

Management of HIV-related oral candidiasis

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ABSTRACT

Opportunistic fungal infections account for a significant amount of morbidity associated with human immunodeficiency virus (HIV) disease. Oral candidiasis is one of the earliest premonitory signs of HIV infection and its diagnosis may have grave prognostic implications for the eventual development of full blown acquired immunodeficiency syndrome (AIDS). It is considered as an important marker of immune suppression and may be the initial manifestation of the disease in about 10% of HIV-infected adults. Careful history taking and detailed examination of the patient's oral cavity are important parts of the physical examination, and diagnosis requires appropriate investigative techniques. Early recognition, diagnosis, and treatment of HIV-associated oral lesions may reduce morbidity. This review is intended to provide information on clinical variants of oral candidiasis and management as dental care providers are likely to be among the first to recognize such manifestations.

Key words: Acquired immunodeficiency syndrome, clinical manifestation, human immunodeficiency virus, management, oral candidiasis

INTRODUCTION

Opportunistic fungal infections account for a significant amount of morbidity associated with human immunodeficiency virus (HIV) disease. The association of oral candidiasis with the HIV infection has been known since the advent of the acquired immunodeficiency syndrome (AIDS) pandemic. Oral candidiasis is one of the earliest premonitory signs of HIV infection and its diagnosis may have grave prognostic implications for the eventual development of full blown AIDS.^[1] Eight species of *Candida* are known to be pathogenic, especially in immunosuppressed persons: *Candida albicans*, *Candida guilliermondii*, *Candida kefyr*, *Candida tropicalis*, *Candida parapsilosis*, *Candida viswanathii*, and *Candida glabrata*.^[2] *Candida albicans* is the best known and by far the most common pathogen of the group.

It is a commensal organism that constitutes a very small proportion of the oral flora in about half of the population. However, under the influence of a wide variety of clinical conditions that affect the host's oral flora or immune response, *Candida albicans* or other *Candida* species can become pathogenic and cause various oral mucosal changes, collectively called oral candidiasis (candidosis). This review is intended to provide information on oral candidiasis and management as dental care providers are likely to be among the first to recognize such manifestations.

CLINICAL VARIANTS OF ORAL CANDIDIASIS

With the increasing frequency of oral candidiasis in HIV infection it has become evident that the disease may present as four distinct clinical variants: Pseudomembranous, erythematous, hyperplastic, and angular cheilitis.

Oral candidiasis in HIV infection presents in multiple oral sites.^[3] Cahn *et al.*,^[4] noted multiple foci in 60% of 105 HIV-positive Argentinian patients with erythematous candidiasis, and Mastrucci *et al.*,^[5] also found it in four of eight Californian children with HIV. One obvious reason for multifocal presentation of

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oral candidiasis in HIV may be the immature defense mechanisms and the virally induced severe T helper cell depletion seen in these individuals.^[1]

CLINICAL FEATURES

Erythematous candidiasis

It appears clinically as a red lesion most frequently affecting the palate and the dorsum of the tongue, with associated depapillation. In one study,^[6] the lesion was present on the hard palate in 60%, on the soft palate in 17%, and on the dorsum of the tongue in 57% of 66 patients with erythematous candidiasis; and, in another study^[4] 49% of 105 patients had this lesion on the hard palate, 42% in the soft palate, and 12% in the buccal mucosa. Prior to AIDS era, erythematous candidiasis was infrequently observed after broad-spectrum antibiotics or rarely, during corticosteroid therapy. It was held that erythematous appearance was a secondary consequence of shedding the plaque of pseudomembranous candidiasis, the primary event.^[1]

Pseudomembranous candidiasis

It presents as semiadherent, whitish yellow, soft and creamy, drop-like or sometimes confluent membranes removable from the mucosa with a gauze swab, leaving a red and slightly bleeding surface.^[1] The disease is usually acute, but in HIV infected cases it may, if untreated, persist for several months when the course appears more chronic. Pseudomembranous lesions may involve any area of the oral mucosa, but most frequently the tongue, hard and soft palate, and the buccal mucosa.^[1] In a study of 106 AIDS patients with this condition, 48 and 42% of the lesions were seen on the dorsum and lateral surface of the tongue, respectively; 20% on the hard palate, 19% on the soft palate, and 15% on the buccal mucosa.^[6]

