

## Oral candidosis: a brief overview

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The advent of the human immunodeficiency virus infection and the increasing prevalence of compromised individuals globally have resulted in a resurgence of opportunistic infections such as oral candidoses. Despite the availability of a number of effective antimycotics for its management therapeutic failure is not uncommon. Hence this paper is an attempt to

provide an overview of clinical variants of oral candidosis and the usage of antimycotics in the management of this condition.

*Key words:* Oral candidosis, anti fungal drugs

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### Introduction

The frequency of life-threatening fungal infections is rising globally and candidosis is by far the commonest oral fungal infection in humans, which manifests in a variety of clinical guises. These include pseudomembranous (thrush) and erythematous variants, *Candida*-induced denture stomatitis, linear gingival erythema associated with HIV infection to median rhomboid glossitis and angular stomatitis, possibly of multi-factorial origin.

The high incidence of oral candidosis may be due to the multiplicity of predisposing factors which facilitates the conversion of commensal *Candida* to a parasitic existence.<sup>1</sup> Hence, all forms of oral candidoses are considered opportunistic. The advent of the human immunodeficiency virus (HIV) infection has also resulted in a resurgence of oral candidal infections. Further, the increasing prevalence

of other compromised patient groups in the community, usage of broad-spectrum antibiotics, cytotoxics and corticosteroids, common endocrine disorders such as diabetes mellitus, and severe nutritional deficiencies have resulted in resurgence of oral candidosis as a relatively common affliction.

A number of effective antifungal agents administered either topically or systemically is available for the management of oral candidosis. These range from the polyenes to the azole group antimycotics, which includes the imidazoles and the triazoles. Despite the availability of these agents, therapeutic failure is not uncommon. The diluent effect of saliva and the cleansing action of the oral musculature often tend to reduce the availability of the antifungals below the effective therapeutic concentrations. Furthermore, *Candida* biofilms on mucosal and inert surfaces may also contribute to failure of drug therapy. Poor patient compliance due to frequent drug administration and associated adverse effects, coupled with possible underlying immunodeficiency can also impair therapy.

The following is a brief description of the clinical manifestations of oral candidosis together with common therapeutic agents that are used in the management of this condition.

### *Candida* and Clinical Manifestations of Oral *Candida* Infections

The most frequent fungal infections of the oral mucosa are those due to species of the genus *Candida*. *C. albicans* is considered the principal species associated with this infection. However non-*albicans* species such as *C.*

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*glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. guilliermondii*, *C. krusei* and *C. dubliniensis*, a recently described species, are also pathogenic to man.

It is generally accepted that oral candidosis can be divided into two broad categories as primary and secondary. Thus, candidal infections confined to oral and perioral tissues are considered primary, and disorders where oral candidosis is a manifestation of generalized systemic candidal infections are categorized as secondary.<sup>3,4</sup> The primary oral candidoses are sub-classified into three major variants viz: pseudomembranous, erythematous and hyperplastic, each of which may manifest as acute or chronic lesions.

### **PSEUDOMEMBRANOUS CANDIDOSIS**

This is classically an acute infection, but it may recur for many months or even years in patients using corticosteroids topically or by aerosol, in HIV-infected individuals, and in other immunocompromized patients. It may also be seen in neonates and among the terminally ill, particularly in association with serious underlying conditions such as leukemia and other malignancies. It appears as white patches on the surface of the buccal and labial mucosa, tongue and the soft palate. The lesions develop and form confluent plaques that resemble milk curd that can be wiped off to reveal a raw, erythematous and sometimes bleeding base.

### **ERYTHEMATOUS CANDIDOSIS**

Erythematous candidosis is associated with corticosteroids, broad spectrum antibiotics and recently with HIV disease. It may arise as a consequence of persistent acute pseudomembranous candidosis, or in HIV infection may precede pseudomembranous candidosis. It is considered the commonest variant of candidosis seen in HIV disease. Erythematous areas are seen on the dorsum of the tongue, palate, or buccal mucosa. Lesions on the dorsum of the tongue present as depapillated areas. Red areas are commonly seen in the palate in HIV disease.

### **HYPERPLASTIC CANDIDOSIS**

Hyperplastic candidosis or *Candida* leukoplakias are chronic, discrete raised lesions that vary from small, palpable, translucent, whitish areas to large, dense, opaque plaques, hard and

rough areas on palpation (plaque-like lesions). They may also present as homogenous or speckled lesions (nodular lesions) that do not rub off. *Candida* leukoplakias usually occur on the inside surface of one or both cheeks at the commissural areas and less often on the tongue. The condition is premalignant and shows varying degrees of dysplasia. Hence, biopsy is vital in its overall management. In a minority of cases, the condition has been associated with iron and folate deficiency and with impaired cell-mediated immunity.

