

# Role of *Candida* Species in Oral Lichen Planus

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## ABSTRACT

*Candida albicans* is the most common fungal pathogen in humans, although other *Candida* species can also cause candidiasis. Patients with symptomatic or erythematous oral lichen planus (OLP) have commonly been associated with these. In recent times, however, there has been a notable shift in the incidence of non-*Candida albicans* (NCA) species which is gaining prominence due to significant differences in their susceptibility to antimycotic drugs. Studies showed that *C. glabrata* and *C. tropicalis* were the most common NCA species isolated in OLP. Treatment failure is common among NCA species in OLP due to its intrinsic resistant or low susceptibility to commonly used antifungal agents. This article reviews the role of *Candida* species in etiology, pathogenesis, clinical features, diagnosis, and management of OLP.

**Keywords:** Oral cancer, Plaque, Potentially malignant disease.

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## INTRODUCTION

*Candida* is a yeast-like fungus that exists in three forms, namely, pseudo-hyphae, yeast, and chlamydo-spore. They are found in the gastrointestinal tract, vagina, and oral cavity.<sup>1</sup> The predominant species of *Candida* isolated from its oral cavity is *Candida albicans* (CA). Apart from CA, there are other non-*Candida albicans* (NCA) such as *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. glabrata*, and *C. dubliniensis* that are frequently found in oral cavity. Oral lichen planus (OLP) is shown to be associated with both types of species.<sup>2</sup> OLP is a T-cell-mediated chronic mucocutaneous disease affecting 2.2% of the world's population. OLP presents in a bilaterally symmetrical manner in the oral cavity.<sup>3</sup> *Candida* isolates alone or together with other factors may exaggerate the development and advancement of OLP. The oral microenvironment may change by the development of OLP and helping in better adaptation allowing the *Candida* to grow vigorously, thus establishing an interconnected relationship between the pathogenesis and the progression of OLP. Studies have also shown that there is a varying capability of both the strains to promote dysplasia.<sup>4,5</sup> NCA has low virulence factors when compared to CA isolates and are known to be more resistant to commonly used antifungal agents.<sup>6</sup> This emphasizes a need for identification of the different phenotypic variants of *Candida* species and their role in OLP.

## Common *Candida* Species in Oral Cavity

*Candida albicans* is the commensal in the oral cavity of normal and diseased individuals (17–75%).<sup>2</sup> The principal *Candida* isolates from normal oral flora are given in Flowchart 1.<sup>7</sup>

## Clinical Presentation of *Candida* Species in OLP

Colonization of *Candida* species in the absence of clinical signs and symptoms may not be indicative of the lesion but at same time can be associated with its progression. All *Candida* species show similar symptoms of mucositis. However, the invasiveness varies considerably among different species.<sup>8</sup> This may also increase the antifungal susceptibilities among species. The role of NCA has become increasingly important, especially in high-risk patients.<sup>9</sup>

Alone or together with other factors, NCA might exaggerate the development and advancement of OLP. Alteration in epithelial cells of OLP promotes adherence of NCA, thus enabling it to overcome

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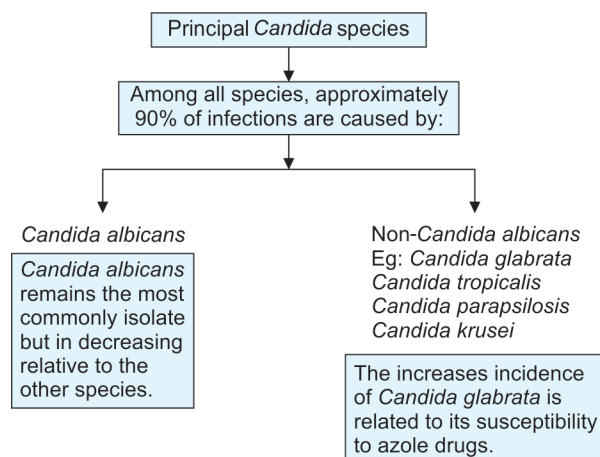
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the normal flushing mechanism of body secretions. They also act as a secondary pathogen due to which the signs and symptoms of OLP like 'burning' sensation or discomfort are also getting aggravated. Endogenous nitrosation product is a potential initiator for oral cancer. Due to its effect on keratinocytes, oral cancer is usually associated with candidal species invasion.<sup>10</sup> Variable members of NCA spp are associated with clinical manifestations of infections they are difficult to differentiate from CA, but several NCA spp. are