Hyperplastic candidiasis

The hyperplastic form of candidiasis in HIV-infected cases is most often seen bilaterally on the buccal mucosa and rarely in the retrocommissural area, which is the classic presentation site in HIV-negatives. The lesions are characterized by irremovable whitish-yellow patches, and the lesions have been related to smoking. This is the least common variant of oral candidiasis in HIV-positives. The chronic hyperplastic candidal variant in HIV-positives or AIDS should be clearly distinguished from hairy leukoplakia which it may resemble. Indeed, on histopathologic examination

candidal hyphae can be demonstrated within the superficial epithelium of hairy leukoplakia lesions and *Candida* species can be recovered from its surface. However, hairy leukoplakia can be differentiated from hyperplastic candidiasis, due to the presence of characteristic histopathologic features as koilocytes.^[1]

Angular cheilitis

Angular cheilitis angular stomatitis is a disease of multifactorial etiology and it may be infective or noninfective in origin. AIDS and HIV infection are added to the list of its causative factors, as cumulative data of four studies^[7-10] indicate that one-eighth of HIV-infected persons present with angular cheilitis. Clinically, the lesions manifest as red fissured crusts with or without ulceration and could be accompanied by subjective symptoms of soreness, tenderness, burning, or pain. Although the infection is generally caused by *Candida* species and/or *Staphylococcus aureus*, to what extent these organisms are involved in HIV-induced angular cheilitis remains to be determined.^[1]

LABORATORY DIAGNOSIS

Confirmation of a clinical diagnosis of oral candidiasis depends on the laboratory identification of the pathogen by mycologic and/or histopathologic techniques. It is important to differentiate between commensal candidal carriage and frank oral candidiasis. Due to a variety of clinical forms of candidiasis a number of differing specimens such as smears, swabs, imprint samples, salivary samples, oral rinse samples, and biopsy specimens may be submitted to the laboratory.

MANAGEMENT OF HIV-RELATED ORAL CANDIDIASIS

Oral candidiasis can be a frequent and significant source of oral discomfort, pain, loss of taste, and aversion to food. For some patients with HIV/AIDS, it may lead to secondary complications, such as esophageal candidiasis. For these reasons, antifungal prophylaxis may be justified in some high-risk patients. HIV-infected patients with CD4 counts <200 cells/mm³ may be at greater risk for oral candidiasis and thus may benefit most from antifungal prophylaxis. Oral candidiasis may be treated either topically or systemically. Treatment should be maintained for 7 days. Response to treatment is often good; oral lesions and symptoms may disappear

in a fairly short period (ranging from 2 to 5 days), but relapses are common because of the underlying immunodeficiency. As with other causes of oral candidiasis, recurrences are common if the underlying problem persists.

Topical agents

The standard antifungal drug regime for oral candidiasis consists of topical administration of either polyene antifungal agents - nystatin or amphotericin or azole compounds - imidazoles (clotrimazole).^[1,11] Topical agents are available in a variety of forms, including oral troches, pastilles, vaginal tablets, rinses, and creams.^[11] Topical therapy requires sufficient contact time (2 min)^[12] between the drug and the oral mucosa as well as the presence of adequate saliva to dissolve the medication in the case of troches, pastilles, and tablets. Sipping water while using the topical antifungal drugs may improve efficacy.^[11] Treatment duration varies from 7 to 14 days, with therapy minimally continued for 2-3 days, beyond the last clinical signs and symptoms. Topical agents have the benefit of few side effects at normal therapeutic doses because of their lack of gastrointestinal absorption.^[12]

Topical treatment may involve nystatin tablets 100,000 unit, three times daily used as lozenges or pastilles, or clotrimazole lozenges (10 mg, five times a day). If the patient has a dry mouth, sucking of the lozenges may be difficult and nystatin dissolved in milk may be used.^[1]

Angular cheilitis could be treated by topical application of amphotericin (cream or ointment) or nystatin (ointment) four times a day to both angles. If *S. aureus* is isolated from the angles then antibiotic sensitivity of the organism should be determined. If the organism is sensitive to fusidic acid then this should be applied daily, and it may be prudent to apply the ointment to the anterior nares to eliminate nasal reservoirs of the causative organisms.^[1] Miconazole gel (an imidazole) can be used if the organism is resistant to fusidic acid as it has some gram positive bacteriostatic action. Microbiologic swabs from the angles should be sent to the laboratory before, and during therapy to ascertain the infective agent and its response to chemotherapy. It is noteworthy that elimination of oral reservoirs of infection is critical to the successful management of angular cheilitis.^[1] Several topical drugs contain sweetening agents such as sucrose or dextrose, and long-term use of these preparations may lead to an increase in caries. The

use of a topical fluoride rinse or gel during therapy with these antifungal agents should be encouraged.^[11]

