RESEARCH PAPER

A Comprehensive Review on Oral Candidiasis: Etiology, Diagnosis, and Management

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ABSTRACT

Oral candidiasis, also known as oral candidosis, is a common opportunistic fungal infection of the oral cavity primarily triggered by *Candida albicans*. Although *Candida* species are normal commensals in the oral microbiota, various predisposing factors such as immunosuppression, diabetes mellitus, poor oral hygiene, prolonged antibiotic or corticosteroid use, and nutritional deficiencies can lead to overgrowth and infection. The clinical presentation of oral candidiasis varies, ranging from pseudomembranous and erythematous forms to chronic hyperplastic and mucocutaneous types, each with distinct pathological features. Early diagnosis through clinical examination and laboratory methods, including microscopy and culture, is essential for effective management. Conventional treatment involves topical and systemic antifungal agents; however, increasing resistance to azoles and recurrent infections have prompted interest in alternative and adjunctive therapies. This review aims to summarize the current understanding of the etiology, classification, diagnostic approaches, and management strategies for oral candidiasis, with emphasis on emerging therapeutic options and preventive measures. A comprehensive understanding of the disease process and related risk factors is crucial for refining patient outcomes and reducing recurrence rates.

Keywords: Oral candidiasis, *Candida albicans*, antifungal therapy, diagnosis, risk factors, oral infection, management.

How to cite this article: Suryawanshi SS, Katkar NR, Magdum DU, Lohar SG, Gat TA, Kamble AA. A Comprehensive Review on Oral Candidiasis: Etiology, Diagnosis, and Management. Int J Drug Deliv Technol. 2026;16(54s): 499-512. DOI: 10.25258/ijddt.16.54s.46

INTRODUCTION

Oral candidiasis, also called candidosis, is one of the furthermost common opportunistic infections that affect the mouth. It is mainly caused by Candida albicans and other species belonging to the Candida family. Usually, the condition appears as a mild infection of the oral mucous membranes, but in some cases, it can become persistent, recurrent, or difficult to treat. This infection is more likely to occur in elderly individuals, people with various underlying health conditions, or those with weakened immune systems.[1] Although more than 150 species of Candida have been identified, about 95% of oral candidiasis cases are caused by Candida albicans.[2] Other species that can also cause infection include Candida dubliniensis, Candida glabrata, Candida tropicalis, Candida parapsilosis, Candida krusei, and Candida guilliermondii can causes infections. Candida colonization usually begins at birth and is most common during infancy and old age.[3] In adults, certain oral conditions such as dry mouth (xerostomia), leukoplakia, and lichen planus, as well as the use of removable dentures, can promote colonization. These dentures often support the formation of biofilms, which are difficult to remove completely.[4]

People who have received chemotherapy, corticosteroids, or antibiotics are more likely to experience increased Candida colonization. This risk is also higher in individuals with diabetes, those who are hospitalized, and people living with HIV.Candidiasis develops when the natural balance between Candida and the host is disturbed. Such disruption can occur due to changes in the oral microbiota (dysbiosis) or damage to the physical and chemical barriers that normally protect the mouth. Fungal colonization and invasion can be facilitated by contemporary medical procedures such as hemodialysis, parenteral feeding, organ transplantation, antineoplastic treatment, and the use of central venous catheters. Different groups have varying rates of oral candidiasis, which is mostly caused by Candida albicans. Approximately 45% of newborns, 45–65% of children, 30–45% of healthy adults, 50–65% of long-term denture wearers, 65–88% of residents of acute and long-term care facilities, 90% of acute leukemia patients receiving chemotherapy, and up to 95% of people with HIV are among the reported rates.[5-10]

Systemic candidiasis is associated with a high mortality rate, ranging from 71% to 79%.[11] It is essential for clinicians, particularly those treating older adults, to be aware of the risk factors, diagnostic criteria, and appropriate management of oral candidiasis. A recent study highlighted

that 30% of clinicians reported they would prescribe nystatin for oral candidiasis at the request of assistant staff, even without examining the oral cavity. Such practices may lead to misdiagnosis, overlooked underlying pathologies, and failure to address predisposing factors, ultimately increasing the risk of recurrent infection. In recent decades, the incidence of oral candidiasis has increased due to the growing population of immunocompromised and medically compromised patients. Diagnosis is typically based on clinical features, supportd by microscopic examination or culture of oral swabs.[11-22]

CLASSIFICATION

Oropharyngeal candidiasis can appear in several forms. Some of the common types include acute pseudomembranous, acute atrophic, and chronic forms such as angular cheilitis, median rhomboid glossitis, and chronic atrophic candidiasis. The transition from harmless colonization of Candida to an actual infection is marked by the appearance of noticeable lesions. [23,24]

Oral candidiasis can be classified into several main types based on its appearance and clinical features:

1. **Acute forms**
   - Acute pseudomembranous candidiasis (trush): Characterized by white creamy patches that can be wiped off, often seen in infants or immunocompromised individuals.
   - Acute erythematous (atrophic) candidiasis : Appears as painful red areas usually following antibiotics use or other disturbance in the oral flora.[25-27]

2. **Chronic forms**
   - Chronic hyperplastic candidiasis (candidal leukoplakia) : Present as persistent white plaques that cannot be scraped off often occurring on the buccal mucosa.[28]
   - Chronic atrophic (erythematous) candidiasis : Commonly associated with dentures wearers leading to redness and soreness beneath the dentures.[29,30]
   - Median rhomboid glossites : A smooth , red rhomboid shaped area on the midline of the tongue caused by chronic candida infection.[31,32]

3. **Angular cheilitis (stomatitis)**

Involve painful fissures or cracks at the corners of the mouth as frequently linked to candida infection and sometimes bacterial co infection.

