Fungal infections in dentistry: Clinical presentations, diagnosis, and treatment alternatives

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Oral candidiasis is a common opportunistic infection that requires knowledge of the various clinical presentations and management strategies for successful treatment.
Numerous local and systemic factors contribute to the development of candidiasis, and the infections can range from superficial mucocutaneous overgrowths to invasive bloodstream infections with a high mortality rate. In addition to *Candida albicans*, various fungal strains have been isolated from the oral cavity, including *C. tropicalis, C. glabrata, C. krusei*, and many others. Antifungal agents are available in various forms, each with differing indications, dosing regimens, adverse effects, and drug interactions. Some antifungal agents are available as oral suspensions, pastilles, or creams, whereas others are administered systemically in capsule or intravenous form. This review describes the various presentations of oral candidiasis and the diagnostic methods and treatment alternatives, with a specific focus on pharmacologic management. Spectra of activity, mechanisms of action, adverse reactions, drug interactions, and dosing regimens are explored in the context of both topical and systemic pharmacotherapy used to treat candidiasis. Polyenes (nystatin, amphotericin B); azoles (ketoconazole, miconazole, clotrimazole, fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole); and echinocandins (caspofungin, micafungin, anidulafungin) are discussed. Novel approaches in antifungal therapy with the use of probiotics are also reviewed. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:533−546)

Candida albicans is the most prevalent *Candida* species isolated from the oral cavity in both health and disease.[1-3] It was first reported in 1838 by the pediatrician Francois Veilleux. *C. albicans* has many clinical presentations, ranging from superficial mucocutaneous overgrowths to deep tissue and invasive bloodstream infections, which have a high mortality rate.[4] *C. albicans* has been isolated in greater than 80% of intraoral lesions.[1,5] Less commonly isolated *Candida* strains from the oral cavity include *C. tropicalis, C. glabrata, C. krusei, C. dubliniensis, C. pseudotropicalis, C. parapsilosis, C. stellatoidea*, and *C. guilliermondii* (Table I).[6-9] In addition to *C. albicans, C. glabrata* is emerging as an important etiology in both mucosal and bloodstream infections.[10]

Candida is an opportunistic yeast that will proliferate in the presence of certain local and systemic factors. The incidence of *Candida* overgrowths gradually increases as immune functioning declines.[11] Local factors, such as dental prostheses, impaired salivary gland function, poor oral hygiene, high carbohydrate diet, inhaled corticosteroids, and topical oral corticosteroids, favor the growth of *Candida* in the oral cavity.[3,12,13] The immunosuppressive effects of inhaled corticosteroids on the oral cavity have been reported to be dose dependent.[14] Systemic factors that favor the transition of *Candida* from commensal to pathogenic include extremes of age (infants and older patients); drugs (broad-spectrum antibiotics, systemic corticosteroids, other xerogenic drugs); endocrine dysfunction (diabetes mellitus, Cushing syndrome); smoking; active malignancies; chemotherapy and radiation therapy; malnutrition; and immunosuppressed states, such as human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) (Table II).[3]

CLINICAL PRESENTATIONS

Oral candidiasis can be divided into pseudomembranous, erythematous, and hyperplastic categories.[16] The remaining clinical presentations, such as *Candida*-associated denture stomatitis, angular cheilitis, and linear gingival erythema, may not respond to antifungals because of underlying diseases and multifactorial etiologies (see Table II). For example, linear gingival erythema may be caused by underlying HIV infection. It is important to recognize that patients may present with a combination of *Candida* infections, such as both erythematous candidiasis and angular cheilitis in denture wearers.

Pseudomembranous candidiasis (thrush)

Pseudomembranous candidiasis, commonly known as *oral thrush*, appears as distinct soft, white plaques that can be easily wiped off, revealing a normal or

Statement of Clinical Significance

Oral candidiasis is a widely prevalent opportunistic infection with various clinical presentations and treatment alternatives. Here, we present a review of *Candida* clinical presentations and an in-depth account of topical and systemic therapies. This will aid clinicians in diagnoses and appropriate pharmacologic management.

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Table I. Oral *Candida* species

C. albicans
C. tropicalis
C. glabrata
C. krusei
C. dubliniensis
C. pseudotropicalis
C. parapsilosis
C. stellatoidea
C. guilliermondii

Table II. Etiologic factors contributing to oral candidiasis

Local	Dental prosthesis trauma/irritation (e.g., poorly fitting dentures)
	Impaired salivary gland function/xerostomia
	Overclosure of the lips (edentulous patients with reduced vertical dimension)
	Chronic topical antimicrobial use
	Inhaled corticosteroids
	Topical corticosteroids
	High carbohydrate diet
	Poor oral hygiene
Systemic	Extremes of age (infants and older adults)
	Immunosuppression (human immunodeficiency virus/acquired immunodeficiency syndrome [HIV/AIDS], transplant recipients, immunosuppressive drugs)
	Endocrine dysfunction (uncontrolled diabetes mellitus, Cushing syndrome)
	Conditions associated with xerostomia (Sjögren syndrome)
	Active malignancies (e.g., leukemia)
	Chemotherapy
	Radiation therapy
	Smoking
	Malnutrition
	Anemia
	Broad-spectrum antimicrobials
	Systemic corticosteroids
	Xerogenic drugs (cytotoxic drugs, anticholinergics, psychoactive drugs, opioids, sympathomimetics, antihypertensives, diuretics)[15]

erythematous surface underneath. The lesions may be acute or chronic, and ulceration is not expected. The plaques contain fungal hyphae, bacteria, inflammatory cells, desquamated epithelial cells, keratin, and fibrin.[17] Common sites are the labial and buccal mucosa, the dorsal tongue, the hard and soft palates, and the oropharynx.[3] Symptoms can range from tenderness and burning to dysphagia, if located in the oropharynx. Oral thrush may also be asymptomatic.

Erythematous (atrophic) candidiasis

Atrophic candidiasis presents as erythematous areas most commonly on the palate.[3] It is usually discovered under dentures and orthodontic retainers but is also found on the buccal mucosa and the dorsal tongue.[3] Patients may be asymptomatic or experience a burning sensation of the involved oral mucosa, commonly under dentures that are left in overnight. Other risk factors include HIV infection, vitamin B_{12} deficiency, corticosteroids, and uncontrolled diabetes (see Table II).