Gentian violet has sometimes been used in pediatric populations and chlorhexidine has been used as a prophylactic agent. Gentian violet causes purple staining of the oral mucosa and there are reports of an association with oral ulcers occurring in neonates.^[13] However, in a study in Zaire of persons with oropharyngeal candidiasis and AIDS, gentian violet eliminated clinical oral candidiasis in 42% compared with 43% in those who took ketoconazole and 9% in those who used nystatin mouthwash. The mechanism of action of gentian violet is unknown and its usefulness has not been studied in detail.^[11]

Chlorhexidine is used as a mouthrinse and is an effective antibacterial agent. Chlorhexidine is not absorbed from the gastrointestinal tract, and its primary side effects are staining teeth and the oral mucosa particularly the dorsal surface of the tongue. It has been shown to be effective as a prophylactic agent in preventing oral candidiasis in a group of patients undergoing bone marrow transplantation.^[11]

Systemic agents

In HIV-infected individuals the response to treatment with polyenes or clotrimazole is transient and relapses are very common. Such failures are mainly caused by the underlying immunodeficiency although poor patient compliance due to frequent administration, gastrointestinal upsets, unpalatable taste, and intolerance may also play a role. Due to these reasons systemic antifungals have been advocated for HIV-related oral candidiasis and two groups of drugs ketoconazole a derivative of the imidazole group and the newer fluconazole and itraconazole belonging to the biazole group are used for this purpose.^[1] They also have an advantage of once daily dosing and simultaneous treatment of fungal infections at multiple body sites. However, these antifungals have more side effects and selection requires consideration of important drug interaction.^[12] Systemic drugs include polyene antifungal agents - nystatin, amphotericin B, and azole compounds - imidazoles and triazoles and are available for both oral and intravenous delivery.

Nystatin

It is currently available as pastilles, vaginal troches, rinses, and creams. Nystatin oral pastilles, 200,000 units, are formulated for oral topical use. One or two pastilles should be dissolved slowly in the mouth

four or five times a day.^[14] The sweetening agent is sucrose. Nystatin oral suspension containing 1,00,000 units/ml is available and contains 50% sucrose. The rinse is often ineffective because of the short contact time with the oral mucosa. Topical therapy should continue for 14 days, and the effectiveness of treatment depends on compliance. In an unpublished study of oral candidiasis in HIV-infected persons, a controlled-release system called MOTS-nystatin that contained 200,000 units of nystatin was more effective than the nystatin pastille.^[15] Nystatin is also available as a cream or ointment containing 100,000 units/g, which can be used for the treatment of angular cheilitis. Some formulations contain both nystatin and triamcinolone. These combination creams may have the advantage of reducing the local inflammatory response. For persons who wear dentures, nystatin powder that is suitable for intraoral use is available for application to the fitting surface of the denture. Side effects from the use of nystatin are unusual as the drug is not well-absorbed from the gastrointestinal tract. Reported side effects include nausea and diarrhea. The use of nystatin pastilles for the prevention of oral candidiasis has also been investigated, and in those persons with a previous history of oral candidiasis, there was a trend toward the nystatin pastille, one or two a day, being more effective than placebo.^[16]

Amphotericin B

Amphotericin B is available as a cream and lotion for topical external use and as a systemic intravenously administered solution. Amphotericin lozenges are proved to be effective in the treatment of denture stomatitis.^[17] Intravenous therapy is usually reserved for systemic candidiasis and for some cases of esophageal candidiasis. It has been used to treat oral candidiasis that has been clinically nonresponsive to other antifungal agents. The intravenous solution has been used topically for the treatment of oral candidiasis that had not responded to other topical or systemic antifungal drugs. Amphotericin B solution was effective in the treatment of oral candidiasis associated with *C. glabrata*, which had not responded to fluconazole.^[18]

Azoles are thought to be fungistatic and to act by inhibiting the synthesis of ergosterol, which thereby changes membrane permeability. The oral azole drugs are effective against *C. albicans*, but may not be as effective against some *Candida* species, such as *C. krusei* and *C. glabrata*.

