Candida and Oral Candidosis—A Review

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Abstract

Oral candidiasis (also called candidosis) is an opportunistic infection affecting the oral mucosa. These lesions are very common and caused by yeast *Candida albicans*. *C. albicans* are normal component of oral microflora and around 30 to 50% carry these organisms. The rate of carriage increases with advancing age of the patient. *C. albicans* are recovered from patient's mouth over the age of 60 years. Other species such as *C. glabrata*, *C. tropicalis*, *C. guilliermondii*, and *C. krusei* are infrequently but consistently isolated. Oral candidosis can be classified into primary and secondary candidiasis. The factors involved in the pathogenicity of *C. albicans* have been reviewed. The pathogenesis of different biotypes and strains of *C. albicans* varies. A relationship has been suggested between the adherence of *C. albicans* to surfaces and its ability to colonize and cause disease. An important aspect of the pathogenicity of *C. albicans* may be its nonspecific affinity and binding to acrylic resin and other plastics. The factors affecting adhesion of yeasts, related to yeast cells, related to host cells and environmental factors, and the main factors which increase the susceptibility of oral candidiasis have been reviewed. The different types of oral lesions, their identification by different methods, management, and treatment of oral candidiasis also have been highlighted. Oral candidosis as a common opportunistic infection has gained importance after the discovery of human immunodeficiency virus infection. Candidiasis was always an endogenous infection. There are few cases of exogenous infection in intravenous drug abusers and contact lens users. Esophageal candidiasis is the earliest and most cases of lesions seen in acquired immunodeficiency syndrome patient. The diagnosis and reporting of oral candidiasis should be done with utmost care. The finding of yeast cells in large numbers and presence of pseudohyphae indicate invasion and causative agent of infection. The diagnosis of Candida infection can be confirmed by various techniques and recently discovered advanced methods.

The confirmation of Candida infection depends on clinical diagnosis, proper collection of specimen, and careful evaluation in methodology and reporting.

Keywords

- *Candida albicans*
- oral candidiasis
- microflora

Introduction

Oral candidiasis (also called candidosis) is an opportunistic infection affecting the oral mucosa. These lesions are very common and caused by yeast *Candida albicans*. *C. albicans* are normal commensal of oral microflora and more than 30% of individuals carry these organisms. The rate of carriage increases with

advancing age of the patient and *C. albicans* has been recovered from oral cavity of most of the adults with bad oral hygiene.^{1,2}

The organism under favorable condition has the ability to transform into pathogenic hyphal form. Conditions that favors this transformation include use of broad spectrum antibiotic therapy, xerostomia, immune dysfunction, overuse of antibiotics, rise of acquired immunodeficiency syndrome,

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increase in organ transplantations and the use of invasive devices, diabetes, and presence of removable prosthesis.³

Other species such as *C. glabrata*, *C. tropicalis*, *C. guilliermondii*, and *C. krusei* are infrequently isolated from various clinical specimens.

Common Species of Candida

Candida albicans

It is the predominant cause of invasive fungal infections. People at risk include those suffering from human immunodeficiency virus (HIV), cancer, and intensive care unit patients who are undergoing major surgery and organ transplants.³

Candida glabrata

It has become important because of its increasing incidence worldwide and decreased susceptibility to antifungals. Its emergence is largely due to an increased population of immune compromised patient and wide spread use of anti-fungal drugs. In many hospitals, *C. glabrata* is the second most common cause of candidemia.⁴

Candida tropicalis

It is the third or fourth most commonly recovered *Candida* species from blood cultures. *C. tropicalis* has progressively been observed to be the most common cause of invasive candidiasis in neutropenic patients such as those with acute leukemia or those who have undergone bone marrow transplantation.⁵

Candida parapsilosis

It is one of the principal causes of invasive candidiasis. In most parts of the world, it is the third most common cause of candidemia especially in patients with intravenous catheters, prosthetic devices, and intravenous drug use. It is also one of the most common causes of candidemia in neonatal intensive care unit.⁶