Median rhomboid glossitis (central papillary atrophy)

Median rhomboid glossitis is an uncommon variant of atrophic candidiasis, also known as *central papillary atrophy*.[18] Median rhomboid glossitis presents as a well-defined symmetric rhomboid area with papillary atrophy and erythema, located on the midline dorsum of the tongue anterior to the circumvallate papilla.[1] The lesions appear in a smooth, shiny pattern as a result of loss of filiform papilla. Patients are often asymptomatic.[19] Median rhomboid glossitis may be associated with "kissing lesion" on the palate, directly related to fungal inoculation.[20]

Denture stomatitis

Previously known as *chronic atrophic candidiasis*, denture stomatitis is characterized by erythema and edema restricted to areas covered by dentures, such as the hard palate and the alveolar ridges.[16] Older denture-wearing patients are at highest risk for denture stomatitis, with symptoms ranging from asymptomatic to pain, burning, and itchiness in some cases. Poorly fitting dentures increase the risk because they impinge on the mucosa and inhibit salivary flow.[19] Lesion are more commonly found on maxillary mucosa compared with the mandible.[20] Denture stomatitis is classified into 3 clinical groups, depending on severity. Type I is described as localized pinpoint petechial hemorrhage and inflammation. Type II presents as diffuse erythema covering the denture bearing area either partially or completely. Type III is defined as papillary hyperplasia or granular lesions of the oral mucosa, located on the alveolar ridge or the middle of the palate.[21]

Hyperplastic candidiasis

Hyperplastic candidiasis is a less common form of *Candida* infection. This variant is often asymptomatic and presents with well-demarcated, raised, white or translucent patches that cannot be wiped off.[22] It may be seen on the anterior buccal mucosa, posterior corners of the mouth, and lateral borders of the tongue. It commonly occurs in middle-aged to older males. The lesions may appear nodular or speckled on clinical examination.[23] If the lesion resembles speckled leukoplakia and there is no response to antifungal therapy, biopsy is indicted. The lesions show varying degrees of dysplasia and may progress to malignancy.[24,25]

Angular cheilitis (angular stomatitis)

Angular cheilitis is characterized by ulcerated lesions at the labial commissures of the mouth and can present unilaterally or bilaterally. The lesions are erythematous, and often, crusting or fissuring is present. Patients typically report pain and soreness caused by fissuring.[19] The infection may last from days to years. Angular cheilitis is common in older patients because of the reduced vertical dimension of occlusion and deep skin folds, both of which pool saliva at the labial commissures and promote the growth of *Candida*.[16] A combination of *Staphylococcus aureus* and *C. albicans* infections is often implicated in the development of this condition.[3] Thus, angular cheilitis can be caused by candidiasis alone, a combination of *Candida* and bacterial infections, or only bacteria.[9] Iron and vitamin B_{12} deficiencies have also been reported to be etiologic factors.[3]

Chronic mucocutaneous candidiasis

Mucocutaneous candidiasis may involve the oral cavity, skin, nails, and mucous membranes. In the oral cavity, lesions may present as angular cheilitis or hyperplastic candidiasis, whereas acral lesions appear as hyperkeratotic erythematous plaques.[19] Mucocutaneous candidiasis demonstrates a poor response to topical antifungal therapy, and the severity of the infection correlates with the level of immune dysfunction.[26] The cases are mostly sporadic, although an autosomal recessive pattern has been identified. Mucocutaneous candidiasis is commonly seen in infants, especially in immunocompromised ones. It has been associated with endocrinopathies, such as hypoparathyroidism, hypothyroidism, Addison disease, and diabetes mellitus.[27]

DIAGNOSIS

A thorough history and clinical assessment of the presenting signs and symptoms are often sufficient to diagnose oral candidiasis. Adjunctive methods to further confirm the diagnosis include exfoliative cytology, culturing, and brush biopsy.[28] Exfoliative cytology, using periodic acid−Schiff staining to detect fungal pseudohyphae, is effective for most *Candida* diagnoses, particularly for pseudomembranous candidiasis.[27,29] In addition to periodic acid−Schiff staining, the microscopic evaluation may be performed with 10% potassium hydroxide or methylene blue staining, which show pseudohyphal components and budding yeast.[19] It is important to note that microscopic evaluation will reveal pseudohyphae or hyphae but will not indicate tissue invasion. Culture with Sabaraud's dextrose agar has been demonstrated as a useful adjunctive method to qualitatively determine the presence of *C. albicans*.[27] However, a positive result on culture is of little diagnostic value because most immunocompetent patients have commensal oral *Candida*. Biopsy is indicated for suspected hyperplastic candidiasis when it presents as speckled leukoplakia with lack of response to antifungal therapy. In some situations, the diagnosis is made after response to treatment has occurred. The clinician must consider the possibility of refractory lesions that persist despite a correct preliminary diagnosis. For such refractory lesions, culture and sensitivity assays may be indicated.

TREATMENT PROTOCOL

The treatment for oral candidiasis varies from nonpharmacologic approaches to topical and systemic pharmacologic agents. Two main treatment principles are (1) identification and removal of contributing factors and (2) reduction of the fungal load. Oral and denture hygiene is essential for successful treatment of oral *Candida* infections. Ill-fitting dentures should be corrected, and nocturnal denture wear should be avoided, and the patient should be encouraged to soak the dentures in chlorhexidine solution (2%) or diluted hypochlorite (0.1%) overnight. When possible, broad-spectrum antibiotic therapy should be avoided. Endocrine dysfunction, such as diabetes mellitus, should be adequately controlled. If related to topical steroid (e.g., inhaler) administration, a volumetric spacer may be used. Simply rinsing the oral cavity after inhaler use helps prevent opportunistic *Candida* infections. Patients with xerostomia should be encouraged to drink water more frequently and chew non−sugar-containing gum to stimulate salivary flow. Saliva contains antimicrobial proteins, such aslactoferrin, sialoperoxidase, histidine-rich polypeptides, and anticandidal antibodies, all of which prevent overgrowth of *Candida*. Adjunctive agents, such as pilocarpine, may be indicated to adequately manage xerostomia and treat oral candidiasis.