Clinical Manifestation of Oral Candidiasis

Pseudomembranous Candidosis

Pseudomembranous candidiasis is characterized by the appearance of soft, creamy white or yellowish patches on the surface of the tongue and other areas of the oral mucosa. The infection presents as milk-curd-like, confluent white plaques that can be easily wiped away, revealing a raw, red (erythematous) surface underneath. Microscopic examination shows that polymorphonuclear leukocytes (PMNLs) and Candida albicans yeast cells and hyphae infiltrate the necrotic tissue and desquamated parakeratotic epithelial layers that form these plaques. As illustrated in the fungal hyphae can extend as deep as the stratum spinosum. Microabscesses and edema are observed in the outer epithelial layers, containing numerous PMNLs. In the deeper layers, acanthosis is evident, while the underlying connective tissue displays an inflammatory response composed of PMNLs, plasma cells, and lymphocytes.This condition most commonly affects infants, the elderly, and terminally ill patients, particularly those suffering from severe underlying diseases such as leukemia, HIV infection, or AIDS. These lesions can vary in size and are often easily wiped off, leaving behind a red, sometimes sore area underneath.[33-37]

Erythematous Candidosis

This condition is most often linked to the use of corticosteroids or broad-spectrum antibiotics. In recent years, it has also become more common among individuals with HIV, accounting for up to 50% of HIV-related candidiasis cases.Clinically, it appears as red, inflamed areas usually on the tongue's dorsum, the palate, or the buccal mucosa without the presence of white plaques. On the tongue, these lesions often show as smooth, depapillated patches. Although this form of the disease is relatively uncommon, the acute type tends to be notably painful. Histopathologically, acute erythematous candidiasis resembles other forms of the infection. Pseudohyphae invade and extend into the superficial layers of the epithelium, while the inflammatory response typically features neutrophils within the epithelial tissue and a lymphocytic infiltration in the underlying connective tissue.[38-41]

Hyperplastic Candidosis

Chronic hyperplastic candidiasis presents as distinct, raised lesions that can vary greatly in appearance and size. They may range from small, translucent whitish patches to large, thick, opaque plaques.Clinically, the nodular (or speckled) type appears as multiple white nodules set against a red, inflamed background, whereas the homogeneous type shows as a smooth, uniform white plaque that adheres firmly to the mucosa. Importantly, neither form can be wiped off.This condition most often affects the inner surfaces of the cheeks, tongue, and oral mucosa. Because chronic hyperplastic candidiasis is considered a premalignant condition and may show varying levels of epithelial dysplasia, performing a biopsy is essential for accurate diagnosis and further management. Histopathological analysis of the lesions shows epithelial hyperplasia and parakeratosis with uneven desquamation. Usually, Candida invasion is limited to the epithelium's outermost layers. A modest, ill-defined chronic inflammatory infiltration, primarily formed of lymphocytes and plasma cells, can be seen in the upper part of the connective tissue (corium). Furthermore, microabscesses small groups of polymorphonuclear cells frequently

develop in the epithelium directly below the regions that contain candidal hyphae. An increase in mitotic activity is frequently seen, despite the fact that the infection is typically limited to the stratum spinosum's basal and suprabasal layers. Epithelial dysplasia is also commonly seen in these cases.The nodular (or speckled) form of the lesion is particularly associated with a higher likelihood of epithelial abnormalities and should be carefully evaluated for potential precancerous changes.[42-45]

Candida-Associated Denture Stomatitis

Chronic redness and swelling of the mucosa that supports the denture especially beneath maxillary dentures is the typical feature of this condition. Most patients usually do not experience significant symptoms, although some may report mild discomfort, and angular cheilitis can occasionally occur.Several additional factors can contribute to the development of denture stomatitis, including bacterial accumulation, reduced salivary defense, and mechanical irritation. Approximately half of all complete denture wearers experience this condition Histological examination of the tissue beneath the denture often shows thinning of the epithelium, reduced keratinization, and either proliferative or degenerative changes. Compared with other forms of oral candidiasis, Candida invasion into the tissue is less common, and only a small number of yeast cells are typically found on the mucosal surface. Most Candida organisms tend to colonize the surface of the denture, with only a few hyphae observed. The condition may, in part, develop as a result of a hypersensitivity reaction.[46,47]

Angular Cheilitis

Clinically, denture stomatitis is often associated with angular cheilitis, which appears as painful, red, and cracked lesions at the corners of the mouth. The condition may also be related to deficiencies in vitamin B12 or iron. Additionally, angular cheilitis is frequently seen in patients with orofacial granulomatosis and can also occur in individuals with AIDS.[48]

Median Rhomboid Glossitis

Median rhomboid glossitis is identified by a smooth, red, elliptical or rhomboid-shaped area of papillary loss, located symmetrically along the midline of the tongue, just in front of the circumvallate papillae. In some cases, the lesion may appear raised, thickened, or lobulated. Histopathologically, Candida hyphae can be observed invading the superficial layers of the parakeratotic epithelium. The epithelial ridges (rete pegs) become elongated and extend into the underlying connective tissue (corium). There is also an infiltration of polymorphonuclear leukocytes within the epithelium and a lymphocytic response in the corium, which extends into the bases of the epithelial projections.[49-51]

Chronic Mucocutaneous Candidosis (CMC)

