A Practical Guide to the Management of Oral Candidiasis in Patients with Plaque Psoriasis Receiving Treatments That Target Interleukin-17

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ABSTRACT

Plaque psoriasis is an immune-mediated inflammatory skin disease associated with the dysregulation of cytokines, especially those involved in the interleukin (IL)-23/IL-17 pathways. In recent years, there has been growing interest in developing biologic therapies that target these pathways. However, inhibition of the cytokines of the IL-23/IL-17 pathways may increase patients’ risk of developing fungal infections, particularly oral candidiasis. Therefore, it is important that dermatology practitioners can effectively diagnose and treat oral candidiasis. In this review, we examine the role of the IL-23/IL-17 pathways in antifungal host defense, and provide a practical guide to the diagnosis and treatment of oral candidiasis in...
patients with psoriasis. Overall, while treatment with anti-IL-17 medications leads to an increased incidence of oral candidiasis in patients with psoriasis, these cases are typically mild or moderate in severity and can be managed with standard antifungal therapy without discontinuing treatment for psoriasis. If applicable, patients with psoriasis should also be advised to practice good oral hygiene and manage or control co-existing diabetes, and should be provided with information on smoking cessation to prevent oral candidiasis.

Keywords: Plaque psoriasis; Candida; Oral candidiasis; Interleukin-17

Key Summary Points

Why carry out this study?
The interleukin-23/interleukin-17 pathways, which are central to the pathogenesis of plaque psoriasis, are also involved in host defense against oral candidiasis.

Given the increased risk of oral candidiasis in patients with psoriasis receiving anti-interleukin-17 therapies, dermatologists should be attentive to clinical signs of oral candidiasis and aware of how to manage cases appropriately.

This review provides a practical guide to the diagnosis and treatment of oral candidiasis in patients with psoriasis being treated with anti-interleukin-17 biological therapies.

What was learned from this study?
Oral candidiasis in patients with psoriasis is typically mild to moderate in severity. In our clinical experience, cases can be managed with standard antifungal treatment without discontinuing biologic psoriasis therapies.

To prevent recurrence of oral candidiasis, patients should be advised to practice good oral hygiene and be provided with information on smoking cessation, if applicable.

INTRODUCTION

Psoriasis is an immune-mediated inflammatory skin disease associated with dysregulation of inflammatory cytokines that affects approximately 41 million people worldwide [1, 2]. The cytokines of the interleukin (IL)-23/IL-17 pathways have been identified as key mediators of psoriasis pathogenesis [3]. Subsequently, there has been growing interest in developing biologic therapies that target these pathways [4, 5]. However, as a result of the roles of IL-17 and IL-23 in antifungal host defense at the oral mucosa, targeting these cytokines may increase patients’ risk of developing fungal infections, particularly oral candidiasis [6].

Here, we provide an overview of the role of the IL-23/IL-17 pathways in antifungal host defense, as well as a practical guide to the treatment of oral candidiasis in patients with psoriatic disease.

This review article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

THE IL-23/IL-17 PATHWAYS AND IMMUNITY

Overview and Role in Psoriasis

The main producers of IL-17, along with T cytotoxic 17 (Tc17) cells, are T-helper (Th)17 cells—a subset of Th cells that differentiate from naive CD4⁺ T cells upon exposure to proinflammatory cytokines [7, 8]. The IL-17 family consists of six ligands (IL-17A to IL-17F) that
bind to receptors (IL-17R) expressed ubiquitously throughout the body [9–13]. IL-17A and IL-17F share the closest homology and can exist as homodimers or heterodimers [5]. While not required for the induction of the Th17 and Tc17 lineages, IL-23 is required for the stabilization and proliferation of these cells [7, 8].

Although the etiology of psoriasis is not fully understood, genetic and environmental factors appear to contribute to atypical activation of the immune system, resulting in disease [14, 15]. The cytokines IL-17A and IL-17F in particular have been identified as key upregulated proinflammatory cytokines in psoriatic lesions; they are thought to recruit immune cells to psoriatic skin, stimulating the hyperproliferation of keratinocytes [16, 17].

**Role in Host Defense Against Candida**

One of the major roles of the IL-23/IL-17 pathways is host defense against fungal infections [18]. The most common species involved, *Candida albicans*, is usually commensal; however, upon conversion to a hyphal state it can cause mucocutaneous candidiasis [19].

