Etiology, pathogenesis, therapy, and prophylaxis of oral yeast infections

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Etiologic factors in oral candidosis are immature antimicrobial host defenses, acquired suppression of immune defense mechanisms (AIDS, immunosuppressive or radiation therapy), or changes of the environmental conditions of the oral cavity (antibiotics, dentures, epithelial changes). After colonization and adhesion of *Candida* to the epithelial surface the subsequent mucosal lesion is due to tissue destruction by potent proteolytic enzymes or toxins and an inflammatory response to *Candida* antigens. Topical antimycotic treatment with nystatin, amphotericin B, or miconazole is important especially to prevent spread of the infection. Chronic *Candida* infections require long-term antifungal therapy, and patient compliance may be difficult to obtain. In denture stomatitis colonization of the fitting denture surface by *Candida* should be controlled by, for example, using a chlorhexidine solution as a denture disinfectant. However, recurrences are frequent if the local or the systemic predisposing conditions are not corrected. Fluconazole, a new bis-triazole, may be important for long-term treatment of immunocompromised patients. □ *AIDS; antimycotics; denture stomatitis; leukoplakia; lichen planus; oral candidosis*

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Candida is an obligate associate of human beings and other warm-blooded animals. Thus, *Candida* is frequently encountered as a harmless commensal of the digestive and vaginal tracts and constitutes a part of the normal microbial flora of the host. In the past two decades an increased prevalence of superficial and invasive candidosis has been attributed to the widespread use of antibiotics and immunosuppressive agents. There is also a parallel between the increased prevalence of candidosis and the use of aggressive cancer chemotherapy, the use of parenteral nutrition, and the frequent practice of invasive surgical procedures. More recently, it has been shown that candidoses are among the oral manifestations often associated with human immune deficiency syndrome (AIDS) and that unresolved candidosis may be one of the earliest signs of HIV/AIDS.

Etiology

Candida species are assumed to cause disease in man by tissue invasion, by inducing a hypersensitive state, or by producing potent *Candida* toxins. For *Candida* to successfully colonize and infect host mucosal surfaces it has to adhere to the epithelial surfaces. In animal experiments it has been shown that treatment with antibacterial agents assists colonization by *Candida* (1). The various factors that may affect the adhesion to epithelial cells have been studied mainly in vitro and include yeast factors (concentration, growth phase, growth medium, species, and strain), epithelial cell factors, and environmental factors (temperature, hydrogen-ion concentration, bacteria, antibodies) (2, 3). Of all *Candida* species *C. albicans*, the most pathogenic *Candida* species, adhere most tightly to the epithelial cells in vitro. This adhesion of *C.*

albicans to the mucosal surfaces appears to involve lectin-like interactions between the protein portion of mannoprotein located in fibrils on the yeast surface and glycoside receptors on epithelial cells (2). The adhesion of *C. albicans* can be enhanced by preincubation of the epithelial cells with certain bacterial species or by adding dietary carbohydrates to the substrate (4, 5). In addition to the specific cell–cell interactions, an important aspect of the pathogenicity of *C. albicans* may be its non-specific affinity and binding to acrylic resin (*Candida*-induced denture stomatitis) and other plastics (catheter-related candidosis) (6). The adhesion to plastic surfaces is also promoted by sugars, which could be an important factor in the almost immediate yeast colonization of the denture surface seen after antifungal therapy (7).

After attachment and colonization *Candida* cells invade the epithelial cells. There is suggestive evidence that hydrolytic enzymes are involved in this process (8). The invasion process is followed by an acute inflammatory response characterized by a predominance of neutrophils. A similar inflammatory response has been observed in experimental oral candidosis in monkeys (9, 10).

Pathogenesis and predisposing conditions

Multiple factors predispose for oral candidal infections (11) (Table 1). During the neonatal period the underlying predisposing condition is probably immaturity of the immune system and lack of a mature oral microflora (12). The infection by *C. albicans* will usually resolve spontaneously without treatment as the commensal bacterial flora is established.

