Review / Derleme

Oral Candidiasis & HIV Infection

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Abstract

The acquired immunodeficiency syndrome (AIDS) pandemic, caused by infection with human immunodeficiency virus (HIV) dramatically illustrates the awesome transmission capabilities of disease. Oral manifestations of HIV have been important in identification of patients harboring the HIV virus and in predicting the decline in their immune system 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. This review is intended to provide information on 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.

Keywords: oral candidiasis, candidosis, HIV, AIDS

INTRODUCTION

The association of oral candidiasis with the human immunodeficiency virus (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)Reference numbers in the text must be in paranthesis, not upper or lower case. Please correct all the numbers in the text [1]

Candida albicans is a common dimorphic organism that can assume either of two forms: yeast-like (blastospore) or filamentous (hypha).[2] In 1887 Audrey was the first to describe both morphologic forms as being one and the same organism with different forms dependent on the growth environment.[3] Berkhout[3] in 1923, proposed the name Candida from the Latin toga candida, which referred to the white robe worn by candidates for the Roman senate. Albicans also comes from the Latin albicare, which means "to whiten". Debate continues over the use of the terms candidiasis versus candidosis. Rippon[4] has suggested that the difference in terminology is geopolitically based, with candidiasis is distinctly American term and candidosis essentially European in origin. At least 20 genera and nearly 90 species of yeasts have been isolated from human beings and have been classified. 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*.[3] *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 like Immune suppression (e.g., HIV infection or systemic treatment of malignant neoplasm), Chronic salivary hypofunction (e.g., Sjogren's syndrome, head/neck radiation therapy, drug side effects), systemic antibiotic treatment, use of systemic or aerosol corticosteroid, uncontrolled diabetes mellitus, untreated anemia, candida infection of the newborn from the birth canal and Removable dentures (with or without any of the conditions above) 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).

EPIDEMIOLOGY

The profound immunodeficiency, particularly affecting the T helper cells during HIV infection precipitates a number of secondary infections in these individuals. Of these, infections by fungi are fairly common and candidiasis particularly affecting the oral mucosa is widely prevalent. The first documented patients with AIDS had oral candidiasis[5] and unexplained oral candidiasis feature prominently in individuals who eventually developed AIDS[6, 7, 8, 9, 10] In one study[11] of 62 HIV infected patients microbiologic recovery of oral *Candida albicans* isolates was 57.5% for Stage I patients; 76.5% for Stage 2 patients and 87.5% for Stage 3 patients.

Iosub et al.[12]found that 50% of 42 children with HIV infection or pediatric AIDS had oral and cutaneous candidiasis in the first year of life, as opposed to 10% of 20 children who were diagnosed as having AIDS after this period. They concluded, therefore, that in very young infants with HIV infection chronic mucocutaneous candidiasis may act as a warning sign for early and severe morbidity. In one study of HIV-infected homosexual and bisexual men who were followed from seroconversion, 4% developed candidiasis within one year, 14% within 2 years, and 26% within 5 years.[13]

Oral candidiasis, particularly the pseudomembranous variety of 'thrush' is not uncommon among otherwise healthy infants and surveys suggest an incidence not exceeding 7% and usually less than 5%.[14, 15, 16, 17] This is generally acknowledged to be due to the immature defense mechanisms of the newborn and it would appear this, together with HIV infection, may act in concert in precipitating severe morbidity, including the oral candidiasis associated with HIV infection.

The data in Table 1 illustrate the high prevalence of candidiasis in adults as well as children with HIV infection.

PATHOGENESIS

Adaptive Response of *Candida*

The primary characteristic of *Candida* that is believed relevant to its pathogenesis is its ability to undergo a morphological transition between yeast-like forms, which divide by budding, and long pseudohyphal or hyphal forms. Both candidal forms are present in the commensal state, found in 40% to 80% of healthy individuals, as well as in the disease state, in which Candida invades the superficial epithelial or endothelial cell layers of the gastroenteric, reproductive, and vascular systems.[36]

Candida as a Mucosal Pathogen

In candidiasis, mucosal infections of the oral cavity take two primary forms, pseudomembranous and erythematous. In the transition from the commensal to the infectious state, the yeast and hyphal cells become more adherent and invasive. Attachment to the mucosa and the subsequent penetration of superficial layers of the epithelium are in part mediated by interactions of cell-surface molecules of *Candida* with the cell-surface molecules of host cells and with molecules of the extracellular matrix (ECM).[36]

