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SPECIAL ISSUE: COLORS AND TEXTURES, A REVIEW OF ORAL MUCOSAL ENTITIES

Candidiasis: Red and White Manifestations in the Oral Cavity

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Abstract
Candidiasis is a very common malady in the head neck region. This review will concentrate on intraoral, pharyngeal and perioral manifestations and treatment. A history of the origins associated with candidiasis will be introduced. In addition, oral conditions associated with candidiasis will be mentioned and considered. The various forms of oral and maxillofacial candidiasis will be reviewed to include pseudomembranous, acute, chronic, median rhomboid glossitis, perioral dermatitis, and angular cheilitis. At the end of this review the clinician will be better able to diagnose and especially treat candidal overgrowth of the oral facial region. Of particular interest to the clinician are the various treatment modalities with appropriate considerations for side effects.

Keywords Candidiasis · Candidosis · Fungal · Thrush · Candidiasis diagnosis · Candidiasis treatment

Introduction

In 1839, Bernhard von Langenbeck was the first to attribute a fungus as the etiologic agent in esophageal and oropharyngeal candidiasis [1]. Since that time, an entire kingdom of fungi with millions of species of heterotrophic and parasitic organisms has been identified.

The terms candidiasis and candidosis are synonyms for the disease process commonly associated with *Candida albicans*. This review will concentrate on candidiasis of the oral cavity, oropharynx, and perioral skin. In general, parasitic infections/infestations end with the suffix -iasis; while mycotic processes generally end with -osis. The term that should be specifically avoided is moniliasis, which incorrectly attributes *Monilia* as the causative organism.

The genus name *Candida* is attributed to the traditional white robes worn by Roman candidates (*candidatus*) running for public office. The term albicans is derived from another Latin word *albico/albicatus*, which means "to be white" or "verge on white." In essence, the term *Candida albicans* is redundant meaning "white to be white" [2]. Most of the species within the genus are dimorphic yeasts and form hyphae or pseudohyphae along with standard blastospore yeast forms. The observation of germ tubes is highly suggestive of *Candida albicans* as the source species [3].

While *Candida albicans* is by far the most common species associated with thrush, at least seven other species within the *Candida* genus have been attributed to the disease in the oral cavity: *C. glabrata, C. guillermondii, C. kruesi, C. lusitaniae, C. parapsilosis, C. pseudotropicalis, C. stellatoidea*, and *C. tropicalis* [4].

In addition, 20 other genera and 80 species have been cultured from human sources [5, 6]. Species-specific culturing and sensitivity testing are primarily used in cases of systemic *Candida* infections and are rarely necessary in overgrowth confined to the oral region [3]. Candidiasis is a very common problem within the population with multiple areas of the body readily affected.

An estimated 30–60% of healthy adults carry *Candida* species within the oral cavity. The vast majority of these microorganisms exist as commensal colonization rather than a pathologic process [7–9]. Most of these epidemiologic studies were performed by culturing for the organisms and many who participated showed no clinical signs or symptoms of *Candida* infection. Because of the background commensal carriage rate among the population at large, culturing for *Candida* species as a diagnostic procedure is likely to

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yield many false positives. This topic is discussed in greater depth during the diagnosis portion of this article.

It is important to recognize the difference between *Candida* species as commensal organisms within the microbiome of the oral cavity versus *Candida* acting as a pathologic entity. When evaluating the patient and making therapeutic choices, the clinician must always consider the difference between commensalism and pathogenesis. The pathologic colonization of *Candida* species is related to a number of factors including, but not limited to: age extremes, malnourishment, metabolic disease, concurrent infections, antibacterial therapy, immunocompromising conditions, radiotherapy, transplant patients, salivary gland hypofunction, and long-term steroid therapy [3].

Advances in fields of medicine such as oncology, organ transplantation and the advent of disease-modifying antirheumatic drugs (DMARDS) have created an ever-increasing number of susceptible hosts; thus advancing the field of medical mycology [10].