The term "chronic mucocutaneous candidiasis" describes a group of conditions characterized by long lasting Candida infections affecting the skin, mouth, and nail beds. In some cases, it can lead to granulomatous nodules on the scalp and face. The main clinical forms include chronic oral candidiasis, chronic cutaneous candidiasis, and chronic vulvovaginal candidiasis.Over 90% of patients with CMC have been found to have oral candidosis. The tongue may expand, crack, and get hyperplastic lateral margins with nodule. Angular cheilitis is often painful. Numerous primary immunodeficiencies, including severe combined immunodeficiency syndrome (SCID), myloperoxidase deficiency, hyperimmunoglobulin E syndrome, Nezelof syndrome (thymic alymphoplasia), DiGeorge syndrome (congenital thymic aplasia), and endocrine disorders, particularly Addison's disease and hypoparathyroidism, are linked to the CMC. The histological characteristics of CMC oral lesions are comparable to those of chronic candidosis. Although additional visceral involvement is uncommon, candidal infections can occasionally move into the pharynx, larynx, or esophagus.[52-55]

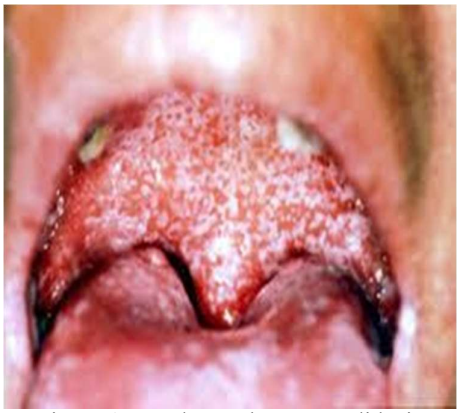

Fig no.1 Pseudomembrane Candidosis

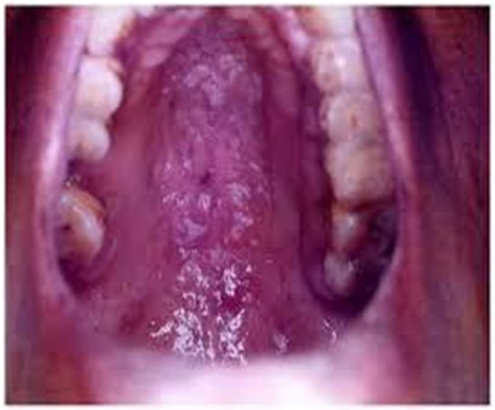

Fig no.2 Erythematous Candidiasis

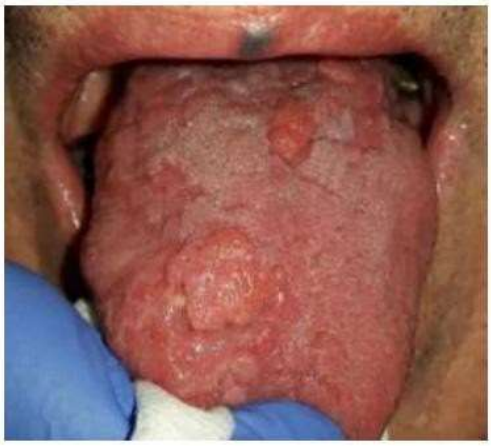

Fig no.3 Hyperplastic Candidosis

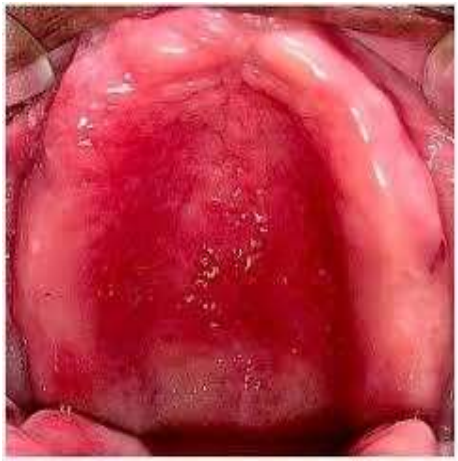

Fig no.4 Candida-Associated Denture Stomatitis

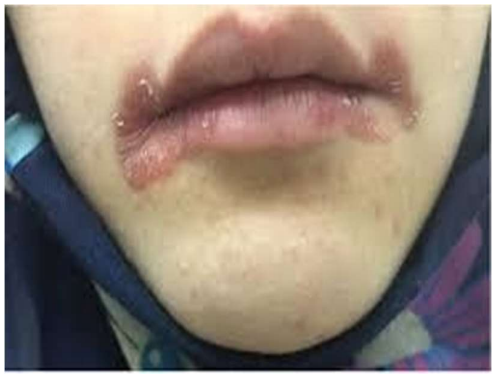

Fig no.5 Angular cheilitis

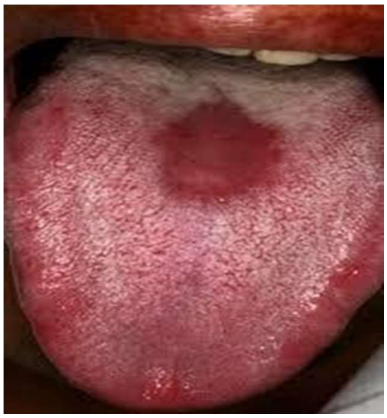

Fig no.6 Median Rhomboid Glossitis

Factors Affecting to Oral Candidiasis

Candida albicans can change from a benign commensal organism to a pathogenic one due to a number of risk factors. The increasing use of broad-spectrum antibiotics, immunosuppressive drugs, and indwelling medical devices like catheters are all contributing factors to the rising frequency of candidiasis. The danger has also increased due to the rise in solid organ transplant and hematopoietic stem cell operations.[56]