Secreted Aspartyl Proteinases as Virulence Factors

One specific set of *Candida* virulence factors, the secreted aspartyl proteinases (SAPS), may play a role in the invasion of the oral mucosa by degrading extracellular matrix (ECM) proteins surrounding the epithelial cells; inhibition of Saps reduces Candida invasion in vitro.[36]

HOST FACTORS ASSOCIATED WITH HIV-RELATED ORAL CANDIDIASIS

Oral candidiasis is a frequent and early manifestation of disease associated with the human immunodeficiency virus (HIV) and has been reported in more than 90% of patients with acquired immunodeficiency syndrome (AIDS). McCarthy GM[37] investigated factors associated with increased frequency of oral candidiasis in a population of 71 HIV- seropositive patients and the most important factors were advanced disease, xerostomia, and cell-mediated immunosuppression as indicated by a low CD4 lymphocyte count.

Immune Function

Increased frequency of oral candidiasis has been noted in patients with cell-mediated immunodeficiencies in the non-HIV-infected population. The principal effect of HIV on the immune system is the depletion of CD4 lymphocytes with advancing disease. As a result, there is a drop in the absolute CD4 count and a reversal of the CD4/CD8 ratio. Oral candidiasis occurs more frequently in HIV infected patients with low CD4 counts. Imam et al. [38] noted a hierarchic association; most oropharyngeal candidiasis occurred when the CD4 count was less than 300/mm^3, and esophageal candidiasis occurred when the CD4 count was less than100 cells/mm^3.

McCarthy GM[37] also found a statistically significant increase in the frequency of HIV-related oral candidiasis in patients with CD4 counts of less than 300 cells/mm^3. An increased frequency of oral candidiasis has also been found to be associated with a reversed CD4/ CD8 cell ratio.

Severe oral candidiasis has also been described in a patient with a low CD4 count, who did not have an HIV infection.[39] Cenci et al.[40] found that CD4 lymphocytes transferred from mice immunized with

Candida albicans provided protection against a challenge with *Candida* species.

Torssander et al.[41]noted a decreased number of CD4 cells in HIV-infected patients, with smears from the oral mucosa that showed pseudomycelial forms of yeast, compared with other HIV infected patients. There is evidence that mucocutaneous pathoses occur with increasing frequency with lower numbers of circulating CD4 lymphocytes. Sindrup et al.[42] found that HIV-related mucocutaneous lesions occurred twice as frequently in patients with a CD4 count of less than 200/mm^3. A significant association between the occurrence of HIV-related oral lesions and a CD4 count of less than 100/mm^3 has also been reported. Granulocytopenia of less than 1 x 10^9 cells/L can predispose to disseminated infection. However, HIV-infected patients usually have normal phagocyte function, and disseminated candidiasis is infrequent. Adhesion of C*andida. albicans* to epithelium is considered necessary for successful infection and this can be inhibited by saliva and enhanced by dietary carbohydrates. However, information regarding the role of diet in the pathogenesis of HIV-related oral candidiasis is lacking.[37]

Role of drugs

There is considerable controversy regarding the role of antibiotics in the etiology of candidiasis. Antibiotics are given to diseased persons, and the disease process may be a more important contributing factor than antibiotic use.

Corticosteroid use has been linked with the onset of candidiasis, and this may be due to impaired macrophage response to a lymphokine that stimulates phagocytosis.

Many HIV-infected patients have iatrogenic anemia as a result of zidovudine (AZT) therapy. McCarthy GM et al.[37] found that the presence of anemia was significantly associated with HIV-related oral candidiasis. However, AZT was provided only for patients in their study who had a CD4 count of less than 300/mm^3, and the apparent associations between AZT / anemia, and oral candidiasis may be largely explained by their association with CD4 count.

Xerostomia

Decreased salivary flow may predispose to oral candidiasis and can occur as a direct result of HIV disease. It may also be induced by drugs and radiotherapy affecting the salivary glands, and may occur as a result of dehydration, depression, or anxiety. Damaged tissue is particularly prone to infection with *Candida* species. Saliva provides mechanical cleansing and lubrication, which can reduce damage to the oral mucosa as a result of trauma.