Endocrine disorders

Of possible predisposing endocrine disorders, diabetes mellitus and glycemic control have been reported to be important factors that affect the rate of candidal carriage (13, 14). Other studies showed no relationship between the carriage rates and the type of treatment of diabetes or the quality of glycaemic control (15, 16), but the carriage rate and the CFU counts of *Candida* were significantly higher in denture wearers than in dentate persons with or without diabetes.

Table 1. Factors predisposing to oral candidosis

Systemic factors
Physiologic
Old age, infancy, pregnancy
Endocrine disorders
Diabetes mellitus, hypothyroidism
Nutritional deficiencies
Iron, folate, or vitamin B_{12} deficiency
Malignancies
Acute leukemia, agranulocytosis
Immune defects, immunosuppression
AIDS, thymic aplasia, corticosteroids
Local factors
Xerostomia
Sjögren's syndrome, irradiation, drug therapy
Broad-spectrum antibiotics
Corticosteroids
High-carbohydrate diet
Leukoplakia, oral cancer
Dentures
Changes in environmental conditions, trauma, denture usage, denture cleanliness
Smoking tobacco

Dietary factors

Iron-deficiency anemia has been proposed as an important factor in the etiology of chronic mucocutaneous candidosis (CMC) (12). In a group of denture wearers a relationship between low plasma iron concentration and unsaturated serum transferrin and *Candida* infection of the angles of the mouth was demonstrated (17). Furthermore, a decreased lymphocyte response to *Candida* antigens was demonstrated in some iron-deficient subjects associated with an increased frequency of *C. albicans* in the oral cavity (18, 19); the immune response was restored once the iron level was again normal. This suggests that iron deficiency may predispose to oral candidosis by depressing cell-mediated immunity.

A high carbohydrate intake has been assumed to predispose to oral candidosis (20). This is supported by in vitro studies showing that the growth of *Candida* in saliva is enhanced by glucose despite the presence

of a nutrient-competing bacterial salivary flora (21). Furthermore, the adhesive properties of *C. albicans* to oral epithelial cells are augmented by dietary carbohydrates (4, 5). In patients with denture stomatitis sucrose mouth rinses have been shown to aggravate existing denture stomatitis and to result in increased yeast counts (22). There is, however, no evidence that pathologically significant yeast overgrowth and infection would result from high carbohydrate consumption alone.

Malignant diseases

Disseminated candidosis is an increasing problem in cancer patients, especially in patients with acute leukemia, in whom fungal infections were determined to be the proximate cause of death in 75% of the patients (23). There are multiple factors responsible for the increasing frequency of candidosis in cancer patients, such as prolonged survival rate due to chemotherapy associated with impaired defense mechanisms depending on the disease and its treatment. It is generally accepted that, although oral candidosis is usually not a life-threatening infection in otherwise normal persons, in patients with generalized immune deficiency problems, this infection can spread to the esophagus, causing ulcerations, perforation, fungemia, and even death (24).

Antibiotics

It is assumed that treatment with broad-spectrum antibiotics is an important predisposing factor in oral candidoses by suppressing the bacterial flora (25). In a double-blind study on the effect of tetracycline in treatment of chronic bronchitis, however, there was no significant differences in the *Candida* carriage rate between the group treated with tetracycline and the placebo group (26). It was suggested that systemic treatment with tetracycline did not produce concentrations of tetracycline high enough to affect the balance of the mixed oral microbial flora.

After topical treatment of oral herpetiform ulcers with tetracycline, acute atrophic candidosis developed in 9 of 14 patients (27). Furthermore, in experimental palatal candidosis in monkeys, prolonged topical treatment with tetracycline resulted in a continuous proliferation of *C. albicans* and a more intense inflammation than that caused by *C. albicans* alone (9); however, tissue invasion was not seen. It seems that depressed microbial defense mechanisms are more important predisposing conditions for oral candidosis than treatment with antibacterial antibiotics.