- **Local Elements**
  - Salivary dysfunction (decreased salivary antibacterial factors and quantitative and qualitative drops in saliva)
  - Dentures that don't fit properly (mucosal trauma) Topical corticosteroid therapy (steroid inhalers, topical gels, or rinse for the treatment of oral mucosal illness)
  - Smoking[57]

- **Systemic Elements**
  - Immunosenescence associated with anging (infants and elderly)
  - Antibiotics with a broad spectrum of action (change in local oral flora)
  - Systemic corticosteroid, biological immunomodulators and immunosuppressive treatments are example of immunosuppressive therapy
  - Chemoradition for cancer of the head and neck
  - Condition that compromises immunity (such as leukemia,graft-versus-host disease, chronic mucocutaneous candidiasis syndromes,hyper – immunoglobulin E (IgE) / Job's syndrome, thymica aplasia, Sjogren's syndrome and HIV/AIDS) neutritional defeciencies(vitamins A,B6,B12,C,folic acid,iron,zinc,magnesium,and selenium)
  - Diabetes, Addison's disease, and hypothyroidism are example of endocrine malfunction.[58]

Local Elements

Salivary Hypofunction

Saliva plays a crucial role in maintaining Candida albicans in its harmless, commensal state. It contains various antimicrobial proteins that prevent the yeast from adhering to the oral epithelial surfaces. Therefore, any reduction in the quantity or quality of saliva is often a key contributing factor in the development of oral candidiasis (OC). With an aging population and the increasing use of multiple medications, cases of salivary gland dysfunction are becoming more common. In addition, immune system compromise such as in individuals with HIV infection and iatrogenic factors like chemotherapy or head and neck

radiation therapy can significantly impair salivary gland function, further increasing the risk and severity of oral candidiasis.[59]

Denture Wearing

Damage to the oral epithelium creates an entry point for Candida infection, making factors such as prolonged denture use, poor denture hygiene, and mucosal trauma significant local contributors to the development of oral candidiasis (OC). The environment beneath dentures provides ideal conditions for Candida growth, leading to denture stomatitis (DS). This area is typically low in oxygen, slightly acidic, and lacks sufficient saliva all factors that promote secreted aspartyl proteinase (SAP) activity, enhancing fungal virulence. DS can occur in both healthy and immunocompromised individuals; however, it is particularly common and recurrent among older adults and those with weakened immune system. Studies indicate that nearly 40% of older denture wearers do not clean their dentures properly or fail to remove them at night. This poor denture hygiene significantly increases their risk by about twofold of developing serious, and potentially life-threatening, pneumonia. The most widely accepted system for classifying denture stomatitis (DS) is Newton's classification, introduced in 1962. It categorizes DS into three main clinical types:

- Type I : Pin-point erythema of the palatal mucosa
- Type II : Diffuse erythema affecting the palatal mucosa
- Type III : Granular-type inflammatory papillary hyperplasia

Research has also shown that patients with mixed Candida species biofilms are approximately five times more likely to experience severe forms of the disease, highlighting the importance of proper oral and denture hygiene in preventing DS.[60]

Topical Corticosteroid Therapy

Topical corticosteroids are the primary treatment for managing chronic inflammatory conditions of the oral mucosa. However, in more severe cases—especially when the disease extends beyond the oral cavity-systemic corticosteroid therapy is often required. Patients undergoing prolonged treatment with either systemic or topical corticosteroids frequently need antifungal prophylaxis to prevent opportunistic infections.Improper or excessive use of steroid inhalers can suppress phagocytic activity and cellular immunity, increasing the risk of developing oral candidiasis (OC). Fortunately, local immune function usually returns to normal once inhaled steroids are discontinued. Overall, the immunosuppressive effects of corticosteroid therapy alter the oral microenvironment, creating favorable conditions for secondary oral candidiasis to develop.[61]

Smoking

Tobacco smokers are known to have significantly higher levels of oral Candida colonization, which increases their risk of developing oral candidiasis (OC). However, the role of newer, non-traditional tobacco products-such as electronic nicotine delivery systems (ENDS)in the development of oral candidiasis remains unclear. Current evidence has not yet established a definitive causal link between ENDS use and oral candidiasis.Further research is needed to better understand the oral mycobiome of ENDS users and to determine whether these individuals harbor potentially carcinogenic Candida strains. Interestingly, recent in vitro studies suggest that ENDS exposure may activate certain C. albicans virulence genes, including SAP2, SAP3, and SAP9, which are associated with increased pathogenicity. Despite these findings, the exact mechanisms through which traditional tobacco smoking contributes to a higher risk of OC are still not fully understood.[62]

Systemic Elements

Age-Related Immunosenescence

Studies have shown that elderly individuals tend to have noticeably reduced activity in their salivary innate defense mechanisms, which play a key role in protecting the mouth. Similarly, infants being at the opposite end of the age spectrum are also more susceptible to developing oral candidiasis.[63]

Broad-Spectrum Antibiotics

Most cases of acute oral candidiasis occur as a result of using broad-spectrum antibiotics. These antibiotics can disrupt the normal balance of microorganisms in the mouth by reducing beneficial bacteria. This disturbance in the oral flora creates an environment that favors the overgrowth of Candida species.