In addition to the foregoing major variants there are a number of other lesions associated with *Candida* infection as described below.

### **CANDIDA-ASSOCIATED DENTURE STOMATITIS**

The characteristic presenting feature is a chronic erythema and oedema of the mucosa in contact with the fitting surface of the denture. It is caused by overgrowth of commensal *Candida* in between the denture surface and the palate, where natural salivary flow is restricted. The mucosa beneath the mandibular dentures is hardly ever involved. Apart from occasional soreness this condition is usually symptomless. However patients may complain of an associated angular stomatitis and burning or tingling sensation beneath the denture. Denture-induced stomatitis is not exclusively associated with *Candida*. Other factors such as bacterial infection, mechanical irritation, or rarely an allergic reaction to the denture base material have also been implicated.

### **ANGULAR STOMATITIS**

Angular stomatitis is characterized by soreness, erythema, and fissuring. It affects the angle of the mouth and is usually associated with denture-induced stomatitis. Both yeasts and bacteria (especially *Staphylococcus aureus*) are involved as interacting and predisposing factors. Angular stomatitis may also present as an isolated initial feature of anemia or vitamin deficiency, such as vitamin B<sub>12</sub> deficiency. Iron deficiency anemia and other vitamin deficiencies may predispose to angular stomatitis. The lesion may also be a result of maceration due to deep, occlusive folds of the skin at the angles of the mouth in individuals with reduced facial height caused by old age or ill-fitting dentures. However, it is seen in young individuals with HIV disease.

## MEDIAN RHOMBOID GLOSSITIS

Median rhomboid glossitis is characterized by an area of papillary atrophy that is elliptical or rhomboid in shape, symmetrically placed centrally at the midline of the tongue, anterior to the circumvallate papillae. The relevance of *Candida* to the etiology of median rhomboid glossitis has been controversial, as a mixed bacterial and/or fungal flora is associated with the condition.

## CANDIDOSIS AND IMMUNOCOMPROMIZED HOSTS

Candidosis is usually restricted to the skin and mucous membranes but may occasionally spread. It is also important to recognize that oral candidal infection can occasionally manifest as a result of systemic candidosis. However most of these complications [with the exception of acquired immunodeficiency syndrome (AIDS)] are rare where candidosis remains superficial, and patients usually do not die from disseminated candidosis. Oropharyngeal candidosis could rarely disseminate to cause *Candida*-associated osteomyelitis in HIV infection, and sometimes in diabetic patients.<sup>5</sup>

Chronic mucocutaneous candidosis is the term given to the group of rare syndromes, sometimes with a definable immune defect, in which there is persistent mucocutaneous candidosis which responds poorly to topical antifungal therapy. In general the more severe the candidosis, the greater the likelihood that immunological defects can be identified.

Since the first clinical definition of AIDS in 1981, the CDC/WHO have recognized oropharyngeal candidosis and candidal infection of the esophagus, trachea, bronchi and lungs as major opportunistic infections and important indicators of the disease. The main cause of oral candidosis in HIV infection is the immune impairment. However *Candida* itself may also induce immunosuppression, and this can influence the prognosis of HIV infection.<sup>6</sup> The manifestations of candidal infections in HIV infection are usually restricted to superficial candidosis with varying degrees of severity. The major clinical oral variants, namely pseudomembranous, erythematous and hyperplastic candidoses, have all been described in HIV infection. Thrush (pseudomembranous candidiasis) and the erythematous variants are the commonest candidal lesions in HIV infection. They may manifest for a variable time

period prior to the development of other life threatening opportunistic infections. *Candida* may also contribute to the development of linear gingival erythema (LGE) or necrotizing ulcerative periododontitis (NUP) in HIV-infected persons.<sup>7,8</sup>

## Treatment of Oral Candidosis

Management of oral candidosis can be usually accomplished with simple topical delivery of antifungals. If this fails treatment should also include systemic medications. However, in patients with recalcitrant infection, it is desirable to continue topical as well as systemic medications. This may allow a lower dose and reduced duration of systemic therapy as the latter carry the risk of toxicity because fungal cell metabolism is similar to that of mammalian cells. Most importantly, antifungal agents, however potent, may be rendered ineffective in the long term if the underlying predisposing factors are not attended to in the first instance. Thus, it should be remembered that antifungal agents are only an adjunct to overall management of oral candidosis.