Corticosteroids and immunosuppressive drugs

The manner in which corticosteroids predispose to infection with *C. albicans* is uncertain, but it seems to be by lowering host resistance rather than by stimulating proliferation of *Candida* (12). Acute pseudomembranous candidosis developed in 6 of 65 patients with recurrent aphthous ulcers or lichen planus who were treated with topical steroids (27). It was noteworthy that the lesions developed where the steroid was commonly held, suggesting a local effect. In an animal experiment it was shown that systemic treatment with the steroid triamcinolone acetonide potentiated oral *Candida* infections, probably by suppressing both non-specific inflammatory responses and cell-mediated immunity against *C. albicans* (28).

Renal transplantation patients treated with immunosuppressive drugs, such as azathioprine, which have a more well-defined immunosuppressive effect by acting selectively on T lymphocytes (29), have an increased susceptibility to fungal infections (12). In experimental palatal candidosis in monkeys systemic treatment with azathioprine resulted in acute pseudomembranous candidosis associated with a depressed cell-mediated immune reaction against *C. albicans* and a strong antibody response (Fig. 1) (10). These studies indicate that topical or systemic treatment with steroids or immunosuppressive drugs, may predispose to oral candidosis and most certainly may have the potential to aggravate existing candidal infections.

Leukoplakia and lichen planus

Oral leukoplakia is considered to be a precancerous lesion that occurs in the mouth as either a homogeneous variety that is usually asymptomatic or as non-homogeneous varieties that may be associated with stinging and burning sensations during food intake (30). *Candida* is usually present in non-homogeneous leukoplakias, and it is believed that the organisms are secondary invaders. There is conflicting information as to the role of tobacco smoking and oral candidosis, but it seems unlikely that tobacco smoking is an important predisposing factor for colonization of the oral cavity by yeasts (31). However, a striking relationship has been shown between tobacco smoking and both invasion of oral leukoplakia by *Candida* and the presence of chronic oral multifocal candidosis (32, 33). It seems, therefore, that tobacco smoking creates the background for invasion of the epithelium by *Candida*.

In patients with oral lichen planus the lesions were relatively frequently infected by *Candida*, and local treatment with amphotericin B resulted in clinical improvement and subjective relief of symptoms (34). The underlying cause of *Candida* infection of these lesions may be structural changes of the epithelial surface or changes in the cell-mediated immunologic response against *C. albicans*.

Dentures

The direct predisposing factor for *Candida*-associated denture stomatitis is the presence of the dentures in the oral cavity. Thus, the infection prevails in patients who are wearing their dentures both by day and night (35), and leaving out the denture will cause the infection to disappear (36).

The outgrowth of yeasts is not caused by a comprehensive change of the oral microenvironment, since the composition of the bacterial flora is essentially the same in dental and denture plaque (37). However, it seems that the relatively acid and anaerobic milieu beneath a close-fitting denture propagates yeast proliferation. It is also possible that a traumatic injury produced by the dentures may reduce tissue resistance against infection and increase the permeability of the epithelium to soluble *Candida* antigens and toxins.

There is reliable evidence that unclean dentures and insufficient hygiene care are significant predisposing factors (35, 38, 39). Furthermore, healing of the lesions has been brought about by chemical plaque control or by instituting meticulous oral and denture hygiene (40, 41). The tissue surface of dentures usually shows micropits and microporosities that harbor microorganisms that are difficult to remove by mechanical or chemical cleansing (42). In vitro studies also indicate that the microbial contamination of denture acrylic resin occurs very quickly and that yeasts adhere well to denture base materials (7, 43, 44).

Angular cheilitis is often correlated to the presence of *Candida*-associated denture stomatitis (38), and it is supposed that the infection may start beneath the maxillary denture and from that area spread to the angles of the mouth (45). It seems, however, that the infection is secondary to local or systemic predisposing conditions such as overclosure of the jaws, nutritional deficiencies, or iron deficiency anemia (46–48).