HIV Infection and AIDS

It is well recognized that individuals living with HIV are significantly more prone to developing oral candidiasis (OC) and tend to exhibit higher levels of Candida colonization within the oral cavity. Among these species, Candida dubliniensis has been identified as having a strong association with OC development in HIV-positive patients.In this group, the severity of oral candidiasis has been shown to correlate directly with CD4 T-cell counts, reflecting the degree of immune suppression. Furthermore, compared with healthy individuals, HIV-positive patients experience a greater incidence of oral candidiasis, largely due to markedly reduced levels of protective antimicrobial peptides such as histatin-5 (Hst-5). Interestingly, linear gingival erythema has been observed as a distinctive clinical feature in HIV-positive individuals, often associated with Candida infection.[64]

Systemic Immunocompromise

Oral candidiasis (OC) can develop as a result of any systemic condition that weakens the immune system. This includes HIV infection, as well as disorders caused by developmental defects, autoimmune or immune-mediated mechanisms, endocrine dysfunction, malignancy, or iatrogenic factors.Some of the conditions associated with an increased risk of oral candidiasis include graft-versus-host

disease, Sjögren's syndrome, agranulocytosis, leukemia, diabetes mellitus, Addison's disease, hypothyroidism, patients undergoing chemoradiation or cytotoxic therapy, those taking immunomodulatory drugs, thymic aplasia, and chronic mucocutaneous candidiasis syndromes—all of which contribute to systemic immunosuppression.

Nutritional Deficiencies

According to reports, eating disorder states, malnutrition, and malabsorption are risk factors for oral candidiasis. In particular, a high-carb diet and hematinic deficits are thought to play a role in the development of oral candidiasis.This elevated risk was linked to the following deficiencies: zinc, iron, vitamins (A, B6, B12, and C), folic acid, magnesium, and selenium.[65]

Diagnostic Approaches for Oral Candidiasis Collection of Specimens

Since older or "burned-out" lesions often lack viable organisms, it is important to collect samples from active lesions for accurate diagnosis. The specimen should be collected under aseptic conditions, ensuring contamination is avoided. A sufficient quantity of the sample must be obtained and placed in sterile containers using sterile instruments. Each specimen should be properly labeled, and all clinical samples must be handled with universal precautions, as they may pose a potential biohazard risk.[66]

Smear Preparation

Smears are collected from the fitting surface of the denture, the corners of the mouth (rhagades), and affected areas of the oral mucosa, preferably using wooden spatulas. Immediately after collection, the smears should be fixed using a spray fixative or a 1:1 ether alcohol solution to preserve the sample.For examination, the prepared smears can be analyzed using the Periodic Acid-Schiff (PAS) staining method or the Gram staining technique, both of which help in identifying fungal elements in the specimen.[67]

Swab

Swabs are typically cultured on blood agar (incubated at 35°C), Sabouraud's agar (at 25°C or room temperature), and Pagano-Levin agar. They may also be placed on Littmann's substrate (at 25°C) or in another medium incubated at 35°C. To ensure recovery of yeast species that do not grow well 1at higher temperatures, incubation at 25°C is often recommended. Sabouraud's dextrose agar is the most commonly used primary culture medium. Pagano-Levin agar and Littmann's substrate serve as useful supplements because they allow differentiation of yeast species based on variations in colony color. This is particularly valuable since mixed yeast infections in the oral cavity are now recognized to be more frequent than previously thought, especially among immunocompromised or debilitated patients.[68]

Biopsy

If persistent hyperplastic candidiasis is suspected, a biopsy sample should be collected and submitted for histopathological examination to confirm the diagnosis.[69]

Imprint culture technique

The technique of imprint culture, Square, sterile plastic foam pads measuring 2.2 by 2.5 cm are dipped in peptone water and put on the study's restricted area for 30 to 60 seconds. The pad is then put straight onto; a container is used for incubation. The O Yeast-Ident system works by measuring enzyme activity with the help of chromogenic substrates. The Rough-N dip slide method operates in a similar way to the MC system but is more sensitive and provides more accurate results.[70]

Impression Culture Technique

This method involves taking alginate impressions of the mandible and maxilla, which are then transported to the laboratory and cast in a 6% enriched agar medium supplemented with Sabouraud's dextrose broth.After preparation, the agar models are incubated at 37°C for 48–72 hours in a wide-necked, sterile, screw-capped container. Once incubation is complete, the number of yeast colony-forming units (CFUs) is counted to assess fungal growth.[71]

Saliva

To get the best disaggregation, the patient is requested to expectorate two milliliters of mixed, unstimulated saliva into a sterile, universal container. The container is then vibrated on a bench vibrator for thirty seconds. The number of Candida, expressed as CFU/ml of saliva, is determined by counting the resultant growth on Sabouraud's agar using either the spiral plating method or the Miles and Misra surface viable counting approach. Patients with clinical signs of oral candidiasis usually have more than 400 CFU/ml.[72]

Paper Point Method

A sterile absorbent paper point is gently inserted into the depth of the periodontal pocket and left in place for about 10 seconds. After removal, the paper points are immediately transferred into a 2 mL vial containing Moller's VMGA III transport medium. This medium supports the survival of both facultative and anaerobic microorganisms, ensuring accurate microbial analysis.[73]

Identification by Histology

In some cases, several serial sections of a biopsy specimen may need to be prepared to confirm the presence of fungal elements. Fungi can be clearly visualized and studied in tissue sections when special staining techniques are used.Candida species do not stain well with the routine Hematoxylin and Eosin (H&E) stain. Therefore, specific fungal stains such as Periodic Acid–Schiff (PAS), Gridley's stain, and Grocott-Gomori's Methenamine Silver (GMS) are commonly employed. These stains highlight fungal

structures more distinctly, making identification in tissue samples easier and more reliable.[74]