Once the underlying contributing factors have been accounted for, pharmacologic therapy may be indicated. Basic pharmacologic principles must not be overlooked by the clinician when prescribing polyene or azole antifungal therapy. The patient's medical history, presenting oral symptoms, and compliance issues should be considered.[23] Topical antifungal therapy is the recommended treatment in mild presentations, as most of these cases are responsive to topical therapy. A recent meta-analysis of mycologic cure rates demonstrated that nystatin, amphotericin B (AmB), ketoconazole, miconazole (tablets and oral gel), clotrimazole, itraconazole (capsules and oral solution) were efficacious in the treatment of oral candidiasis. Researchers concluded that fluconazole is superior to other drugs, showing a statistically significant improvement in its therapeutic effect on oral candidiasis.[30]

Fungal lesions that are refractory to one form of antifungal agent may be susceptible to another class of agents. Removal of underlying factors, patient compliance, and the correct diagnosis should all be confirmed

before administering an additional course of antifungal therapy. If lesions are refractory to treatment or frequently recur, it is prudent for the general dentist to refer the patient to an oral and maxillofacial pathologist or surgeon because therapy with systemic antifungal agents may be indicated at this stage. Systemic antifungal therapy should also be considered in immunocompromised patients at risk of candidemia.

Adjunctive Agents

Adjunctive agents include sialagogues (e.g., pilocarpine, cevimeline, bethanechol) and antiseptic mouth rinses (e.g., chlorhexidine gluconate). Pilocarpine is a parasympathomimetic agent (muscarinic agonist) used to treat salivary gland hypofunction by promoting exocrine gland secretion (salivary, sweat, and lacrimal glands). Adverse reactions are related to the widespread effect on exocrine glands, combined with stimulation of the urinary tract and gastrointestinal (GI) smooth muscles. These reactions include increased sweating, lacrimation, flushing, nausea, dizziness, urinary frequency, and pulmonary secretions.[15] Pilocarpine is commonly administered as a 3- to 5-mg dose 3 times daily. Pilocarpine should be avoided in hypersensitive patients and those with uncontrolled asthma and narrow-angle glaucoma. Chlorhexidine gluconate may be used to prevent recurrent *Candida* infections. Chlorhexidine gluconate (0.12%) oral rinse is prescribed as a 475-mL solution, with instructions to the patient to rinse with 15 mL for 1 minute 2 times daily for 2 weeks. Prolonged chlorhexidine use can lead to alterations in taste, mucosal erosion at high doses, and, most commonly, brown discoloration of teeth, restorative materials, and the tongue.

ANTIFUNGAL PHARMACOTHERAPY

In each of the following sections, both the topical and systemic antifungals are presented to gain a more comprehensive understanding of antifungal pharmacotherapy. Dosing regimens for topical antifungals will be reviewed, followed by a more detailed account of their mechanism of action, pharmacokinetics, drug interactions, and adverse effects. Systemic antifungals are discussed in the context of oral administration and other methods, such as intravenous (IV) administration. Some of the modalities described are reserved for life-threatening fungal infections treated in acute hospital care settings, rather than in general dental practice.

Gentian violet

Gentian violet solution (0.5%) is a topical fungicidal agent that also targets staphylococcal infections.[19] It is prescribed as a 1.5-mL dose used 2 times daily. It is important to note that skin irritation, oral ulcers, and purple staining of clothes and skin may result.[19]

Polyenes: nystatin, AmB

Two polyene fungicidal agents, nystatin and AmB, were discovered in the 1950s but remain to be widely used to treat *Candida* infections. Polyene molecules are produced by *Streptomyces nodosus*, and they specifically bind to the ergosterol molecules in the fungal cell membrane, inducing cell necrosis by increasing permeability and leakage of intracellular contents (Ca^{2+}, Na^{+}, K^{+}) (Figure 1).[31] Both nystatin (C_{47} H_{75} NO_{17}) and AmB (C_{47} H_{73} NO_{17}) have large chemical structures, resulting in poor water solubility and oral absorption.

Nystatin. Nystatin is available in various topical forms, such as suspensions, creams, and pastilles, all of which have a bitter taste. Flavoring agents have been added to improve patient compliance. Nystatin has minimal adverse effects because of poor systemic absorption when in contact with the skin, mucous membranes, or GI tract. Parenteral administration is highly toxic, rendering nystatin unsuitable for treating systemic *Candida* infections. Nystatin oral suspension (100,000 units/mL) or pastilles (100,000 IU) may be prescribed topically as a first-line agent. Nystatin suspension (200 mL) is administered as 1 tablespoon (15 mL) for 2 to 3 minutes 4 times daily, for 10 days. Patients should not eat or drink for 30 minutes after intake. If nystatin is swallowed, patients may experience nausea, vomiting, and diarrhea (Table III). Nystatin pastilles are dissolved and taken 4 times daily for 7 to 14 days. For the treatment of angular cheilitis and fungal infections residing under dentures, nystatin cream (100,000 units/g) may be dispensed (30 g). For angular cheilitis, cream is applied to the labial commissures 3 times daily for 10 to 14 days. A thin layer of nystatin cream may be applied to the intaglio surface of dentures after meals for 10 to 14 days.

Amphotericin B. AmB is poorly absorbed orally and is commonly administered topically in the form of an oral suspension (100 mg/mL) or lozenges (10 mg). AmB suspension is swished and swallowed as a 100- to 200-mg dose for as long as possible after meals, 4 times daily for 14 days. AmB lozenges are dissolved and taken after meals, 3 times daily for 14 days. It is important to note that lozenges may contain sucrose, which should be avoided in patients with uncontrolled diabetes mellitus or high caries risk.[23] AmB lozenges (10 mg) may be combined with nystatin ointment (100,000 units/g) or miconazole gel (2%). Topical AmB therapy rarely results in adverse effects because of negligible absorption in the GI tract. However, it may also be administered intravenously to treat systemic *Candida* infections. It can act either fungicidally or fungistatically, depending on the organism and the dose delivered. AmB has a broad spectrum of