Antifungal agents that are available for treatment of candidosis fall into three main categories. They are the polyenes (nystatin and amphotericin B) the azoles (miconazole, clotrimazole, ketoconazole, itraconazole and fluconazole) and the DNA analogue 5-fluorocytosine. The principal antifungals used against oral mycoses belong to the polyenes and the azoles.<sup>9</sup>

## POLYENE ANTIFUNGAL AGENTS

Two polyenes, namely amphotericin B and nystatin could be used for the treatment of oral candidosis.

## AMPHOTERICIN B

This drug acts by inhibiting fungi through an interaction with ergosterol. This effect results in the loss of membrane selective permeability and intracellular components which in turn causes impairment of barrier functions, leakage of cellular components and cell death. As mammalian cell membranes also contain sterols, this drug accounts for a certain degree of host toxicity. However the polyenes bind more effectively to ergosterol, the principal sterol in fungal membranes.<sup>12-14</sup> Amphotericin B is poorly absorbed from the intestinal tract

and is usually administered intravenously or topically.

Though not very popular, topical amphotericin B oral preparations (lozenges, mouthwashes, creams, ointments) are available for treatment of oral candidosis. While topical therapy may be useful in its own right in primary oral candidosis, it could be used as an adjunct to parenteral therapy in secondary candidosis which manifests both systemically as well as on mucosal surfaces.

The most common and most serious adverse effect of systemic amphotericin B is nephrotoxicity. Hypokalemia and mild anemia are also common. Other rare adverse effects include acute hypersensitivity reactions including anaphylaxis, fever and headache, vomiting, anorexia, backache, seizures and thrombophlebitis at the site of injection.<sup>12,13</sup> Amphotericin B may potentiate nephrotoxicity of other agents such as aminoglycosides and cyclosporin while concomitant administration of glucocorticoids may exacerbate electrolyte disturbances, especially hypokalemia. Mechlorethamine and other anticancer agents may potentiate the nephrotoxic and hypotensive effects of amphotericin B.<sup>14</sup>

Available preparations for oral delivery of amphotericin B include an ointment, suspensions, creams and lozenges. The oral dose for adults is 100-200 mg 6 hourly. Lozenges (Fungilin 10 mg) can be given 8 hourly to a maximum of 80 mg/day. Also 1 ml of oral suspension (Fungilin 100 mg/ml) retained in the mouth (after food) especially in contact with the lesion 8 hourly is recommended. Intravenous infusions can be administered with care to adults and children at 0.25 mg/kg daily.<sup>12</sup>

#### NYSTATIN

Nystatin has an identical mode of action as amphotericin B and is probably the most popular agent for treating superficial fungal infections caused by *C. albicans*. Nystatin is used topically in the treatment of infections caused by *C. albicans*.

Nystatin is available in the form of creams, tablets, suspensions, oral rinses, gels and pastilles. The ointment contains perfumes and other agents and is not suitable for intraoral use, but has been used for treatment of angular cheilitis. Nystatin tablets (500,000 IU) are commonly used for treatment of oral candidosis

and so are unflavored vaginal tablets (100,000 IU). The latter is highly efficacious when used orally as long as the patient is persuaded to take them; the bitter taste of the tablets, however, results in poor patient compliance.<sup>2</sup> The suspension can be used for young children or in patients where there is poor compliance, although its rapid clearance from the oral cavity results in concentrations falling to sub-therapeutic levels fairly quickly. Similarly the oral rinse is relatively ineffective, because of the short contact time with the oral mucosa. Further, it contains sugar and increases the risk of dental caries.<sup>2</sup> In contrast the pastilles and lozenges can be sucked slowly and hence have a longer duration of action. Additionally, the sweetened formulations of pastilles and lozenges result in better patient compliance and due to its prolonged retention pastilles can be expected to be a better fungicidal agent than the suspension. Nystatin pastilles are ideal for the treatment of *Candida* associated denture stomatitis and could be used to prevent outbreaks or recurrence of oral candidosis in HIV-infected patients. However as these are also sweetened with sucrose they will increase the risk of developing dental caries, and long-term use may be contraindicated in dentate, caries-prone individuals.

A number of topical preparations of nystatin can be used in the treatment of oral candidosis. These include dissolved vaginal tablets (100,000 IU) 1 tablet 3 times a day, dissolved pastille (100,000 IU) 1 pastille 4 times a day, ointment/cream to be applied to commissures 3 times a day, and oral suspension (100,000 units/ml) 4 times a day, continued for several days after clinical healing.

#### AZOLE ANTIFUNGAL AGENTS

These agents are classified into two groups:

1. Imidazoles: clotrimazole, econazole, fenticonazole, isoconazole, ketoconazole, miconazole, sulconazole and tioconazole.
2. Triazoles: fluconazole and itraconazole.

