic variability either by gene regulation or genetic
changes including chromosomal alterations, mutations, and loss of heterozygosity (LOH). In fact, LOH events lead to *MTL* homozygosis, azole resistance and microevolution during infection passage through a mammalian host or *in vitro* exposure to physiologically relevant stresses.

*C. albicans*, *C. parapsilosis*, and *C. tropicalis* remain susceptible to polyenes, azoles, and echinocandins. However, *C. glabrata* and *C. krusei* show reduced triazole susceptibility. In addition, the majority of isolates of *C. albicans* are less susceptible to fluconazole.

*Candida albicans* is the yeast pathogen most frequently isolated from patients with vaginitis. Recently, an increase in other species, including *C. tropicalis*, *C. glabrata*, *C. krusei*, and *C. parapsilosis*, which are the cause of the opportunistic infection oropharyngeal candidiasis (OPC), has been observed. *C. glabrata* has become a prominent pathogen in some institutions. It is therefore of the utmost importance to rapidly and reliably identify *C. albicans* as well as other Candida species in routine clinical microbiology practice.[10, 11]

**Candida as Pathogen:** We know that colonization is the first step for disease (invasion preceded by colonization). Infection models of candidiasis in animals suggest that *C. albicans* is the most pathogenic species, and also expresses higher levels of putative virulence factors compared with other Candida species. Several potential virulence factors have been proposed in the pathogenicity of Candida species with adhesion to host surfaces, secretion of proteinases and hyphal formation apparently the most significant. Adherence of Candida to host surfaces is required for initial colonization and contributes to persistence of several host cell types, including epithelial, endothelial and phagocytic cells. Candida species secrete several hydrolytic enzymes associated, including secreted aspartyl proteinases, phospholipases, lipases, phosphomonoesterase and hexosaminidase which results in pathogenicity. Aspartyl proteinases is considered to be important in the development of Candida infection. In contrast with other types of proteinases, secreted aspartyl proteinases show proteolytic activity only under acidic conditions (pH < 4.0). Secreted aspartyl proteinases are produced by certain Candida species, with *C. albicans* secreting nine distinct aspartyl proteinases, often at much higher levels compared with other species, strains of *C. albicans* isolated from clinically apparent oral candidiasis have been shown to produce higher levels of secreted aspartyl proteinases compared with strains obtained from carriers with no mucosal signs. These findings suggest that strains of *C. albicans* that are actively involved in candidiasis could be inherently more virulent than commensal strains, possibly by
being able to upregulate secreted aspartyl proteinase gene expression. In contrast, there is no conclusive evidence that proteinase activity is always associated with infection, and this probably reflects the multifactorial nature of Candida infections. Phospholipases hydrolyse one or more ester linkages of glycerophospholipids. Phospholipase activity has been demonstrated for many fungal pathogens, including Candida species. It has been reported that the phospholipase activity is enhanced when hyphae are in direct contact with host tissue.

**Virulence factors associated with Candida and oral Candidiasis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
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<tr>
<td>Relative cell-surface hydrophobicity</td>
<td>Non-specific adherence process</td>
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<tr>
<td>Cell surface adhesin molecules</td>
<td>Specific adherence mechanisms</td>
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<td>High-frequency phenotypic switching</td>
<td>Antigenic modification through frequent cell-surface changes</td>
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<tr>
<td>Hyphal development</td>
<td>Promotes invasion of oral epithelium</td>
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<td>Secreted aspartyl proteinase production</td>
<td>Secretory IgA destruction</td>
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<td>Binding of complement molecules</td>
<td>Host cell and extracellular matrix damage</td>
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<td></td>
<td>Antigenic masking</td>
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**Candida non albicans**

