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Review Article

ORAL CANDIDIASIS: A REVIEW

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ABSTRACT

Candidiasis, a common opportunistic fungal infection of the oral cavity, may be a cause of discomfort in dental patients. The article reviews common clinical types of candidiasis, its diagnosis current treatment modalities with emphasis on the role of prevention of recurrence in the susceptible dental patient. The dental hygienist can play an important role in education of patients to prevent recurrence. The frequency of invasive fungal infections (IFIs) has increased over the last decade with the rise in at-risk populations of patients. The morbidity and mortality of IFIs are high and management of these conditions is a great challenge. With the widespread adoption of antifungal prophylaxis, the epidemiology of invasive fungal pathogens has changed. Non-albicans Candida, non-fumigatus Aspergillus and moulds other than Aspergillus have become increasingly recognised causes of invasive diseases. These emerging fungi are characterised by resistance or lower susceptibility to standard antifungal agents. Oral candidiasis is a common fungal infection in patients with an impaired immune system, such as those undergoing chemotherapy for cancer and patients with AIDS. It has a high morbidity amongst the latter group with approximately 85% of patients being infected at some point during the course of their illness. A major predisposing factor in HIV-infected patients is a decreased CD4 T-cell count. The majority of infections are due to C. albicans although other species such as C. glabrata, C. tropicalis, C. krusei and C. parapsilosis are increasingly isolated. The systemic azoles, ketoconazole, fluconazole and itraconazole, have been an important benefit in treatment. To date, resistance has primarily been a problem with fluconazole in AIDS. However, it is important that measures are instituted to prevent the spread of resistant strains and the development of cross-resistance. Although the NCCLS has established a reference method to measure in vitro susceptibility, besides already published papers, more data are necessary to demonstrate that resistance correlates with clinical failure.

Keywords: Candidiasis

INTRODUCTION

Oral candidiasis is one of the most common, treatable oral mucosal infections seen in persons with human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)[1].Oral candidiasis can be a frequent and significant source of oral discomfort, pain, loss of taste, and aversion to food. Candida albicans carriage and a history of oral candidiasis are other significant risk factors for oral candidiasis[2]. The infection is caused by Candida Albicans, a dimorphic fungal organism that typically is present in the oral cavity in a non-pathogenic state in about one-half of healthy individuals. Normally present as a yeast, the organism, under favorable conditions, has the ability to transform into a pathogenic (disease causing) hyphael form. Conditions that favor this transformation include broad-spectrum antibiotic therapy, xerostomia, immune dysfunction (secondary to systemic diseases such as diabetes or the use of immune suppressant medications), or the presence of removable prostheses. Furthermore, about one in four patients with lichen planus will have superimposed candidiasis. Unless the patient is severely immunocompromised, the infection is generally limited to the superficial mucosa and skin. Invasive candidiasis infection is rare, with disseminated disease even more so. This superficial nature of the infection makes oral candidiasis so amenable to treatment. Several antifungal agents can be used topically. For topical agents, successful therapy depends on adequate contact time (2 minutes) between the agent and the oral mucosa. Treatment duration varies from 7 to 14 days, 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. However, sucrose containing topical agents can be cariogenic when used over prolonged time periods[3], such that adjunctive topical fluoride therapy may be needed. Systemic antifungals have the 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 interactions. The present work reviews the common clinical types of oral candidiasis, its diagnosis, and current treatment modalities with emphasis on the role of prevention of recurrence in the susceptible dental patient. The dental hygienist can play an important role in the education of patients to prevent recurrence. Candidiasis is a common oral and perioral opportunistic infection that usually results from overgrowth of endogenous Candida fungal microorganisms. There are many species of Candida (Table 1)[4] but C. albicans is the fungal microorganism most often encountered in the ambulatory general practice dental patient. Changes in the oral environment that can predispose or precipitate oral candidiasis include: antibiotics, corticosteroids, dry mouth (xerostomia), diabetes mellitus, nutritional deficiencies, and immunosuppressive diseases and therapy[1]. Saliva contains antifungal proteins including histatins and calprotectin that help protect patients from Candida infections[5]. These protective proteins are absent in a patient who has xerostomia. Individuals who use corticosteroid asthma inhalers must rinse their mouths with water after each use to reduce their chances of developing oral candidiasis. Excellent oral hygiene, including brushing and flossing of the teeth twice daily and maintenance of adequate intraoral moisture, is critical in the prevention of candidiasis recurrence in the susceptible patient.