Candida krusei

It is the fifth most common bloodstream isolate, although less common (1–2%). *C. krusei* is of clinical significance because of its intrinsic resistance to fluconazole and reduced susceptibility to most other antifungal drugs. It is frequently recovered from patients with hematological malignancies complicated by neutropenia and tends to be associated with higher mortality rates (49 vs. 28% with *C. albicans*) and lower response rates (51 vs. 69% with *C. albicans*).⁷

Candida guilliermondii

It has been isolated from environmental surfaces and from the skin and nails of health care workers. It has been shown to cause hematogenously disseminated candidiasis.⁸

Proposed Revised Classification of Oral Candidosis⁹

Primary Oral Candidosis (Group 1)

Acute symptoms are classified into pseudomembranous and erythematous and chronic symptoms are classified into

erythematous, pseudomembranous, hyperplastic, nodular, and plaque-like *Candida*-associated lesions, which include angular cheilitis, denture stomatitis, and median rhomboid glossitis.

Keratinized primary lesions superinfected by *Candida* are leukoplakia lichen planus and lupus erythematosus.

Secondary Oral Candidoses (Group 2)

Oral manifestations of systemic mucocutaneous candidiasis are due to diseases like thyroid aplasia and candidiasis endocrinopathy.

Pathogenicity of *Candida* Species¹⁰

The factors involved in pathogenicity of *C. albicans* have been reviewed. The pathogenesis of different biotypes and strains of *C. albicans* varies.

Enzymes of *Candida*

It has been suggested that *C. albicans* produces endotoxin, but the levels of endotoxin produced in vivo may not be sufficient to produce toxic effects. Alternatively, the organisms may produce enzymes that facilitate penetration of the mucous membrane. *Candida* certainly have the ability to produce phospholipases and these are concentrated at the tip of the fungal hyphae and localized in the vicinity of the host cellular compartments where active invasion occurs. These enzyme activities were found in most *C. albicans* strains but not in organisms known to be less virulent than *C. albicans* such as *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*.

Extracellular proteinases have also been implicated in the pathogenicity of *C. albicans*. Proteinase-deficient strains are noninvasive, and pattern of adherence also reflects the expression of secretory proteinase. Salivary proteins including immunoglobulin A (IgA) can be almost completely degraded by acidic proteinases of *Candida* especially under low pH conditions. Recently, it has been shown that parotid saliva is more resistant to the proteolytic action of *Candida* proteinase when compared with mixed saliva. Acid proteinase (aspartyl proteinase) production is increased by *C. albicans* isolated from later stage of HIV infection and may contribute to candidosis.¹¹

Temperature Variations

The virulence of *C. albicans* can also be influenced by the temperature at which it is grown. Virulence is associated with increased germ tube production by yeast grown at lower temperature. These in turn display enhanced adherence characteristics compared with parent yeast mainly in the blastospore phase. Yeasts grown at room temperature are more resistant to killing by polymorphonuclear leukocytes.

Adhesion of *Candida*^{12,13}

A relationship has been suggested between the adherence of *C. albicans* to surfaces and its ability to colonize and cause disease. An important aspect of the pathogenicity of *C. albicans* may be its nonspecific affinity and binding to acrylic resin and other plastics. The mechanism of attachment is believed to involve the interaction of cell wall components of *C. albicans* with the target surface.

Factors Affecting Adhesion of Yeasts^{14,15}

Factors related to yeast cells are medium in which it is grown, its phenotype, and capacity to form germ tube or pseudo-hyphae extracellular polymeric material such as flocculator fibrillar surface layers mannan, chitin, hydrophobicity, and cellular lipids. Factors related to host cells are cell source, mucosal cell size and viability, fibronectin, fibrin, sex hormones, and yeast carriers versus patients with overt candidosis. Environmental factors affecting adhesion are cations, pH, sugars, saliva, humoral antibody and serum, antibacterial drugs, and lectins.