Severe systemic involvement of *Candid*a species can cause significant morbidity and mortality most notably in immunocompromised hosts [10–12]. *Candida albicans* associated candidemias have mortality rates that may exceed 30% in certain populations. Severely neutropenic patients, intensive care unit (ICU) patients, and neonatal ICU patients tend to harbor less common pathologic genera of *Candida*. Choosing the correct broad-spectrum antifungal agent for prophylaxis in these patients is literally a life-saving decision [13]. When host defenses are lowered, the dimorphic nature of *Candida albicans* allows the organism to switch from a commensal to pathogenic state largely through the formation of biofilms. These biofilms, by virtue of their three-dimensional structures, are very resistant to even high concentrations of antifungal drugs. Embedded microorganisms on either host or abiotic surfaces (catheters, indwelling implants, etc.) often break off and enter the systemic circulation. In severely immunocompromised patients, oral mucosal infections can likewise cause candidemia, which is also associated with a high mortality rate [14].

Clinically, these authors prefer the use of cytologic preparations for standard mucosal candidiasis. The cytologic preparation gives information on the prevalence of fungal organisms within the preparation in addition to the microbiome burden of bacterial elements. In general, the morphologic forms of the *Candida* species are the most significant finding in the preparation with the bacterial load being an interesting, but minor finding. A modified version of periodic acid Schiff (PAS) with a light green counter stain as described by the Armed Forces Institute of Pathology (AFIP) is one recommended method [15].

The azole class of antifungal medications (e.g. itraconazole, clotrimazole, fluconazole) exert their mechanism of action by preferentially inhibiting fungal cytochrome P450, an essential element to continued ergosterol production and growth of the organism. However, in cases resistant to azole medications, cytologic preparations may reveal the absence of hyphal elements. This would be the case with *Candida glabrata* as well as rare pathologic species such as *Candida tropicalis or Candida parapsilosis*, although the latter two may form pseudo-hyphae (Figs. 1, 2, 3, 4).

In the event of unusual cytologic findings, culturing for specific species and drug sensitivity may be appropriate. Certain pathologic genera of *Candida* are resistant to even the newer azoles (voriconazole, posaconazole, isavuconazole). In such cases, the polyene medications such as nystatin or amphotericin B may be more effective. These medications are not well absorbed from the gastrointestinal tract, but are effective topically [10]. The echinocandin class of antifungals is preferred in cases of severe *Candida* infections where fungi are dependent on beta-1,3 D-glucan synthetase. By inhibiting the production of this glucan, the drugs affect the cell walls of many fungi including *Candida*. At this time, no oral forms of echinocandin drugs are available [10].

Cytologic preparations are simple, non-invasive, and cost effective; but due to clinicians' lack of exposure to the technique, they are often underutilized. While inappropriate for many diagnostic work-ups, in the correct clinical setting, they can serve as a useful adjunct to obtain a diagnosis.

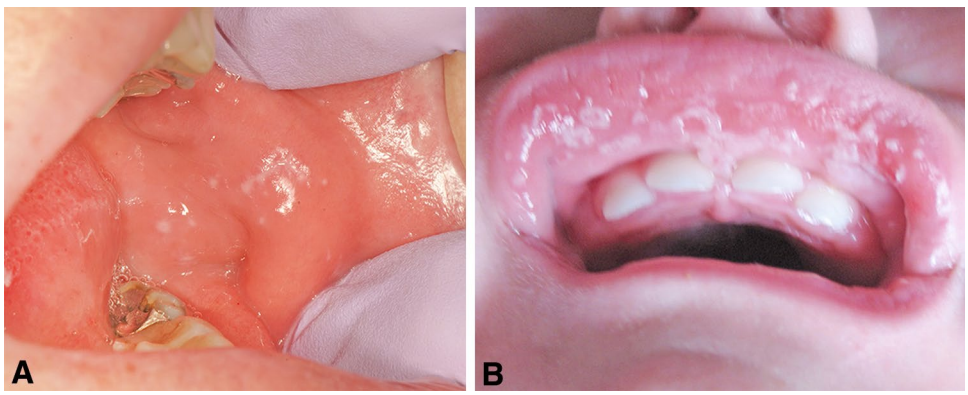

Fig. 1 **a** Pseudomembranous candidosis left cheek. **b** Pseudomembranous candidosis infant