Fluconazole, a novel bis-triazole antifungal agent introduced in 1990, has systemic effects that may be beneficial for other fungal infections. Subjects in the fluconazole prophylactic arm of one antifungal placebo-controlled trial showed improvement of dermatophytoses, such as tinea pedis, onychomycosis, and tinea cruris[6]. In addition, systemic fluconazole prophylaxis may prevent esophageal and vaginal candidiasis[7], cryptococcemia, histoplasmosis, and other deep fungal infections. Unlike ketoconazole, fluconazole is not altered by changes in gastric acidity and carries less risk of hepatotoxicity; however, many of the same drug interactions are possible. A newly raised concern about the wide spread use of fluconazole is the potential for development of azole-resistant Candida albicans and selection of non-albicans Candida species, which also increase in prevalence with immune decline and further complicate management of some individuals[8,9,10].

Causative organisms

Candida spp.

Among the fungal pathogens, Candida spp. are the most predominant causes of invasive infections. The annual incidence of Candida associated BSIs ranged from 6 to 23 per 100 000 persons in the USA[11,12] and from 2.53 to 11 per 100 000 persons in European countries[13]. In various reports, Candida spp. accounted for 8–10% of nosocomial BSIs[11]. Rising incidences of candidaemia have been reported throughout the world in the past two decades[11,13,14]. The

major predisposing factors included surgical intervention, intensive care treatment, solid tumour or haematological malignancies, use of steroids and premature birth[13]. Crude mortality rates remain high despite advances in medical care, ranging from 30% to 50%[11,12,13]. More than 95% of Candida-associated BSIs are caused by five major species: C. albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis and Candida krusei[12,13,15,16]. Candida parapsilosis occurs with high frequency in premature neonates and in patients with vascular catheters [17,18]. Candida glabrata infections are rare in infants and children but are significantly more common in the elderly[19]. Candida tropicalis plays an important role as a cause of invasive diseases in patients with haematological malignancy[20]. Overall, the non-albicans Candida spp. have shown an increasing trend as causative pathogens in BSIs[21] with a 10–11% increment over a 6.5-year period in a global report[21]. With the more widespread use of fluconazole, the emergence of C. glabrata and C. krusei has been reported in the USA[22,23]. However, the role of species with lower susceptibility to azoles has been limited in other areas. New triazoles, such as voriconazole and posaconazole, and the echinocandins are active against these two species, although cross-resistance was noted within the azoles in some C. glabrata strains.

Aspergillus spp.

Aspergillus spp. are commonly found in soil, water and decaying material all over the world. Unlike invasive candidiasis, invasive aspergillosis (IA) occurs predominantly in highly immunocompromised patients[24,25,26]. The main affected populations are patients with haematological malignancies and/or those receiving haematopoietic stem cell transplantation (HSCT)[27]. IA is also an emerging condition in patients with other causes of immunosuppression, such as solid organ transplantation, advanced acquired immunodeficiency syndrome (AIDS) and treatment with newer immunosuppressive agents such as infliximab[28]. The usual route of infections for IA is inhalation of Aspergillus conidia. The most frequently involved sites of IA are sinuses, lungs, brain and disseminated infection. IA is associated with a high mortality rate, which exceeds 50% in most reports. Higher mortality rates were noted in patients receiving HSCT compared with patients receiving solid organ transplants (68% vs. 41%; $P < 0.0001$), in patients with central nervous system disease (88% vs. 53%; $P = 0.0005$) and in non-neutropenic compared with neutropenic patients (89% vs. 60%; $P < 0.05$)[29].

Other moulds

Zygomycetes are fungi belonging to the order Mucorales, which form broad hyphae and are generally non-septate. Genera that are able to cause invasive diseases include Rhizopus, Rhizomucor, Absidia and Cunninghamella[30,31]. Infections due to zygomycetes are classically characterised by vascular invasion, leading to thrombosis and tissue necrosis. Zygomycetes are susceptible to amphotericin B but generally resistant to most triazoles and the echinocandins. Breakthrough zygomycosis has been reported in patients receiving voriconazole or caspofungin prophylaxis, as these agents lack activity against zygomycetes[32,33]. Voriconazole and posaconazole have been reported as successful treatments for fusariosis.