Switching Phenomenon¹³

C. albicans frequently exhibits variant colonial forms when grown in vitro. A smooth colony forming yeast when inoculated onto an agar surface may produce a proportion of colonies with rough surfaces. It is known that switching can be triggered by low doses of ultraviolet radiation, and once triggered into the high-frequency switching mode, *C. albicans* exhibit high rates of alterations in colony morphology. Thus, *C. albicans* has the capacity to switch frequently and reversibly between several variants, heritable, and phenotypes. Switching is associated with change in micromorphology, and physiological properties as well as several putative virulence traits. One switching system, "white-opaque" transition has been examined for the capabilities of two phenotypes to adhere to oral epithelial cells.

There are three general factors which helps the *C. albicans* infection to develop in the patient's body. They are immune status of the patient, oral mucosal environment, and strain of *C. albicans*.

The main factors which increase the susceptibility of oral candidiasis are¹⁴ immunosuppression, endocrinopathies, nutritional deficiency, malignancies, dental prosthesis, epithelial alteration, high carbohydrate diet, infancy and old age, poor oral hygiene, and heavy smoking.

Xerostomia saliva contains IgA which inhibits binding of *C. albicans* to mucosal surfaces. It also provides a flushing action which removes *C. albicans* from the oral cavity. In case of xerostomia, both these actions are absent because of lack of saliva production, so chances of candidiasis is more in oral cavity. Xerostomia is also seen in case of anticancer treatment and irradiation which increases the proliferation of candidal cells and resistance of candidal cells to antifungal drugs. Xerostomia is also seen in case of Sjogren's syndrome because of lymphocytic infiltration and destruction of salivary glands.¹⁶

Diabetes Mellitus

Growth of *C. albicans* thrives on increased levels of glucose in saliva which increases the ability of *C. albicans* to adhere to oral mucous membranes.

Medicines

Prolonged use of antibiotics depletes normal oral flora and enables proliferation of *C. albicans* in the oral cavity. In asthmatic patients due to use of steroid inhalers, steroid aerosols interfere with the normal balance of microflora and favor the

proliferation of *C. albicans*, whereas systemic steroids cause suppression of the Candida.

Pseudomembranous Candidiasis

Pseudomembranous candidiasis or oral thrush is the most commonly diagnosed and most easily recognizable form of oral candidiasis. In this type of infection, the mucosa is covered in a white or yellow pseudomembrane consisting of fibrin, desquamated epithelial cells, inflammatory cells, and sometimes bacteria or food debris.¹⁴ The plaque is also heavily infiltrated by fungal hyphae. With some pressure, the membrane can be removed and underneath the mucosa is erythematous which is inflamed. If removal of the membrane reveals bleeding mucosa, the patient is most likely suffering from additional conditions such as erosive lichen planus or pemphigus, which are often associated with oral candidosis in affected areas.

The infection can often be asymptomatic and other times the patient will describe discomfort such as burning sensation, tenderness, or changes in taste when large parts of the mucosa are involved. Most commonly affected are the buccal mucosa, tongue, soft palate, and oropharynx.

Erythematous Candidiasis¹⁵

Erythematous candidiasis is probably the most common form of oral candidiasis. Due to its less pathognomonic appearance, however, it is not as easily diagnosed as its pseudomembranous counterpart. Erythematous candidiasis appears as red, more or less circumscribed lesion in the hard palate or dorsum linguae. An ill-fitted denture is also a contributing factor, as repeated trauma against the mucosa can cause an increase in penetration of Candida antigens and toxins. The lesion is restricted to the mucosa covered by the denture and is typically asymptomatic.

When erythematous candidiasis affects the tongue, a smooth red patch appears where the filiform papillae atrophy. If this patch is round or oval, and is located in the middle of the tongue, it is called median rhomboid glossitis or central papillary atrophy. This type of lesion may be caused by bacteria as well as Candida and other fungi, so the etiology is not completely clear. Predisposing factors for this particular type of lesion is smoking and the use of steroid inhalers.

