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Review Article

Candidiasis and Oral Cavity: A Review

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ABSTRACT

Oral Candida is opportunistic pathogen. Oral candidiasis is one of the common fungal infections, affecting the oral mucosa and is caused by Candida albicans. Candida pathogenicity is facilitated by a number of virulence factors, the most important of which are those for adherence to host tissues and medical devices, biofilm formation and secretion of hydrolytic enzymes. Assessment of predisposing factors plays a crucial role in the management of candidal infection. Carefully recording the medical history is important Topical antifungal therapy is the recommended first line treatment for uncomplicated oral candidiasis.

Keywords: Candida, pathogenicity, predisposing, antifungal

INTRODUCTION

Oral infections caused by the yeast of genus Candida have been recognised throughout recorded history.[1] Oral Candida is opportunistic pathogen.[3] Oral candidiasis is one of the common fungal infection, affecting the oral mucosa and are caused by Candida albicans.[2] The fungus now known as Candida albicans was isolated by Bennet(1844) from the sputum of a tuberculosis patient.[15] Candida albicans are the normal components of oral microflora and around 30% to 50% people carry this organism.[11] Xerostomia, local trauma, malnutrition, use of broad spectrum antibiotics, denture users and presence of HIV predisposes to candidal infection.[10] Depending on the host defence mechanisms or local oral microenvironment, Candida can transform from a harmless commensal to the pathogenic organism causing oral mucosal infection.[3] Overgrowth of candida can lead to local discomfort, an altered taste sensation, dysphagia from oesophageal overgrowth resulting in poor nutrition, slow recovery, and prolonged hospital stay.[5] Although nystatin and amphotericin B are commonly used, fluconazole is proving to be very effective in the treatment of oral candidiasis.[4]

PATHOGENESIS

The most common fungal species responsible for invasive infections is candida species.[10] The genus Candida includes characteristically white asporogenous yeasts capable of forming pseudohyphae.[15] Seven Candida species are of major medical importance and of these C.albicans, C. Tropicalis, and C.glabrata are the most frequently isolated (more than 80%) from medical specimens.[6] C.albicans exist in the mouth in three different morphological forms : the yeast cell ,also called blastopore, the septate filamentous form called pseudohypha, and the non-septate filamentous form, the hypha.[16] There have been extensive research to

identify pathogenic factors in fungi, particularly in C.albicans. Candida pathogenicity is facilitated by a number of virulence factors, the most important of which are those for adherence to host tissues and medical devices, biofilm formation and secretion of hydrolytic enzymes.[17] In C.albicans, the yeast cell is commensal, does not invade the oral epithelium and in a healthy host, induces regulatory immune responses mediated by keratinocytes and epithelial immunocytes releasing into the local microenvironment many biological agents, which induce protective immune responses, preventing the development of clinical infection.[16] Virulence in C .albicans and other pathogens includes host recognition, which enables the pathogen to bind to host cells and proteins. Degradative enzymes play a special role in virulence.[17] The transition from commensal yeast form to pathogenic filamentous form occurs in response to local microenvironmental stress signals.[16]

Table 1-Predisposing factors for oral candidiasis:[1,5,6,11,16]

LOCAL FACTORS	SYSTEMIC FACTORS
Ill-fitting dentures, reduced salivary flow, high sugar diet, inhaled steroids, smoking, poor oral hygiene, oral cancer, leukoplakia, lichen planus, radiotherapy of head and neck	Malnutrition, iron deficiency, extremes of age, endocrine disorders, immunosuppressive conditions, broad spectrum antibiotics