Clinical spectrum of the disease

Infection with Candida Albicans presents mainly in any of four forms: pseudomembranous candidiasis, hyperplastic candidiasis, erythematous candidiasis, or angular cheilitis. Patients may exhibit one or a combination of any of these presentations. Angular cheilitis, for example, will frequently be seen in combination with erythematous candidiasis in denture wearers (Table 3).

Pseudomembranous candidiasis

Pseudomembranous candidiasis, commonly known as "thrush," is the form often seen in neonates. It can also be seen in patients receiving topical corticosteroid therapy or in immune suppressed patients. In fact, the presence of pseudomembranous candidiasis in a seemingly healthy adult may be an indication of underlying systemic disease, such as infection with the human immunodeficiency virus (HIV). Pseudomembranous candidiasis presents as multiple white plaques of material resembling cottage cheese that can easily be wiped away. These plaques consist of tangled aggregates of hyphae. The underlying mucosa may be erythematous, but ulceration would not be expected. While symptoms are typically mild for this form of infection, patients may complain of a slight tingling sensation or a foul taste. Identification of the fungal pseudohyphae within exfoliative cytologic preparations, often utilizing periodic acid Schiff and/or Papanicolaou stained preparations, is the optimal standard for the diagnosis of all candidiasis, although the highest yield of positive cytology smears is with pseudomembranous candidiasis[34].

Atrophic Candidiasis

Atrophic candidiasis exhibits a diffusely reddened, often relatively dry mucosa. The red areas are often confined to mucosa underlying dental appliances such as partial dentures or orthodontic retainers. Approximately 26% of patients with complete dentures have atrophic candidiasis[35].

Hyperplastic candidiasis

This form has been referred to as "candidal leukoplakia," although this terminology should probably be avoided. Like leukoplakia, hyperplastic candidiasis will present as a white plaque that cannot be wiped away by the clinician. Unlike leukoplakia, however, lesions should completely resolve with routine antifungal therapy.

Erythematous candidiasis

Many conditions fall under the spectrum of erythematous candidiasis. As the term implies, lesions clinically appear red or erythematous. While any mucosal site may be affected, erythematous candidiasis commonly involves the tongue and palate. A form of erythematous candidiasis that is especially common involves the hard palate and gingiva beneath a denture or removable partial denture.

Angular cheilitis

The final clinical presentation of oral candidiasis infection is angular cheilitis. This form presents as cracking, peeling, or ulceration involving the corners of the mouth. It will frequently be seen in combination with one of the other forms of candidiasis infection, such as the erythematous type. Patients with a reduced vertical dimension of occlusion, secondary to severe attrition or worn dentures, are particularly susceptible to the development of angular cheilitis. This is due to the increased folding of the soft tissue that is frequently seen at the corners of the mouth, creating a haven for the organism.

Several over-the-counter (OTC) medications including miconazole nitrate and clotrimazole creams, and prescription nystatin or ketoconazole creams are available to topically treat angular cheilitis. Topical miconazole nitrate 2% cream is valuable in that it is effective against both Candida and Staphylococcus aureus. Dental professionals should be cautious when recommending OTC topical antifungals to patients who are using the anticoagulant warfarin. The combination increases the risk of excessively prolonged coagulation periods, due to interference with the liver enzymes that aid in the metabolism of warfarin[36]. Angular cheilitis is typically clinically diagnosed based on the uni- or bilateral presence of asymptomatic or painful red cracks or fissures at the corners of the mouth. Angular cheilitis may be caused by candidiasis (20%), mixed candidial bacterial infections (60%), or bacteria alone (20%)[37].

Treatment

For the normal healthy patient, the treatment of oral candidiasis is relatively simple and effective. Typically, topical medications are adequate. A commonly prescribed anti-fungal agent, nystatin oral suspension, will usually resolve most infections. However, topical medications must be in contact with the organism to eliminate it. Since patients are usually unable to hold liquids in their mouths more than briefly, clotrimazole troches are an effective alternative. These are dissolved slowly in the oral cavity, allowing the drug to be present for greater length of time.