Linear Gingival Erythema

Linear gingival erythema is a specific type of oral fungal infection that most frequently affects patients with HIV. The lesion is red band stretching along the gingival margin, and can be mistaken for gingivitis. Though the diagnostic criteria are not entirely clear, linear gingival erythema is defined as a nonplaque-induced gingivitis presenting a distinct erythematous band of at least 2 mm along the margin of gingivae, with either diffuse or punctuate erythema of the attached gingivae. Improved oral hygiene, even with regular professional cleaning, is not an efficient treatment. The fungus *Saccharomyces cerevisiae*, *Candida dubliniensis*, and opportunistic bacteria are thought to be the pathogens associated with this type of lesion.

Hyperplastic Candidiasis

Hyperplastic candidiasis is the least common form of oral candidiasis, but its malignant potential makes it an important one. It is also called candidal leukoplakia, and like ordinary leukoplakia, it appears as white lesion that cannot be rubbed off. Its appearance varies greatly, from small translucent, slightly raised lesions, to large, plaque-like areas that feel hard and rough on palpation. It is most commonly found on the buccal mucosa and is associated with smoking. Though it cannot be rubbed off, it can be separated from leukoplakia by microbiological tests, attempting treatment with antifungal medicine, or by taking a biopsy for histological examination. The fungi's hyphae often invade the oral epithelium which is hyperplastic. As previously mentioned, the lesion of hyperplastic candidiasis can sometimes turn malignant, but there is controversy regarding the importance of *Candida* species as a contributing risk factor.

Angular Cheilitis

Angular cheilitis is a multifactorial condition that can be caused by bacteria, especially *Staphylococcus aureus*, fungi, or combination of both. It is also affected by the loss of vertical dimension, vitamin B12 deficiency, and iron deficiency anemia. The connection between folic acid deficiency and angular cheilitis was made in 1971 by J.A Rose, who found a significantly higher occurrence of folic acid deficiency in patients with angular cheilitis. Folic acid therapy was also found to heal the lesions, though this occurred in only two of the patients, and thus was not conclusive.

Angular cheilitis affects the corners of the mouth and the surrounding skin and mucosa. Folds in the skin create a constantly moist environment, with perfect growth conditions for both bacteria and fungi. The result is a red, sensitive lesion, with fragile skin that can rupture when stretched, such as when opening the mouth wide during dental treatment. Treatment of the fungal infection will often cure the lesion, but if the vertical dimension is not improved (denture relining), or the nutrient deficiencies are not treated, the lesions will most likely recur.

Laboratory Diagnosis of Oral Candidiasis

Specimen Collection¹⁷

The specimen should be collected from any part of active lesion. Sufficient specimen under aseptic precautions should be collected. Sterile collection devices and containers should be used. The specimen should be appropriately labeled. All clinical specimens should be handled with care using standard precautions.

The specimen should be sent immediately or stored in a refrigerator at 4°C. Due to variety of clinical forms of oral candidiasis, several different types of specimen may be submitted to the laboratory.

Smear

Smears are collected from infected oral mucosa, rhagades, and fitting side of denture, preferably with wooden spatulas. Smears were fixed immediately and stained by Gram stain method

and Gridley's periodic acid-Schiff (PAS) technique. Yeast cells appear dark blue in Gram stain and red in PAS preparation.

Swabs

Swabs are collected from any part of the lesion inoculated on Sabouraud's dextrose agar incubated at 25°C and on blood agar at 37°C. Incubation at 25°C is done to ensure recovery of species growing badly at 35°C. Since mixed yeast infections are seen in oral cavity more frequently, particularly in immune compromised and debilitated patients, Pagano-Levin agar or Littmann substrate are useful supplements because they enable distinction of yeasts on the basis of difference in colony color.

Biopsy

Biopsy specimen should be taken for histopathological examination when chronic hyperplastic candidiasis is suspected.

