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Practical Update on Treatment of Oral Candidiasis

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ABSTRACT

Dermatologists are likely to periodically encounter candidiasis in clinical practice, especially given the increased risk with the use of new broad-spectrum IL-17 blocking psoriasis agents such as bimekizumab. Oral candidiasis may be white or red, classically presenting as cottage-cheese consistency plaques associated with symptoms of a burning mouth and dysgeusia. Standard first- and second-line antifungal medications can easily and safely be prescribed by dermatologists. In this article, we summarize clinical presentations and treatment algorithms for oral candidiasis relevant to the dermatologist. We also present indications and criteria for infectious disease referral or hospitalization.

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INTRODUCTION

Many commonly administered, older biologics for psoriasis target interleukin (IL)-17 and IL-23, which are essential to neutrophil recruitment for fungal defense, predisposing patients to mostly oral candidiasis.[1–3] Such drugs are less likely to result in vulvovaginal candidiasis, which relies less on IL-17 and more on S100A8 alarmin and IL-1β.[4,5] With the advent of new, more potent psoriasis agents like bimekizumab that block both IL-17A and IL-17F, there is an increased risk of candidiasis, estimated between 8 and 18%.[6] Bimekizumab achieves over 90% reduction in Psoriasis Area and Severity Index (PASI) scores more frequently than other agents, and it is expected to be widely used given its recent approval.[7–9] As such, dermatologists must prepare to treat oral candidiasis (though unlikely esophagitis) that may result from broad-spectrum IL-17 blocking agents.[6,7]

Presentation and Diagnosis of Oral Candidiasis

Oral candidiasis can present as white or red.[10] The two major forms of white candidiasis include the pseudomembranous variant, which is the most common, classical form of white, cottage cheese consistency plaques that can be scraped off, revealing an erythematous surface underneath.[10–12] The plaques can cover the soft and hard palates, buccal mucosa, and extend into the oral segment of the pharynx.[10,13] The other type of white candidiasis is hyperplastic, which also presents with white plaques on the buccal mucosa, except these plaques may also be found at the labial commissures.[10–12] Lesions can be speckled, nodular, small, large, translucent, or opaque, and cannot be scraped off.[10] Therefore, the challenge lies in differentiating these lesions from oral leukoplakia and lichen planus.[10,11,14] Erythematous candidiasis affects the buccal mucosa, tongue, or

TABLE 1.

Non-Triazole Treatment Recommendation Summary for Oropharyngeal Thrush[20,22–37]

Agent (First/ Second Line)	Route	Dose/Duration	Side Effects	Contraindications	Relative Cost	Appropriate Patient Characteristics	Kidney/ Liver Adjustments	Next Drug in Line after Failure (First/ Second Line)
Clotrimazole (First)	Troche	10 mg 5x daily; 7-14 days	Hepatic enzyme elevation	--	$	Mild disease Pregnancy	--	Fluconazole
Miconazole (First)	Buccal Tablet	50 mg 1x daily; 7-14 days	Local site reactions (burning, pain, bad taste)	--	$$$$ (no generic)	Mild disease Pregnancy	--	Fluconazole
Nystatin (Second)	(1) Suspension (2) Pastilles	(1) 400,000-600,000 units 4-6x daily; 7-14 days (2) 1-2 pastilles (200,000 units each) 4x daily; 7-14 days	Dental caries	--	$	Mild disease Pregnancy	--	Fluconazole

TABLE 2.

Triazole Treatment Recommendation Summary for Oropharyngeal Thrush[20,22-37]

