Recurrent candidal intertrigo: challenges and solutions

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Abstract: Intertrigo is a common inflammatory dermatosis of opposing skin surfaces that can be caused by a variety of infectious agents, most notably candida, under the effect of mechanical and environmental factors. Symptoms such as pain and itching significantly decrease quality of life, leading to high morbidity. A multitude of predisposing factors, particularly obesity, diabetes mellitus, and immunosuppressive conditions facilitate both the occurrence and recurrence of the disease. The diagnosis of candidal intertrigo is usually based on clinical appearance. However, a range of laboratory studies from simple tests to advanced methods can be carried out to confirm the diagnosis. Such tests are especially useful in treatment-resistant or recurrent cases for establishing a differential diagnosis. The first and key step of management is identification and correction of predisposing factors. Patients should be encouraged to lose weight, followed up properly after endocrinologic treatment and intestinal colonization or peri-orificial infections should be medically managed, especially in recurrent and resistant cases. Medical treatment of candidal intertrigo usually requires topical administration of nystatin and azole group antifungals. In this context, it is also possible to use magistral remedies safely and effectively. In case of predisposing immunosuppressive conditions or generalized infections, novel systemic agents with higher potency may be required.

Keywords: Candida, intertrigo, recurrent candidal intertrigo, candidiasis, candidosis, candidal predispositions

Background
Intertrigo (intertriginous dermatitis) is a clinical inflammatory condition that develops in opposing skin surfaces in response to friction, humidity, maceration, or reduced air circulation. This common skin disorder may be localized in a small area or involve larger surfaces. Lesions mostly develop in the neck, axilla, sub-mammary fold, and perineum, while other sites may also be involved including antecubital, umbilical, perianal, and interdigital areas as well as abdominal folds, eyelids, and the retroauricular area.

The main factor in the development of the lesions is the mechanical friction on the skin that initially appears as a minimal erythema of the folds. Heat, reduced aeration, humidity, and maceration facilitate intertrigo. Although the condition may occur in both genders and all races, it is more common in diabetic obese individuals residing in hot and humid climates and in bed-ridden or elderly subjects. Urinary or fecal incontinence, inadequate personal hygiene, malnutrition, immunosuppression, and occlusive clothing are among other predisposing factors. Infants are also more likely to develop intertrigo due to drooling and short neck structure with prominent
skin folds and a flexed position. Many yeasts (particularly *Candida*) and molds, bacteria, and viral infectious agents may aggravate intertrigo by colonizing on the skin (Table 1).

Intertrigo may transform into a life-long chronic condition. It generally has an insidious onset with symptoms such as itching, pain, burning, or pricking sensations in skin fold areas. Initially it presents itself as mildly erythematous papillae or plaques, quickly developing into an exudative erosion, fissures, macerations, and crusts. Erythema due to secondary infections, increased inflammation, papullo-pustules, and bad odor may develop.1,2,7

Diagnosis of intertrigo and its complications are generally based on clinical manifestations and basic microbiological investigations. Microbiological cultures, potassium hydroxide (KOH) preparation, and Gram’s staining may guide the therapy when used for differentiating primary and secondary infections. Wood’s light examination can be used to identify a Pseudomonas, Malassezia, or erythrasma infection more quickly than would a culture. Despite the absence of a characteristic histopathological appearance, biopsy may be required in treatment-resistant cases of intertrigo in order to exclude other skin disorders such as psoriasis or lichen planus.1,2

Treatment of intertrigo should generally focus on the removal of predisposing factors, followed by appropriate use of topical or systemic antimicrobial agents as well as low-potency corticosteroids, if required.