Imprint Culture Technique¹⁸

This technique uses a sterile plastic foam pad of known size (2.5 × 2.5 cm), dipped in Sabouraud's broth, and placed on the restricted area under study for 30 to 60 seconds. Thereafter, the pad is placed directly on Pagano-Levin or Sabouraud's agar, and left in situ for the first 8 hours of at 37°C. Then, the candidal density of each site is determined by a Gallenkamp colony counter and expressed as colony-forming units (CFUs) per mm². Thus, it yields yeasts per unit mucosal surface. It is useful for quantitative assessment of yeast growth in different areas of the oral mucosa and is thus useful in localizing the site of infection and estimating the candidal load on a specific area.

Impression Culture Technique¹⁵

This method is totally a research tool and is useful in quantifying the relative distribution of yeast on oral surfaces such as teeth and palate. Maxillary and mandibular alginate impressions are taken and transported to the laboratory and casting is done in 6% fortified agar with incorporated Sabouraud's dextrose broth. The agar models are then incubated in a wide-necked sterile screw topped jar for 48 to 72 hours at 37°C and the CFU of yeasts estimated.

Salivary Culture Technique

This simple technique involves requesting the patient to expectorate 2 mL of mixed unstimulated saliva into a sterile universal container, which is then vibrated for 30 seconds on a bench vibrator for optimal disaggregation. The number of *Candida* expressed as CFU/mL of saliva is estimated by counting the resultant growth on Sabouraud's agar using either the spiral plating or Miles and Misra surface viable counting technique. The carriers and patient with oral candidiasis can be distinguished reliably on the basis of quantitative culture. Patients who display clinical signs of oral candidiasis usually have more than 400 CFU/mL.¹⁹

Oral Rinse Technique

It was described by Samaranayake.²⁰ The concentrated oral rinse culture technique has advantages over imprint

technique. It is simple to perform and it does not involve the clinicians in judgment of sampling size.

Paper Points

An absorbable sterile point is inserted to the depth of the pocket and kept there for 10 seconds and then the points are transferred to the transport medium, which also facilitates survival of facultative and anaerobic bacteria.

Commercial Identification Kits

Rapid commercial system such as Microstix-Candida and Oricut-N were used for diagnosis of oral candidosis in the clinical setting particularly when microbiology laboratories are not within easy access.²¹

Histological Identification

Demonstration of fungi in biopsy specimens may require several serial sections to be cut. Fungi can be easily demonstrated and studied in tissue sections with special stains. The routinely used hematoxylin and eosin stain candida species poorly. The specific fungal stains such as Gridley's PAS stain and Gomori's methenamine silver are widely used for demonstrating fungi in the tissues.

Physiological Tests¹⁷

The main physiological tests used in definitive identification of Candida species involve determination of their ability to assimilate and ferment individual carbon and nitrogen sources and formation of germ tube in the presence of human serum or better in egg white.

Phenotypic Methods²²

Serotyping should prove useful for studying the epidemiology of candidiasis in hospitalized patients.

Serotyping is limited to two serological groups (A and B), a fact that makes it inadequate as an epidemiologic tool. It has recently been shown that there can be wide discrepancies in results obtained with different methods of serotyping.

Resistogram Typing

This method is based on the differences in resistance of Candida isolates to six selected organic and inorganic chemicals incorporated in agar medium. Thirteen resistogram strains of *C. albicans* were found among isolates obtained from mouth. Resistogram do not correlate with pathogenic potential, and even though improvement have been made in the method, growth endpoints often present problems because of inoculum size, interpretation, and reproducibility.