Physiological Tests
The main physiological methods used to accurately identify Candida species involve evaluating their ability to utilize and metabolize different sources of carbon and nitrogen. These tests help distinguish between species based on their unique metabolic profiles. These tests are based on the metabolic activities, growth behavior, enzyme production, and biochemical characteristics of the fungal organism. Unlike simple microscopic examination, physiological tests provide detailed information about biological nature and pathogenic potential of Candida species. [75]

METHODS OF PHENOTYPING
Serotyping
Only two serotypes, A and B, are recognized for Candida species. However, because of this limited classification, serotyping is not considered a reliable tool for epidemiological studies. Recent research has shown that different serotyping methods may yield varying results, indicating inconsistency in this approach.[76]

Resistogram Typing
Resistogram typing, which evaluates antimicrobial resistance patterns, does not reliably reflect the pathogenic potential of Candida species. Although the method has seen some improvements, challenges remain, particularly regarding growth end-points, which can be affected by inoculum size, interpretation, and reproducibility.[77]

"Killer Toxin" Yeast Typing
To differentiate among 100 strains of Candida albicans, researchers initially used nine killer strains to generate a triple-code system, identifying twenty-five killer-sensitive types. Later, the method was expanded by incorporating thirty killer strains along with three antifungal agents, which improved its ability to distinguish a larger number of C. albicans strains.[78]

Biotyping
Williamson (1987) introduced a simpler identification method consisting of three tests: the APIZYM system, the API 20C system, and a plate test to assess resistance to boric acid. Using this approach, it was possible to differentiate up to 234 biotypes of Candida albicans. Among 1,430 isolates collected from oral, genital, and skin samples, 33 distinct biotypes were identified.[79]

Protein typing
Typing proteins are those that undergo non-lethal mutations during the yeast cell cycle, leading to variations in their physicochemical properties among different strains. These differences can be detected using one- or two-dimensional gel electrophoresis. Such techniques have been successfully used to distinguish Candida albicans at the subspecies level.[80]

Genetic methods
The earliest molecular methods used to identify Candida albicans strains included restriction fragment length polymorphism (RFLP), restriction endonuclease analysis (REA), and karyotyping. In arbitrarily primed polymerase chain reaction (AP-PCR), also known as randomly amplified polymorphic DNA (RAPD) analysis, genomic DNA serves as the template. A single short primer, typically 9 to 10 bases long with an arbitrary sequence, is used for amplification at a low annealing temperature.[81]

Serological tests
Serological tests for invasive candidiasis.[82]

Detection of Antibodies
Antibodies can be detected using several immunological techniques, including:

- **Slide agglutination –** a rapid method used to identify antigen-antibody reactions by visible clumping on a slide.
- **Immunodiffusion –** a technique where antigens and antibodies diffuse through a gel to form visible precipitation lines.
- **Phytohemagglutination –** a process that uses plant-derived lectins to detect immune responses based on cell agglutination.
- **Coelectrosyneresis –** a method that combines electrophoresis and diffusion to identify antigen-antibody interactions.
- **Immunoprecipitation -** is a laboratory technique used to isolate and study a specific antigen from a mixture using its corresponding antibody. In this process, an antibody binds to its target antigen to form an immune complex, which then precipitates out of the solution. This method is commonly used to identify, purify, or analyze proteins and their interactions within a sample.
- • **Latex agglutination -** is a technique used to detect nonspecific Candida antigens through visiblev clumping reactions on latex particles. Immunofluorescence tests - including types A and B, help identify Candida species by using fluorescently labeled antibodies that bind to specific fungal components.
- **Immunoblotting** is another method used to detect Candida cell wall components, such as cell wall mannoproteins (CWMP) and β (1,3)-D-glucan. It can also be employed to test for the presence of the Candida enolase antigen, an important marker in the diagnosis of Candida infections.[83]

Immunodiagnosis
Within minutes, specific antibodies labeled with fluorescent stains can accurately identify pathogenic organisms. However, producing purified polyclonal or monoclonal antibodies and specialized antisera requires advanced technical expertise and resources. Therefore, their use is generally reserved for cases where achieving a highly precise diagnosis has important therapeutic value (Olsen

and Stenderup, 1990).[84]
That said, the usefulness of antibody testing in diagnosing oral candidiasis remains uncertain, especially since more reliable, sensitive, and simpler diagnostic techniques are now available (Silverman et al., 1990).[85]

Traditional Methods of Treating Oral Candidiasis
The treatment of oral candidiasis depends on how severe the infection is. Topical antifungal agents, such as nystatin and amphotericin B (both polyenes), are commonly used for mild to moderate infections, while systemic antifungals like fluconazole (an azole) are prescribed for recurrent or severe cases. Polyenes act by damaging the fungal cell membrane, whereas azoles block the production of ergosterol, an essential component of the fungal membrane, thereby inhibiting growth. A newer class of antifungal drugs, echinocandins (such as micafungin and caspofungin), target the fungal cell wall and are effective against drug-resistant strains, though their use is limited due to high cost and their availability only as injectable formulations.[86]

Despite their effectiveness, antifungal drugs have several limitations, including drug toxicity, recurrence of infection, and the emergence of resistance, particularly in immunocompromised patients. Resistance to azoles, especially fluconazole, has become increasingly common, making treatment more challenging in these vulnerable populations.[87]