Imidazoles

Clotrimazole

Clotrimazole is available as a 10 mg oral troche (mycelex) that should be dissolved slowly in the mouth five times a day. Clotrimazole has also been shown to be effective used as a 10 mg troche taken three times a day, to prevent oral candidiasis in persons with leukemia who are undergoing chemotherapy. Nausea, vomiting, and pruritis have been reported as side effects. Clotrimazole is available as a cream that can be used for the treatment of angular cheilitis.^[11]

The systemic azoles are effective anti-candida agents because they inhibit the enzyme lanosterol 14 α -demethylase, which leads to destabilization of the fungal membrane.

Ketoconazole

Ketoconazole was the first truly, orally active azole antifungal introduced in 1979, and when administered, therapeutically useful blood and tissue levels has to be given. This drug has dramatically improved the therapeutic prospects of recalcitrant candidiasis such as chronic mucocutaneous candidiasis and candidal infections in compromised patients.^[1]

Oral ketoconazole (Nizoral) is normally given in doses of 200-400 mg daily, and it is usually recommended that the drug is taken with food.^[19,20]

Ketoconazole therapy is associated with a number of side effects such as nausea, rashes, pruritus, and hepatitis and of these the latter is arguably, the most significant. Because of the relatively high frequency of transient alterations in liver function (usually elevation in serum transaminase) it is essential to monitor liver function regularly in all patients on ketoconazole for more than a few days. Ketoconazole is also available as a topical cream that can be used for the treatment of angular cheilitis.^[11] Its use is also contraindicated with isoniazid, phenytoin, and rifampicin because of its decreased antifungal effect. Astemizole is also contraindicated if the patient is taking ketoconazole. Use of ketoconazole with HIV protease inhibitors that are normally metabolized through the cytochrome P450-3A4 enzyme system on which the ketoconazole acts may produce increased levels of the protease inhibitors. Ketoconazole is to be taken with food,^[21] and since gastric acid is essential for its dissolution and absorption it may not be adequately absorbed by persons with reduced gastric acidity.^[11] Periodic

liver function tests are recommended to monitor for hepatotoxicity.^[12]

Triazoles

Fluconazole (Diflucan) and itroconazole (Sporanox) are very recently introduced bis-triazole antifungals with different pharmacokinetic properties. They are water soluble, bind to proteins minimally, and are principally excreted through the kidney. Fluconazole has been shown to be effective at a dose nine times lower than ketoconazole in resolving palatal candidosis in rats. One of the drawbacks with both the imidazoles and the triazoles is the frequent relapse of the condition after clinical recovery and cessation of treatment.^[1]

Fluconazole

Fluconazole, a novel bis-triazole antifungal agent introduced in 1990, has been shown to prevent adhesion of *Candida* to buccal epithelial cells in healthy volunteers. It is available as an orally administered systemic tablet and as an intravenous solution. Increase in gastric pH does not affect the absorption of fluconazole^[20] and it carries less risk of hepatotoxicity; however, many of the same drug interactions are possible fluconazole is excreted mainly through the kidney and side effects include nausea, vomiting, abdominal pain, and skin rash. Several studies report effective therapy with 50 mg a day, 100 mg a day what is the duration, and 150 mg as a single dose.^[20]

In addition, systemic fluconazole prophylaxis may prevent esophageal and vaginal candidiasis, cryptococemia, histoplasmosis, and other deep fungal infections.^[12]

One study has shown that fluconazole 100 mg a day was effective in treating oral candidiasis and that there was a longer time to relapse in the participants who received fluconazole than in those who received clotrimazole.^[22] Other studies have shown that fluconazole 50 mg a day taken for 14-28 days is effective.^[23] For persons who are HIV-seropositive, therapy should be for a minimum of 14 days.

Relapses are common, and the optimum regimen using fluconazole to prevent oral candidiasis has yet to be established. Fluconazole has been investigated for use as a prophylactic agent in doses ranging from 50 mg a day and 50 mg every other day to 100 mg a day.^[24-26] In HIV-infected persons who had never had

oral candidiasis, 50 mg of fluconazole daily or every other day was equally effective. However, in those with a history of oral candidiasis, 50 mg daily was more effective in preventing candidiasis.^[27] Several cases of oropharyngeal candidiasis that are resistant to treatment with fluconazole have been reported. Many of these cases have been in patients with advanced HIV disease with CD4 counts <100^[28] and with severe immune suppression (e.g. CD4 < 50).^[29] Some of these cases are due to the emergence of species, such as *C. glabrata* that are known to be less susceptible to fluconazole.