The key role of IL-17 signaling in host defense against *Candida* is supported by observations from patients with primary immunodeficiencies leading to defects in the Th17 pathway, who present with a form of chronic mucocutaneous candidiasis (CMC) termed CMC disease (CMCD) [20]. These patients are prone to recurrent oral and esophageal candidiasis, suggesting a pivotal role of IL-17 in defense against candidiasis in the mucosa of the upper digestive tract [20]. However, these patients are not prone to systemic or vulvovaginal candidiasis, leading to an emerging consensus that the IL-23/IL-17 pathways are not essential to immune defense against these infections [19, 21–23]. These patients also rarely display any other severe diseases [24].

According to the current model of host defense against oral candidiasis, conversion of *C. albicans* to a hyphal state results in the activation of immune cells in response to damage [25]. These cells then produce proinflammatory cytokines such as IL-23, inducing the proliferation of Th17 cells and the release of IL-17A and IL-17F as well as IL-22. Neutrophils are then recruited to the infection site by these cytokines, inducing the secretion of antifungal proteins (Fig. 1) [19, 26]. Therefore, through the inhibition of IL-17 or its receptors, anti-IL-17 medications prescribed for psoriasis can increase the risk of oral candidiasis through inhibition of these Th17 cell-mediated antifungal pathways.

**Epidemiology of Candida Colonization and Infection in Psoriasis**

There is some evidence of increased *Candida* colonization of the oral cavity in patients with psoriasis versus those without psoriasis. In a systematic literature review and meta-analysis of nine studies, statistically higher rates of *Candida* colonization of mucosal membranes were observed in patients with psoriasis [27]. For example, rates were reported as 69% versus 44% for those without psoriasis in a study conducted in Jordan [28], and 47.2% versus 19.5% in a study conducted in Germany [29]. This trend was consistent with another study where patients with psoriasis receiving systemic treatment were excluded (20.0% versus 2.8%) [30]. The reason for this association is unclear. Notably, there was considerable heterogeneity in these studies, and most measured the presence of *Candida* colonization rather than true candidiasis [27].

**Risk of Candidiasis in Patients Receiving Biologic Treatments for Psoriasis**

In recent years, several monoclonal antibodies targeting IL-17 (e.g., brodalumab, ixekizumab, and secukinumab), IL-23 (e.g., guselkumab, risankizumab, and tildrakizumab), and IL-12/23 (e.g., ustekinumab) have been approved for treatment of psoriatic disease [4].

A systematic review of previous trials of anti-IL-17 medications in psoriatic disease found that overall incidence of candidiasis was increased in patients treated with anti-IL-17 medications versus placebo (1.7–4.0% versus 0.3%, respectively) [31]. The majority of
Candida infections were oral and not vulvovaginal. Moreover, most oral candidiasis cases were mild to moderate in severity [31]. There was also no increase in the risk of esophageal or systemic candidiasis, further supported by a systematic review of all IL-17 and IL-23 inhibitors [31, 32].

Bimekizumab, an anti-IL-17 medication recently authorized in Europe for the treatment of moderate to severe plaque psoriasis [33], inhibits IL-17F in addition to IL-17A [34]. Dual inhibition of IL-17A and IL-17F has demonstrated superior levels of skin clearance compared with targeting IL-17A alone with secukinumab in a head-to-head in patients with plaque psoriasis [35]. As expected, as a result of the roles of both cytokines in antifungal host defense, dual neutralization was also associated with an increased incidence of mild to moderate oral candidiasis as compared with previously approved anti-IL-17 medications [36–38].

Despite both bimekizumab and brodalumab inhibiting the activity of IL-17A and IL-17F, differences have been observed in the rates of oral candidiasis. This could be a consequence of the mechanistic differences between these two biologics. One hypothesis is that, as brodalumab inhibits IL-17R, it blocks the function of all additional IL-17 cytokines, including IL-17E which may indirectly suppress Th17 responses [13]. Furthermore, if IL-17R is not fully blocked at the end of a dosing cycle, it is possible that residual IL-17 may confer host protection against Candida. However, further research into this topic is needed.