**Flowchart 1:** Principal *Candida* isolates from normal oral flora



both inherently or acquire resistance to commonly used antifungal drugs.<sup>9</sup>

**Prevalence of *Candida* Species in OLP and in Healthy Individuals**

A single general estimate of the world prevalence of CA and NCA species in OLP is difficult to determine. But there is limited data on the actual prevalence of the various NCA species in OLP. Table 1 is a review of some studies on the prevalence of the various CA and NCA species in patients with OLP. All studies showed that the prevalence of CA was higher than NCA in OLP patients. Thus, although less virulent in nature, NCA need to be differentiated and identified to emphasize the initiation of adequate and appropriate therapeutic modalities in treating OLP cases. As there are significant differences in their susceptibility to antimycotic drugs, identification of different *Candida* species maybe the need of the hour.

**Pathogenesis**

*Candida* species present in many parts of the body, including the oral cavity, as a normal commensal, but its growth is prevented by innate immune system of the body.<sup>20</sup> The pathogenicity of *Candida* species depends upon two major factors, including the immune status of the host and virulence of the pathogen which are also responsible for the conversion of *Candida* spp. from normal commensal to potent pathogen. The virulence factor includes adherence to buccal epithelial cell (ABEC), hemolytic activity, biofilm formation, and production of extracellular hydrolytic enzymes (coagulase, phospholipase, and proteinase)

(Table 2). In comparison to CA, NCA lacks many of the virulence factors such as ability to form hyphae and phenotypic switching. They have low capacity of adherence to buccal epithelial cell as well as vascular endothelial surfaces and secrete less proteinases. Biofilm formation in *Candida* spp. is implicated as an important virulence attribute, as it increases the significant resistance to antifungal therapy and also ability to resist the host defense response.<sup>6</sup> This prompted researchers to identify and differentiate CA from NCA for better therapeutic management in cases of OLP due to considerable variations in their susceptibility to antimycotic drugs.

**Risk Factors**

Risk factors that are responsible for increased *Candida* carriage in OLP are advanced age, female gender, wearing of dentures, immune suppression, iron deficiency, steroid treatment, poor oral hygiene, systemic diseases (e.g., diabetes mellitus), and tobacco usage (Table 3).<sup>24</sup>

**Laboratory Identification**

Identification of CA and NCA is of utmost importance owing to difference in their susceptibility to antifungal drugs. A number of laboratory techniques are used to identify *Candida* species in oral tissues which includes direct (Table 4) and indirect microscopic examination (conventional and molecular diagnostic techniques) (Table 5). All methods are enlisted in Flowchart 2. However, conventional techniques stay the mainstay of *Candida* species identification in most clinical microbiology laboratories.<sup>22,27,28</sup>