Agent (First/ Second Line)	Route	Dose/ Duration	Side Effects	Contraindications	Relative Cost	Appropriate Patient Characteristics	Kidney/ Liver Adjustments	Next Drug in Line after Failure (First/ Second Line)
Fluconazole	Oral (Tablets)	100-200 mg 1x daily; 7-14 days	Hepatotoxicity Dermatologic reactions: rash, SJS/TEN, DRESS, AGEP, Sweet's syndrome, alopecia Prolonged QT interval Torsades de Pointes	Pregnancy Drugs that prolong the QT interval (erythromycin, pimozide, quinidine)	$	Mild disease with HIV Moderate to severe disease	Kidney: For creatinine clearance ≤50 mL/minute, normal dosage for loading dose; reduce maintenance dose by 50%	Itraconazole (First) Posaconazole (First) Voriconazole (Second)
Fluconazole	Oral (Tablets)	100 mg 1x daily; 3x weekly	Hepatotoxicity Dermatologic reactions: rash, SJS/TEN, DRESS, AGEP, Sweet's syndrome, alopecia Prolonged QT interval Torsades de Pointes	Pregnancy Drugs that prolong the QT interval (erythromycin, pimozide, quinidine)	$	Recurrent infection	Kidney: For creatinine clearance ≤50 mL/minute, normal dosage for loading dose; reduce maintenance dose by 50%	--
Itraconazole	Oral Solution	200 mg 1x daily; 28 days	Nausea Headache Abdominal pain	Pregnancy Non life-threatening indications in patients with ventricular dysfunction Significant drug interactions; consult database	$$	Moderate to severe disease Fluconazole refractory	--	Voriconazole
Posaconazole	Oral Suspension	400 mg 2x daily; 3 days, THEN 400 mg 1x daily; 28 days	Gastrointestinal side effects (nausea, vomiting, diarrhea) Hypokalemia Fever Hepatic enzyme elevation	Pregnancy Statins, pimozide, astemizole, quinidine, terfenadine, efavirenz, fosamprenavir, ergot alkaloids, drugs the prolong the QTc interval Proarrhythmic conditions: cardiomyopathy and QTc prolongation Monitoring and dosage adjustment with some drugs	$$$	Moderate to severe disease Fluconazole refractory	--	Voriconazole
Voriconazole	Oral (Tablets)	200 mg 2x daily*	Visual abnormalities Hepatic enzyme elevation Skin reactions: Photosensitivity	Pregnancy Carbamazepine, rifampin, long-acting barbiturate, sirolimus, pimozide, astemizole, quinidine, terfenadine Severe hepatic impairment* Monitoring and dosage adjustment with some drugs	$$	Moderate to severe disease Fluconazole refractory	Liver: Standard loading dose for mild-moderate insufficiency[a] Reduce maintenance dose by half Do not give in severe insufficiency[b]	IV echino-candins (refer/admit)

Abbreviations: SJS: Stevens-Johnson Syndrome; TEN: Toxic epidermal necrolysis; DRESS: Drug reaction with eosinophilia and systemic symptoms; AGEP: Acute generalized exanthematous pustulosis
*Requires trough concentrations during therapy; consider referral for drug administration
[a]Child-Pugh A and B
[b]Child-Pugh C

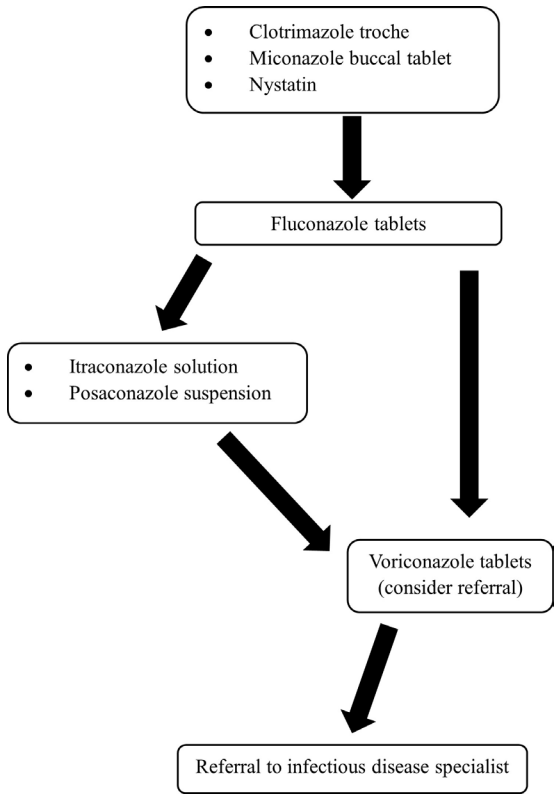
hard palate, presenting with either reddish papules or macules or both.[11,12]

Patients with oral candidiasis may complain of easy mucosal bleeding or a burning sensation in the mouth, taste changes, or a sour taste. Erythematous candidiasis can present with sore lips and/or tongue or with angular cheilitis.[10,15,16] They may also present asymptomatically, especially in chronic candidiasis.[10,11] In all cases, an oral physical examination should support clinical suspicion and should be sufficient for diagnosis. As *Candida albicans* is frequently part of the normal oral flora, a positive culture is not of much significance, though recommended by some infectious disease societies.[2]

Treatment

Oropharyngeal thrush has multiple treatment options, including topical and tablet options, with doses and other administration details summarized in Tables 1 and 2. First-line options include clotrimazole troche and miconazole buccal tablets. Nystatin may also be used second line (Table 1). Fluconazole is classically used (Table 2), although the potential for resistant strains of *C. albicans* is growing.[17,18] As such, alternative therapies to fluconazole (itraconazole, posaconazole) are included in Table 2. Unlike fluconazole, these drugs also do not require adjustments for kidney function. Additionally, fluconazole has potential drug-drug interactions due to its CYP2C9 inhibition, and therefore, topical therapies are offered first-line in Table 1 (clotrimazole, miconazole). However, agents typically used in cases of fluconazole failure similarly interact with many other medications.[19] In cases of fluconazole, itraconazole, and posaconazole failure, voriconazole can be given. For patients with HIV, continuing concurrent antiretroviral therapy to avoid recurrent thrush is recommended.[20] Angular cheilitis can be treated with topical antifungal creams (clotrimazole, miconazole, or any of the many other newer azoles).[10,15,21] Finally, as agents used for severe oropharyngeal candidiasis are contraindicated in pregnancy, intravenous amphotericin B can be given to pregnant patients to treat severe thrush.[20] Accordingly, dermatologists should refer to an infectious disease specialist in such cases. Figure 1 depicts the sequential next steps for unresponsive oropharyngeal thrush. Criteria for referral or hospital admission are detailed in Table 3.