Anti-IL-23 biologics do not seem to increase the risk of Candida infections as much as anti-IL-17 biologics [39]. This may be because anti-IL-23s do not block IL-23-independent sources of IL-17, such as IL-17 produced by innate lymphoid cells [3, 39]. However, IL-23-independent sources of IL-17 are increasingly thought to play a significant role in the pathogenesis of immune-mediated inflammatory diseases, which may explain the higher efficacy of some anti-IL-17 medications compared with IL-23 blockers axial spondyloarthritis and joint outcomes in psoriatic arthritis [40, 41].
DIAGNOSIS AND TREATMENT OF ORAL CANDIDIASIS

Given the increased risk of oral candidiasis in patients with psoriasis treated with anti-IL-17 medications, it is important that dermatology practitioners can effectively diagnose and treat these infections. On the basis of a review of the literature and clinical experience, we propose the diagnosis and treatment algorithm for oral candidiasis shown in Fig. 2.

Clinical Presentations of Oral Candidiasis

**Pseudomembranous Candidiasis**

Pseudomembranous candidiasis (or “thrush”) is sometimes referred to as the classic presentation of candidiasis [42], and in our clinical experience is most commonly identified in patients with psoriasis receiving anti-IL-17 treatment. It is characterized by the presence of white, curd-like plaques that can be dislodged with gentle scraping, revealing underlying erosions of the oral mucosa (Fig. 3A) [43–46]. Patients are often asymptomatic; however, pain, a burning sensation, and in some cases a metallic taste may be present [46].

**Erythematous Candidiasis**

Erythematous candidiasis is the most common form of oral candidiasis [46]. There are four subtypes: acute erythematous candidiasis, chronic erythematous candidiasis, angular cheilitis, and median rhomboid glossitis.

Acute erythematous candidiasis presents as painful reddened lesions which occur throughout the oral cavity (Fig. 3B) [43–46]. In chronic erythematous candidiasis (or “denture stomatitis”), these lesions are localized to the fitting surface of dentures [43–46]. Angular cheilitis, most commonly seen in elderly patients with over-closure of the jaw, is characterized by reddened lesions at the corner of the mouth.

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Fig. 2 Algorithm for the diagnosis and management of oral candidiasis in patients with plaque psoriasis. aIn the case that administration of anti-IL-17 treatment falls on the same day in which the antifungal treatment for oral candidiasis is initiated, administration of anti-IL-17 can be postponed for 3–4 days to prioritize resolution of oral candidiasis.
Finally, the least common subtype, median rhomboid glossitis, presents as a rhomboid-shaped area of atrophy and erythema on the midline posterior tongue dorsum [43, 45].

Chronic Hyperplastic Candidiasis
Chronic hyperplastic candidiasis is a rare form of oral candidiasis that presents as a thickened white plaque, most frequently at the commissural region of the mouth or the dorsum of the tongue. However, unlike in pseudomembranous candidiasis, this plaque cannot be removed by gentle scraping [42–47]. Plaques may be smooth and isolated (homogeneous) or nodular and speckled (heterogeneous) [45–47].

Risk Factors for Oral Candidiasis
The presence of predisposing factors, other than treatment with anti-IL-17 medications, can also inform diagnosis of oral candidiasis. These factors are divided into two categories: local factors that affect the local oral environment and microflora and systemic factors that affect the host’s immune status (for a full list see Table 1) [43].

Local Predisposing Risk Factors
One of the most common local risk factors is the use of dentures, which can create a favorable environment for Candida growth, especially if denture hygiene is poor [43, 48, 49]. It is estimated that up to 75% of adults who wear dentures have some form of erythematous candidiasis, although most are unaware of it [48].

Another common local predisposing factor is the use of steroid inhalers, which may cause alterations in the oral microflora and is commonly associated with pseudomembranous candidiasis [42, 43, 49, 50]. Incidence of oral candidiasis in users of steroid inhalers generally ranges from 1% to 7% in the literature [51].

Patients who use or smoke tobacco have significantly increased oral Candida carriage levels and rates of oral candidiasis [49, 52]. Hyperplastic candidiasis is almost exclusively found in patients who smoke [47]; however, the exact underlying mechanism remains unclear [52].

Systemic Predisposing Risk Factors
The best-characterized systemic predisposing factors for oral candidiasis are human immunodeficiency virus (HIV) and chemotherapy and radiotherapy for cancer [49, 53, 54]. Antibiotic use is also associated with oral candidiasis, particularly acute erythematous candidiasis (commonly referred to as “antibiotic sore mouth”) [43–46, 49].

Other major systemic predisposing factors for oral candidiasis are extremes of age; both elderly patients and infants have increased risk of oral candidiasis due to lower levels of protective salivary defenses [43]. Elderly patients may also have a loss of vertical dimension of occlusion, increasing the risk of developing angular cheilitis [43].