Intraoral candidiasis

Topical agents include nystatin suspension and clotrimazole troches, which should be allowed to dissolve slowly in the mouth five times daily for 14 days. Patients should avoid eating or drinking for 20 minutes after using clotrimazole troches. Intraoral appliances should

be removed during the treatment as the medication works topically and must be in contact with the tissue. Systemic prescription antifungal agents include ketoconazole[38], fluconazole[39], and itraconazole[40].

Prosthodontic appliances

With any case of oral candidiasis, if the patient utilizes a removable prosthodontic appliance it is important to disinfect the appliance, because the porous material or surface biofilm can serve as a reservoir of fungal microorganisms and contribute to relapse or reinfection[41]. Disinfection of dental appliances is a two-step process. First, the appliance should be free of debris and concretions. Household chlorine bleach, although effective and inexpensive, can cause damage to dental metals, acrylic, and tissue-conditioning materials[42]. To avoid damage to prosthetic appliances, a germicide deodorizer containing sodium benzoate, citrate, and disodium phosphate (Oral Safe, Great Lakes Orthodontics, Tonawanda, NY) can be used to soak the appliance for six hours. This solution can be reused for one week and is harmless if ingested[43]. Another technique utilizes five minutes of microwave irradiation. Applying 60 Hz at full power to a complete acrylic denture in eight ounces of water can effectively sterilize acrylic and most soft denture liners[44].

Table 1: Species of Oral Candida

Species of Oral Candida
C. albicans
C. glabrata
C. guillermondii
C. krusei
C. parapsilosis
C. pseudotropicalis
C. stellatoidea
C. tropicalis

Table 2: Topical antifungal medications

Topical antifungal medications	
Dosage form/ strength	Indication
OTC	
Miconazole cream 2%	Angular cheilitis
Clotrimazole cream 1%	Angular cheilitis
Prescription	
Ketoconazole cream 2%	Angular cheilitis
Nystatin ointment 100,000 units/gram	Angular cheilitis
Nystatin topical powder 100,000 units/gram	Denture stomatitis
Nystatin oral suspension 100,000 units/gram	Intraoral candidasis
Betamethasone dipropionate clotrimazole cream	Chloronic angular cheilitis
Clotrimazole troches 10 mg	Intraoral candidasis
Amphotericin B 100 mg/ml	Intraoral candidasis

Table 3: Clinical classification

Clinical classification
Angular chelitis
Chronic atrophic (erythematous)
Denture stomatitis
Endocrine-candidiasis syndrome
Hyperplastic (Candidial leukoplakia)
Inflammatory papillary hyperplasia
Median rhomboid glossitis
Mucocutaneous
Pseudomembranous

Xerostomia

Such patients may require maintenance therapy of twice daily 0.12% chlorhexidine gluconate mouthrinses after an acute or chronic episode of oral candidiasis is under control.

Recent developments

For many years, amphotericin B deoxycholate remained the mainstay of treatment for IFIs[27]. The major limitations of its usage are the substantial adverse effects such as fever, chills, nausea and vomiting, electrolyte abnormalities and, most importantly, nephrotoxicity[45]. In the 1990s, the introduction of the two azoles fluconazole and itraconazole represented a considerable advance in antifungal therapy. However, the use of fluconazole is hampered by its narrow spectrum, and the use of itraconazole is limited due to absorption problems[46]. New therapeutic agents have now been developed that provide better antifungal activities and lower toxicities (Table 2, 4 and 5).

Extended-spectrum triazoles

Second-generation triazoles act predominantly by inhibition of the cytochrome P450 (CYP450)-dependent conversion of lanosterol to ergosterol[47]. This leads to an accumulation of toxic 14- -methylsterols and a depletion of membrane-associated ergosterol. This change in cell membrane properties results in inhibition of cell growth or cell death. Antifungal agents in this class include voriconazole, which was approved for the treatment of fungal infections in 2002, and posaconazole, which received US Food and Drug Administration (FDA) approval in September 2006. Clinical trials of ravuconazole have not

yet been completed. Voriconazole is available both in intravenous (i.v.) and oral formulations.