According to Barnett *et al.* Several *non-albicans Candida* spp. are also known to be pathogenic and responsible for disease in man, while several others cause disease occasionally. The NCAC (non Candida *albicans* Candida) species are a heterogenous group of organisms and different from each other and also from *C.albicans*. Earlier, it was considered that *C.albicans* was the only species causing infection and *C.parapsilosis, C.tropicalis* and *C.guilliermondii* were considered only as occasional pathogens. The development of new medical therapies, treatments for cancer, the increase in invasive medical, the emergence of human immunodeficiency virus (HIV) and AIDS, and the widespread use of broad-spectrum antibiotics, however, lead to the increasing recovery of many other NCAC species causing mucosal infections. The NCAC species are thought to cause candidiasis of less virulence explained by the fact that they lack, totally or partially, some virulence factors that the most virulent species *C.albicans* has the ability to form hyphae. *C. dubliniensis* was originally identified by[9] in oral specimens from Irish HIV-infected and AIDS patients with recurrent oral candidiasis. However, the earliest known isolates of *C. dubliniensis* precede the AIDS pandemics and there have been one isolate deposited in the Central Bureau voor Schimmelcultures in Holland as *C. albicans, Candida dubliniensis*, a new fungal pathogen 209 in 1952[10] the British National Collection for Pathogenic Fungi as *Candida stellatoidea* in 1957.[11] This emphasizes the problem of misidentification of *C.*
dubliniensis isolates due to its phenotypic similarity with C. albicans. The most common clinical manifestations of oral C. dubliniensis infection are the erythematous and pseudomembranous forms. Recently, C. dubliniensis has also been implicated. This species can also cause oral disease in non-HIV-infected persons and be an oral colonizer at low incidence levels in normal healthy individuals. Redding described a mixed infection of C. dubliniensis and C. albicans in a patient undergoing head and neck radiation for oral cancer who developed oropharyngeal candidiasis. Willis et al. (2001) reported that 70% of 414 insulin-using diabetes mellitus patients also carried Candida species in their oral cavity. Colonization with multiple Candida species was common, and C. dubliniensis was present in both carriage and disease states. Isolates of C. dubliniensis also have been recovered from cases of systemic disease in both HIV- and non-HIV-infected patients and from vaginal, urinary and fecal specimens. Polacheck described the isolation of five C. dubliniensis strains, one of the five isolates was recovered from urine, and while the remaining four were recovered from upper respiratory tract and oral specimens. None of the patients was HIV positive, but all were receiving broad-spectrum antibacterial agents at the time of C. dubliniensis isolation. A case of a C. dubliniensis candidemia in a non-neutropenic patient have described by Salesa. Although the portal of entry for candidemia was unknown, the authors believed that it might be related to the intravenous use of cocaine by the patient. The clinical importance of C. dubliniensis requires further investigation of its epidemiology and virulence, and these studies should be facilitated by the development of reliable identification techniques. C. dubliniensis cells grown at 37 °C on Sabouraud dextrose agar, have the ability to coaggregate in vitro with cells of the oral bacterium Fusobacterium nucleatum. C. albicans cells fail to grow with this species at this temperature. Other tests were also used which allow the discrimination of C. dubliniensis and C. albicans include pyrolysis mass spectrometry and Fourier transform infrared spectroscopy which has shown a great reliability among the phenotypic methods. To discriminate between these two closely related yeast species a new method was developed by Paltroche-Llacsa huanga, a fatty acid methyl ester analysis using gas-liquid chromatography (Sherlock Microbial Identification System; Inc., USA). Although the chromatograms of these two species revealed no specific differences when applying fatty acid methyl ester analysis, a new library (CADLIB) was created by the authors using Sharlock Library Generation Software (MIDI). Using this method, only 9.4% isolates of C. albicans were misidentified as C. dubliniensis, but all the isolates of C. dubliniensis were correctly identified. Resulting differentiation
accuracy was 90.6% available at clinical diagnostic laboratories for \textit{C. albicans} and 100% for \textit{C. dubliniensis}.

3.1 \textbf{Candida dubliniensis}

\textit{C. dubliniensis} species was first described in 1995. This species is also associated with oral lesions in HIV-infected individuals and closely related to \textit{C. albicans} phenotypically and genotypically. Like \textit{C. albicans} it produce germ tubes and chlamydomospores but grow poorly at 42°C. It is the only Candidal species except \textit{C. albicans} that forms true hyphae.

The isolates of \textit{C. dubliniensis} recovered from HIV-patients receiving fluconazole therapy shows decreased susceptibility or resistivity.[9, 26, 27]

![Images of some Candida species showing morphological differences.](image)

3.2 \textbf{Candida glabrata.}

Most commonly isolated from the oral cavities of HIV-infected individuals. It is the second-most common agent of candidemia and have ability to develop resistance to fluconazole quickly.