**Table 1:** Summary of studies

Author	Total no of cases		Positive cases of <i>Candida</i>		No of <i>Candida albicans</i>		No of non- <i>Candida albicans</i>	
	OLP patients	Healthy individuals	OLP patients	Healthy individuals	OLP patients	Healthy individuals	OLP patients	Healthy individuals
Lundstorm et al. 1984 <sup>11</sup>	41 OLP patients	30 healthy individuals	18 (44%)	11 (37%)	15 (83%)	–	3 <i>C. tropicalis</i> (02), <i>C. glabrata</i> and <i>C. parapsilosis</i> (01)	–
Krogh et al. 1987 <sup>12</sup>	Percentage of <i>Candida</i> species—47%							
Hatchuel et al. 1990 <sup>13</sup>	185 OLP patients	–	33 (17.8%)	–	–	–	–	–
Jainkittivong et al. 2007 <sup>14</sup>	30 OLP patients	30 healthy individuals	23 (76.7%)	13 (43.3%)	21 (91.3%)	12 (40%)	2 (4.3%), <i>C. tropicalis</i> (01), <i>C. glabrata</i> (01)	1 <i>C. lusitaniae</i>
Zeng et al. 2009 <sup>15</sup>	300 OLP patients	128 healthy individuals	86 (28.67%)	26 (20.31%)	86	26	–	–
Mehdipour et al 2010 <sup>16</sup>	21 OLP cases	21 healthy individuals	20(33.3 %)	21 (28.5%)	20 (33.3%)	21 (28.5%)	–	1 <i>C. krusei</i>
Masaki et al. 2011 <sup>17</sup>	15 OLP patients	7 healthy individuals	12 (80%)	2 (29%)	9	2	3 <i>C. glabrata</i> (01), <i>C. fukuyamaensis</i> (01), <i>C. parapsilosis</i> (01)	0
Shivanandappa et al 2012 <sup>10</sup>	34 OLP patients	0	15 (44.11%)	0	–	0	–	0
Artico et al. 2014 <sup>18</sup>	Percentage of <i>Candida</i> species—29%							
Ebrahimi et al 2014 <sup>19</sup>	37 OLP patients	0	18 (49%)	0	7(37%)	0	12(63%)	0
Arora et al. 2015 <sup>2</sup>	80 OLP patients	80 healthy individuals	26 (33%)	0	19 (73%)	0	7 (27%) <i>C. parapsilosis</i> (02), <i>C. glabrata</i> (03), <i>C. krusei</i> (01) <i>C. dubliniensis</i> (01)	0

**Table 2:** Virulence factors associated with *Candida* species<sup>21–23</sup>

Virulence factor	Effect	Mechanism of action
Adherence to buccal epithelium.	<ul style="list-style-type: none"> <li>• First step in the pathogenesis of infection.</li> <li>• Promotes retention in the mouth.</li> </ul>	Binding of the <i>Candida</i> to host cells, host cell proteins, or microbial competitors prevents or at least reduces the extent of clearance by the host's defense mechanisms
Biofilm formation	<ul style="list-style-type: none"> <li>• Increases the ability to withstand host defenses and also confers significant resistance to antifungal therapy.</li> </ul>	After adhesion, proliferation of these yeast cells occur followed by formation of hyphal cells, extracellular matrix accumulation and finally, dispersion of yeast cells from the biofilm complex.
Hemolytic activity	Survival and persistence.	<i>Candida</i> uses hemolysins to degrade hemoglobin and obtain elemental iron which helps pathogens to survive and persist.
Production of extra-cellular hydrolytic enzymes:	Play an important role in adherence, tissue penetration, invasion, and the destruction of host tissue.	
Enzyme coagulase	Enzyme coagulase binds plasma fibrinogen and activates a cascade of reactions that induce clotting of plasma. Phospholipases and proteinases are the most important hydrolytic enzymes which are produced by <i>Candida</i> spp.	
(i) Phospholipases	Host cell membrane and hence facilitate invasion of tissue.	Enzymes hydrolyze phospholipids into fatty acids and also expose receptors on host cell membrane to facilitate adherence and damage the host cell membrane.
(ii) Proteinase	Facilitates <i>Candida</i> invasion and colonization of host tissue.	Disruption of host membrane and by degrading important structural and immunological defense proteins.