### Candida species

Taxonomically, *Candida* belongs to the phylum Ascomycetes, class Blastomycetes, order Cryptococcales, family Cryptococcaceae, and genus *Candida*. These microorganisms have a diameter of 3–5 μm with a two-layered cell wall. Among more than 200 *Candida* species identified, only 15 may be associated with primary *Candida* infections. Yeasts associated with *Candida* species can be found in the normal flora of human skin as well as in the mucosal covering of the gastrointestinal system, genito-urinary system, and respiratory system, in addition to the soil and a variety of foods. Human colonization starts on the first day after birth and continues throughout the life-cycle as an opportunistic pathogen. *Candida albicans* is responsible for the majority of *Candida*-related noninvasive skin and mucosal candidiasis. However, a more than 50% increase in the incidence of non-albicans *Candida* species have recently been reported including *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. lusitaniae*, *C. dubliniensis*, and *C. guilliermondii*. Each of these organisms exhibits characteristic virulence potential, antifungal susceptibility, and epidemiology.

#### Pathogenesis of candidal infection

*C. albicans* is a part of the normal flora in skin and genital and/or intestinal mucosa in 70% of healthy individuals. Similar to many other opportunistic microorganisms of the skin, it exists as a commensal yeast in individuals with an intact immune system. It may lead to mucocutaneous or systemic infections under appropriate conditions.

Many *Candida* species are known to produce virulence factors like proteases. Species lacking these virulence factors are considered less pathogenic. Mechanisms of pathogenicity for *Candida albicans* may be summarized as below: secretion of hydrolases, molecules that mediate adhesion to with concomitant invasion into host cells, the yeast-to-hypha transition, biofilm formation, contact sensing and thigmotropism, phenotypic switching, and a variety of fitness attributes.

As is the case with all pathogens, the innate immunity of the skin represents the first step of the host defense against *Candida*. Pathogenic invasion is a rather complex process and is initiated through disruption of the physical barrier by the transformation of *Candida* on the skin from yeast to hypha form. The capability of the yeasts to adhere to epithelium is a strong stimulant for the hyphal transformation and represents the most important step in tissue penetration. Hyphae of *C. albicans* exhibit stronger epithelial adhesion than yeasts.

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Species</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td><em>Candida</em></td>
<td><em>C. albicans</em>, <em>C. glabrata</em>, <em>C. tropicalis</em>, <em>C. krusei</em>, <em>C. parapsilosis</em>, <em>C. dubliniensis</em>, <em>C. famata</em></td>
<td>4–11</td>
</tr>
<tr>
<td><em>Fusarium</em></td>
<td><em>F. oxysporum</em>, <em>F. solani</em></td>
<td>12–18</td>
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<tr>
<td>Dermatophytes</td>
<td><em>Trichophyton</em> spp., <em>Microsporum</em> spp., and <em>Epidermophyton</em> floccosum</td>
<td>2,8,9,15,19,20</td>
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<tr>
<td>Malassezia</td>
<td>Mostly <em>M. furfur</em>, <em>M. globosa</em> or <em>M. sympodialis</em></td>
<td>9,21–23</td>
</tr>
<tr>
<td>Bacteria</td>
<td><em>S. aureus</em>, <em>S. epidermidis</em>, <em>S. haemolyticus</em>, <em>S. pyogenes</em>, or other streptococcal species <em>Pseudomonas</em> spp., <em>Proteus</em> spp., <em>E. coli</em>, <em>Pseudotreptococcus</em> spp., <em>Corynebacterium</em> spp., <em>Acinetobacter</em> spp., etc.</td>
<td>2,11,24–26</td>
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</table>

**Abbreviation:** HPV, human papillomavirus.
More aggressive *C. albicans* species that have no ability to produce hyphae cannot attach to epithelium. Breakdown of the physical barrier with fungal invasion allows the spread of *C. albicans* to underlying vascular tissues, and then to distant organs. While transformation into the hypha form is a critical virulence factor both for epithelial penetration and phagocyte attachment of *C. albicans*, the yeast form is required for the development of systemic infection and dissemination.38,41

The contest between the host and *Candida* involves more specific and complex molecular mechanisms; the recognition of fungal cell wall components, activation of the immune cell signal pathways of the host, and release of cytokines and chemokines.41 Formation of hyphae by *C. albicans* is also known to represent a very important factor that induces cytokine responses from epithelial cells.42 The importance of cytokine and chemokine production has been underlined almost universally in all studies investigating the epithelial responses to *C. albicans*. Infected epithelial cells have been found to produce IL-α/β, IL-6, G-CSF, GM-CSF, and TNFα, in addition to chemokines and cytokines such as RANTES, IL-8, and CCL20.38,43-45