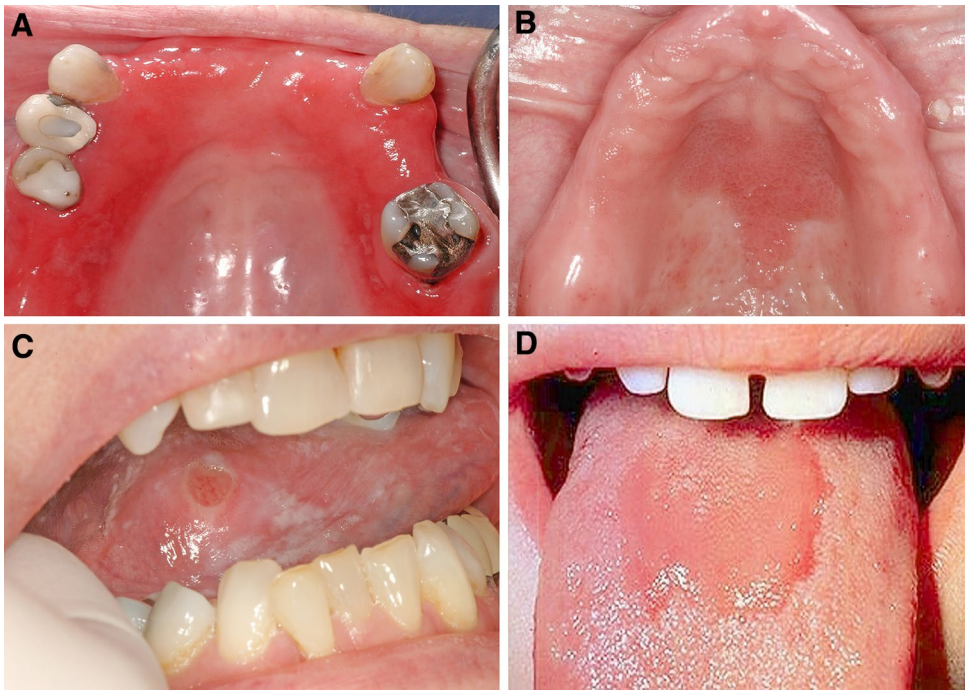

Fig. 2 **a** Chronic atrophic candidosis. **b** Inflammatory papillary hyperplasia (IPH). **c** Hyperplastic candidosis with traumatic ulcer and frictional changes. **d** Median rhomboid glossitis

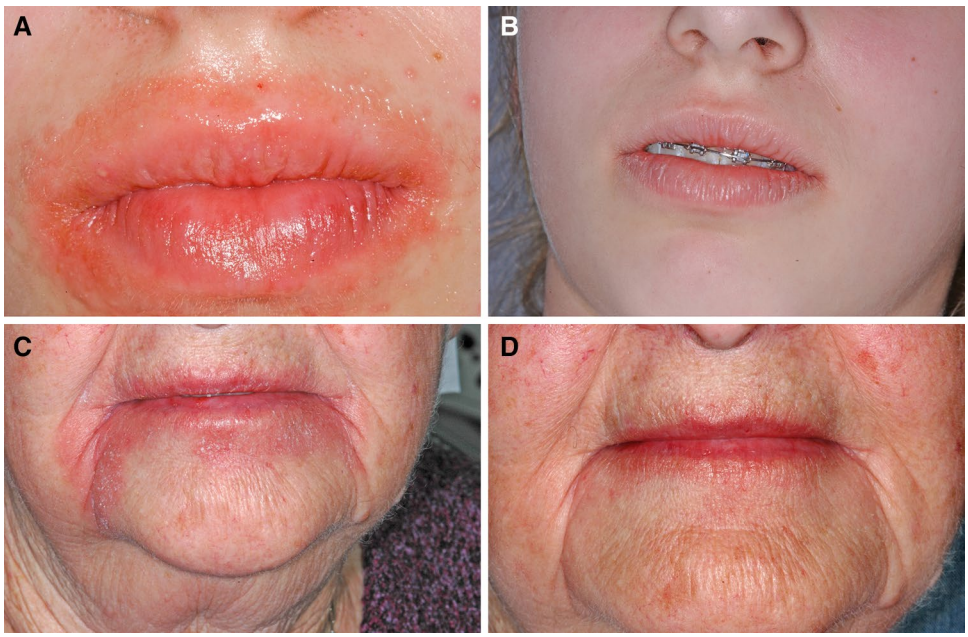

Fig. 3 **a** Circumoral dermatitis Case 1 before treatment. **b** Circumoral dermatitis Case 1 after treatment. **c** Circumoral dermatitis Case 2 before treatment. **d** Circumoral dermatitis Case 2 after treatment

Clinical Presentation and Diagnosis

The classic presentation of candidiasis is that of pseudomembranous candidiasis, commonly known as thrush. Thrush is a colloquial term derived from a family of birds with characteristic white spots on their breasts. Other forms of candidiasis, such as the chronic erythematous form, can be a diagnostic challenge for clinicians, especially in the absence of a dental prosthesis. The determination of the origin of the erythema as a pathological process induced by *Candida* overgrowth versus *Candida* as a commensal organism may require a therapeutic trial of an antifungal agent. However, in the erythematous cases, the use of cytologic preparations is especially helpful.