**Table 3:** Risk factors associated with *Candida* species<sup>25,26</sup>

Risk factors	<i>Candida</i> species	Mechanisms
Advanced age	Extremes of age may predispose to <i>Candida</i> infection.	Due to immature or weakened immunity.
Prolong use of denture	<i>Candida albicans</i> is commonly associated with denture use followed by <i>Candida glabrata</i> , are frequently recoverable from dentures and underlying mucosal tissues.	Produces a microenvironment conducive to the growth of <i>Candida</i> with low oxygen, low pH and anaerobic environment. This may be due to enhanced adherence of <i>Candida</i> species to acrylic, reduce salivary flow under denture
Drugs	Topical corticosteroid application is associated with a growing number of different species of <i>Candida</i> in OLP patients, whose predominant pathogen is <i>C. albicans</i> . Undoubtedly, non- <i>Candida albicans</i> strains, such as <i>C. parapsilosis</i> , <i>C. tropicalis</i> , <i>C. krusei</i> , and <i>C. glabrata</i> , are frequently detected during the OLP therapy.	Less virulence factors of NCA causes increase in ability to withstand host defenses response and significant resistance to antifungal therapy
Habits	The rate of oral <i>Candida</i> carriage is higher among smokers and smokeless tobacco users as compared to non-smokers	Tobacco usage leads to an increase in thickness of epithelial keratinized layer, decrease in levels of salivary immunoglobulin A, and suppression in functions of polymorphonuclear leukocytes, thus facilitating the proliferation of <i>Candida</i> species. It is also hypothesized that cigarette smoke enhances adhesion, growth and biofilm formation of <i>C. albicans</i> .
Diabetes	Non- <i>C. albicans</i> species are frequently isolated from subjects with diabetes.	Poorly controlled DM causes increased glycogen levels and other metabolic alterations, which lower oral PH resulting in <i>Candida</i> colonization at a rate higher than that of commensal bacteria and infection.
Iron deficiency	<i>C. albicans</i> species are more frequently isolated from subjects with iron deficiency.	Due to impaired cellular immunity.
Other factors	Persons with increased blood group H antigen, old age, pregnancy and nutritional status of the patients.	

**Table 4:** Direct microscopic examination<sup>22,27,28</sup>

Type	Methodology	Interpretation	Significance
Potassium hydroxide (KOH) wet mount	Smear of the representative area is taken. A drop of potassium hydroxide solution is placed on a slide and examined under microscope.	<i>Candida</i> seen as yeast cell with or without budding or pseudohyphae	Used to differentiate between yeast and bacterial growth
Gram stain	Smear taken from the lesional site is heat fixed on to microscope slides and then stained by the gram stain for microscopic examination.	Gram positive organisms appear dark violet whereas gram negative organisms appear pink in color.	To differentiating between yeast and hyphal forms smear is consider important tool but is less sensitive than cultural methods

