ORAL CANDIDIASIS: A REVIEW

YUVRAJ SINGH DANGI1, MURARI LAL SONI1, KAMTA PRASAD NAMDEO1

Institute of Pharmaceutical Sciences, Guru Ghasidas Central University, Bilaspur (C.G.) - 49500 Email: yuvv1206@gmail.com

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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 etiology of invasive fungal pathogens has changed. Non-albicans Candida, non-fumigatus Aspergillus and moulds other than Aspergillus have become increasingly recognized 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 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): Oral candidiasis can be 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. 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, 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 peroral opportunistic infection that usually results from overgrowth of endogenous Candida fungal microorganisms. There are many species of Candida (Table I) 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. Saliva contains antifungal proteins including histatins and calprotectin that help protect patients from Candida infections. 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 a one antifungal placebo-controlled trial showed improved development of dermatophytes, such as tinea pedis, onychomycosis, and tinea cruris. In addition, systemic fluconazole prophylaxis may prevent esophageal and vaginal candidiasis; cryptococcosis, 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 ofazole-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.

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 USA1,2 and from 2.53 to 11 per 100 000 persons in European countries3. In various reports, Candida spp. accounted for 6–10% of nosocomial BSIs. Rising incidences of candidaemia have been reported throughout the world in the past two decades. The
major predisposing factors included surgical intervention, intensive
care treatment, solid tumour and haematological malignancies, use of
steroids and premature birth\(^{13}\). Crude mortality rates remain high
despite advances in medical care, ranging from 30% to 50%\(^{12,23,24}\).
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\(^{7,18}\). Candida glabrata infections are rare in infants and
children but are significantly more common in the elderly\(^{21}\). Candida
tropicalis plays an important role as a cause of invasive diseases in
patients with haematological malignancy\(^{25}\). Overall, the non-albicans
Candida spp. have shown an increasing trend as causative pathogens
in BSIs\(^{27}\) with a 10–11% increment over a 6.5-year period in a global
report\(^{31}\). 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
it is difficult to determine whether this reflects true cross-resistance
or whether some isolates have altered susceptibilities to azoles.

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)\(^{26}\). 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\(^{29}\). The usual route of infections for IA is inhalation of
Aspergillus conidia. The most frequently involved sites of IA are sinuses,
the 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
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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
clinical candidiasis, although the highest yield of positive cytology smears is
with pseudemembranous candidiasis\(^{34}\).

Atrophic Candidiasis

Atrophic candidiasis exhibits a diffusely reddened, often 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

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 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
nitrile and clotrimazole creams, and prescription nystatin or
toconoazole 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 unilateral 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 oral lesion 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
Prophylactic removal

During treatment as the medication works topically and must be in contact with the tissue. Systemic prescription antifungal agents include ketoconazole, fluconazole, and itraconazole.

Prostodontic appliances

With any case of oral candidiasis, if the patient utilizes a removable prostodontic 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. 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. 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. 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.

Table 1: Species of Oral Candida

<table>
<thead>
<tr>
<th>Species of Oral Candida</th>
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<tbody>
<tr>
<td>C. albicans</td>
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<tr>
<td>C. glabrata</td>
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<tr>
<td>C. guilliermondii</td>
</tr>
<tr>
<td>C. krusei</td>
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<tr>
<td>C. parapsilosis</td>
</tr>
<tr>
<td>C. pseudotropicalis</td>
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<tr>
<td>C. stellatoidea</td>
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<tr>
<td>C. tropicalis</td>
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Table 2: Topical antifungal medications

<table>
<thead>
<tr>
<th>Topical antifungal medications</th>
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<tbody>
<tr>
<td>Dosage form/strength</td>
</tr>
<tr>
<td>OTC</td>
</tr>
<tr>
<td>Miconazole cream 2%</td>
</tr>
<tr>
<td>Clotrimazole cream 1%</td>
</tr>
<tr>
<td>Prescription</td>
</tr>
<tr>
<td>Ketoconazole cream 2%</td>
</tr>
<tr>
<td>Nystatin ointment 100,000 units/gram</td>
</tr>
<tr>
<td>Nystatin topical powder 100,000 units/gram</td>
</tr>
<tr>
<td>Nystatin oral suspension 100,000 units/gram</td>
</tr>
<tr>
<td>Betamethasone dipropionate clotrimazole cream</td>
</tr>
<tr>
<td>Clotrimazole troches 10 mg</td>
</tr>
<tr>
<td>Amphotericin B 100 mg/ml</td>
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</tbody>
</table>