Using multivariate logistic regression analysis, McCarthy GM et al.[37] showed that the presence of xerostomia was an independent and statistically significant predictor of HIV related oral candidiasis. It was also a better predictor than CD4 count (categorized as <300, 300 to 500, and >500 cells/mm^3), indicating the importance of saliva in the control of HIV-related oral candidiasis. Xerostomia was considered to be present if there was a subjective complaint of dry mouth and reduced pooling of saliva, and if the oral mucosa appeared dry on clinical examination.

Saliva contains antimicrobial proteins including lysozyme, lactoperoxidase, immunoglobulins, lactoferrin, and histatins. Histatins appear to have potent antifungal activity, and although these proteins may have the potential to protect against oral candidiasis, their roles have not been elucidated.[37]

Changes in salivary function of HIV-infected patients have been documented. Elevated levels of antimicrobial proteins in patients with HIV have been noted. However, Wray et al.[43] found that levels of IgA are lower in patients with oral candidiasis and that this is particularly marked in HIV-infected persons. There is some evidence that salivary IgA inhibits oral adhesion of *Candida albicans.* The benefits of this may be lost as pathogenic forms of *Candida* can produce proteinases to break down salivary IgA. Interactions between whole saliva and Candida are most relevant to the pathogenesis of candidiasis. It is difficult to investigate these because many of the constituents of whole saliva also interact.

Sociodemographic Factors

Increased susceptibility to candidiasis has been noted in very young or very old persons. These groups are rarely represented in studies of HIV infected patients in World Health Organization pattern I countries. HIV-infected patients older than 35 years were twice as likely to have oral candidiasis compared with younger persons, and this difference was statistically significant. This concurs with evidence of increased carriage of Candida species in middle-aged and elderly persons.

Marital status and risk group may influence the occurrence of oral candidiasis. McCarthy GM et al.[44] found that the never-married group of HIV-infected patients had a significantly lower frequency of candidiasis compared with the sometime-married group. These differences can be partly explained by the confounding effect of age. They may also reflect social practices or indicate that female-to-male transmission of *Candida* species may be occurring. The lowest frequency of oral candidiasis was noted in the homosexual risk group. This is in contrast to the results of Moniaci et al.[45] who found lower incidence of oral mycotic lesions in the heterosexual risk group compared with intravenous drug abusers and homosexuals.

Habits

Tobacco smoking may facilitate the invasion of oral epithelium by Candida species and has been associated with a reduction in salivary IgA. In a study by McCarthy GM et al.[44] the frequency of HIV-related oral candidiasis was higher in cigarette smokers and persons consuming more than 8.5 L of absolute alcohol per year, but these differences were not statistically significant. They found an increasing frequency of candidiasis with increasing values of plaque index, but the association was not statistically significant with their sample size.

Dentures

The use of dentures is associated with oral candidiasis and increased carriage of *Candida* species. McCarthy GM et al.[44] found that HIV-related candidiasis was less likely to develop in patients with dentures.

ANTICANDIDAL ACTIVITIES OF SALIVARY SECRETIONS

Salivary secretions play important roles in the maintenance of oral hard and soft tissues. Oral candidiasis is a greater problem in patients with chronic salivary hypofunction. The antifungal qualities of saliva have been traced to specific salivary proteins. Lysozyme, salivary peroxidase, and lactoferrin, which also occur in other tissues and body fluids, are minor salivary proteins with limited antifungal activity. In addition, immunoglobulins, specifically secretory IgA (sIgA), the predominant immunoglobulin of salivary secretions, may contribute to the antifungal activity of saliva, although precise data on sIgA's antifungal role are lacking. Recent discoveries in salivary research have led to the identification and characterization of a major group of salivary proteins with antifungal and antibacterial activities known as histatins, this low-molecular-weight, histidine-rich proteins are present in both parotid and submandibular/sublingual secretions of humans and certain subhuman primates.[36]

Anticandidal activity of Histatins

The major proteins of this family are histatins 1, 3, and 5, accounting for 85% to 90% of all histatins. The dimorphic nature of *Candida albicans* necessitates that bioassays measure fungicidal effects on both blastoconidia and germinated cells. In addition, they should measure effects on the inhibition of germination (the transformation from blastospore to germ tube), since the latter form of *Candida albicans* is considered to be more infective. Histatins are most effective in killing blastospores, less effective in killing germ tubes, and least effective in inhibiting germination. Comparison of the three major histatins indicates that histatin 5 is the most candidacidal histatin for either of the cellular forms, whereas histatin 3 is slightly more effective in inhibiting germination than histatin 1 or histatin 5.[36]