Denture Hygiene
Proper denture hygiene is essential for preventing and managing oral candidiasis. Effective cleaning methods include brushing with mild soap and soaking in disinfectant solutions. Among chemical disinfectants, chlorhexidine gluconate and sodium hypochlorite are the most commonly used. Chlorhexidine offers strong antifungal activity with minimal side effects, while sodium hypochlorite is highly effective at killing fungi and bacteria but may damage denture materials over time. Combining regular denture cleaning with antifungal therapy is the most effective way to reduce Candida colonization and prevent recurrence of infection.[88]

Other Options for Treating Oral Candidiasis
Because removable dentures can serve as reservoirs for infection, several alternative approaches have been explored alongside conventional antifungal therapy. Physical methods like microwave irradiation and photodynamic therapy have proven to be effective, fast, safe, and cost-efficient for disinfecting dentures. Additionally, emerging adjunctive treatments including vaccines, immunotherapy, and natural bioactive compounds are being investigated to support antifungal therapy and help reduce the risk of recurrent infections.[89]

Denture Disinfection Using Microwave Irradiation
Microwave irradiation is a simple and effective method for disinfecting dentures using just a household microwave and water. Research has shown that short exposures typically 3 minutes at 650W can successfully eliminate Candida species, including resistant strains such as C. glabrata and C. krusei, without affecting the mechanical properties of acrylic denture materials. Clinical studies have demonstrated that microwaving dentures significantly reduces Candida colonization on both the dentures and the palatal tissues, easing inflammation and achieving results comparable to topical nystatin treatment. Importantly, this method also lowers the risk of mycelial invasion and reinfection, common contributors to recurrent oral candidiasis.[90]

Benefits of Microwave Disinfection
Microwave disinfection offers several advantages over chemical or drug-based treatments. Its broad, non-selective antimicrobial activity targets not only Candida but also bacteria that can contribute to infection, such as Pseudomonas aeruginosa, Escherichia coli, and Staphylococcus aureus (including MRSA). The method works through a combination of effects: thermal impacts from water molecule vibrations, alterations in fungal cell membranes and metabolism, and possible non-thermal disruption of cell walls. Being a physical disinfection technique, microwave irradiation also avoids the development of antifungal resistance, making it a safe, effective, and reliable alternative or complement to conventional oral candidiasis treatments.[91]

Photodynamic Therapy for Oral Candidiasis and Denture Disinfection
Photodynamic therapy (PDT) is an innovative approach for treating infections like oral candidiasis. The process involves applying a photosensitizer (PS) to microbial cells, followed by exposure to a specific wavelength of light in the presence of oxygen. This generates reactive oxygen species that are toxic to the microbes and make the development of resistance unlikely. Various PS compounds, including phenothiazinium dyes (methylene blue and toluidine blue O), porphyrins, and natural substances like curcumin, have been successfully used against Candida species, even those resistant to fluconazole. PDT works by disrupting fungal cell membranes, inhibiting germ tube formation, and reducing biofilm production, making it a promising non-drug treatment option for managing oral candidiasis and disinfecting dentures.
PDT has proven effective against a range of Candida species, including C. albicans, C. tropicalis, and C. dubliniensis, in both laboratory and animal studies. Interestingly, the hyphal forms of C. albicans are generally more susceptible to PDT than the yeast forms. The therapy has also been successfully applied for denture disinfection in vitro, reducing fungal colonization without damaging acrylic materials. Animal studies further show that PDT is safe for oral tissues, causing less epithelial damage and fewer inflammatory responses, highlighting its potential as a gentle yet effective treatment for oral candidiasis.[92-95]
Despite some limitations, clinical studies have shown encouraging results. PDT using Photogem or methylene blue combined with LED or laser light effectively reduced

Candida on dentures and palatal tissues, achieving results comparable to topical nystatin. Animal studies have also highlighted the potential of curcumin-mediated PDT against Candida biofilms. While PDT offers a non-drug, resistance-free alternative for managing oral candidiasis, further clinical research is needed to confirm its effectiveness and optimize treatment protocols.[96]

Supplementary Approaches for Oral Candidiasis

Immunotherapy offers another potential strategy for managing candidal infections, especially in high-risk patients whose weakened immune systems may limit the effectiveness of antifungal drugs. Advances in understanding the body's immune defenses against fungal pathogens have enabled the development of therapies that use antibodies and cytokines to boost host protection against Candida.Most of the research on immunotherapy is still at the preclinical stage, primarily involving animal models. Only a few clinical studies have been conducted, and these have mainly explored immunotherapy as a complementary treatment alongside conventional antifungal medications rather than a standalone therapy.[97]

Vaccine Research for Candida

Researchers are also exploring vaccines against Candida using live attenuated strains and cell wall antigens. Preclinical studies, mostly in mice, have shown promising results. However, humans naturally carry Candida species as commensals, meaning they live in the body without causing disease, unlike in controlled mouse models. Additionally, the human immune system differs significantly from that of mice, making it challenging to translate these findings directly to humans.[98]

To develop effective vaccines for people, more diverse animal models are needed. Early-phase (Phase I) clinical trials are beginning, but progress faces hurdles, including the high cost of producing antigens under proper manufacturing standards and limited commercial interest in funding such trials.[99]

Management

Effective management of oral candidosis begins with identifying and addressing the underlying risk factors, such as immune deficiencies, diabetes, and nutritional deficiencies like low iron, folate, or vitamin B12 levels. A comprehensive medical and dental history is crucial to guide appropriate treatment. Patients using corticosteroid inhalers should be advised to rinse their mouths after each use, and whenever possible, medications contributing to the condition should be replaced with safer alternatives. Emphasizing and maintaining good oral hygiene is equally important. When it's not possible to correct the underlying cause such as in individuals with HIV or those undergoing immunosuppressive therapy antifungal treatment becomes necessary, with the choice of medication depending on the infection's severity, the patient's overall health, and their ability to follow the treatment plan.[100]