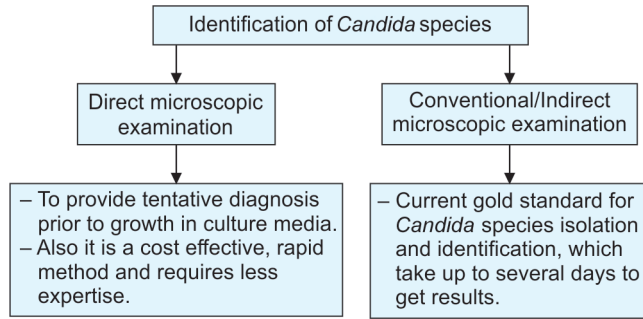


**Table 5:** Conventional/indirect microscopic examination<sup>22,27-29</sup>

Type	Methodology	Interpretation	Significance
<b>(A) Microbiological test</b>			
Culture: Sabouraud's dextrose agar (SDA) with Chloramphenicol	Swab from the representative area is inoculated on SDA plate and incubated aerobically at 37°C for 24–48 hours	<i>Candida</i> develops as cream, smooth, pasty convex colonies on SDA	SDA culture is the most frequently used primary isolation medium for <i>Candida</i> . Although permitting growth of <i>Candida</i> , it suppresses the growth of many species of oral bacteria due to its low pH
Germ tube test	The culture of <i>Candida</i> species is mixed with sheep or normal human serum and incubated at 37°C for 2–4 hours. A drop of suspension is examined on the slide under the microscope.	Examined for sprouting yeast cells that is tube-like outgrowths from the cells (known as germ tubes).	Differentiating of <i>C. albicans</i> from other <i>Candida</i> species.
Thermo-tolerant test	Heavy inoculum of <i>Candida</i> isolate is inoculated on SDA plates and incubated at 45°C for 24–48 hours and examined for the growth.	Growth indicates <i>C. albicans</i> whereas no growth indicates <i>C. dubliniensis</i> .	Differentiate between <i>C. albicans</i> and <i>C. dubliniensis</i>
Sugar assimilation and fermentation test	Carbohydrate assimilation test is based on the use of carbohydrate-free yeast nitrogen base agar and observing for the presence of growth on carbohydrate containing media after an appropriate period of incubation.	The ability to ferment sugar was shown by the presence of acid (indicator becomes pink) and gas trapped in the Durham tubes	Is a "gold standard" for speciation of <i>Candida</i> species but, it can take several days for identification.
<b>(B) Serological tests</b>			
	Candidal antigen from either cell-wall mannan or cytoplasmic constituents helps for identification of species.	The detection of IgA and IgM antibodies is important to identify <i>Candida</i> species.	Variability in antibody production was seen in immunosuppressed individuals and hence in such case the use of an antigen detection test is recommended.
Examples: Enzyme linked immunosorbent assay (ELISA) and radio immuno assay (RIA).			
<b>(C) Molecular diagnostic techniques</b>			
	Genetic based identification of <i>Candida</i> species were done by analyzes of restriction fragment length polymorphisms (RFLPs) and electrophoretic karyotype differences using DNA–DNA hybridization or gel electrophoresis.	Results can be obtained based on final PCR product sizes, PCR product sequence variation or gel electrophoresis resolution, following cutting of PCR sequences with restriction endonucleases.	Sensitivity and specificity of this technique is 98.7– 100% and 100% respectively, allowing for the discrimination of <i>C. albicans</i> from the phenotypically similar <i>C. dubliniensis</i> .
Examples: Fluorescence in situ hybridization with peptide nucleic acid method (PNA Fish), pulsed field gel electrophoresis (PFGE), random amplified polymorphic DNA (RAPD) analysis and repeat sequence amplification PCR (REP).			
<b>(D) Histopathological features (special stains)</b>			
Gomori's methenamine silver (GMS)	Deparaffinize section. Oxidized in 5% aq chromic acid, 2 hour. Washing in tap water. Rinse in 1% sodium metabisulfate. Wash in tap water 5 minutes. Placed in preheated silver incubating solution in a dark place, upto 1 hour. Rinse well in distilled water. Tone in 0.1% gold chloride for 4min. Place in 3% sodium thiosulfate, 5 min. counterstain in Arzac's stain, 15–30 seconds. blot, dehydrant, clear and muont.	Fungi, pneumocystis, melanin— black. Mucin and glycogen— grey-black. RBCs—yellow. Background—pale green	Screening test for fungi. It stains nonviable and even degenerated fungi with better contrast.
Periodic acid–Schiff (PAS)	Deparaffinize two section. Treat one control with Amylase (25 minutes). Wash in running water (20 minutes). Oxidize with periodic acid (5 minutes). Rinse in distilled water. Treat with Schiff's reagent (5 minutes). Wash in running water (10 minutes). Stain the nuclei with Mayer's hematoxylin 1 minute (no need to blue). Wash in water. Dehydrate, clear and mount.	PAS-positive materials can simply be recognized by their shape (morphology), e.g., fungal hyphae (rose pink)	Screening test for fungi. It actually demonstrates fungal morphology better than the silver stains



**Flowchart 2:** Methods for identification of *Candida* species



**Table 6:** *Candida* species resistance to antifungal agents<sup>9,31,32</sup>

<i>Candida</i> species	Resistance to antifungal agents
<i>Candida albicans</i>	Amphotericin B
<i>Candida glabrata</i>	Isavuconazole
<i>Candida tropicalis</i>	Fluconazole
<i>Candida krusei</i>	Itraconazole
<i>Candida parapsilosis</i>	Fluconazole