Diabetes and poor glycemic control have also been associated with oral candidiasis; patients with poorly controlled diabetes often exhibit reduced salivary pH and increased...
Table 1  Predisposing risk factors for oral candidiasis

| Local risk factors                                      | Systemic risk factors                                                                 |
|--------------------------------------------------------|----------------------------------------------------------------------------------------|
| Dentures                                               | HIV                                                                                   |
| Poor denture hygiene, ill-fitting dentures, and prolonged wearing of dentures are all associated with increased risk of oral candidiasis. Denture use is particularly associated with chronic erythematous candidiasis, also referred to as 'denture stomatitis' [43] | Oral candidiasis is one of the most common opportunistic infections in patients with HIV [54] |
| Topical corticosteroids (e.g., steroid inhalers)       | Chemotherapy                                                                          |
| May cause local alterations in the oral microflora, thereby predisposing the host to Candida overgrowth and particularly pseudomembranous candidiasis [43, 51] | Patients receiving chemotherapy or radiotherapy, especially of the head and neck region, are at increased risk of oral candidiasis [53] |
| Smoking                                                | Antibiotics                                                                            |
| Individuals who smoke or use tobacco are known to have significantly higher oral Candida carriage levels and experience higher rates of oral candidiasis [52]. However, the exact mechanism of this increase is unclear. Hyperplastic candidiasis is almost exclusively seen in patients who smoke [47] | Antibiotic use is particularly associated with acute erythematous candidiasis, which is commonly referred to as 'antibiotic sore mouth' [43] |
| Poor oral hygiene                                      | Extremes of age                                                                         |
| Can create a favorable environment for Candida growth. Many cases of oral candidiasis can be prevented by good oral hygiene [43, 56] | Both elderly patients and infants have lower levels of protective innate salivary defenses and reduced vertical dimension of occlusion, both of which are predisposing factors for angular cheilitis [43] |
| Salivary hypofunction                                  | Endocrine disorders (level of glycemic control)                                        |
| Reductions in the production of saliva are implicated in the development of oral candidiasis. This often occurs in older patients [43] | Patients with poorly controlled diabetes exhibit reduced salivary flow, reduced salivary pH, and increased salivary glucose levels, all of which facilitate Candida overgrowth [55] |
|                                                        | Nutritional deficiencies                                                                |
|                                                        | Malnutrition and deficiencies in iron, zinc, magnesium, selenium, folic acid, and vitamins A, B<sub>6</sub>, B<sub>12</sub>, and C have all been linked to increased risk of oral candidiasis [43, 55] |
|                                                        | Carbohydrate-rich diet                                                                  |
|                                                        | It has been suggested that such a diet facilitates the adherence of Candida to the oral mucosal epithelial cells [55] |

HIV human immunodeficiency virus
salivary glucose levels, facilitating Candida proliferation [49, 55].

**Confirmation of Diagnosis**

Oral candidiasis is typically diagnosed according to the presence of clinical signs and symptoms in patients with predisposing factors [45, 56]. If there are diagnostic doubts, diagnosis can be confirmed via microbiologic examination [45, 49]. Fresh samples from the oral tissues can be taken and examined microscopically using 10% potassium hydroxide (KOH) [45]. This method is useful for distinguishing erythematous manifestations of oral candidiasis from conditions with similar presentations, such as thermal traumatic lesions, lupus erythematosus, erythema multiforme, or epithelial dysplasia [57]. Alternatively, it is possible to culture samples using Sabouraud dextrose agar (SDA), from which the Candida species can be identified [45, 47]. This can be useful if infection shows resistance to antifungal agents, as some rarer Candida species (e.g., Candida glabrata) may show enhanced resistance to treatment [47].

In rare cases (0.32% of otherwise healthy individuals in a retrospective single-center study of 88,125 individuals in South Korea) [58], oral Candida infections may extend to the esophagus. Esophageal candidiasis appears endoscopically as thick white plaques on the esophageal mucosa. Symptoms include difficulty or pain upon swallowing or pain behind the sternum [49, 59]. Patients presenting with these symptoms should be referred for esophagoscopy to exclude esophageal candidiasis [49, 60].

If a patient presents with clinical signs of hyperplastic candidiasis, a biopsy should be conducted because of the proposed link between this presentation and malignancy [56].