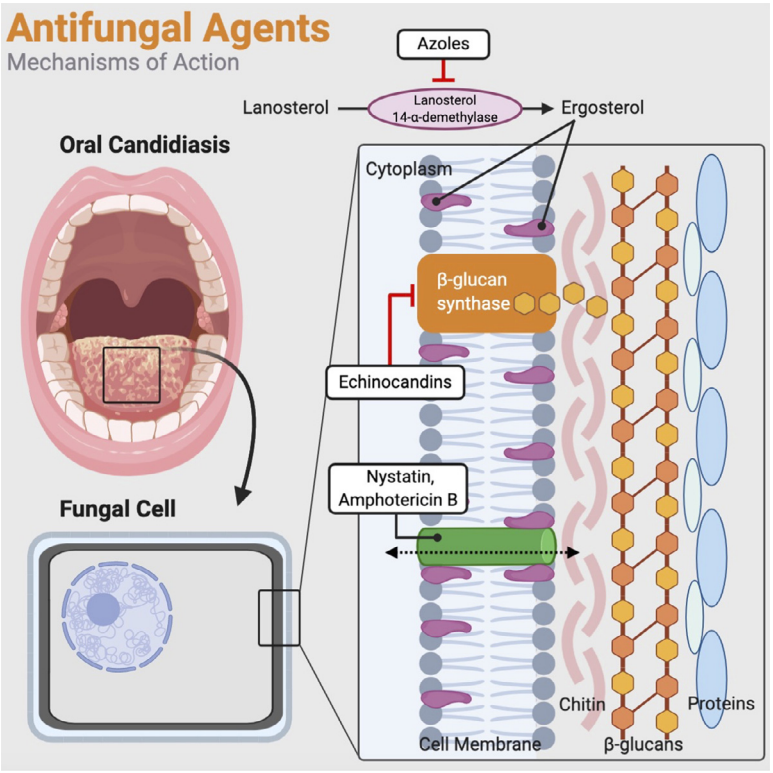

Fig. 1. Various antifungal mechanisms of action, targeting the fungal cell membrane and the fungal cell wall.

activity against yeasts and molds. It is both fungistatic and fungicidal against most *Candida* and *Aspergillus* species.[32] It also targets *Blastomyces dermatitidis, Cryptococcus neoformans, Coccidioides immitis*, and *Histoplasma capsulatum* (see Table III). It is highly bound to plasma proteins and penetrates tissues poorly. AmB is metabolized hepatically and excreted in urine slowly and has a half-life of 15 days. AmB is not metabolized by cytochrome P450 (CYP450) enzymes, minimizing drug interactions through CYP450 mechanisms. The original AmB formulation, developed in the 1950s, has several adverse effects, most notably nephrotoxicity (see Table III). Pharmacologic agents with nephrotoxicity will cause added adverse renal effects and should be avoided when administering IV AmB. These may include, but are not limited to, cyclosporine, vancomycin, and aminoglycosides. An effort was made in the 1990s to minimize its adverse effects, leading to the introduction of lipid formulations, such as AmB colloidal dispersion, lipid complex, and liposomal AmB. AmB colloidal dispersion was discontinued in 2011, and the remaining lipid formulations have been reported be as efficacious as the original AmB formulation with the advantage of less nephrotoxicity.[31,32] It is important to note that renal toxicity is dose dependent and reversible but can become irreversible with exceedingly high doses.

Infusion-related adverse effects are common in the majority of patients receiving IV AmB. These include headache, rigors, fever, bronchospasm, hypotension, nausea, vomiting, diarrhea, weight loss, muscles aches or spasms, and pain at the site of injection with potential thrombophlebitis. Less common reactions include cardiac dysrhythmia, hemolytic anemia, convulsions, neuropathy, hearing loss, and hypersensitivity (see Table III). Liver functional tests (LFTs), complete blood counts, and analysis of several serum parameters (creatinine, potassium, sodium, magnesium) should be performed because of the wide range of toxicities (see Table III). To minimize infusion-related effects, AmB should be infused slowly over 4 to 6 hours with prior administration of acetaminophen, diphenhydramine, and corticosteroids. Meperidine has also been suggested for rigors. Prehydrating with 500 mL of normal saline may aid in reducing nephrotoxicity.

Azoles: imidazoles and triazoles

Imidazoles (ketoconazole, miconazole, and clotrimazole) and triazoles (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole) are pyrrole ring agents that have a broad spectrum of activity and are commonly used to treat candidiasis. They are synthetic fungistatic agents that inhibit CYP450 enzyme lanosterol 14-α-demethylase, preventing the conversion of lanosterol to ergosterol (see Figure 1). These

Table III. Review of antifungal agents: polyenes, imidazoles, triazoles, and echinocandins (various sources)

Class/Drugs	*Indications/Spectrum of activity*	*Dose*	*Half-life*	*Adverse effects*
Polyenes				
Nystatin (oral suspension, pastille, cream) *Mycostatin oral suspension* *Mycostatin pastilles*	**Dental:** Oropharyngeal thrush, cutaneous candidiasis **Systemic**: N/A	**Suspension (100 units):** 15 mL PO rinse 2−3 min QID for 10 days **Pastille:** Dissolve after meals QID for 7−14 days **Cream:** Apply directly to area of infection TID−QID	N/A	Negligible absorption from GI tract. If Nystatin swallowed, may experience nausea, vomiting, diarrhea
Amphotericin B (oral suspension, lozenge, cream, IV) *Fungizone oral suspension*	**Dental**: Oral Candidiasis **Systemic**: Wide spectrum: Disseminated *Candida* and *Aspergillus* species, *Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis*	**Suspension (100 mg/mL):** 100−200 mg PO swish for maximum duration QID for 14 days **Lozenge (10 mg):** Dissolve after meals TID for 14 days **Cream:** Apply directly to area of infection QID for 14 days	15 days	Negligible absorption from GI tract when taken orally **When administered IV:** Headache, fever, chills, dermal rash, muscle and joint pain, hypotension, hypokalemia, hypomagnesemia, seizure, cardiac arrhythmias and arrest, nephrotoxicity, anemia, thrombocytopenia, thrombophlebitis, hypersensitivities, including anaphylaxis
Imidazoles				
Ketoconazole (cream, oral tablets) *Nizoral tablets*	**Dental:** Oral candidiasis **Systemic:** Blastomycosis, chronic mucocutaneous candidiasis, chromomycosis, coccidioidomycosis, paracoccidioidomycosis, and histoplasmosis	**Cream (2%):** BID−TID for 14−28 days **Tablet:** 200−400 mg QD for 14 days	7−10 hours	**Topical:** Skin irritation and headache **Systemic:** Nausea, vomiting, dermal rash, pruritus, adrenal insufficiency, gynecomastia in some males, and severe hepatotoxicity requiring LFTs Pregnancy risk FDA category C
Miconazole (oral gel, cream, tablets)	**Dental**: Oropharyngeal candidiasis	**Oral Gel (2%):** Apply directly to area of infection TID−QID for 14−21 days **Cream (2%):** Apply directly to area of infection BID for 14−21 days **Tablets:** 50 mg QID 14 days	N/A	**Topically:** Skin irritation and burning