Histatin Concentration and AIDS

The concentrations of histatins in saliva vary within ranges, which is typical or all salivary proteins, considering variation among individuals and dependency on flow rate. The proteolytic activities of proteases in whole saliva reduce the concentration of histatins significantly. Conditions of reduced salivary flow and high proteolytic activity in the oral cavity are likely to lessen the host's protection by histatins.[36]

Higher concentration of histatins has been found in submandibular/sublingual secretions from HIV-l-positive patients which could be due to a direct effect of the virus on the gland or could represent a compensatory response to changes in the oral cavity. [36]

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. [46] Cahn et al[47]noted multiple foci in 60% of 105 HIV- positive Argentinian patients with erythematous candidiasis, and Mastrucci et al[34] also found it in four of eight Californian children with HIV. One obvious reason for multifocal presentation of oral candidiasis in HIV may be the immature defence mechanisms and the virally induced severe T helper cell depletion seen in these individuals.[48]

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[51], 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[47] 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.[48]

Pseudomembranous candidiasis

It presents as semi-adherent, 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. 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.[48] 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.[51]

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 hyperplasic candidiasis, due to the presence of characteristic histopathologic features as koilocytes.[48]

Angular cheilitis

Angular cheilitis (angular stomatitis) is a disease of multifactorial etiology and it may be infective or non-infective in origin. AIDS and HIV infection are added to the list of its causative factors, as cumulative data of four studies [32, 26, 27, 29] indicate that ⅛ with HIV infection present with angular cheilitis. Prior to HIV infection these lesions were most commonly seen in elderly individuals as a complication of denture-induced stomatitis (chronic atrophic candidiasis) and the disease was relatively rare among younger age groups. 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.[48]

HISTOLOGICAL FEATURE

Histologically, candidal infection in HIV-infected patients frequently shows a remarkably weak inflammatory reaction. The epithelium may be invaded by numerous hyphae or pseudohyphae without the characteristic massive infiltrate of polymorphonuclear leukocytes. Likewise, areas of subepithelial inflammation often contain few or no leukocytes.[48]

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.

Table 3 shows the sampling techniques easily available to the clinician which are necessary to confirm as far as possible the presence or absence of a specific clinical variant of oral candidiasis.

DIMORPHISM OF C. ALBICANS IN VIVO

Many reports state or imply that only the hyphal phase of *Candida* is invasive or pathogenic while yeast cells or blastospores are merely harmless commensal[52]which means the presence of yeast cells in a specimen is harmless whilst 'hyphae' imply a pathogenic process or an active infection. Some workers[53] found a positive correlation between hyphae and oral candidosis whereas others[54]were unable to demonstrate this relationship. Torssander et al.[55] in their study were unable to show a positive correlation between hyphae (or mycelia) and disease state in HIV-infected patients with oral candidosis. In one half of the subjects with mycelial elements in smear the clinical picture was normal while positive 'hyphal' smears

were found in several subjects without any evidence of immune deficiency. When the subjects with positive 'hyphal' smears were re-examined after 12-18 months they still yielded 'hyphal' elements in the absence of any symptoms. These workers state that oral hyphal/mycelial findings in these patients most likely represent a variant of non-pathologic commensal colonization. Candida species such as C. glabrata and C. krusei whose pathogenic status is well established are unable to form hyphae/mycelia either in vitro or in vivo.[48]

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/mm^3 may be at greater risk for oral candidiasis and thus may benefit most from antifungal prophylaxis. *Candida albicans* carriage and a history of oral candidiasis are other significant risk factors for oral candidiasis.[56] Factors considered in decisions for prophylaxis against oral candidiasis and choice of prophylactic agent includes the following[56]:

1. The impact of oral fungal disease recurrences on the patient's quality of life and well-being.
2. The need for prophylaxis for other fungal infections
3. Cost
4. Convenience of drug dosing
5. Toxicities
6. Drug interactions
7. The potential to induce antifungal drug resistance.

A wide variety of agents are available for the treatment of oral candidiasis. Some of these antifungal drugs are used topically, others are used systemically either by the oral route or intravenously.