Resistance can be both innate and acquired. Its infections are associated with systemic infections having a high mortality rate and are difficult to treat. Unlike \textit{C. albicans}, \textit{C.}}
*glabrata* have a lower oral keratinocyte adherence capacity. The virulence factors and host-parasite interactions of *C. glabrata* are not known.\(^{28,29}\)

### 3.4 Candida krusei

*C. krusei* causes infection mainly in critically ill patients and is most often isolated in hematologypatients with severe neutropenia. It is an uncommon pathogen causing candidemia. Isolates have been reported to be resistant to both fluconazole and itraconazole and resistant strains to amphotericin B. The widespread use of fluconazole to prevent fungal infections in HIV-infected patients has lead to a significant increase in *C. krusei* infections.\(^{30,31}\)

### 3.5 Candida lusitaniae

It is a very rare pathogen and a very few studies have been performed on this species. It is not much pathogenic as *C. tropicalis* and *C. parapsilosis* are and infect mainly immunocompressed hosts with prolonged administration of broad-spectrum antibiotics, hospitalization, cytotoxic or corticosteroid therapy, or granulocytopenia. *C.lusitaniae* may develop resistance to amphotericin B, but the data are contradictory.\(^{30}\)

### 3.6 Candida parapsilosis

*C. parapsilosis* affects neonates who are critically ill and surgical intensive care unit patients.\(^{32}\)

*C.parapsilosis* shows susceptibility to azoles and polyenes, tolerance to amphotericin B.\(^{33}\) Sarvikivi et al. reported the emergence of fluconazole resistance in *C. parapsilosis* strains in a neonatal intensive care unit. Fluconazole prophylaxis was used in low doses and this lead to resistant strains over a 10-year period.

### 3.7 Candida tropicalis

*C. tropicalis*, their ability to adhere to epithelial cells *in vitro* and its ability to secrete moderate levels of proteinase make this species most virulent among NCAC.\(^{29}\) Usually isolated from the oral cavity and skin. Sometimes esophagus infections may also occur. The latter cases, have been shown to correlate with systemic disease.

**Identification of candidal species**

The conventional methods of identifying yeasts to the species level in the clinical microbiology laboratory rely on criteria such as morphology, growth characteristics and
carbon source assimilation or fermentation, as well as appearance on differential isolation media. Isolates of C. albicans are typically identified by their ability to form germ tubes (GT) or chlamydospores under the appropriate conditions. It has also been demonstrated that the Murex C. albicans (MC) (Murex Diagnostics), Albicans-Sure (AS) (Clinical Standards Laboratories), and BactiCard Candida (BC) (Remel) test kits can be used for the rapid, presumptive identification of Candida albicans. To identify other species of Candida, commercial carbohydrate assimilation systems, such as the ID 32C system and API 20C test kit, are widely available.

**Useful phenotypical characteristics for identification of Candida dubliniensis**

Candida produced germ tube and chlamydospores (features for definitive *C. albicans* identification), carbohydrate assimilation profiles that not correlated precisely to *C. albicans* or any other yeast species included in these databases. These isolates known now as *C. dubliniensis* are closely related to *C. albicans*\(^{[26]}\) and differentiation between the two species in the clinical laboratory remains difficult.

*C. dubliniensis* produces chlamydospores more readily and abundantly on Rice agar than *C. albicans*.

A high frequency of chlamydomspore formation has been observed in approximately 57% of *C. dubliniensis* isolates and only in approximately 15% of *C. albicans* isolates. *C. dubliniensis* have the to produce rough colonies and chlamydomspores on STAIB agar (Syn. *Guizotia abyssinica* creatinine agar) provided a simple means of differentiating it from its close relative *C. albicans*.

On these agar plates, *C. dubliniensis* formed rough colonies due to mycelial growth and produced abundant chlamydospores whereas *C. albicans* grew only in smooth colonies and without chlamydomspore formation.

All of the *C. albicans* isolates grew as smooth, shiny colonies on STAIB agar after 48–72 h at 30 °C, while most *C. dubliniensis* isolates grew as rough colonies, many with a hyphal fringes.