(*continued on next page*)

Table III. Continued

Class/Drugs	*Indications/Spectrum of activity*	*Dose*	*Half-life*	*Adverse effects*
Clotrimazole (troche, solution, cream) *Mycelex oral troches*	**Dental**: Oropharyngeal candidiasis	**Troche:** 10 mg dissolved PO 5 × /day for 14 days **Solution (1%):** 5 mL QID for 14 days **Cream (1%):** Apply directly to area of infection BID−TID for 21−28 days	N/A	**Topically:** Nausea, vomiting, and skin irritation
Triazoles				
Fluconazole (oral, IV) *Diflucan tablets*	**Dental:** Oral thrush, chronic severe esophageal/oropharyngeal candidiasis **Systemic:** Bone marrow transplant prophylaxis, vulvovaginal candidiasis, candidemia, coccidioidomycosis, mucocutaneous candidiasis, cryptococcal meningitis	**Capsules:** Loading dose of 200 mg; 100 mg QID for 7−14 days thereafter	25 hours	Headache, nausea, vomiting, diarrhea, dermal rashes, hepatotoxicity, drug interactions Pregnancy risk FDA category C
Itraconazole (oral capsule, oral suspension, IV) *Sporanox capsules* *Sporanox oral solution*	**Dental:** Oral candidiasis, oropharyngeal candidiasis **Systemic**: *Aspergillus, Candida, Cryptococcus*, and *Sporothrix* infections Blastomycosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, chromomycosis	**Capsule:** 100 mg QID for 14 days **Refractory Infection**: 200 mg loading dose TID for 3 days, followed by dosing above **Suspension:** 100−200 mg swish and swallow BID for 7−14 days	24−42 hours	Headache, nausea, vomiting, dermal rashes, hypertension, edema, hypokalemia, and hepatotoxicity Pregnancy risk FDA category C
Voriconazole (oral, IV)	**Dental:** Esophageal candidiasis **Systemic:** Invasive candidiasis, *Fusarium* and *Scedosporium* infections	**Oral:** 200 mg BID for 28 days **IV**: 6 mg/kg BID loading dose, followed by 4 mg/kg BID	6 hours	Dermal rashes, visual disturbances, hallucinations, QT prolongation, may require LFTs
Posaconazole (oral suspension, IV)	**Dental:** Oropharyngeal candidiasis refractory to Itraconazole	**Oral suspension:** 100 mg BID on first day; 100 mg QD for 13 days thereafter	25 hours	GI upset, neutropenia, hepatotoxicity requires LFTs FDA pregnancy category C

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Table III. Continued

Class/Drugs	*Indications/Spectrum of activity*	*Dose*	*Half-life*	*Adverse effects*
	or Fluconazole **Systemic:** Invasive *Scedosporium* and *Zygomycetes* infections, prophylaxis against invasive *Candida* and *Aspergillus* infections in immunocompromised patients	**Refractory Infection**: 400 mg BID loading dose for 3 days; 400 mg QD for 25 to 28 days thereafter **IV**: 6 mg/kg BID loading dose, followed by 4 mg/kg BID		
Isavuconazole (oral, IV)	**Dental:** None **Systemic:** Invasive A*spergillosis* and *Mucormycosis*	**IV**: 372 mg TID 2-day loading dose, followed by 372 mg/day	130 hours	Headache, nausea, vomiting, diarrhea, and hypokalemia
Echinocandins				
Caspofungin (IV)	**Dental:** Angular cheilitis **Systemic:** Candidemia, invasive aspergillosis Mucocutaneous candidiasis	**IV:** 70 mg loading dose, followed by 50 mg/day	9−11 hours	Nausea, vomiting, fever, dermal rash, thrombophlebitis Histamine-like reaction when rapidly infused
Micafungin (IV)	**Dental:** Esophageal candidiasis **Systemic:** Candidemia, prophylaxis in hematopoietic stem cell transplants, mucocutaneous candidiasis	**IV:** 150 mg/day (no loading dose)	11−15 hours	Nausea, vomiting, fever, dermal rash, thrombophlebitis, hepatotoxicity Histamine-like reaction when rapidly infused
Anidulafungin (IV)	**Dental:** Esophageal candidiasis refractory oropharyngeal candidiasis **Systemic:** Candidemia	**IV:** 100 mg loading dose followed by 50 mg/day	24−48 hours	Nausea, vomiting, fever, dermal rash, thrombophlebitis Histamine-like reaction when rapidly infused

FDA, U.S. Food and Drug Administration; *GI,* gastrointestinal; *IV,* intravenous; *LFT,* liver function test; *N/A,* not available; *PO,* oral; *QID,* 4 times daily; *TID,* 3 times daily.

agents possess a broad spectrum of activity but have significant drug interactions because of inhibition of human CYP450 enzymes. Different drug interactions are demonstrated by each azole, depending on the CYP450 isoenzymes that are targeted (Table IV). By inhibiting CYP450 enzymes, azoles increase the concentration of drugs that rely on the same enzymes for metabolism. Conversely, drugs that inhibit or induce CYP450 enzymes will alter the concentration of certain azoles that are substrates for these enzymes (see Table IV). Azoles can prolong the QT interval. Thus, concomitant administration of azoles with QT-prolonging agents should be avoided, with the exception of isavuconazole (does not prolong the QT interval).[33] Classes of drugs that may prolong the QT interval include antifungals (ketoconazole, miconazole, itraconazole, posaconazole, voriconazole); antiarrhythmics (amiodarone); antibiotics (erythromycin, clarithromycin, azithromycin); antipsychotics (haloperidol, quetiapine); antidepressants (amitriptyline, nortriptyline, fluoxetine, citalopram, escitalopram, venlafaxine, mirtazapine); antiemetics (dolasetron, droperidol); protease inhibitors; antihistamines (hydroxyzine); adrenergic agonists (albuterol, ephedrine, metaproterenol); cocaine; methadone; and chloroquine.[34-37] Azoles are teratogenic and, thus, should be avoided in pregnant patients when the risks to the mother outweigh the benefits.