FIGURE 1. Next steps for Oropharyngeal Thrush Unresponsive to Treatment.[20]



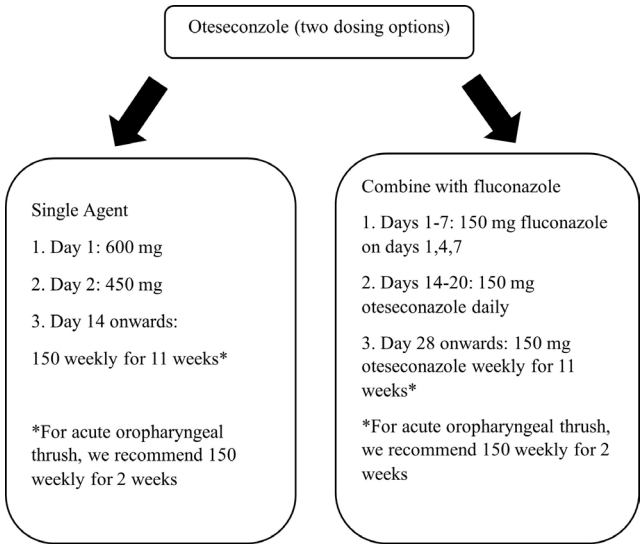
Other Considerations

Novel agents now on the market to treat vulvovaginal candidiasis may show promise in the treatment of oral thrush, given their success in the therapy of vaginal mucosal disease.[22] Ibrexafungerp is now FDA-approved for acute vulvovaginal thrush as an alternative oral therapy to fluconazole, especially for resistant strains. Ibrexafungerp is a first-in-class triterpenoid that blocks the formation of an adequate fungal cell wall by inhibition of 1,3-β-D-glucan synthase.[23–27] Although trials specifically evaluating the use of ibrexafungerp for oral thrush have yet to be published, the phase 3 FURI trial to investigate its efficacy for fungal infections refractory to standard treatment, including mucocutaneous infections, is currently underway.[28,29]

TABLE 3.

Indications for Referral or Hospital Admission for Oral Thrush[20,38–40]
Infectious Disease Referral
• Esophageal disease: symptoms include retrosternal pain, odynophagia, and dysphagia • Severe thrush in pregnant women • Recurrent disease unresponsive to fluconazole, itraconazole, posaconazole • Can consider referral for voriconazole administration
Hospital Admission
Systemic Candidemia • Symptoms: fever unresponsive to antibiotics or antifungals and general non-specific symptoms of infection in the correct setting (risk factors or history of thrush) • Risk factors: indwelling central venous catheter, immunosuppression, total parenteral nutrition, use of broad-spectrum antibiotics, dialysis, recent surgery, necrotizing pancreatitis

FIGURE 2. Oteseconazole Dosing.[35]



Ibrexafungerp is dosed as two 150 mg tablets, twice daily for one day.[23] We recommend this dosing for oropharyngeal disease.

Oteseconazole, a newly FDA-approved oral azole drug, has shown promise for the management of recurrent vulvovaginal candidiasis, with less toxicity due to selective cytochrome P450 inhibition.[30–34] It is given as a 600 mg dose for 1 day, followed by a 450 mg dose the next day, and then, starting on day 14 of treatment, 150 mg once weekly for 11 weeks. It may also be combined with fluconazole in a more complicated dosing regimen, detailed in Figure 2.[35] For acute oropharyngeal thrush, we recommend the 600 mg dose, followed by the 450 mg dose, then 150 mg per week for 2 weeks.

CONCLUSION

Oral candidiasis is likely to present to the dermatologist given the risks attendant to the routine use of dermatologic medications (psoriasis biologics, specifically bimekizumab). In suggestive clinical contexts, dermatologists should evaluate and treat patients for candidiasis. Numerous inexpensive first- and second-line antifungal agents are available for oropharyngeal candidiasis, including for recurrent and initially resistant cases. However, dermatologists should remain aware of indications and criteria for further referral to an infectious disease specialist.

DISCLOSURES

Dr Zamil and Dr Rosen do not declare any conflicts of interest. The views expressed in the submitted article are the views of the authors and not the official position of their respective institutions.

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