An examination of the immune mechanisms of the skin against *C. albicans* reveals that the defense barrier initiated with the stromal cells such as keratinocytes and melanocytes as well as the defense proteins released by these cells continues with the pattern recognizing receptors such as Dectin-1 and Toll-like receptor. Individuals with mutations or gene polymorphisms in pathways of these receptors have been found to be more susceptible to *Candida* infections.46 The major mechanisms of innate immunity against candida infections include neuropeptides such as calcitonin gene-related peptide (CGRP) released in areas where the physical barrier is disrupted, IL-23 release from the dendritic cells, and activation of neutrophils recruited via IL-17 release from γδ T cells that is stimulated by the release of IL-23. On the other hand, IL-17 pathways represent an important component of the adaptive immunity against *Candida* infections through induction of effector and cytotoxic T lymphocytes.35

**Predisposing factors for candidal infections**

The main determinant of the non-pathogenic commensal colonization versus pathogenic behavior is the balance between fungal proliferation and the innate and adaptive defenses of the host.41 This balance is disturbed in favor of *Candida* as a result of various factors that predispose the individual to intertrigo (Table 2).

**Clinical forms of candidal skin infection**

*C. albicans* is responsible for approximately 80–90% of all skin infections caused by *Candida* species. It is an oval-shaped thermal dimorphic yeast with a diameter of 2–6×3–9 μm that can produce budding cells, pseudo-hyphae, and true hyphae. Skin infections encompass numerous forms with varying clinical terminology used to describe them. Although the clinical variants of skin infections have been clearly defined in the literature, currently no consensus regarding a standard classification system exists. In a 1996 classification by the American Academy of Dermatology’s Guidelines/Outcomes Committee,47 the infections have been defined on the basis of their location and appearance as follows: cutaneous (intertriginous agents), oral (intra-oral mucosa), genital (vagina and penis), nail unit, and chronic mucocutaneous. However, different clinical classification systems have been proposed in many dermatological or other textbooks, or reviews.31,49-51,57,58,62-65

Regardless of the size of the lesion, *Candida* infections involving skin folds should be classified under the candidal intertrigo heading, based on the definition intertriginous dermatitis (Table 3).

**Candidal intertrigo**

*C. albicans* has a predilection for moist and macerated skin folds. The most frequent type of clinical presentation in hairless skin is intertrigo. Pruritic, erythematous, macerated skin areas are observed in intertriginous areas with satellite vesicopustules. The characteristic pustulae rapidly rupture, leading to the formation of collaret type erythematous surface, from which the necrotic epidermis may be easily removed.9,87

Candidal intertrigo of larger skin folds usually involves the axilla, gluteal, infra-mammary, and genito-crural fold (Figure 1). The moisture and increased temperature on the surface of opposing skin folds provide a suitable medium for the growth of *Candida* and bacteria. Humid and hot weather, tight underclothes, poor hygiene, and inflammatory skin conditions such as psoriasis may increase the risk of candidal infections.9 Diabetes mellitus and obesity represent the leading predisposing factor. Xerostomia, hyperhidrosis, occlusive wearings, occupational factors, use of corticosteroids or wide spectrum antibiotics, and immunosuppression including HIV infection may also increase the risk.5,51,68,88,89

**Diaper candidiasis**

Diaper dermatitis is an acute and inflammatory skin reaction in the diaper area (Figure 2). It is generally caused by
the yeast colonizing in the gastrointestinal system. Chronic occlusion with wet clothes facilitates the infection. With prevalence ranges between 7 and 35%, it most commonly occurs in infants between 9 and 12 months of age, and may also be seen in adults requiring incontinence pads. Infants with Candida diaper dermatitis generally have colonization in their gastrointestinal system with positive stool cultures for Candida. In infants with very low birth weight ≤ 1500 g, candidal colonization of the rectum and stools can be detected in 21–62.5%. Lesions typically start in the perianal region, and spread over the perineum and inguinal area. Not all cases of diaper dermatitis may be caused by Candida, but diaper dermatitis due to candidiasis involves the skin folds. Multiple small
Recurrent candidal intertrigo

erythematous desquamated pustules and satellite lesions extending along the borders of large maculae represent significant findings for diagnosis.\textsuperscript{51,88,90}