Imidazoles: ketoconazole, clotrimazole, miconazole

Ketoconazole. Ketoconazole is the first imidazole developed that is absorbed systemically after oral administration. It is available in cream (2%) and tablet preparations. The cream may be applied directly to the infected area 2 or 3 times daily for 14 to 28 days, whereas the tablet is taken orally, at a dose of 200 to 400 mg 4 times daily for 14 days (see Table III). Indications for ketoconazole include chronic mucocutaneous candidiasis, vaginal candidiasis, and oral candidiasis. It is well absorbed from the GI tract, with widespread tissue penetration. High doses are required to achieve central nervous system penetration. Ketoconazole is inactivated in the liver and excreted in bile and urine and has a half-life of 7 to 10 hours. The main adverse effect is severe hepatotoxicity, warranting LFTs during therapy. Hepatic enzymes should especially be monitored in patients taking oral ketoconazole for longer than 2 weeks.[19] Ketoconazole is an inhibitor of CYP2 C8, CYP2 C19, and P-glycoprotein, as well as being both a substrate and a strong inhibitor of CYP3 A4 (see Table IV). This results in potentiation of drugs that rely on CYP450 for metabolism, such as cyclosporin, phenytoin, triazolam, and warfarin (see Table IV). Other adverse effects include nausea, vomiting, anorexia, cutaneous rash, pruritus, menstrual irregularities, and impotence. Minimal adverse effects are experienced after topical administration but may include skin irritation and headache (see Table III). Because of its severe hepatotoxicity, numerous drug interactions, and potential teratogenicity, ketoconazole should be avoided in treating routine oral candidiasis. It is generally reserved for treatment of chronic mucocutaneous candidiasis, chromomycosis, coccidioidomycosis, and histoplasmosis (see Table III).

Clotrimazole and miconazole. The two most commonly used topical azoles are clotrimazole and miconazole, both available over the counter. Oral clotrimazole is an alternative to nystatin and has a more favorable taste and, more importantly, antistaphylococcal activity.[21] Clotrimazole disturbs amino acid transport into the fungus by acting on the cell membrane. Clotrimazole is available topically as troches, solutions, or cream forms. Systemic use is avoided because of GI and neurologic toxicities.[19] Clotrimazole troche (10 mg) is dissolved slowly in the oral cavity 5 times daily for 14 days. Clotrimazole solution (1%) is swished as a 5-mL dose 4 times daily for 14 days, and the cream (1%) is applied directly to the area of infection 2 or 3 times daily for 21 to 28 days (see Table III).

Miconazole is available for topical use in oral gel (2%) and cream (2%) formulations because it is not absorbed from the GI tract. The antistaphylococcal effects of miconazole, in addition to its fungicidal effects, make it particularly useful in treating angular cheilitis. Miconazole oral gel (2%) is applied topically to the lesion as a 2.5-mL dose 3 or 4 times daily for 14 to 21 days. Miconazole gel may also be swished around in the mouth for as long as possible or applied to the intaglio surface of dentures affected by *Candida* infection. Miconazole cream (2%) is applied directly to the area of infection 2 times daily for 14 to 21 days (see Table III). High amounts of miconazole absorbed through topical administration may potentiate the anticoagulant effects of warfarin and result in life-threatening hemorrhage (see Table IV). Additionally, interactions with terfenadine, cisapride and astemizole are possible. Miconazole should be avoided in pregnancy and porphyria.[21]

Triazoles: fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole

Triazoles, such as fluconazole and itraconazole, were developed in the 1990s and have been widely used to treat fungal infections, including oral candidiasis.[38] Extended-spectrum triazoles, such as voriconazole and posaconazole, were later introduced in 2002 and 2006, respectively. Voriconazole and posaconazole are

Table IV. Interaction of azoles with phase I and II biotransformation enzymes and transport proteins

Azole antifungal	Phase I	Phase II	Transport proteins	Resulting drug interactions
Ketoconazole	(-/s) CYP**3 A4** (-) CYP**2 C8** (-) CYP**2 C19**		(-) P-gp	Decreased ketoconazole levels with antacids, proton pump inhibitors, antihistamines **CYP3 A4 inhibition**: ↑ Cyclosporine, triazolam, methylprednisolone, betamethasone, fluticasone, buprenorphine, bromocriptine, calcifediol, cannabis, codeine, maraviroc, meperidine, propafenone, ranolazine **CYP2 C8 inhibition**: ↑ Repaglinide **CYP2 C19 inhibition**: ↑ Clobazam **P-gp inhibition**: ↑ Colchicine, naldemedine, prucalopride, talazoparib, tegaserod, venetoclax ketoconazole may ↑ warfarin, midazolam ***Several more drug interactions; not complete list***
Miconazole	None known			Miconazole may ↑ fosphenytoin, phenytoin, and warfarin serum concentrations Miconazole may enhance the hypoglycemic effect of sulfonylureas
Clotrimazole	(-) CYP**3 A4**			**CYP3 A4 inhibition**: ↑ Dofetilide, flibanserin, lomitapide, tacrolimus, triazolam
Fluconazole	(-/s) CYP**3 A4** (-/s) CYP**2 C9** (-/s) CYP**2 C19**	(-)UGT	(s) P-gp	Increased fluconazole levels with CYP inhibitors (amiodarone, cisapride, pimozide, erythromycin, mizolastine) **CYP3 A4 inhibition**: ↑ Ergot alkaloids, vinca alkaloids, midazolam, HMG-CoA reductase inhibitors, cyclosporine, tacrolimus, and sirolimus **CYP2 C9 inhibition**: ↑ Warfarin **UGT inhibition**: ↑ Zidovudine **CYP and/or P-gp inhibition**: ↑ Venetoclax
Itraconazole	(-/s) CYP**3 A4**		(-/s) P-gp (-) BCRP	Increased itraconazole levels with CYP inhibitors (amiodarone, cisapride, pimozide, erythromycin, mizolastine) **CYP3 A4 inhibition**: ↑ Alfuzosin, ergot alkaloids, ibrutinib, vinca alkaloids, midazolam, HMG-CoA reductase inhibitors, cyclosporine, tacrolimus, sirolimus, vardenafil, methylprednisolone, oxybutynin **P-gp inhibition**: ↑ Digoxin, quinidine **CYP, P-gp, and/or BCRP inhibition**: ↑ Venetoclax
Voriconazole	(-/s) CYP**3 A4** (-) CYP**2 B6** (-/s) CYP**2 C9** (-/s) CYP**2 C19**			Increased voriconazole levels with CYP inhibitors (amiodarone, cisapride, pimozide, erythromycin, mizolastine) Decreased voriconazole levels with CYP inducers (carbamazepine, phenobarbital, rifampicin, rifabutin, efavirenz, etravirine, ritonavir, St. John's wort, phenytoin) **CYP3 A4 inhibition**: ↑ Alfuzosin, ergot alkaloids, ibrutinib, vinca alkaloids, midazolam, HMG-CoA reductase inhibitors, cyclosporine, tacrolimus, sirolimus, phenytoin **CYP2 C9 inhibition**: ↑ Warfarin **CYP inhibition**: ↑ Venetoclax
Posaconazole	(-) CYP**3 A4**	(s)UGT	(-/s) P-gp (-) BCRP	Increased posaconazole levels with CYP inhibitors (amiodarone, cisapride, pimozide, erythromycin, mizolastine) Decreased posaconazole levels with CYP and UGT inducers (Phenytoin) **CYP3 A4 inhibition**: ↑Alfuzosin, ergot alkaloids, ibrutinib, vinca alkaloids, midazolam, HMG-CoA reductase inhibitors, cyclosporine, tacrolimus, sirolimus, phenytoin **CYP, P-gp, and/or BCRP inhibition**: ↑ Venetoclax
Isavuconazole	(-/s) CYP**3 A4** (-) CYP**2 B6**	(-)UGT	(-) P-gp (-) BCRP (-) OCT2	Decreased isavuconazole levels with CYP inducers (carbamazepine, phenobarbital, rifampicin, rifabutin, efavirenz, etravirine, ritonavir, St. John's wort) **CYP3 A4 inhibition**: ↑ Vinca alkaloids, midazolam, cyclosporine, tacrolimus, and sirolimus