Two isolates showed reduced susceptibility to fluconazole, but not to ketoconazole even though there had been no prior exposure to azoles.^[30] Other cases suggest that the strains are resistant to fluconazole, both clinically and by *in vitro* susceptibility testing.^[22,31,32]

The choice of therapy for these fluconazole-resistant cases is limited. Alternatives include higher doses of fluconazole (200-600 mg per day), itraconazole (200-400 mg per day), or ketoconazole (400 mg per day).^[33] Intravenous amphotericin B is reserved for failures. Recurrence of oral candidiasis in an HIV-infected person should not immediately be assumed to be a result of resistance to fluconazole because other azoles have also been associated with the development of resistance.^[34]

De Wit *et al.*,^[35] in a randomized, prospective, double-blind study compared the efficacy and toxicity of ketoconazole (200 mg daily) with fluconazole (50 mg daily) in 37 patients with either AIDS or AIDS-related complex (ARC). Clinical cure at end of therapy was seen in all fluconazole-treated patients and 75% of the ketoconazole group, and cultures were negative in 87% of the fluconazole group and 69% of the ketoconazole group. One of 18 fluconazole-treated and four of 19 ketoconazole-treated patients had transient rise in alanine or aspartate transaminase indicating hepatic affection. They concluded that, fluconazole was more effective than ketoconazole in the treatment of oral thrush among AIDS and ARC patients. The rate of relapse however, was high both after fluconazole as well as ketoconazole therapy. Subsequent prospective, randomized studies by Esposito *et al.*,^[36] in 50 HIV positive patients and Gritti *et al.*,^[37] in 16 AIDS and ARC patients confirmed the finding that fluconazole may be superior in treating AIDS-related oral candidiasis than ketoconazole.

A number of studies have been done employing different treatment regimes for fluconazole ranging from 50 mg per day for a few days or weeks to 400 mg given as a single dose. A regime of 50 mg per day (single dose therapy) of fluconazole for a period of 2-3 weeks has been found to be adequate to prevent or suppress oral candidiasis in HIV infected patients. Indeed 50 mg per day is the dosage recommended by the drug manufacturers for oral candidiasis. Nevertheless, either maintenance therapy or intermittent therapy with fluconazole is essential to prevent relapses after cessation of treatment although, some workers^[35] feel that maintenance therapy is not warranted and intermittent therapy is adequate.

Itraconazole

Itraconazole is a new antifungal agent and is available as a 100-mg capsule. Studies have shown that itraconazole 200 mg a day^[6,38] is as effective as ketoconazole 200 mg a day and as effective as clotrimazole 10 mg troches five times daily in the treatment of oral candidiasis. Those who were taking itraconazole had a faster response to therapy and a longer period before relapse than those taking clotrimazole.^[39] Plasma levels of itraconazole were reduced in persons with AIDS when compared with controls, which suggests that higher doses of itraconazole may be necessary for effective treatment.^[40] Side effects include nausea, headache, and altered results of liver function tests.

Drug interactions have been reported with the azoles, either because of interference with the absorption of the azole or because of alteration of liver enzyme functions. A partial list of these drugs includes antacids, H₂ receptor antagonists, sucralfate, phenytoin, rifampin, cyclosporin, terfenadine, astemizole, and warfarin.^[11]

Resistant flora of the candida species to bis-triazoles has been reported. Korting *et al.*,^[34] examined the susceptibilities of 62 oral *C. albicans* isolates from patients infected with HIV and they found three strains which were resistant to itraconazole, one strain resistant to ketoconazole, and another to flucytosine. The development of cross resistance of *C. albicans* to different imidazoles during treatment with one single azole derivative has been described previously.^[41] It is therefore important to keep the behavior of *C. albicans* in mind when planning treatment protocols involving azoles against candidiasis in HIV infected or any other

patient group.

CONCLUSION

Opportunistic fungal infections account for a significant amount of morbidity associated with HIV disease. Oral candidiasis which is often the first manifestation of HIV infection and dental care providers are likely to be among the first to recognize such manifestations. By recognizing such manifestations it will help to provide optimal and appropriate dental care, ensure early medical intervention, and ultimately prolong a patient's life and enhance its quality.

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