Granuloma gluteale infantum is a reaction developing 
\textit{Candida} that causes opaque, reddish, irregular papules and/or nodules on the background of an erythematous surface in the diaper area. This is a reactive condition developing due to chronic irritant contact dermatitis caused by urinary incontinence or chronic diarrhea.\textsuperscript{63,89,91} Diagnosis is generally straightforward, and biopsy may be required to rule out mast cell tumors, pseudolymphoma, lymphoma, and leukemic infiltration.\textsuperscript{92}

Angular cheilitis (perleche)

This condition is characterized by erythema, maceration, transverse fissures, and pain in the corners of the mouth. Although it is localized in the skin folds on the lips, it is classified within the group of oral candidal infections. Recurrent oral candidiasis is a common finding in HIV-infected subjects and is an important prognostic marker.\textsuperscript{78} In HIV-positive patients, it may occur without other signs when the CD4+ lymphocyte count declines below 200/\(\mu\)L.\textsuperscript{93} Frequently, it occurs due to use of lip liners in younger individuals, while skin sagging may be a causative factor in the elderly. Tooth loss, ill-fitting dental fixtures, and malocclusion represent other predisposing factors.\textsuperscript{78,88,89} It may occur concomitantly with submental and cervical intertrigo, particularly in infants and debilitated patients with salivary discharge.

\textbf{Erosio interdigitalis blastomycetica}

Candidal intertrigo settling between the fingers, also termed as erosio interdigitalis blastomycetica (EIB), is an infectious condition that may develop by a candidal or polymicrobial infection. It usually affects the third and fourth fingers or toes due to physical inactivity, moisture, soap, water retention, or disruption of the skin barrier. The moisture under a ring may cause maceration and irritation, facilitating secondary infections with \textit{C. albicans}. Lesions may cause oval, macerated, whitish lesions that may extend to the lateral borders. Generally, one or more fissures with a reddish-base are present in the middle of the lesions. As the disease progresses the macerated skin is peeled off, leaving an eroded area in which the protruding epidermis is surrounded by a white collar.\textsuperscript{51} Microbiological cultures suggest that \textit{Candida} and gram negative bacilli play a role in the development of this condition.\textsuperscript{94} Very often, it develops as an occupational disease due to chronic maceration in individuals with chronic contact
with water such as cooks, barmen, barmmaids, dishwasher, housewives, or dentists. Diabetes mellitus is a predisposing disease for EIB, and EIB is an important cutaneous manifestation of diabetes. Thus, in patients diagnosed with EIB, a diagnosis of de novo or uncontrolled diabetes should be considered. The differential diagnosis includes erythrasma and irritant contact dermatitis.

**Toe web candidiasis**

It is an EIB-like intertriginous *Candida* infection, commonly occurring in the fourth interdigital space of the toes. It may be asymptomatic or cause mild symptoms. Moist working conditions and use of tight and closed shoes for prolonged periods of time may induce this condition. The skin exhibits white, macerated, and thickened epidermis. Its appearance is very similar to that of tinea pedis, and significant erythema and desquamation may occur as well.

**Perianal, perineal and intergluteal candidosis**

Perianal, perineal, and genitocrural areas are naturally moist areas of the skin. Intertrigo may develop as an extension of vulvovaginal or intestinal candidiasis or due to spreading from one area to another. Initially, it may present as severe perineal and anal pruritus accompanied by severe itching and burning sensation. An erythematous, oozy dermatitis together with maceration is observed in involved areas (Figure 3). Also satellite lesions in the form of papules or pustules may be observed in the margins of erythematous-macerated plaques and eroded areas. Absence of satellite lesions does not rule out a diagnosis of candidiasis.

In cases where the cause of the condition is vulvovaginal or intestinal candidiasis, the disease may exhibit a recurrent and chronic course. Acute genitocrural intertrigo may also develop as a maculopapular eruption in HIV-infected subjects.