It should be recognized that both denture stomatitis and angular cheilitis have a varied etiology, that multiple predisposing conditions may be present, and that both bacteria and yeasts may be involved as pathogens. However, *Candida* species often play an important role. Although denture stomatitis and angular cheilitis do not usually reflect a serious predisposing abnormality or disease, the dentures being the primary predisposing condition, it should be realized that severe infections may occur in the immunocompromised host.

Treatment of oral candidosis

There are six preparations that are widely used in candidosis therapy: the polyene macrolides nystatin and amphotericin B, the imidazole derivatives clotrimazole, ketoconazole, and miconazole, and 5-

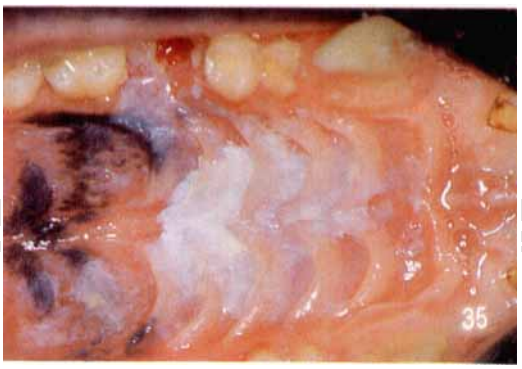

Fig. 1. Experimental palatal candidosis in an immunosuppressed (azathioprine) monkey produced by inoculation of *Candida albicans* beneath an acrylic plate. The infection is characterized by formation of extensive thrush-like plaques.

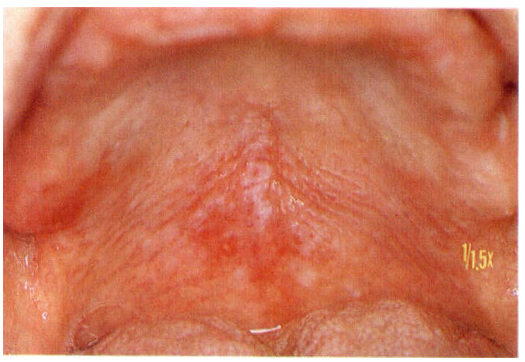

Fig. 3. Same patient as in Fig. 2. Plaque-like lesion of the soft palate.

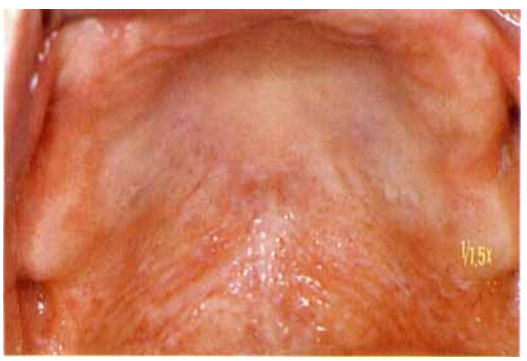

Fig. 5. Same patient as in Fig. 2 after systemic treatment with fluconazole for 2 weeks. The plaque-like lesion and the inflammation have disappeared.

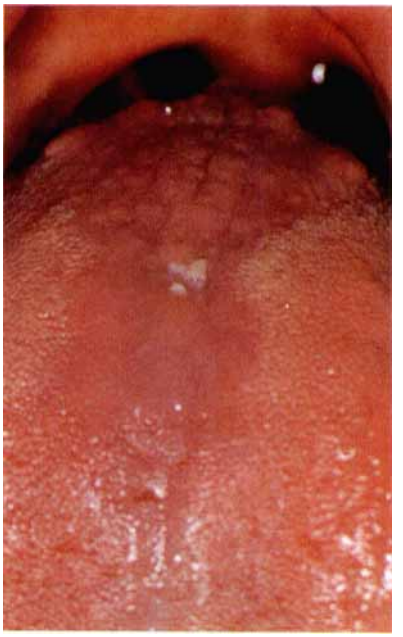

Fig. 2. Chronic oral multifocal candidosis. Erythematous lesion and a nodular lesion of posterior part of dorsum of the tongue.