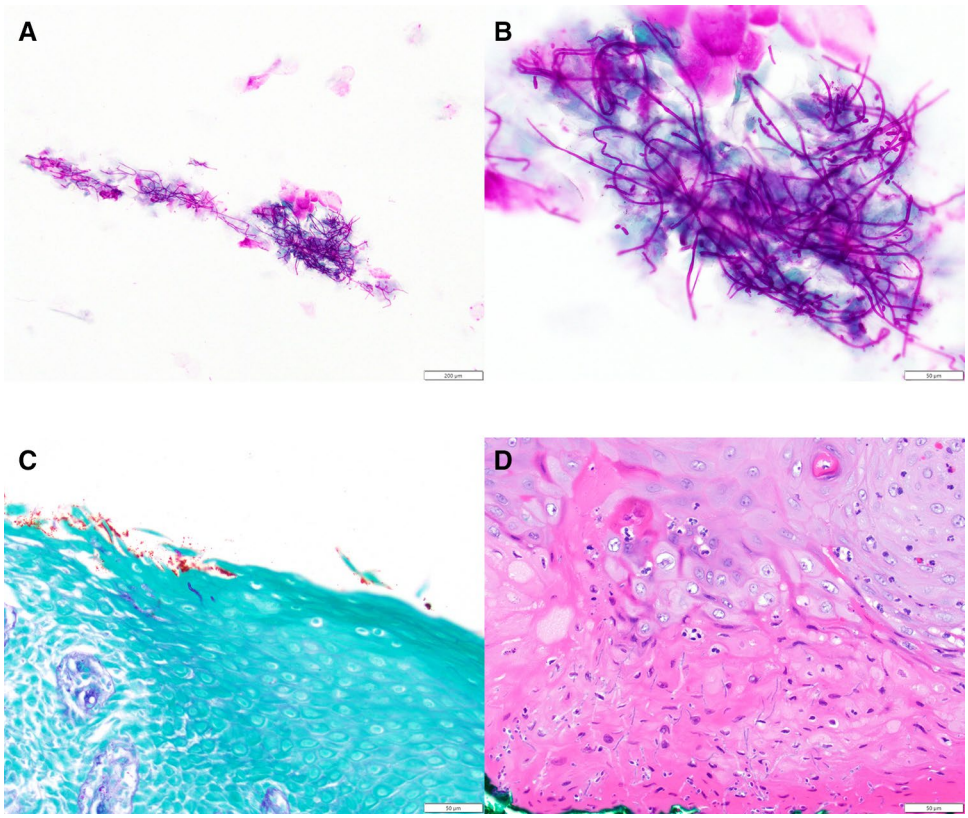

Fig. 4 **a** Candida cytology PAS medium-power. **b** Candida cytology PAS high-power. **c** Candida tissue rare hyphae PAS high-power. **d** Candida tissue numerous hyphae H&E

Acute Pseudomembranous Candidiasis

Acute pseudomembranous candidiasis is the form of candidiasis classically seen in newborns and immunocompromised patients. This infection may be associated with steroid inhalers, rinses, gels, and ointments. Salivary gland hypofunction and xerostomia may also be causative factors to this acute presentation. Many of these cases are asymptomatic; however, patient using topical steroid preparations for vesiculoulcerative or autoimmune diseases such as erosive lichen planus or mucous membrane pemphigoid, often experience significant discomfort.

After initiation of topical steroids, these patients often experience reduced symptoms of their condition. 1–3 weeks into their therapeutic regimen, patients may relay that their symptoms have worsened. Classically, this second bout of symptoms is due to a *Candida* infection. The risk of iatrogenically induced acute pseudomembranous candidiasis varies by patients in accordance with the number of risk factors mentioned above. Most patients are advised of an approximate 20% risk associated with use of intraoral steroids. In patients with multiple risk factors, a prescription antifungal may be written in anticipation of candida overgrowth.