BCRP, breast cancer resistance protein; *CYP,* cytochrome P; *HMG-CoA,* 3-hydroxy-3-methyl-glutaryl-coenzyme A; *P-gp,* permeability glycoprotein; *UGT,* uridine 5′-diphospho-glucuronosyltransferase.

broad-spectrum antifungals, with a fungicidal effect against most yeasts and filamentous molds.[39] Triazoles have a similar mechanism of action as imidazoles because they inhibit the synthesis of ergosterol, thereby destroying the integrity of the fungal cell membrane (see Figure 1). The newest triazole is isavuconazole, which is the active form of its prodrug isavuconazonium sulfate.

Fluconazole. Fluconazole was the first triazole antifungal agent to be developed and is known to be limited by its spectrum of activity. Fluconazole is available as an oral capsule and an IV agent. Oral capsules are indicated in moderate to severe oral candidiasis, delivered as a 200-mg loading lose, followed by 100 mg 4 times daily for 7 to 14 days (see Table III). Fluconazole is effective against candidiasis, especially *C. albicans* and *C. parapsilosis* infections, as well as others, such as fungal meningitis and most forms of mucocutaneous candidiasis. It may be used as a single-dose oral treatment for vulvovaginal candidiasis. Fluconazole is water soluble, is completely absorbed from the GI tract, and has excellent bioavailability after oral administration. Fungicidal concentrations can be achieved in saliva, skin, nails, and vaginal fluids. Fluconazole is excreted unchanged in urine and has a half-life of 25 hours. The adverse effects are milder compared with those of ketoconazole because fluconazole does not inhibit CYP enzymes to the same extent. Adverse effects include mild headache, GI upset, dermal rashes, and hepatotoxicity (see Table III). However, fluconazole is both a substrate and an inhibitor of CYP3 A4, CYP2 C9, and CYP2 C19, resulting in drug interactions that must be considered (see Table IV). Unfortunately, systemic antifungals, such as fluconazole, have been shown to fail in the treatment of *Candida* infections, primarily because of their inability to penetrate *Candida* biofilms.[40,41]

Itraconazole. Itraconazole has a broader spectrum of action compared with fluconazole (see Table III). Itraconazole is indicated in refractory candidiasis and is delivered as an oral capsule with a 200-mg loading dose, 3 times daily for 3 days, followed by 100 mg for the remaining 11 days (see Table III).[19] The capsules may also be indicated for resolving initial candidiasis, administered at a dose of 100 mg 4 times daily for 14 days. In addition to oral capsules, an oral suspension and IV formulations are available. Patients are instructed to swish and swallow 100 to 200 mg of the oral suspension 2 times daily for 7 to 14 days (see Table III). There is variable absorption in the GI tract after oral administration. Itraconazole is taken with acidic beverages and food, as decreased pH conditions promote its absorption.[21] IV administration is another method of overcoming variable GI absorption. Once absorbed, itraconazole undergoes extensive hepatic metabolism and is excreted in urine and feces and has a half-life of 24 to 42 hours. It has good distribution in adipose and bone tissues. The most notable adverse effect is hepatotoxicity, with significant drug interactions resulting from its activity as both a substrate and an inhibitor of CYP3 A4 (see Table IV). Other adverse effects include headache, GI disturbances, dermal rashes, hypertension, edema, and hypokalemia (see Table III).

Voriconazole. Voriconazole is an extended-spectrum triazole that is available in oral and IV formulations. It is indicated in refractory oral candidiasis, delivered orally at a dose of 200 mg 2 times daily for 28 days (see Table III). Its broad spectrum of activity includes its activity against invasive *Candida* and *Aspergillus*, as well as serious infections caused by *Scedosporium* and *Fusarium* species (see Table III). Similar to oral fluconazole, voriconazole displays excellent bioavailability. It has good tissue penetration and is excreted in urine and has a half-life of 6 hours. Many drug interactions have been documented because voriconazole is a substrate for CYP3 A4, CYP2 C9, and CYP2 C19 (see Table IV). Its use with several drugs, such as rifampin, carbamazepine, and St. John's wort, is contraindicated because of interactions. Adverse effects include visual disturbances and QT interval prolongation. Voriconazole may require LFTs during treatment (see Table III).

Posaconazole. Similar to voriconazole, posaconazole is an extended-spectrum triazole, available in oral and IV formulations. Posaconazole may also be indicated in the treatment of refractory candidiasis, administered orally at a loading dose of 400 mg 2 times daily for 3 days, followed by 400 mg 4 times daily for 25 to 28 days.[19] For initial cases, it is prescribed at 100 mg 2 times on the first day, followed by 100 mg 4 times daily for the next 13 days (see Table III). Posaconazole is also indicated for the treatment of invasive *Scedosporium* and *Zygomycetes* infections and for prophylaxis against invasive *Candida* and *Aspergillus* infections in immunocompromised patients (see Table III). Posaconazole has low bioavailability and is, therefore, commonly administered with fatty foods to increase its bioavailability (400%).[42] Initially, posaconazole was only available in an oral liquid formulation but is now available in an IV form and as a sustained-release capsule to further increase its bioavailability. Posaconazole is primarily metabolized hepatically through glucuronidation and excreted in feces and has a half-life of 25 h.[42] Posaconazole inhibits CYP3 A4, resulting in several drug interactions (see Table IV).