**Differential diagnosis of candidal intertrigo**

Numerous infectious agents, mainly bacteria and dermatophytes, may lead to similar clinical presentations in the areas affected by *Candida* intertrigo in addition to a variety of mucocutaneous disorders that can mimic the inflammation in the lesions. Some of these conditions have been presented in Table 4 according to the involved site in intertrigo.

**Preventing recurrent infections**

Preventive measures for recurrent intertrigo are used to support the therapy and represent the first step in management.

![Figure 3 Perianal and intergluteal candidal intertrigo of a man.](https://www.dovepress.com/)

The affected area(s) should be kept dry, clean, and cool with good airing and minimization of skin friction at the fold site. Good hygiene should be maintained in the infected area. Patients should be advised to wear cotton underwear, light clothing in hot and humid weather conditions, and should be warned regarding outdoor activities. Open shoes may help to prevent intertrigo of the toes.

Maceration or irritation due to incontinence should be minimized or eliminated totally if possible. Cleansers, driers, emollients, and skin barrier creams may prove to be useful in such cases.

**Laboratory diagnosis of intertrigo**

The clinical appearance of candidal intertrigo usually suffices for a diagnosis. However, laboratory investigations and confirmatory tests may be required, particularly in chronic, resistant, and recurrent cases. The simplest examination technique involves identification of the presence of pseudo-hyphae or yeast forms under direct microscopic examination of the samples obtained through scraping and smears that have been prepared with KOH and calcofluor white staining. Also, fluorescent microscopy and trypan blue examination may be used for that purpose. Differentiation between the species, assimilation and fermentation tests are applied on Candidal cultures. More advanced techniques...
rarely required in the clinical practice include PCR, electron microscopy, and microchip diagnostic tests. Biopsy may be performed for the differential diagnosis from psoriasis as well as from dermatoses and dermatophytoses such as tinea. Identification of septa-free hyphae and yeast forms in PAS-stained histopathological samples is diagnostic for Candida.

**Treatment of candidal intertrigo**

Specific treatment of candidal intertrigo depends on the location, severity, and depth of the infection. Also, the treatment may be guided by the stage of the infection, i.e., acute, subacute, or chronic. Initially, the active *Candida* infection should be medically managed, followed by skin drying measures to reduce the risk of recurrence, and finally by the correction of predisposing factors (Table 3).

Topical anti-fungal agents are the mainstay of treatment in Candidal intertrigo. Topical anti-fungal agents represent the first step in management in mild cases of candidiasis. Nystatin and azole topical antifungals including miconazole, ketoconazole, or clotrimazole may be used twice daily for 2–4 weeks. Time-tested magistral preparations may also aid in treatment. In acute lesions, Domeboro® solution (Moberg Pharma North America LLC, Cedar Knolls, NJ, USA), Castellani paint (ICM Pharma, Singapore), or vinegar–water solutions may be applied twice daily for 5–10 minutes. After drying, a mixture of zinc oxide, talc, and glycerin may be administered twice daily. In subacute lesions, after cleansing with benzoyl peroxide, Castellani stain, or vinegar, topical antifungals may be administered. In chronic lesions, rinsing lotion containing zinc-talk applied twice daily may be beneficial. Also, night-time application of antifungal/corticosteroid combinations may be recommended. For itchy and painful lesions, an antifungal agent combined with corticosteroids (mostly hydrocortisone) may also be added to the treatment. In cases with local hyperhidrosis, anti-perspiration agents such as 20% aluminum chloride can be used in the long term. If maceration or moisture is present, astringent and antiperspirant solutions may be applied following antifungal creams.