The first line of treatment of acute pseudomembranous candidiasis in adults is generally clotrimazole 10 mg troches with secondary choices being systemic. For therapeutic "cure" of acute pseudomembranous candidiasis, a 14 day course of five troches a day is prescribed. Compliance with a five times daily medication is difficult for many patients. For this reason, it is acceptable for the patient to dissolve two troches in the morning, one in the afternoon and two at bedtime. Patients are instructed to remain NPO (nothing by mouth) for 30 min after use. They also may catch up on doses as needed during the daytime as rigid dosing schedules are not necessary. Patients who have friable tissue and/or sore mouths are instructed to take a sip of water prior to dissolving the tablets to hasten the dissolution process and soften the hard surface of the compressed troche.

In iatrogenic cases where the inductive medication (antibiotics, topical steroids, cyclosporine, etc.) will be continued due to the underlying disease process, a preventive antifungal regimen will be necessary. For clotrimazole maintenance two troches may be dissolved at bedtime daily to prevent overgrowth. Nystatin suspension is usually only a first line drug in newborns. Chronic use of nystatin suspension is discouraged in dentate patients due to high sucrose content (30–50%).

Acute Atrophic Candidiasis

This form of candidiasis is generally diagnosed due to an acute presentation and is most likely secondary to antibiotic use or other iatrogenic therapeutic agent. Examination shows

erythematous mucosa, but no evidence of pseudomembranous overgrowth and can be localized or generalized. The painful nature of this form is what will bring the patient into the clinic. An acute version of burning mouth/tongue type symptoms are symptomatically described as tenderness of the mucosa as well as increased sensitivity to various foods and flavoring agents. Cytologic diagnostic testing can be performed, though an empiric clinical diagnosis is often enough to begin therapy. The same therapeutic approach as acute pseudomembranous candidiasis is applied.

Chronic Atrophic Candidiasis

This is the most common form of candidiasis in denture patients and is usually asymptomatic. Occasionally this form may be associated with orthodontic retainers, but the vast majority of patients are wearing their dentures 24 h a day. In addition to the long-term use of the dental appliances, there are other etiologic factors. Oral hygiene is often poor. Additionally, there is chronic infestation of the appliance with the organism. Changes in mucosa are generally limited to the area covered by the dental appliance. The hyphae/yeast forms may invade into the superficial epithelium. Due to the asymptomatic nature of chronic atrophic candidiasis, the dentist is most often the first to identify the problem. The clinician may be concerned with the edematous nature of the inflammatory process, especially at the time of denture fabrication.

In order to reduce mucosal changes, treatment of both the oral mucosa and the appliance are necessary. In treatment of the mucosa, antifungal creams or ointments are applied directly to the denture. Clotrimazole 1% cream is recommended and available as an over-the-counter product. It should be noted that this product is labeled for jock itch and athletes' foot; therefore patients should be counseled on the rationale behind use of the product.

Nystatin ointment may also be used long-term as the yellow hue and poor taste are not factors since the denture is essentially being used as a splint. With either medication, directions to the patient should be to apply a thin film to the tissue surface of the denture 2–4 times daily.

Various methods of denture sanitation have been recommended. There are a number of commercial products available. Nystatin suspension is not an effective denture cleaner as the acrylic pores of the appliance are much smaller than the size of the nystatin molecule.

Cleaning the prosthesis with a denture brush/toothbrush is always a good idea prior to use of either the topical antifungal as well as prior to the overnight denture sanitation [16]. Patient compliance in all the steps can also be very unpredictable as most clinicians already realize.

Chronic atrophic candidiasis can also be associated and concomitant with inflammatory papillary hyperplasia (IPH). This is often secondary to poorly fitting dentures. Inflammatory papillary hyperplasia creates ideal areas for the fungal elements to flourish and is perhaps induced by the chronic fungal/bacterial overgrowth. Elimination of IPH is usually not a reasonable therapeutic goal. Though surgical removal of IPH has been advocated [17–20], there have also been some nonsurgical protocols for the more severe cases of IPH. The method described by Orenstein et al. appears be very reasonable. Orenstein utilized a method where the [19] IPH was addressed by relieving stone model (a step in denture fabrication) where the mucosal alteration is noticed. This resulted in an ill-fitting denture initially requiring use of a denture adhesive on initial denture insertion. They also utilized sanitizing agents and routine cleaning of the denture with denture brush/toothbrush. When the papillary hyperplasia was reduced or eliminated, they then relined or re-based the denture for proper fit.