Adverse effects include GI disturbances, neutropenia, and hepatotoxicity and require LFTs (see Table III).

Isavuconazole. Isavuconazole is the newest triazole, available in oral and IV formulations. It is administered as the prodrug isavuconazonium, which is quickly hydrolyzed by esterases in blood to isavuconazole. Isavuconazole has a broad spectrum of activity and is indicated for use against invasive aspergillosis and mucormycosis. It displays excellent bioavailability and good distribution into tissues. The half-life is 130 hours. Isavuconazole inhibits CYP3 A4, CYP2 B6, and many other phase II and transport proteins, resulting in drug interactions (see Table IV). Common adverse effects are headache, GI disturbances, and hypokalemia (see Table III).

Echinocandins: caspofungin, micafungin, anidulafungin

Echinocandins are a newer class of antifungal agents that are synthetic derivatives of echinocandin B found in *Aspergillus nidulans*. Echinocandins disrupt the formation of the fungal cell wall by inhibiting the synthesis of β-(1,3)-D-glucan (see Figure 1). The resultant fungal cell wall lacks integrity and osmotic stability, ultimately leading to cell lysis and death.[43] Mammalian cells do not contain β-(1,3)-D-glucan and are, therefore, not targeted. Caspofungin, micafungin, and anidulafungin are the 3 echinocandin agents available, all of which as IV formulations only and taken once daily (see Table III). Echinocandins are reserved for life-threatening *Candida* infections. The spectrum of action includes most *Candida* species, including *C. albicans, C. tropicalis, C. glabrata, C. krusei*, and *C. dublinensis*. A loading dose is recommended for caspofungin and anidulafungin, but not for micafungin (see Table III).[44] They should be infused slowly to avoid histamine-like reactions. Echinocandins are fungicidal for *Candida* and fungistatic for *Aspergillus*. Caspofungin and micafungin are metabolized hepatically, whereas anidulafungin undergoes metabolism in blood. Importantly, these agents are poor CYP450 substrates, minimizing drug interactions compared with the azoles.[45] However, caspofungin uses the OATP-1 B1 transporter, leading to various drug interactions with antiretrovirals, immunosuppressants, antiepileptics, and rifampin.[46,47] Caspofungin is effective in treating invasive candidiasis and is used to treat invasive aspergillosis when attempts with AmB and azoles have failed.

NOVEL ANTIFUNGAL THERAPIES

Recent studies have investigated novel antifungal treatment alternatives, such as probiotics, photodynamic therapy, and plant derivatives.[48-51] The most notable is the use of probiotics, postulated as an alternative for prophylaxis and treatment of oral candidiasis. Probiotics can be administered in various forms, such as mouth rinses, lozenges, and capsules. A recent double-blinded, placebo-controlled, randomized trial demonstrated that probiotic capsules containing *Lactobacillus bulgaricus, Streptococcus thermophilus, Lactobacillus acidophilus*, and *Bifidobacterium bifidum* significantly reduced candidal loads in patients with Sjögren syndrome.[52] This study was the first to administer probiotics systemically by using capsules. Previous studies found that probiotics effectively reduce *Candida* levels in older denture wearers and children receiving broad-spectrum antibiotics.[53-55] In complete denture wearers, daily consumption of cheese supplemented with probiotics also reduced *Candida* loads.[56] Probiotics have been studied in combination with nystatin, showing an increase in the reduction of *Candida*-associated stomatitis compared with conventional therapy.[57] A significant increase in anti-candida immunoglobulin A levels has also been demonstrated after consuming the probiotics *Lactobacillus casei* and *Bifidobacterium breve*.[55] An additional study concluded that epithelial cells acquire improved defense functions after intake of probiotics.[58] Further research is required to understand the species that are therapeutically efficacious in the prophylaxis and treatment of oral candidiasis.

DRUG DEVELOPMENT AND FUTURE CONSIDERATIONS

The 3 classes of antifungal agents (polyenes, azoles, echinocandins) that are currently the mainstay in the treatment of fungal infections both present unique limitations, such as toxicity, low selectivity, and emerging resistance.[59,60] Fortunately, there have been advances in the development of novel antifungal agents. Two new glucan synthesis inhibitors, ibrexafungerp (SCY-078) and rezafungin (CD101), are currently undergoing clinical trials.[61] Ibrexafungerp is a triterpenoid that is orally administered and has demonstrated promising results against multidrug resistant *Candida*, such as *C. glabrata, C. auris*, and *Aspergillus* species.[38,62] Rezafungin is an echinocandin with a prolonged half-life and a spectrum of action against *Candida* and *Aspergillus* that is similar to that of currently available echinocandins. Manogepix (APX001 A) is a novel antifungal agent that targets fungal cell walls by inhibiting Gwt1, a key enzyme in the glycosylphosphatidylinositol biosynthesis pathway.[63] Development of new classes of antifungal agents has been the main approach to addressing evolving fungal resistance and the limitations of the currently available antifungal agents. A significant amount of knowledge regarding the pathogenicity and host immune response to *Candida*

infections remains to be uncovered.[59,64] Future pharmacologic development will benefit from these discoveries and should be integrated with new trends in administering antifungal probiotics. A multidimensional approach to target *Candida* infections allows clinicians to individualize antifungal therapy and appropriately manage each clinical presentation.

CONCLUSIONS

Oral candidiasis is a prevalent opportunistic infection with differing clinical presentations and various topical and systemic treatment alternatives available to clinicians. In the present report presented here, we briefly reviewed the clinical features of various oral *Candida* presentations and provided an in-depth account of the topical and systemic pharmacologic therapies used in treatment. The 2 important treatment principles are identification and removal of contributing factors and reduction of the fungal load. After the contributing factors are dealt with, pharmacotherapy may be indicated. Topical antifungal therapy includes gentian violet, nystatin, AmB, ketoconazole, miconazole, and clotrimazole. Systemic therapy for oral candidiasis includes fluconazole, itraconazole, and, very rarely, ketoconazole. Basic pharmacologic principles must not be overlooked by clinicians when prescribing polyene or azole antifungal therapy.

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