Yeast Killer Toxin Typing

Owing to its reliability, economy, and versatility, this method can be used as an alternative biotyping method in laboratories lacking the financial and training resources. Initially, the method used nine killer strains, now it has expanded to using 30 killer strains and 3 antifungal agents, which appeared

to discriminate between sufficient number of strains of *C. albicans*.^{22,23}

Morphotyping

It is a simple and easy typing method using Sabouraud triphenyltetrazolium agar as a tool for differentiation and morphotyping of Candida subspecies. This method has been used in a study of morphotypes of 446 strains of *C. albicans* isolated from various clinical specimens.²⁴

Biotyping

It is a simpler method. This system is comprised of three tests, the API ZYM system, the AP20C system, and a plate test for resistance to boric acid. This system was found to distinguish a possible of 234 biotypes which can be distinguished by one- or two-dimensional gel electrophoresis. These methods have been used to separate *C. albicans* at the subspecies level.²⁵

Genetic Methods

The earliest molecular methods used for fingerprinting *C. albicans* strains were karyotyping, restriction endonuclease analysis, and restriction fragment length polymorphism. In arbitrarily primed polymerase chain reaction (PCR) analysis, the genomic deoxyribonucleic acid is used as a template and amplified to a low annealing temperature with the use of single short primer (9–10 bases) of an arbitrary sequence. Multiplex PCR has been used to identify various candida species. Real-time PCR has demonstrated that Candida biofilms can exert resistance to many commonly employed antifungals in clinical setting.

Serological tests for detection of invasive candidiasis agar gel diffusion, whole cell agglutination, and counterimmunoelectrophoresis are of lesser importance. Candida enolase antigen or antibody detection are of importance for differentiating colonization and oral candidiasis and they are found in biofilm also.²

Immunodiagnosis

The use of specific antibodies labeled with fluorescent stain permits causative organisms to be diagnosed accurately within minutes. However, the preparation of specific antisera and purified polyclonal or monoclonal antibodies entails a much more extensive technical outlay, so the application of these reagents need only be considered when a very precise diagnosis is of therapeutic consequence.

Management

Assessment of predisposing factor plays a crucial role in the management of candida infection. Mostly, the infection is simply and effectively treated with topical application of antifungal ointments. However, in chronic mucocutaneous candidiasis with immunosuppression, topical agents may not be effective. In such instances, systemic administration of medications is required.

Treatment: When topical therapy does not show good result then start with systemic therapy because failure of drug response is the initial sign of underlying systemic disease. Follow-up after 3 to 7 days is important to check the effect of drugs. Always continue the treatment for 2 weeks after resolution of the lesions. Main goals of treatment are to identify and eliminate possible contributory factors, to prevent systemic dissemination, to eliminate any associated discomfort, and to reduce load of *Candida*.⁴

Primary Line of Treatment

Nystatin is the drug of choice as a primary line of treatment, and for the mild and localized candidiasis other drugs includes clotrimazole which is available as lozenges and amphotericin B as oral suspension.

Nystatin: It is available as cream and oral suspensions. It is to be applied four times a day and allowed to act approximately for 2 minutes in the oral cavity and then it is to be swallowed. Nystatin shows no significant drug interaction or side effects.

Amphotericin B: Amphotericin B is available as lozenge (Fungilin 10 mg) and oral suspension (100 mg/mL) which is to be applied three to four times daily. It inhibits the adhesion of *Candida* to the epithelial cells. It is a nephrotoxic drug.

Clotrimazole: Clotrimazole reduces the fungal growth because this drug inhibits the synthesis of ergosterol which is a part of cell membrane of fungi. It is not indicated for systemic infection. This drug is available as creams and lozenges (10 mg).

Second line of treatment: The second line of treatment is used for severe, localized, immune suppressed patients and patients who respond poorly to primary line of treatment. Drugs mainly used in second line of treatment are ketoconazole, fluconazole, and itraconazole.

Fluconazole: It is used in oropharyngeal candidosis.

Itraconazole: It is one of the broad spectrum antifungal drugs. It is contraindicated in pregnancy and liver disease.

Prognosis: The prognosis is good for oral candidiasis with appropriate and effective treatment. Relapse, when it occurs, is more often than not due to poor compliance with therapy, failure to remove and clean dentures appropriately, or inability to resolve the underlying predisposing factors to the infection.

Conflict of Interest

None.

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