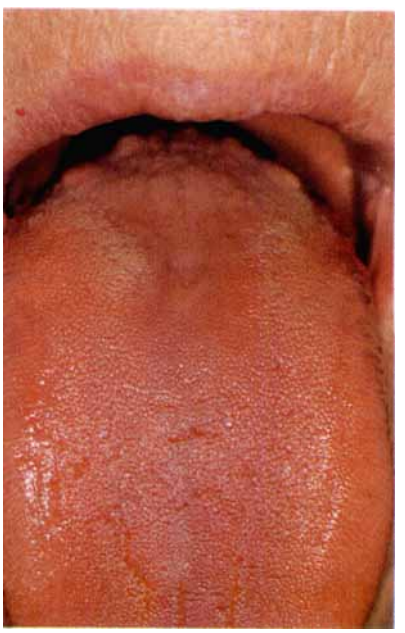

Fig. 4. Same patient as in Fig. 2 after systemic treatment with fluconazole for 2 weeks. The nodular lesion has disappeared and the inflammation regressed.

[*Facing page 64*]

fluorocytosine. More recently, a new oral bis-triazole antifungal drug, fluconazole, has been introduced. Furthermore, chlorhexidine gluconate has been widely used, particularly for treatment of *Candida*-associated denture stomatitis. Of the antifungal antibiotics nystatin and miconazole are only for topical use, amphotericin B, ketoconazole, and clotrimazole for systemic or topical use, and 5-fluorocytosine and fluconazole primarily for systemic use (Table 2). Resistance of yeasts has been observed regularly only against 5-fluorocytosine, and this drug, therefore, should be reserved solely for use in systemic candidosis (12).

Guidelines for antimycotic treatment have been listed by Dreizen (49). Lesions of acute pseudomembranous candidosis will usually heal after oral treatment with nystatin in a dose of 100,000 units six times a day as a vaginal troche that is allowed to melt slowly in the mouth. Clotrimazole is given as a dissolvable 10-mg troche five times a day, and amphotericin B as lozenges of 10 mg, three to four times a day. The recommended dose of ketoconazole is one 200-mg tablet per day, and ketoconazole cures thrush faster and more effectively than nystatin (50). The required treatment time is 1–2 weeks. It is recommended that patients with severe *Candida* infections that fail to respond to topical therapy should be hospitalized and treated systemically with ketoconazole, fluconazole, or amphotericin B.

Table 2. Antifungal agents for treatment of oral candidosis

	Topical	Systemic
Polyenes		
Nystatin	+	
Amphotericin B	+	+
Imidazoles		
Miconazole	+	
Clotrimazole	+	
Ketoconazole		+
Triazoles		
Fluconazole		+
Antiseptics (for denture disinfection)		
Chlorhexidine gluconate	0.2%	
Sodium hypochlorite	0.5%	
Chloramine	0.5%	
Denture cleansers		
Alcalase (Enzydent®)		

In children with acute leukemia acute pseudomembranous candidosis has been treated successfully by using a mouthrinse or painting with 0.2% chlorhexidine gluconate (51).

The acute erythematous candidosis will often subside spontaneously after withdrawal of the offending antibiotic (49), but the time of resolution could be reduced by antimycotic treatment.

The chronic nodular or plaque-like types of oral candidosis generally need long-term antifungal therapy and surgical resection of persistent lesions. The effect of treatment with amphotericin B has been studied thoroughly by Holmstrup & Besserman (33). They used a median length of treatment of 44 days to obtain mycologic cure, but only the erythematous lesions showed complete clinical cure. Thus, the nodular and the plaque-like lesions showed only partial remission. Three and 6 months after antimycotic treatment there was a high incidence of recurrence, particularly of the palatal lesions of non-denture wearers and the commissural lesions. It was suggested that tobacco smoking had a significant pathogenic role both for the initial infection and the high recurrence rate.