Antimicrobial proteins in saliva such as lactoferrin, sialoperoxidase, lysozyme, histidine rich polypeptides, and specific anticandida antibodies, interact with the oral mucosa and prevent overgrowth of candida. The conditions which causes decrease salivary flow, such as Sjogren's syndrome, can cause this disease.[11] Drugs such as inhaled steroids can increase the risk of oral candidiasis by possibly suppressing cellular immunity and phagocytosis.[5] Topical, systemic and aerosolized corticosteroids are all important in this respect, and excessive use of antibacterial mouthwashes can also be followed by oral yeast infection.[6] The local mucosal immunity reverts to normal on discontinuation of the inhaled steroids.[5] Pancreatic juices aid in maintaining the integrity of mucosa of small intestine and protect it from parasites and microorganisms. In patients with chronic candidiasis, it is highly recommended to restore the normal hydrochloric acid, pancreatic enzyme levels to prevent development of candidiasis.[10] Prosthetic dentures predispose to infection with candida in as many as 65% of elderly people wearing full upper dentures.[11] Other factors are oral cancer, leukoplakia and a high carbohydrate diet. Growth of candida in saliva is enhanced by the presence of glucose.[5] A variety of nutritional factors, including deficiencies of iron, folic acid, and vitamins have been implicated in the pathogenesis of oral candidal infections. Host defence mechanisms are impaired by the malignant process and its chemotherapy, which in turn can lead to disordered numbers and dysfunction of polymorphonuclear and mononuclear phagocytes and to oral candidiasis.[6]

CLINICAL PRESENTATION

Pseudo membranous form: also known as oral thrush. Thrush forms soft, friable, and creamy plaques on the mucosa that can be wiped off, leaving a red, raw or bleeding, and painful surface. The buccal mucosa, palate and tongue are common locations. [7] Discrete white pseudo membranous patches that may become confluent are seen and they comprise candidal elements, desquamated epithelial cells, fibrin, inflammatory cells and debris.[16] Diagnosis is usually based on clinical criteria. Burning sensation in the mouth is present which increases on taking spicy food. Direct smear microscopic examination with potassium hydroxide and culture are helpful.[7] The clinical presentation of acute and chronic pseudomembranous candidiasis are indistinguishable. The chronic form emerged as a result of human immunodeficiency virus (HIV) infections as patients with this disease may be affected by a pseudomembranous candida infection for

a long period of time.[13] The infection has traditionally, been regarded as an acute condition, often affecting newborn babies where there is an immature immune system. In older individuals, acute pseudomembranous candidosis often occur when there is a nutritional limitation, local immune suppression (eg: steroid inhaler administration for treatment of asthma) or an underlying disease most notably HIV infection and AIDS.[9]

Erythematous form: also known as acute atrophic candidiasis. It appears as red, raw looking area which is tender.[10] It may arise as a consequence of persistent acute pseudomemebranous candidiasis. It is characterised by erythematous areas generally on the dorsum of tongue, palate or buccal mucosa. Lesions on the dorsum of tongue present as depapillated areas. Red areas are often seen in the palate in HIV disease.[6] Burning sensation can be present. A form of erythematous candidiasis that is especially common involves the hard palate and gingiva beneath a denture or removable partial denture.[8]

Hyperplastic candidiasis (chronic form): resembles leukoplakia, hence also known as candidal leukoplakia.[10] A white patch is present, that cannot be rubbed off and can affect any mucosal site.[16]

Angular cheilitis: There is crackling or ulcerations seen around the corners of mouth.[10] It manifests as erythematous fissures or macerations affecting both mucosa and skin at the corner of the mouth.[16] Both yeasts and bacteria (especially Staphylococcus aureus) are involved, as interacting, predisposing factors. However, it is very occasionally, an isolated and initial sign of anemia and vitamin deficiency, such as vitamin B12 deficiency, and resolves when the underlying disease has been treated.[6]

Median rhomboid glossitis: Midline glossitis, or glossal central papillary atrophy, is characterised by an area of papillary atrophy that is elliptical or rhomboid in shape, symmetrically placed centrally, at the midline of the tongue, anterior to circumvallate papillae.[6] It is made up of atrophic filiform paillae. Biopsy of this area usually yields candida in over 85% of cases. It tends to be associated with smoking and the use of inhaled steroids.[5]

Denture stomatitis: also known as chronic atrophic candidiasis, it is characterised by localised chronic erythema of tissues covered by dentures.[5] The most prevalent site for denture stomatitis is the denture bearing palatal mucosa. It is unusual for the mandibular mucosa to be involved. It is further classified into three types:

Type I is localised to minor erythematous sites caused by trauma from denture.