*Candida dubliniensis*, a new fungal pathogen grow well at 30–37 °C, as creamy white colonies on solid media, such as Glucose SABOURAUD agar or Potato dextrose agar, but these colonies are indistinguishable from those of *C. albicans*. However, unlike *C. albicans*
colonies, C. dubliniensis do not grow or grow with difficulty at 45 °C. 1% C. albicans isolates failed to grow at 45 °C. However 36% C. albicans isolates did not grow at this temperature. This discrepancy could be a reflection of the inaccuracy of temperature readings and heat distribution in many laboratory incubators. Although it is impossible to distinguish between C. albicans and C. dubliniensis colonies in conventional solid media, the introduction in the clinical microbiology laboratories of chromogenic agars, as CHROM agar Candida has proven to be helpful in the identification of C. dubliniensis isolates, particularly following primary culture from clinical specimens. While C. albicans colonies are a light blue green color on CHROMagar Candida, C. dubliniensis colonies are a much darker green (particularly pronounced after 48 h).

Recently, Odds and Davidson\cite{34} examined the color of colonies of nine Candida species on CHROM agar Candida incubated for 24–72 h at 25 °C, 30 °C or 37 °C. Colors and colony forms characteristic of C. albicans and C. dubliniensis were formed most rapidly and were best differentiated at 37°C. They concluded that incubation of this chromogenic medium at temperatures below 30°C is not reliable for presumptive identification of Candida sp. Other culture media, as methyl blue-sabouraud agar (Schoof et al. 1997) or candida agar (quindós et al. 2001), have been proposed for discriminating C. dubliniensis from C. albicans. On Methyl blue-SABOURAUD agar, C. albicans isolates produced yellow fluorescence when exposed to long wave ultraviolet light, whereas C. dubliniensis isolates did not produce fluorescence. Unfortunately fluorescence was not visible in all C. albicans isolates when recovered from storage or repeated subcultures.\cite{35} On Candida ID agar, most C. dubliniensis isolates showed clear turquoise blue colonies, in contrast to C. albicans deep blue colonies. However, a small number of C. dubliniensis isolates grew as white colonies complicating their identification on this agar medium.\cite{36}

<table>
<thead>
<tr>
<th>Different media or sources</th>
<th>Candida. albicans</th>
<th>Candida. Dubliniensis</th>
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<tbody>
<tr>
<td>CHLAMYDOSPORE</td>
<td>+</td>
<td>+ More readily and abundant on rice agar</td>
</tr>
<tr>
<td>Growth at STAIB AGAR</td>
<td>15% Smooth colonies without chlamydospore</td>
<td>57% Rough colonies with abundant chlamydospore</td>
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<tr>
<td>Growth at 45°C</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>CHROM AGAR</td>
<td>Light blue color colony</td>
<td>Dark green color colony</td>
</tr>
<tr>
<td>METHYLENE –BLUE SABRO UDS DEXTROSE AGAR</td>
<td>Yellow fluorescence on exposure to long wave U.V light</td>
<td>–</td>
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<tr>
<td>CANDIDA ID AGAR</td>
<td>Deep blue colonies</td>
<td>Turquoise blue colonies</td>
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*Figure: 2 Images showing the growth of Candida albicans and Candida dubliniensis on different media sources.*
Polimorphic Nature of Candida: - *C. albicans* is a dimorphic species that can grow as yeast or filamentous forms, and is only one of the two Candida species capable of forming true hyphae, the other species being *C. dubliniensis*, the closest relative of *C. albicans*. Hyphae are considered to play important roles in infection processes such as adhesion and tissue invasion. Comparison of both species in both mucosal and systemic infection models have demonstrated that in spite of the ability of both species to produce hyphae, *C. albicans* is a significantly more successful pathogen.