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) [48,57]Topical agents are available in a variety of forms, including oral troches, pastilles, vaginal tablets, rinses, and creams.[57] Topical therapy requires sufficient contact time (2 minutes)[56] 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.[57] Treatment duration varies from 7-14 day, with therapy minimally continued for 2 to 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.[56]

Topical treatment may involve nystatin tablets 100,000 unit, 3 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.[48]

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.[48] 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.[48] 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.[57]

Gentian violet has sometimes been used in pediatric populations and chlorhexidene 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. 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.[57]

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.[57]

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 bis-triazole group are used for this purpose.[48] 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.[56] Systemic drugs include Polyene Antifungal Agents -- Nystatin , Amphotericin B and Azole compounds - Imidazoles, Triazoles and are available for both oral and intravenous delivery.

Nystatin - Nystatin is the only topical polyene antifungal drug suitable for intraoral use available in the United States. Nystatin was discovered to be an effective antifungal agent in 1951[58] and 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.[59] 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.[60] Nystatin is also available as a cream or ointment containing 100,000 units/ gm, 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.[61]

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 not available in the United States, but they are effective in the treatment of denture stomatitis.[62] 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. A solution of 1 mg of amphotericin B was prepared in 5 ml of syrup. Rinsing four times a day with 5 ml of this preparation produced clearing of the oral lesions.[63]

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 *Candida albicans* but may not be as effective against some Candida species, such as *Candid. krusei and Candida glabrata*.

Imidazoles

1. 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 l0-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.[57] The systemic azoles are effective anticandida agents because they inhibit the enzyme lanosterol 14α-demethylase, which leads to destabilization of the fungal membrane.

3. 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.[48]

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.[64, 65]

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.[57] Ketoconazole may interfere with the metabolism of cyclosporine, tacrolimus, and, warfarin increasing their toxicity. 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 P450-34A enzyme system on which the ketoconazole acts may produce increased levels of the protease inhibitors. Absorption of ketoconazole requires gastric acidity, such that the concomitant use of antacids, H_2 antagonists, omeprazole, or sucralfate significantly reduces its bioavailability, resulting in treatment failure. Ketoconazole is to be taken with food[75], and since gastric acid is essential for its dissolution and absorption it may not be adequately absorbed by persons with reduced gastric acidity.[57] Periodic liver function tests are recommended to monitor for hepatotoxicity.[56]

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.[48]

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[65] 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, and 150 mg as a single dose.[65]

Subjects in the fluconazole prophylactic arm of one antifungal placebo-controlled trial showed improvement of dermatophytoses such as *tinea pedis, onchomycosis and tinea cruris.* In addition, systemic fluconazole prophylaxis may prevent esophageal and vaginal candidiasis, cryptococcemia, histoplasmosis, and other deep fungal infections.[56]

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.[66] Other studies have shown that fluconazole 50mg a day taken for 14 to 28 days is effective.[67] 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.[68, 69, 70] 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.[71] 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[72] and with severe immune suppression (e.g. CD4< 50).[73] 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.[74] Other cases suggest that the strains are resistant to fluconazole, both clinically and by in vitro susceptibility testing.[75, 76, 77] Results of in vitro testing depend on the method used, and susceptibility testing is not well standardized.

The choice of therapy for these fluconazole-resistant cases is limited. Alternatives include higher doses of fluconazole (200 mg to 600 mg per day), itraconazo1e (200 mg to 400 mg per day), or ketoconazole (400 mg per day).[78] 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.[79]

De Wit et. al.[80] 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 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 4 of 19 ketoconazole-treated patients had transient rise in alanine or as 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.[81] in 50 HIV positive patients and Gritti et al.[82]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 and it is derived that the regime of 50 mg per day (single dose therapy) of fluconazole for a period of 2-3 wks may 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[80] feel that maintenance therapy is not warranted and intermittent therapy is adequate.

2. Itraconazole - Itraconazole is a new antifungal agent and is available as a 100-mg capsule. Studies have shown that itraconazole 200 mg a day[48, 83] 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.[84] 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.[85] 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, terfanidine, astemizole, and warfarin.[57]

Resistant flora of the candida species to bis-triazoles has been reported. Korting et al.[11] examined the susceptibilities of 62 oral *Candida albicans* isolates from patients infected with HIV and they found three strains which were resistant to itroconazole, one strain resistant to ketoconazole and another to flucytosine. The development of cross resistance of *Candida albicans* to different imidazoles during treatment with one single azole derivative has been described previously.[86] It is therefore, salutary to keep the behavior of *Candida albicans* in mind when planning treatment protocols involving azoles against candidiasis in HIV infected or any other patient group.

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