For mild or localized cases of oral candidosis, topical antifungal agents like Nystatin oral suspension (100,000 IU/ml) are commonly prescribed. The medication is typically used four times daily for 7–14 days and continued for a few extra days after symptoms resolve to ensure complete recovery. However, because Nystatin contains a high amount of sucrose, it is not recommended for patients with diabetes or cancer. In such cases, Fluconazole (5 mg/ml) serves as a suitable alternative. Additionally, mouth rinses containing 0.2% chlorhexidine gluconate can help control fungal growth, though they should be used at least 30 minutes apart from Nystatin to avoid reduced effectiveness. If topical treatments fail to produce results, it may indicate an underlying systemic condition, requiring systemic antifungal therapy with Fluconazole, which is effective due to its excellent penetration into saliva and oral tissues.[101]

The management of denture stomatitis involves a combination of antifungal medication, maintaining proper oral and denture hygiene, and ensuring that dentures fit correctly. Patients are advised to remove their dentures at night and clean them thoroughly using chemical or antimicrobial cleansers, such as alkaline peroxides or hypochlorites, to help reduce fungal buildup. Dental professionals play a key role in diagnosing and managing the condition through clinical examination, cytology, or culture tests. If topical antifungal treatments fail to provide relief, systemic antifungal therapy should be considered, and patients should be evaluated for any underlying systemic conditions that might be contributing to the infection. Regular follow-up appointments are essential to monitor treatment effectiveness and prevent the infection from returning.Niosomal formulations improve both the efficacy and safety of nystatin. They serve as a promising alternative to liposomes and enable parenteral (injectable) administration through niosomal encapsulation, expanding therapeutic possibilities for antifungal treatment.[102]

Marketed preparations

Marketed Preparations for Oral Candidiasis with Antifungal Drugs:[103-105]

Table no.1 Marketed Formulation

Sr. No	Antifungal Drug	Brand Name	Manufacture	Dosage form
1.	Clotrimazole	Candid mouth paint	Glenmark pharma	Oral paint
2.	Clotrimazole	Clocip mouth paint	Cipla Ltd	Oral paint
3.	Clotrimazole + Lignocaine	Mycoderm – N	Zydus Candila	Mouth paint
4.	Clotrimazole	Candid mouth Gel	Glenmark	Oral gel
5.	Amphotericin B	Fungizone	Bharat Serums & vaccines	Oral suspension

6.	Miconazole	Micogel Oral Gel	Glenmark	Oral gel
7.	Miconazole	Daktarin oral gel	Johnson & Johnson	Oral gel
8.	Nystatin	Mycostatin	GlaxoSmithKline (GSK)	Oral suspension
9.	Nystatin	Nystat	Pfizer	Mouth Paint
10.	Fluconazole	Diflucan	Pfizer	Capsule
11.	Itraconazole	Candiforce100/200	Mankind pharma	Capsule
12.	Posaconazole	Posacad	Cadila Healthcare	Oral suspension
13.	Posaconazole	Posanol	Merck	Oral suspension
14.	Ketoconazole	Ketoderm	Sanofi	Cream

CONCLUSION

Oral candidiasis remains one of the most prevalent opportunistic fungal infections of the oral cavity, particularly affecting individuals with compromised local or systemic immunity. Although Candida species most notably Candida albicans are common commensals of the oral microbiota, a disturbance in host defense mechanisms and oral ecological balance can transform these organisms into pathogenic agents. This thesis has comprehensively reviewed the etiology, classification, clinical manifestations, diagnostic modalities, and management strategies of oral candidiasis, highlighting its multifactorial nature and clinical significance. The wide spectrum of clinical presentations, ranging from acute pseudomembranous and erythematous forms to chronic hyperplastic candidiasis and denture-associated stomatitis, emphasizes the importance of accurate clinical recognition supported by appropriate laboratory investigations. Advances in diagnostic approaches, including histopathology, culture techniques, and molecular methods, have significantly improved species identification and understanding of pathogenic mechanisms, thereby aiding targeted therapy.

Conventional antifungal agents such as polyenes and azoles remain the cornerstone of treatment; however, their limitations including drug toxicity, recurrence, patient non-compliance, and emerging antifungal resistance pose ongoing therapeutic challenges. The increasing prevalence of azole-resistant Candida strains underscores the urgent need for alternative and adjunctive treatment strategies. In this context, non-pharmacological approaches such as improved denture hygiene, microwave irradiation, and photodynamic therapy have shown promising results, particularly in managing biofilm-associated infections and reducing recurrence rates. Furthermore, emerging therapeutic avenues including immunotherapy, vaccine development, nanocarrier-based drug delivery systems, and natural bioactive compounds represent potential future directions for more effective and sustainable management of oral candidiasis. Nevertheless, most of these approaches remain in experimental or early clinical stages, warranting further large-scale, well-designed clinical trials to establish their safety, efficacy, and practical applicability. In conclusion, effective management of oral candidiasis requires a holistic approach that integrates early diagnosis, appropriate antifungal therapy, correction of predisposing factors, and preventive oral healthcare practices. Increased awareness among healthcare professionals, patient education, and interdisciplinary collaboration between dental and medical practitioners are essential to reduce disease burden, prevent recurrence, and improve overall patient outcomes. Continued research into host–fungal interactions and novel therapeutic strategies will be pivotal in addressing the evolving challenges associated with oral candidiasis.

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