The azoles are increasingly becoming popular in the management of oral candidosis. In spite of the introduction of novel antifungal agents, fluconazole could still be considered the drug of choice in the treatment of oropharyngeal candidosis in HIV infection. The azole antifungals act by inhibition of cytochrome p-450 enzyme that is involved in cell membrane

synthesis in fungi. The principal target is 14-<sup>o</sup>demethylase, which converts 14-<sup>o</sup>methylsterols to ergosterol in the fungal cell membrane. Therefore they cause alteration of the fungal cell membrane by blocking the 14-<sup>o</sup>demethylation step in the synthesis of ergosterol, an important constituent of fungal cell membrane which thus becomes permeable to intracellular constituents and leads to alterations in a number of membrane-associated functions. Imidazoles, in addition, interfere with fungal oxidative enzymes to cause lethal accumulation of hydrogen peroxide. The selective toxicity of azoles is due to their differential affinity for mammalian and fungal cytochrome p-450.<sup>12-14</sup>

### CLOTRIMAZOLE

Clotrimazole has a broad-spectrum of activity, anti-candidal as well as anti-staphylococcal, and is primarily fungistatic. It is mainly used in the management of superficial infections caused by *Candida*. It is effective in particular in managing oropharyngeal candidosis, especially in the immunocompromized such as HIV-infected patients and recipients of renal transplants. As a cream it is particularly useful in the treatment of angular cheilitis, due to its dual action on both yeasts and staphylococci.<sup>2,10</sup>

When applied topically clotrimazole is well tolerated. Adverse reactions are minor and rare, and include local skin irritation, vomiting, and nausea. Abdominal cramps, increased urination and elevated liver SGOT levels have also been reported.<sup>13</sup>

Clotrimazole is available in the form of 1% cream which can be applied to commisures three times a day and oral troche (10 mg) to be used dissolved, 5 times a day. Other forms such as lozenges, vaginal creams and vaginal tablets are also available for topical use.<sup>14</sup> The most common method of delivery of clotrimazole in oral candidosis is the use of a troche, available in 10 mg units. Slow dissolution in the mouth is thought to result in binding of clotrimazole to the oral mucosa, from which it is gradually released to maintain fungistatic concentrations for several hours.

### MICONAZOLE

Miconazole, like clotrimazole, has a broad spectrum of activity against fungi, including *C. albicans*. It is also effective against some gram-positive bacteria such as staphylococci and

hence useful in the management of angular cheilitis where concurrent bacterial and fungal infection may be present.

Miconazole is used and is effective in all types of oral candidosis including chronic mucocutaneous candidosis. However, the use of miconazole systemically has been largely superseded by the availability of other less toxic drugs such as ketoconazole and fluconazole.

Side effects after topical use of miconazole are few and uncommon. Burning and skin maceration can occur following cutaneous use. Itching, burning, urticaria, headache and cramps have been associated with the use of vaginal preparations. The most common side effect after intravenous use is thrombophlebitis. Nausea may develop in some cases. Rarely, anaphylaxis and cardiotoxicity can occur.

Antifungal drugs of the azole group are known to enhance the anticoagulant effect of warfarin. Recently it has been reported that the concurrent use of miconazole oral gel for the treatment of oral candidosis resulted in potentially life threatening derangement of warfarin.<sup>15</sup>

Tablets, oral gel, intravenous injections, and topical and vaginal preparations are available for treatment. Miconazole cream is a very effective delivery mode for angular cheilitis lesions caused by *Candida* and *Staphylococcus aureus*.

### KETOCONAZOLE

Ketoconazole is effective against a wide spectrum of fungi and yeasts including *Candida* spp. Unlike other imidazoles, it is readily absorbed after oral administration, which is favored by an acidic pH. It has been used in the management of cutaneous, oral, esophageal, and vaginal *Candida* infections.<sup>14</sup> Ketoconazole has no place in the treatment of primary oral candidoses, and its main indication is in secondary oral candidoses such as in chronic mucocutaneous candidosis.<sup>10</sup>

The commonest adverse reactions to ketoconazole are gastrointestinal intolerance with nausea and vomiting. Hepatotoxicity is not uncommon but is generally asymptomatic with reversible elevation of serum transaminase. Care has to be taken during usage of ketoconazole as fatal hepatotoxicity and nephrotoxicity have been reported. Liver function tests should

be performed throughout any prolonged ketoconazole therapy, and treatment should be discontinued in patients with progressively increasing transaminase levels.<sup>6</sup> Ketoconazole blocks steroid synthesis in host cells, with subclinical adrenocorticosteroid deficiency. Depression of testosterone biosynthesis can manifest as painful gynecomastia, loss of libido and sometimes loss of hair.<sup>12</sup> It is also a potential teratogenic agent.