Table 3: Clinical classification

<table>
<thead>
<tr>
<th>Clinical classification</th>
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<tbody>
<tr>
<td>Angular cheilitis</td>
</tr>
<tr>
<td>Chronic atrophic (erythematous)</td>
</tr>
<tr>
<td>Denture stomatitis</td>
</tr>
<tr>
<td>Endocrine-candidiasis syndrome</td>
</tr>
<tr>
<td>Hyperplastic (Candidal leukoplakia)</td>
</tr>
<tr>
<td>Inflammatory papillary hyperplasia</td>
</tr>
<tr>
<td>Median rhomboid glossitis</td>
</tr>
<tr>
<td>Mucocutaneous</td>
</tr>
<tr>
<td>Pseudomembranous</td>
</tr>
</tbody>
</table>

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. The major limitations of its use are the substantial adverse effects such as fever, chills, nausea and vomiting, electrolyte abnormalities and, most importantly, nephrotoxicity. In the 1990s, the introduction of the 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. 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. This leads to an accumulation of toxic 14α-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 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. 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). 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. Posaconazole is excreted mainly in the faeces and a minor portion is metabolised in the liver through glucuronidation. Dosage adjustment for oral voriconazole and posaconazole is not necessary in patients with renal insufficiency or in patients receiving dialysis. 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. 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. Voriconazole and posaconazole are very active against most Candida spp., including C. krusei, C. glabrata and those strains that are resistant to fluconazole. 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. They are active against some but not all strains of opportunistic moulds.

Table 4: Systemic antifungal medications

<table>
<thead>
<tr>
<th>Systemic antifungal medications</th>
<th>Dosage form / strength</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>50,000 units/ml vaginal tablet</td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50 mg/ml oral suspension</td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>40 mg/ml oral suspension</td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>100 mg ml oral suspension</td>
<td>Oral candidiasis</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>100 mg/ml oral suspension</td>
<td>Oral candidiasis</td>
</tr>
</tbody>
</table>

Table 5: Antifungal drugs for treatment of oropharyngeal candidiasis

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Proprietary name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Fungonex</td>
<td>100 mg/ml oral suspension</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Mycelex</td>
<td>10 mg troche</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Mycelac</td>
<td>10 mg/ml oral suspension</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Sporanox</td>
<td>10 mg/ml oral suspension</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nizoral</td>
<td>10 mg/ml oral suspension</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Mycostatin</td>
<td>200 mg ml oral suspension</td>
</tr>
</tbody>
</table>

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 mammal. Inhibition of 1,3-d-glucan synthase interferes with fungal cell wall synthesis, which leads to osmotic instability and death of the fungal cell. 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. The three agents share similar pharmacological characteristics, with some variation. A once-daily dosing regimen is optimal based on concentration-dependent pharmacodynamics and prolonged post-antifungal effects.

A loading dose is recommended for caspofungin (75 mg loading on Day 1 followed by 50 mg/day) and micafungin (200 mg loading on Day 1 followed by 100 mg/day), but not for micafungin (50–150 mg/day). Caspofungin and micafungin are degraded mainly in the liver whilst anidulafungin uniquely undergoes chemical degradation in the blood. 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. Echinocandins have very low MICs against clinically significant Candida spp., including C. albicans, C. tropicalis, C. glabrata, C. krusei, C. lusitaniae and Candida dubliniensis.

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. Indeed, several trials have demonstrated that fluconosine is included in the treatment regimen, the dose of amphotericin B could be reduced, thereby decreasing somewhat its toxicity.

The dose of amphotericin B was subsequently increased and response rates to therapy, with or without fluconosine, improved. At present, we are faced with an increasing incidence of serious invasive fungal mycoses and a high mortality rate secondary to these infections.