Treatment of chronic mucocutaneous candidosis includes immunologic therapy such as thymus transplants, injection of thymic extracts, infusion of lymphocytes from immunocompetent donors, and transfer factor to correct the immunologic defects (49). Systemic therapy with adequate doses of amphotericin B or ketoconazole combined with topical oral treatment with clotrimazole has been efficient in inducing remission of cutaneous and mucous membrane lesions. However, the patients usually relapsed within a few weeks after cessation of treatment. So far, a combination of antifungal chemotherapy and transfer factor from *Candida*-sensitive donors seems to provide the most safe and effective therapeutic schedule for these patients (52).

In denture stomatitis the most important therapeutic measure is institution of an efficient oral and denture hygiene, as the

major etiologic factor is the presence of a denture. However, antimycotic treatment should be instituted in immunocompromised patients, in patients with more widespread infection of the oral mucosa, and in patients who respond poorly to hygienic measures.

The antimycotic treatment includes the use of antifungal antibiotics and antimicrobial agents for denture disinfection (53). Topical treatment with antifungal antibiotics such as nystatin, amphotericin B, miconazole, and ketoconazole has produced a significant reduction of the inflammation and concomitant clearing of oral symptoms, angular cheilitis, and glossitis. Antifungal antibiotics also produced a reduction of the inflammation of the granular type of denture stomatitis, but the hyperplasia usually persisted. It was a consistent finding, however, that the infection was often reestablished a few weeks after antimycotic treatment had been withdrawn.

In an extensive mycologic study carried out by culture of yeasts from the angles of the mouth, the denture-bearing mucosa, the denture base, the throat, and the gastrointestinal tract in patients with denture stomatitis similar yeast species were isolated from the oral sites and the feces (54). After topical oral treatment with nystatin there was a suppression of yeast growth both in the oral sites and feces. This suggests that in patients with *Candida*-associated denture stomatitis the entire alimentary tract tends to be colonized by *Candida* and that the denture plaque serves as a reservoir for *Candida*.

In a recent study the effect of oral administration of fluconazole, a systemic antifungal antibiotic with low toxicity, was studied in a controlled double-blind placebo experiment (55). A significant reduction of the erythema and the concentration of yeast cells was observed among the patients in the fluconazole group, who received 50 mg fluconazole per day orally for 14 days (Figs. 2–5). However, yeasts were cultured in most of the patients at the end of the 2-week treatment period, but extensive changes of the composition of the yeast species and *C. albicans* biotypes were observed only in the fluconazole group. The results indicate that there are differences in the fluconazole susceptibility between various yeast species and that therapeutic concentrations of the drug were not reached within the plaque. Similarly, *Candida* has been shown to be able to survive in denture plaque after 2-week topical treatment with amphotericin B ointment (56).

These studies indicate that to obtain a more prolonged effect of antimycotic treatment, it is important to control plaque development on the oral mucosa and the dentures and, possibly, to continue antimycotic treatment for at least 4 weeks.

In treatment of angular cheilitis antimycotic antibiotics such as nystatin, amphotericin B, or pimafucin have been effective when used topically (57–59). Angular cheilitis will usually clear when a concurrent *Candida*-associated denture stomatitis is treated by local or systemic antimycotic antibiotics or chlorhexidine, and no specific treatment has to be prescribed for the angular lesions (55, 59). It was recently shown that angular cheilitis associated with *C. albicans* and *Staphylococcus aureus* responded to treatment with nystatin, whereas fusidic acid was efficient in lesions with *S. aureus* as the only detected pathogen (60). It was found that a poor or late response to treatment was associated with a more extended length of the angular skinfolds and dry skin.