**Antifungal Susceptibility Profile of *Candida* Species in OLP**

OLP patients treated by corticosteroid therapy can have superimposed and/or secondarily infected candidiasis. Studies show that topical corticosteroid application in OLP has been associated with increase in different *Candida* species.<sup>2</sup> Also, NCA species have shown to be immune to commonly used antifungal agents. NCA species are more commonly found in erosive OLP cases. Studies show that in erosive OLP lesion, the yeast strongly adheres to the epithelial cells when compared to healthy subjects or transplanted patients even in absence of corticosteroid therapy.<sup>2,11,15</sup> Lundstorm et al. reported both transformation of erosive lesions to the reticular form and clinical improvements in 90% of cases after antifungal treatment. Li et al. suggested that the genotypes and antifungal susceptibility test of *Candida* isolates in OLP was considered for the use of an antifungal agent.<sup>30</sup> Studies show that among NCA species, *C. tropicalis* and *C. glabrata* were more commonly isolated from OLP patients.<sup>2,11</sup> The incidence of *C. glabrata* was highest in azole resistance among *Candida* isolates. This may be due to decrease in intrinsic resistance to the azole class of antifungals, including the isavuconazole (newest addition to the class). Another study showed that the *C. tropicalis* has greater ability for biofilm formation when compared to CA due to which they show variable resistance to antifungal therapy, mainly fluconazole, as they increase its capacity to withstand host defenses. As antifungal agents especially fluconazole is resistance to variable *Candida* species, it has made susceptibility testing of *Candida* important.<sup>9,31,32</sup> The testing shows significant progress. For species-specific breakpoints for each agent, broth dilution, E test, microtiter method, and disk diffusion are now available. Evaluations of susceptibility to antifungal agents are carried out for azoles, such as fluconazole, itraconazole and/or voriconazole.<sup>33</sup> Hence, for initiation of adequate and appropriate therapeutic modalities in treating OLP cases, it is important to differentiate and identify *Candida* species (Table 6).

**Treatment**

To treat symptomatic OLP, various treatments modalities have been employed, but complete resolution is difficult to achieve. The first line of treatment for OLP is usually topical corticosteroids, but its prolonged use causes decrease in the immune mechanism of mucosa along with reduction in salivary flow, leading to altered microflora, thus enhancing candidal growth.<sup>14</sup> Various other drugs have found to be effective in certain *Candida* species. For all these *Candida* species, nystatin is the most effective antifungal drugs. Singh and Chakraborty also found that more effective drugs against NCA species (80%) was clotrimazole, which is analogous to the study done by Ajitha et al., where they found that around 67% of NCA species were sensitive to clotrimazole. Susceptibility to antimycotic drugs was significantly different in various *Candida* species. Singh and Chakraborty conducted the antifungal susceptibility test which revealed that amphotericin B exhibited a higher sensitivity against CA, *C. dubliniensis*, respectively, and hence concluded that this drug can be a good adjuvant for CA and *C. dubliniensis* infections. This finding is analogous to the opposite studies done by Kaur et al. and Mondal et al. However, high degree of resistance against amphotericin B was shown by NCA and non-dubliniensis.<sup>34</sup>

The current drug regimen seems to be only palliative and has also shown to have various adverse effects, including colonization of *Candida* species. To avoid such effects, valuable natural therapies, such as curcumin and aloe vera, have been considered for effective treatment, as they show antifungal effects that would prevent the development of *Candida* infection over the OLP lesions.<sup>35</sup>

**CONCLUSION**

*Candida* species are not just present in OLP but also play a role in its progression. Prevalence of CA is high when compared to other species. However, ongoing increase within the incidence of NCA species isolate in OLP may be a rising concern. This rising trend is not going to wane, given the unwarranted use of antifungal drugs and patient susceptibility. The exact mechanisms behind the role of CA and NCA in OLP are unknown. Hence, a thorough research and understanding is needed for better therapeutic management and results.

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