Type II affects a major part of denture covered mucosa.

Type III affects mostly denture covered mucosa and also central part of the palate.[13]

There is no apparent age limit and some studies show women are affected more frequently than men.[21]

Chronic mucocutaneous candidiasis: It is a group of different forms of the infection, some of which may have multiple features in common, although they can usually be seperated as entities. In general, it is characterised by chronic candidal involvement of the skin, scalp, nails and mucous membranes.[21] It is the term given to the group of rare syndromes, sometimes with a defineable immune defect, in which there is persistent mucocutaneous candidosis that responds poorly to topical treatment. These syndromes are Familial chronic mucocutaneous candidiasis, Diffuse chronic mucocutaneous candidiasis, Candidiasis Endocrinopathy syndrome, Candidosis thymoma syndrome.[6]

Oral candidiasis associated with HIV: More than 90% of acquired immune deficiency syndrome (AIDS) patients have had oral candidiasis during the course of their HIV infection, and the infection is considered a portent of AIDS development. The most common types of oral candidiasis in conjunction with HIV are pseudomembranous candidiasis, erythematous candidiasis, angular cheilitis

and chronic hyperplastic candidiasis.[13] The main cause of infection in HIV disease is the immune impairment, but candidosis is found approximately three times more frequently in patients who also have xerostomia. Recent studies have shown that oral Langerhans cells are infected by HIV (Braathen et al,1987) and may also play a role in candidosis.[6] Identification of the fungal pseudohyphae within exfoliative cytologic preparations, often utilizing periodic acid schiff and/or Papanicolaou stained preparations ,is the optimal standard for the diagnosis of all candidiasis, although the highest yield of positive cytology smears is with pseudo membranous candidiasis. Oral manifestations, especially candidiasis, has been found to be significantly correlated to a reduced CD4 cell count below 200 cells/mm^3.[12] Mc Carthy et al(1991) have shown that 92% of patients with a diagnosis of AIDS have oral candidosis, compared with only 24% of HIV infected patients who had not developed AIDS.[6]

TREATMENT

Assessment of predisposing factors play a crucial role in the management of candidal infection.[2] Acquiring a thorough medical history is an essential component in the management process.[1] Potentially malignant oral disorders lesions associated with Candida should be treated with great caution as it shows a higher rate of malignant transformation.[3] General treatment guidelines include after the completion of early diagnosis, the correction of predisposing factors or underlying disorders, maintaining good oral hygiene, using antiseptic agents, such as Chlorhexidine, as well as removing dentures at night.[4] Topical antifungal therapy is the recommended first line treatment for uncomplicated oral candidiasis and where systemic treatment is needed topical therapy should continue as this reduces the dose and duration of systemic treatment required.[5] In the 1990s,the introduction of the two azoles, fluconazole and itraconazole, represented a considerable advance in antifungal therapy. However, the use of fluconazole is hampered by its narrow spectrum, and the use of itraconazole is limited due to absorption problems.[8] Topical antifungal agents are available as rinses, tablets and creams. Oral rinses are useful for patients with dry mouth who may have difficulty in dissolving tablets.[6] Polyenes include the drugs amphotericin B and nystatin and their mode of action is through direct binding to the sterol ergosterol found within fungal cell membranes. Polyene binding to ergosterol induces leakage of cytoplasmic contents, leading to fungal cell death.[1] Nystatin represents an antifungal antibiotic with fungicidal effect, significantly against yeasts of Candida, Rhodotorula, and Trichosporon species, sufficiently against Aspergillus species. It is a light yellow or brownish powder, hygroscopic, thermolabile, and sensitive to moisture, light, oxygen and extreme pH.[19] Nystatin can be given in following doses:[10]

Nystatin ointment 100,000 units/gram
Nystatin topical powder 100,000 units/gram
Nystatin oral suspension 100,000 units/gram