Many drug interactions are seen with ketoconazole. It is capable of decreasing the hepatic metabolism of non sedative antihistamines such as terfenadine and astemizole, which can lead to increased levels of the latter with resultant arrhythmias and tachycardia. Similarly ketoconazole can suppress the metabolism of cyclosporine leading to elevated concentrations and accompanying profound immunosuppression and renal dysfunction. Absorption of ketoconazole may be reduced by antacids and H<sub>2</sub>-receptor blockers such as cimetidine and ranitidine. Rifampin, a potent inducer of hepatic metabolizing enzymes can decrease ketoconazole concentration in serum.<sup>14</sup>

Tablets, suspensions and creams of ketoconazole are available for usage, and 2% cream could be applied to commisures three times a day in chronic hyperplastic candidosis. Depending on the infection 200-400 mg tablets once daily is the dosage for systemic use.<sup>2</sup>

#### OTHER AGENTS USED IN ORAL CANDIDOSIS

Chlorhexidine has been used as an adjunct in the management of oral candidoses. For instance, 0.2% chlorhexidine gluconate has been successfully employed as a mouth rinse in the treatment of *Candida*-associated denture stomatitis and in pseudomembranous candidosis, while 2% suspension is used as an overnight denture disinfectant. Chlorhexidine gluconate has a bimodal action on *Candida*. Firstly, it is fungicidal even at very low concentrations. Secondly, it is capable of significantly suppressing candidal adhesion to both inorganic and organic substrates. Due to its multifaceted anti-candidal action, mouth rinses containing chlorhexidine have been proposed as an appropriate alternative to conventional antifungals in the management of oral candidosis.<sup>18</sup> However, it is worth noting that chlorhexidine and nystatin should not be used simultaneously as they form chlorhexidine-

nystatin complexes rendering both agents ineffective against *Candida*.<sup>19</sup>

#### Conclusion

In the management of patients with oral candidosis especially the compromised, a sensible selection should be made from the antimycotic agents currently available. The mechanism of action of the drug is a vital factor when treating patients who are chronically immunocompromised, such as those with HIV infection, where azoles, especially fluconazole may be the drug of choice. The polyenes could be routinely used in empirical therapy of primary oral candidoses as the inappropriate use of the more useful azoles as the first choice drug may result in emergence of resistant strains thus rendering the latter drug worthless. Hepatotoxicity is common to most antifungals, and the potential for endocrine toxicity exists, particularly at high doses. Another consideration is the cost. However, by prescribing these agents according to their pharmacodynamic properties, it is possible to achieve maximal antifungal activity. An ideal antimycotic for treating oral candidoses is not yet available. But certain agents are better than others with respect to efficacy, tolerability, patient compliance, and cost effectiveness. Most importantly however, antifungal agents may be rendered ineffective if the underlying predisposing factors are not attended to in the first instance.

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### CME/CPD Questions

After you have completed reading the article *Oral candidosis: A brief review*, take the test given below. Circle T (True) or F (False) in the answer sheet (page 42) to show the correct answer to each question. Questions 11 to 20 are related to the content in this article.

11. Organisms other than *C. albicans* are NOT of major concern as pathogens in candidal infection in humans.
12. The classical clinical presentation of pseudomembranous candidosis is a recurrent infection in HIV-infected individuals, immunocompromized patients and the terminally ill.
13. The majority of patients who present with hyperplastic candidosis can be successfully treated with iron and folate supplements.
14. Allergic reaction to denture base materials or chemical irritation by incompletely processed denture materials is the primary cause of denture stomatitis.
15. Disseminated candidosis is a clinical presentation often observed in immunocompromized patients.
16. The resistance developed by the infecting organisms to the common antifungal preparations has made topical delivery of the therapeutic agent ineffective in the treatment of candidosis.
17. The degree to which Amphotericin B is absorbed through the intestinal tract is adequate for the satisfactory management of oral candidosis.
18. Nystatin in the form of suspensions or oral rinses produces adequate therapeutic levels of the therapeutic agent for treating patients with oral candidosis.
19. Newer antifungal agents have largely replaced fluconazole as a drug of choice in the treatment of oropharyngeal candidosis.
20. Ketoconazole is readily absorbed following oral administration, thus making it useful for treating a variety of clinical presentations of oral candidosis.