Since denture stomatitis is associated with an establishment of yeasts in the plaque on the fitting surface of the denture and on the underlying mucosa, a combination of intraoral treatment with antimycotic antibiotics and extraoral disinfection with chlorhexidine (0.2%) has been recommended (59). An amphotericin B/chlorhexidine combination has been standard treatment of infectious denture stomatitis in Scandinavia for more than 15 years and has been shown to be superior to other treatment modalities (61). It was concluded that to obtain better future treatment results, emphasis should be placed on the use of imidazoles and triazoles that act systemically after a single daily oral dose. Such treatment should be combined with meticulous denture hygiene, including disinfection of the dentures with chlorhexidine.

Prevention

Antifungal prophylaxis may be indicated to prevent colonization or multiplication of *Candida* in a susceptible host, to prevent primary infection, and to prevent reinfection after antimycotic treatment. It should be realized, however, that oral topical treatment with antimycotic antibiotics usually has a temporary effect only, since the oral sites tend to become reinfected from *Candida* harbored in the digestive tract. Furthermore, reinfection is likely if the primary predisposing conditions are not corrected, which, of course, is not always possible.

Prophylactic measures against acute oral candidosis in immunosuppressed patients with cancer and patients with acute leukemia undergoing chemotherapy and against acute and chronic candidosis in HIV-infected patients have been reviewed recently by Holmstrup (62). Most data indicate that it is not justifiable to use local or systemic antimycotic antibiotics as a routine prophylactic measure, since it is not possible to obtain total systemic protection and since oral candidosis usually responds immediately to treatment with antimycotic antibiotics. In immunocompromised patients it rather seems to be important to carry out careful clinical and mycologic evaluation to be able to institute treatment with antimycotic antibiotics when the patients develop manifest oral candidosis, to reduce the risk of systemic candidosis. Fluconazole, which has recently been introduced for systemic treatment of oral candidosis (55) and which has an extremely low toxicity, might be useful as a prophylactic antimycotic agent in severely immunocompromised patients.

Candida-associated denture stomatitis is usually not a serious condition. However, it is important to prevent this disorder, as an inflamed oral mucosa is a poor support for a denture and because the inflammation may possibly contribute to resorption of the underlying bone. Furthermore, denture wearers are mostly elderly people, and debilitating diseases may increase their susceptibility to oral and systemic candidosis. It should also be recognized that colonization of the dentures and the underlying mucosa by yeasts may contribute to colonization of the gastrointestinal tract by yeasts (54).

Patients with recurrent infections should be persuaded not to use their dentures at night but rather leave them exposed to air, which seems to be a safe and efficient means of preventing yeast colonization (63).

There is no substantial evidence that harmless commercial denture cleansers are efficient in preventing colonization of the dentures by microorganisms (64). However, a recently developed enzyme cleanser, Enzydent®, has been shown to be an efficient adjunct to denture brushing in preventing microbial plaque and yeast colonization of the dentures (65). Finally, polishing or glazing of the tissue surface of removable dentures should be considered as a routine step in prosthodontic treatment to facilitate denture cleansing by brushing (66).

Conclusions

Candidosis is by far the most common mycotic infection of the human oral cavity. As *Candida* organisms occur as commensals and constitute a part of the normal oral flora, the reasons for infection are precipitating factors such as depressed host defenses, endocrine disorders, mucosal lesions, ill-fitting dentures, poor oral and denture hygiene, and protracted use of antibiotics, corticosteroids, or antineoplastic drugs. The variety of the clinical manifestations of oral candidosis reflects the diversity of the predisposing conditions.

Most types of oral candidosis are easily treated by topical application of nystatin, amphotericin B, or miconazole. In chronic nodular and plaque-like candidoses long-term treatment is important. In *Candida*-associated denture stomatitis, treatment involves denture hygiene measures, not wearing the dentures during night, denture soaking in chlorhexidine, and antifungal antibiotic therapy. It should be recognized that recurrence of the infection is frequent if the underlying predisposing conditions are not corrected. Prophylactic measures include efficient oral hygiene care and chlorhexidine mouthrinses. In severely immuno-

compromised hosts prophylactic treatment with fluconazole, a systemic antimycotic antibiotic with low toxicity, may be an important means to control oral candidosis.

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