**Table 4: Most common differential diagnoses for intertriginous dermatitis on skin-fold areas**

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Large skin folds (axilla, inframammary, umbilical, intergluteal, and genitocrural)</th>
<th>Diaper intertrigo</th>
<th>EIB</th>
<th>Toe web intertrigo</th>
<th>Perianal and perineal intertrigo</th>
<th>Intertrigo of the neck folds</th>
<th>Eyelids and retroauricular</th>
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<td>Atopic dermatitis</td>
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<td>Fusarium spp. infections</td>
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<td>Syphilis</td>
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<td>Verrucous carcinoma</td>
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**Note:** Data taken from several studies. Abbreviations: HPV, human papillomavirus; EIB, Erosio interdigitalis blastomycetica
In extensive, severe, and resistant intertrigo, systemic anti-fungal treatment is required. Oral fluconazole at a dose of 50–100 mg/day or itraconazole at a dose of 200 mg/day may be recommended for a total duration of 2–6 weeks until symptoms resolve. For pediatric cases, the recommended fluconazole and itraconazole doses are 6 mg/kg/day and 5–10 mg/kg/day, respectively.84

**Diaper candidiasis**
Diaper candidiasis can be generally managed with topical antifungal agents. Nystatin ointment or powder is commonly used, with a clinical cure rate of approximately 85%.90 Treatment with other azoles such as clotrimazole and miconazole may also give successful results. Despite similar mycological cure rates, miconazole is more effective than nystatin for symptomatic relief.79,80

For concomitant bacterial infections or irritation, combination of 1% hydrocortisone with antimicrobial agents such as sodium fusidate or clioquinole may be used. If recurrent diaper candidiasis is related to oral and intestinal colonization, addition of oral nystatin suspension may elicit a clinical response.51

**Angular cheilitis (perleche)**
Angular cheilitis (perleche), when secondary to a *Candida* infection of the oral mucosa, should be brushed regularly, together with twice daily administration of an antiseptic oral rinse solution such as chlorhexidine gluconate (0.12%, suspension) or Gentian violet 0.5% solution.59,104 Patients with xerostomia should be encouraged to increase water consumption, and sugar-free lozenges should be advised to increase salivation.39

**Interdigital candidiasis (EIB and toe web candidiasis)**
Special applicators may be recommended for drying the inter-toe spaces in interdigital candidiasis (EIB and toe web candidiasis).9 Also, triggering factors should be avoided. For treatment, topical antifungal agents (azole antifungals) are generally adequate. Good outcomes have been reported with filtering paper adsorbed with Castellani stain.51,105 In recurrent or resistant cases, systemic itraconazole, terbinafine, or amorolfine may be used.

**Correction of predisposing factors**
Obese patients should be encouraged to lose weight, and diabetes should be under good control.7,81 Patients with large and sagging breasts may benefit from breast reduction surgery.2,106 For excessive sweating between the breasts, sweat-absorbing towels may be utilized. If present, predisposing factors (malocclusion, teeth loss, etc.) should be corrected in patients with angular cheilitis. For anatomical problems, the depth of skin folds may be reduced by injection of cosmetic filling material.9 Topical or systemic administration of corticosteroids may also lead to chronic or recurrent candidiasis via immune suppression.47,62,78 Wide spectrum antibiotics may also lead to *Candida* colonization and pathogenicity by disrupting the saprophytic flora of the skin and mucosal membranes. A detailed history of medication should be obtained to avoid unnecessary use of antibiotics and corticosteroids.47,50,62,64,107 If high doses are involved, oral contraceptives with lower estrogen content should be preferred. For the recurrent intertrigo of the perianal area and its surroundings due to intestinal colonization, nystatin may be given.32 Nutritional deficiencies such as iron and B2 deficiency may facilitate mucocutaneous candidiasis.58,59,53

Patients wearing rings should be recommended to keep the skin under the ring dry and clean. Good aeration with open shoes may be recommended for toe web intertrigo. In cases with chronic incontinence, regular and absorbing hygienic products should be utilized for skin care.

**Prognosis**
Candidal intertrigo has a good prognosis in healthy immunocompetent individuals with no co-morbidities, and complete resolution of symptoms may be achieved with correct diagnosis and appropriate topical treatment. Ideally, in all cases with intertriginous candidiasis, all predisposing and provoking factors should be totally eliminated; if that is not possible, then these factors may be reduced. In more severe and recurrent cases of vaginal, oral, or chronic mucocutaneous candidiasis, systemic antifungals generally yield good results.

**Disclosure**
The authors report no conflicts of interest in this work.

**References**