Chronic Hyperplastic Candidiasis

Chronic hyperplastic candidiasis (CHC) is a white lesion that does not wipe off. CHC has an increased incidence in those who use tobacco but many white lesions are increased overall in this population. The diagnosis of CHC is sometimes problematic because any rough surface within the oral mucosa can create an ideal place for candidal elements to proliferate. Squamous papillomas are commonly associated with hyphal elements histologically, for example. Likewise, entities such as focal keratosis, epithelial dysplasia and squamous cell carcinoma, verrucous carcinoma and others may be associated with candida hyphae. Though it would take culture methods to confirm the species, such hyphae are presumed to be candidal in origin. The hyphal overgrowth/invasion can create reactive changes leading to some question as to whether the changes are dysplastic or reactive in origin. Chronic hyperplastic candidiasis is often found on the lateral tongue and the buccal mucosa. These are also areas of increased friction, which predispose them to candida colonization.

For definitive diagnosis of CHC a course of antifungal therapy should completely resolve the lesion. Then, and only then, can the diagnosis be confirmed as primary. Otherwise an underlying etiology must be explored. In cases where dysplastic changes are seen, re-biopsy following antifungal therapy is suggested to confirm whether or not the changes were reactive or actually dysplastic. The recommended treatment for CHC is clotrimazole troches, dissolved five times daily for 14 days followed by long-term prophylactic therapy of two troches dissolved together at bedtime. Therapy should continue as long as predisposing factors remain. However,

systemic antifungal therapy agents may be appropriate as per clinical-pathologic correlation.

Angular Cheilitis

Angular cheilitis (AC) is very common and is readily amenable to treatment. However, the patient must be informed that this is often a long-term management issue and a single therapeutic regimen will not prevent further recurrence.

The standard predisposing conditions for *Candidiasis* hold true for angular cheilitis. Important additional predisposing factors include a decrease in vertical dimension, as well as increases in dermal laxity due to aging. This creates a situation where salivary contamination of the skin is unavoidable. Long dental procedures requiring extensive opening, especially with cheek retraction, may be an initiating factor. The patient may be asymptomatic or present with tenderness, erythema, and fissuring at the labial commissures. Angular cheilitis may or may not be associated with concomitant intraoral candidiasis.

Many clinicians have a preferred and successful method of managing this condition. In our experience, the combination of both antifungal and antibacterial agents provides the best clinical outcomes.

The application of a mixture of clotrimazole 1% mixed in a one-to-one ratio with mupirocin 2% has been very effective and predictable in clinical practice. Admittedly, the use of an antifungal alone is often effective. The clinical choice of a nystatin mixed with a steroid however, raises a pharmacotherapeutic dilemma. The steroid reduces the inflammation but can also contribute to increased bacterial or fungal colonization. Because the fungal colonization is being controlled by the nystatin, the main concern is with bacterial colonization. Topical corticosteroids should not be used for the management of angular cheilitis. Many practitioners still use nystatin 100,000 U/g with triamcinolone acetonide 0.1% cream (MycologII®) for AC. In addition to the increased bacterial colonization issues associated with the steroid component, the patient may become predisposed to circumoral/perioral dermatitis (below).

Circumoral Dermatitis/Perioral Dermatitis

Circumoral dermatitis (CD), for purposes of this discussion, is defined as relatively minimal dermal erythematous changes around the mouth with or without vermilion involvement. The skin involvement and erythematous changes are generally symmetric and uniform. Perioral dermatitis (PD) may extend further away from the vermilion borders of the lips and is asymmetric. Management of these two entities is generally the same. Some controversy exists as to the organisms associated with this condition. Clinical experience reveals, these entities are similar in origin to angular cheilitis with the possibility of pure fungal involvement, pure bacterial involvement and also mixed fungal and bacterial involvement. It may best to treat the patient for all three possibilities.

There is a strong correlation to the overuse of topical steroids in the perioral region and the emergence/persistence of CD/PD. Therefore, topical steroids should be avoided in AC as well.