Formation of Biofilm

Fungal biofilms and their role in infection and drug resistance have received increasing amounts of interest in the past years. Biofilms are structured microbial communities, tightly adhere to a mucosal surface and are embedded within a of extracellular polymers matrix.\(^{[39]}\) The formation of Candida biofilms begins with the attachment of the fungal cells to each other, followed by the formation of germ tube and extracellular matrix. At last the formation of hyphae and pseudohyphae by the yeast cells takes place. The mature biofilm shows a three dimensional structure having a depth of several hundred microns. It is gel-like, highly hydrated so that the micro-organisms in it are largely immobilized. *C. dubliniensis* biofilms also have similar 3-D structures as *C. albicans*. *C. parapsilosis* biofilm shows different architecture to that of *C. albicans*. It consists of mushroom-shaped biofilm patches in communities rather than biphasic arrangement of discrete layers. Biofilms are less susceptibility to the host immune system, disinfectants, and drugs. All of the commonly used antifungal agents have been reported to have a decreased activity against candidal biofilms.\(^{[40]}\) The mechanism of resistance in the biofilms is not fully understood. There have been many suggestions including restricted penetration of drugs through the matrix, phenotypic changes in the cells, and activation of resistance genes.\(^{[37]}\) The resistance increases during stages of biofilm maturation.

The biofilm state is the mode for growth of microorganisms in natural environments and recent reports have linked biofilms with over 65% of hospital-acquired infections. It has also been suggested that Candida strains have a high ability to form biofilms are generally more virulent than others. The explanation for this is likely to be multifactorial and relate to the differences observed between biofilm cells and their free-living or planktonic counterparts. Indeed, it is now known that significant phenotypic differences occur between biofilm and planktonic lifestyles. Perhaps the most important of these are those factors that relate to the
promotion, persistence and virulence of the organisms within the host environment. A recent investigation of candidaemia highlighted the importance of biofilms in infection, with higher mortality rates evident when a Candida biofilm was present. In the oral cavity, adherent biofilm cells will not be only protected from the normal mechanical flushing action of saliva and gingival cervical fluid, but the biofilm itself is a defensive barrier prevents the penetration of host immune factors and administration of antimicrobials. Candida biofilms exhibit resistance to many antifungals. The exact mechanism of biofilm resistance to antifungals remains unclear, but it is probably multifactorial. The extracellular polysaccharide of the biofilm could serve as an inhibitor to diffusion of an antimicrobial agent or ionically bind the drug as it diffuses through the biofilm, thereby effectively reducing its bioavailability. A feature of multilayered biofilms is the reduced activity and growth rates of cells that are in areas of limited exposure to required gases and nutrients, and it could readily be envisaged how these cells would be less susceptible to an antimicrobial that relies on inhibiting biochemical pathways associated with actively growing cells. These cells could represent the persister cells that have been suggested to be the resistant phenotype within a biofilm community. Conversely, other studies have demonstrated that biofilm resistance mechanisms are actually not completely dependent on changes in growth rates, and may be the result of upregulation of particular genes by biofilm cells. Indeed, the genes encoding ATP-binding cassette (ABC) transporter proteins that are particularly associated with azole drug resistance by efflux pump mechanisms in C. albicans have been shown to be upregulated in biofilms.

Among the many adhesions expressed by C. albicans, agglutinin-like sequence proteins have been implicated in pathogenesis and biofilm formation. These cell wall-bound adhesions bind to diverse mammalian peptide ligands, causing cellular aggregation through homotypic adhesion, and also co-aggregate with other microbial pathogens to mediate polymicrobial infection.

**CONCLUSION**

Although an increase in the prevalence of non- *albicans* spp. has been noted during the past decade, because of the extensive use of anti mycotic drugs particularly azoles, for prolonged periods makes non albicans species may consider as the survivor of the fittest (Darwins natural selection theory). Therapeutic courses has led to changes in the relative prevalence of various candida spp. with a decrease in the proportion of *C. albicans* as the etiological agent.
of candidiasis and an increase in the proportion of non *albicans* spp. such as *C. glabrata* and *C. krusei*, *C. glabrata* is associated with severe complications than other species. The newly recognized *C. dubliniensis* is an opportunistic pathogen causing oropharyngeal candidiasis in HIV infected patients. *Candida*, overcome two main obstacles to be a successful pathogen, host mechanisms to interfere the adhesion of *Candida* to human tissues and the production of hydrolytic enzymes. The first step in the initiation of and invasive process in oral cavity and other human mucosae is the microbial adherence to mucosal surfaces. *C. albicans*, the most adherent and pathogenic species of *Candida*, uses a diversity of mechanisms to adhere to human surfaces.

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