The bioavailability of the oral formulation is >90% but is decreased to 80% by fatty foods[48]. Both i.v. and oral formulations are given as a twice-daily dosage. A loading dose is needed to achieve steady-state concentration rapidly (6 mg/kg twice daily on Day 1 followed by 4 mg/kg twice daily)[48]. Posaconazole is available only in oral formulation (400–800 mg/day in divided doses). Administering posaconazole with a meal, in a suspension rather than a tablet and in divided doses increases its oral bioavailability[49]. Posaconazole is excreted mainly in the faeces and a minor portion is metabolised in the liver through glucuronidation[49]. Dosage adjustment for oral voriconazole and posaconazole is not necessary in patients with renal insufficiency or in patients receiving dialysis[50,51]. The concentrations of voriconazole in cerebrospinal fluid (CSF) are ca. 50% of plasma concentrations, and concentrations in brain tissue are higher than those in the CSF[52]. Voriconazole and posaconazole are very broad-spectrum antifungal agents. As with other azoles, they appear to be fungistatic against most yeasts but have a fungicidal effect against the filamentous moulds[53]. Voriconazole and posaconazole are very active against most Candida spp., including C. krusei, C. glabrata and those strains that are resistant to fluconazole[54,14]. For Aspergillus spp., voriconazole and posaconazole are very potent against many species, including A. terreus, which is resistant to amphotericin B, and A. fumigatus, which is resistant to itraconazole[55,56]. They are active against some but not all strains of opportunistic moulds[56,57,58,59,60].

Table 4: Systemic antifungal medications

Systemic antifungal medications	
Dosage form/ strength	Indication
Ketoconazole tablet 200 mg	Intraoral candidasis
Fluconazole tablet 100 mg	Intraoral candidasis
Itraconazole tablet 100 mg	Intraoral candidasis

Table 5: Antifungal drugs for treatment of oropharyngeal candidiasis

Generic name	Proprietary name	Formulation
Amphotericin B	Fungizone	100 mg/ml oral suspension
Clotrimazole	Mycelex	10 mg troche
Fluconazole	Diflucan	100 mg tablet
		10 mg/ml oral suspension
		40 mg/ml oral suspension
Itraconazole	Sporanox	100 mg capsule
		10 mg/ml oral suspension
Ketoconazole	Nizoral	200 mg tablet
Nystatin	Mycostatin	100,000 units/ml oral suspension
		200,000 units/ml pastille
		500,000 units/ml tablet
		100,000 units/ml vaginal tablet

Echinocandins

The echinocandins are large lipopeptide molecules that inhibit synthesis of -1, 3-d-glucan, which is an essential component of the cell wall of many fungi but is absent in mammals[61]. Inhibition of -1,3-d-glucan synthase interferes with fungal cell wall synthesis, which leads to osmotic instability and death of the fungal cell[61]. Until now, caspofungin, micafungin and anidulafungin are the only echinocandin agents approved for clinical use. All echinocandin preparations to date are for i.v. use only[62]. The three agents share similar pharmacological characteristics, with some variations[62]. A once-daily dosing regimen is optimal based on concentration-dependent pharmacodynamics and prolonged post-antifungal effects[53,63,64].

A loading dose is recommended for caspofungin (75 mg loading on Day 1 followed by 50 mg/day) and anidulafungin (200 mg loading on Day 1 followed by 100 mg/day), but not for micafungin (50–150 mg/day)[65,64]. Caspofungin and micafungin are degraded mainly in the liver[64] whilst anidulafungin uniquely undergoes chemical degradation in the blood[65]. All three agents are poor substrates for the hepatic CYP450 enzyme system. Therefore, unlike triazoles, the CYP450-independent metabolism and degradation of echinocandins reduces concern about drug–drug interactions[61]. Echinocandins have very low MICs against clinically significant Candida spp., including C. albicans, C. tropicalis, C. glabrata, C. krusei, C. lusitaniae and Candida dubliniensis[66,59,67,68].

Rationale for and against antifungal combinations

The original use of antifungal combination therapy was in the treatment of cryptococcal meningitis in patients who did not have AIDS. Amphotericin B was the first agent available for successfully treating invasive mycoses, but there have been major problems with systemic toxic reactions associated with its infusion and nephrotoxicity[69]. Indeed, several trials have demonstrated that when flucytosine is included in the treatment regimen, the dose of amphotericin B could be reduced, thereby decreasing somewhat its toxicity[70,71].

The dose of amphotericin B was subsequently increased and response rates to therapy, with or without flucytosine, improved[72,73]. At present, we are faced with an increasing incidence of serious invasive fungal mycoses and a high mortality rate secondary to these infections[74,75,76,77].

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