Nystatin constitutes primary line of treatment but since it has higher systemic toxicity, it is used only locally. Nausea and bad taste in mouth are the only side effects. It has been combined with tetracyclines for the prevention of superinfection (due to Candida) diarrhoea. However, routine use of such combination is not justified.[14] Amphotericin B is polyene antibiotic and is available as Lozenge(10mg) and oral suspension (100mg/ml) which is to be applied 3-4 times daily.[11] The polyenes possess a macrocyclic ring, one side of which has several conjugated double bonds and is highly lipophilic, while the other side is hydrophilic with many OH groups.[14] Amphotericin is not absorbed from the gut, and although it can be given intravenously(for systemic candidosis), there is considerable risk of toxicity, which may manifest as fever, vomiting and renal, bone marrow, cardiovascular and neurological toxicity.[6] The long term toxicity includes nephrotoxicity. It occurs

fairly uniformly and is dose related, its manifestations are azotemia, reduced glomerular filtration rate, acidosis, hypokalemia and inability to concentrate urine. Anemia can also develop.[14] Poor compliance, however, is common because of the bitter taste and multiple daily dosing.[18] Clotrimazole is an imidazole, it reduces the fungal growth because this drug inhibits the synthesis of ergosterol which is a part of the cell membrane of the fungi.[11] For oropharyngeal candidiasis,10 mg troche of clotrimazole is allowed to dissolve in the mouth 3-4 times a day. It is well-tolerated by most patients. Local irritation with stinging and burning sensation occurs in the same. No systemic toxicity is seen after topical use.[14] Ketoconazole forms second line of treatment and is absorbed from the gastrointestinal tract and metabolized in the liver and blocks ergosterol synthesis.[11] It is first orally effective broad spectrum antifungal drug, useful in both dermatophytosis and deep mycosis. The usual dose is 200mg once or twice daily(for two weeks),higher doses are sometimes required.[14] Adverse effects includes nausea, rashes, pruritus, and hepatotoxicity.[6] Fluconazole is a newer water soluble triazole having a wider range of activity than Ketoconazole.[14] This drug inhibits fungal cytochrome P450 sterol C-14 alpha demethylation.[11] Adhesion of Candida to epithelial cells widely recognised as the essential step in the process of candidal colonization and subsequent infection is significantly inhibited by fluconazole.[6] Clinical cure rates of 80-90% have been reported for fluconazole in children with oropharyngeal candidosis. A suspension formulation of fluconazole allows for more convenient dosing in patients who have difficulty in swallowing tablets or capsules.[18] Fluconazole is 94% absorbed, oral bioavailability is not affected by food, it is primarily excreted unchanged in urine. Fungicidal concentrations are achieved in nails, vagina and saliva; penetration into brain and cerebrospinal fluid is good.[14] In patients with chronic atrophic oral candidosis, fluconazole is effective, particularly when administered concurrently with an oral antiseptic such as chlorhexidine.[6] Dose is 50-200mg per day for 7-14 days(swish and swallow). Possible side effects are nausea, vomiting, abdominal pain, diarrhoea, headache, skin rash.[16]

Table2-list of some antifungal agents used in the treatment of oral candidiasis[14,16]

ANTIFUNGAL AGENT	DOSAGE
Nystatin(cream, oral suspension)	1-2 mL 4-5 times/day,7-14 days
Amphotericin B(Lozenges)	10 mg,14-21 days
Clotrimazole(Lozenges)	10 mg,14 days
Fluconazole(tablets)	200 mg per day,7-14 days
Ketoconazole(tablets)	200-400 mg daily,7-14 days
Itraconazole(capsules)	100 mg per day,7-14 days

CONCLUSION

Dental clinicians play an important role in the diagnosis and management of oral fungal diseases.[20] Carefully recording the medical history is important in identifying this clinical problem. Predisposing factors should be treated or eliminated where feasible.[9] In most of the cases, oral candidiasis is a cause of secondary superficial infection which can easily be resolved with antifungal therapy and proper oral hygiene maintenance.[11] A candidal infection may often be the first clinical sign of HIV infection.[12] It is preferable to start treatment with topical agents as their side effects and interactions with other drugs are less significant than those of systematically administered antifungals.[16]

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