**Treatment of Oral Candidiasis**

Patients with psoriasis are encouraged to practice good oral and denture hygiene to prevent the occurrence of oral candidiasis. However, if oral candidiasis occurs, a number of treatments are available, with some applied topically and others administered orally [56]. Generally, as per guidelines from the Infectious Diseases Society of America and Centers for Disease Control and Prevention in the USA, and the UK National Institute for Health and Care Excellence, initial topical antifungal treatment for 7–14 days is recommended [49, 56, 61, 62]. This can include miconazole oral gel (50 mg mucoadhesive tablet applied daily [USA], or 2.5 mL, four times daily [UK]), clotrimazole troches (10 mg, five times daily [USA]) or “swish and swallow” treatments such as nystatin suspension (100,000 U/mL, 4–6 mL [USA] or 1 mL [UK] four times daily) [61, 62]. If candidiasis does not resolve, oral fluconazole (100–200 mg once daily for 7–14 days [USA], or 50–100 mg once daily for 7 days [UK]) is recommended [49, 61, 62]. Itraconazole (200 mg once daily [USA] or 100–200 mg twice daily [UK]) can be prescribed as an alternative to fluconazole [61, 62]. As the labels of anti-IL-17 medications recommend pausing administration until an infection is resolved, if administration of anti-IL-17 treatment falls on the same day as initiation of antifungal treatment, administration of anti-IL-17 can be postponed for a few days to prioritize resolution of oral candidiasis.

Depending on local guidelines, fluconazole may be prescribed as a first-line treatment for oral candidiasis, as it is highly effective in treating fungal infections and has a simpler dosing schedule compared with topical antifungal treatments [56]. In our experience, shorter durations of fluconazole treatment (e.g., 100–200 mg daily for 3–5 days) can be an effective first-line treatment for oral candidiasis. However, any potential drug–drug interactions should be carefully considered, especially if a patient with psoriasis presents with other comorbidities. If oral candidiasis shows resistance to fluconazole, fungal characterization via SDA culture can be carried out, as previously described [45, 47]. In the case that a fluconazole-resistant Candida species is identified, alternative antifungal treatment should be prescribed.

While the majority of patients respond to these antifungal treatments with quick resolution [56], in certain cases oral candidiasis may...
be recurrent. If recurrent, measures should be taken to confirm adherence to antifungal treatment and correct any predisposing factors if applicable. This includes education in proper oral and denture hygiene, smoking cessation, rinsing the mouth after use of steroid inhalers, and proper management of diabetes [62]. Poor oral and denture hygiene, in particular, are key risk factors of oral candidiasis and so should be amended in order to prevent reinfection if relevant.

If recurrence continues within a 3-month period following initial treatment, and there is insufficient treatment response with alternative modes of psoriasis treatment, initiation of prophylaxis can be considered. In our clinical experience, this could include administration of any of the aforementioned treatment measures repeated once weekly or monthly for short or longer periods, guided by need and response.

The effectiveness of prophylaxis for the prevention of recurrent oral candidiasis has most frequently been demonstrated in patients with HIV [63]. In these patients, fluconazole prophylaxis has been shown to reduce recurrence as compared with no treatment or placebo [64–68]. However, there is concern that continuous treatment may lead to fluconazole resistance. Indeed, one study found decreased susceptibility of Candida isolates to fluconazole in 56% of patients who received continuous therapy. Nevertheless, the vast majority of patients in this study still showed clearance of oral candidiasis in response to fluconazole [69]. Furthermore, in another study, similar proportions of patients with HIV receiving continuous (4.1%) or episodic (4.3%) fluconazole developed fluconazole-refractory oral candidiasis [70]. For fluconazole-refractory infections, treatment with non-azole antifungals can be considered [61].

**CONCLUSIONS**

Given the increased risk of oral candidiasis in patients with psoriasis receiving anti-IL-17s, dermatologists should be attentive to clinical signs of oral candidiasis and aware of how to manage cases appropriately.

Oral candidiasis in patients with psoriasis is typically mild to moderate in severity. In our clinical experience, cases can be managed with standard antifungal treatment without discontinuing biologic psoriasis therapies. Furthermore, anti-IL-17 treatment is generally not associated with an increased risk of systemic candidiasis or serious infections.

To prevent recurrence of oral candidiasis, patients should be advised to practice good oral hygiene and be provided with information on smoking cessation, if applicable. Prophylaxis with antifungal agents can be considered if there is insufficient treatment response with alternative modes of psoriasis treatment.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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