First line therapy for CD/PD is the 1:1 combination of clotrimazole 1% cream with mupirocin 2% ointment by a pharmacist. A thin film of this mixture is applied 2–3 times daily until resolved. If erythematous changes continue to be a problem, a nonsteroidal anti-inflammatory drug may be added to the therapeutic regimen. For refractory cases, 0.1% tacrolimus or pimecrolimus can also be added to supplement the therapeutic regimen above. The tacrolimus or pimecrolimus can be applied 10 to 15 min before or after the mupirocin and clotrimazole mixture. The dilutional effect of simply mixing three different topical agents is generally not preferred but can be utilized per clinical-pathologic correlation and for compliance issues. Both tacrolimus and pimecrolimus have FDA black box warnings for the theoretical risk of lymphoma and the patient should be advised accordingly. This is also a reason why a trial course of the clotrimazole and mupirocin mixture alone is generally preferred.

Median Rhomboid Glossitis

Median rhomboid glossitis is a cosmetic problem only and no treatment is necessary. If there are some tongue sensitivity issues topical agents can be employed as outlined in acute atrophic candidiasis.

Considerations for systemic antifungal medications

If the clinician believes systemic antifungals are needed, potential drug–drug and drug-disease state interactions must be considered. A summary of some of the considerations follows.

Notably, clotrimazole troches are not considered systemic because of their poor absorption from the GI tract. Some nausea (5%) and diarrhea may occur, but overall the troches are well-tolerated [21].

In 2013 the FDA issued a black box warning for potential fatal liver injury, drug interactions and antiandrogenic issues associated with the azole drug ketoconazole.

In 2012, 600,000 prescriptions for ketoconazole tablets were written in the U.S. The FDA now limits the use of oral ketoconazole tablets to serious fungal infections, not amenable to other treatments [22].

Fluconazole and itraconazole are the two other commonly prescribed systemic azole antifungal agents. These drugs are also associated with serious and fatal drug interactions, but their lower affinity for the human cytochromes P450 (CYPs) render them safer than ketoconazole.

Human cytochromes P450 (CYPs) are the membrane-associated hemoproteins that comprise one of the major metabolic pathways of drugs. While most drugs are biotransformed to inactive substances by the CYPs, these isozymes also form active/toxic metabolites and activate prodrugs. CYP3A4 is the predominant subfamily, responsible for the metabolism of over 30% of drugs.

While a complete discussion of drug metabolism interactions is beyond the scope of this text, all clinicians must be thoroughly familiar with the metabolic profiles of the drugs they prescribe and the potential effects of these drugs on other prescription, OTC, homeopathic, dietary supplement substances as well as concomitant disease states of the patient.

The major source of adverse drug interactions is the concomitant administration of medications that affect the same CYP subfamily. Medications can act as substrates, inducers, and inhibitors of the CYP sub families. Substrates are drugs that are metabolized by an enzyme system.

Inducers are agents that enhance P450 expression by increasing the biosynthesis or reducing the rate of enzyme degradation. Upon repeated administration, inducers will cause accelerated substrate metabolism, resulting in decreased pharmacological action of the inducer and co-administered agents. Conversely, inducers will increase the formation of reactive metabolites, potentially resulting in toxicity.

Strong inducers of sensitive substrates will decrease the body's exposure to the parent drug (area under the plasma drug-concentration time curve [AUC]) by > 80%, moderate inducers by 50–79% and weak inducers by 20–49%.

Drugs can inhibit cytochrome P450 activity via multiple mechanisms, the end result being increased exposure to the parent drug and potential toxicity. Repeated dosing of strong inhibitors of CYP3A (itraconazole, voriconazole, clarithromycin, etc.) can result in a 10-fold increase in the AUC of sensitive substrates. Moderate CYP3A inhibitors (fluconazole, ciprofloxacin, etc.) can increase the AUC between two- and fivefold. Toxicity and enhanced adverse effects of sensitive substrates can occur. An example would be increased risk of developing rhabdomyolysis and acute renal failure when fluconazole is administered with simvastatin.

Conclusion

The various forms of oral candidiasis are extraordinarily common. Sometimes the therapeutic regimen is simple discontinuation of the predisposing agent. But unfortunately, the predisposing cofactors such as salivary gland hypofunction, dentures, medications, etc. are inherently long-term and unchangeable.

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Compliance with Ethical Standards

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Research Involving Human and Animal Participants This article does not contain any studies with human participants or animals performed by any of the authors.

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