

Oral candidosis: an update on diagnosis, aetiopathogenesis and management

SADJ August 2016, Vol 71 no 7 p314 - p318

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ABSTRACT

Candidosis is the most common oral opportunistic infection and can be caused by any member of the heterogeneous genus *Candida*. Diagnosis is based on clinical features and on microscopic identification of the candidal hyphae or pseudohyphae on a smear or in a biopsy specimen of the lesional tissue. Although *candida* in both commensal and pathogenic forms has similar immunogenic properties, commensal yeasts generate a state of immune tolerance while pathogenic hyphae or pseudohyphae provoke an immuno-inflammatory reaction.

The first step in the treatment of oral candidosis is to moderate any local and systemic predisposing factors, and to prescribe a course of topical antifungal agent. Systemic antifungal treatment should be considered only if topical treatment has been unsuccessful or in cases of severe oral candidosis in debilitated or immuno-compromised subjects.

In this paper, we briefly describe the clinical variants, the diagnosis and the management of oral candidosis, and discuss the commonly used pharmacotherapeutic agents.

Key words: oral candidosis, commensal organism, hyphae, nystatin, miconazole, fluconazole, amphotericin B

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INTRODUCTION

Candidosis is a common opportunistic oral infection. It is caused by members of the fungal species *Candida*, most commonly by *C.albicans*. The tongue, palate and the buccal mucosa are the oral sites most frequently colonised by the fungus.¹⁻⁴ *C.albicans* is a unicellular dimorphic fungus that can undergo morphogenetic transition from a commensal yeast form to pathogenic filamentous pseudohyphae or hyphae which can invade tissue and cause symptomatic clinical infection.^{3,5-8} The pathogenic filamentous forms, but not the commensal yeasts, express genes encoding virulent proteins that can facilitate invasion of oral keratinocytes.⁹

The mere presence of *C.albicans* in whatever form but without clinical evidence of tissue abnormality cannot be considered to be clinical infection.^{10,11} Ultimately, the interplay between micro-environmental conditions, systemic and local host factors, and fungal genetic factors will determine whether the candidal micro-organisms will become virulent with the capacity to cause oral candidosis.^{6,8,11-13}

The purpose of this article is to discuss some aspects of the aetiopathogenesis and the management of oral candidosis, focusing on topical antifungal agents.

DIAGNOSIS

Diagnosis of oral candidosis is based on the clinical features of the lesion and on microscopic identification of filamentous fungal elements either in a smear preparation or in a biopsy specimen from the suspected lesion.^{11,14,15} Although simple and convenient, the sensitivity of the cytological smear tests for erythematous candidosis is low, in contrast to its high sensitivity for pseudomembranous candidosis.⁶

Although a biopsy is by no means essential for routine diagnosis of oral candidosis, a definitive diagnosis can be made by demonstration of filamentous fungal elements invading the epithelium, with inflammation of the underlying lamina propria. *Candida* can be seen when stained with periodic acid-Schiff (PAS) or with Gram and Gomori methenamine silver, but not with haematoxylin and eosin. The various species of *candida* can be differentiated by the macroscopic characteristics of cultured colonies, by the microscopic morphology of the fungus, by immunohistochemical techniques, and by the polymerase chain reaction technique.^{6,16,17}

Table 1: Clinical variants of oral candidosis.^{6,7,18,30}**Pseudomembranous candidosis (thrush)**

Discrete white pseudomembranous patches that may become confluent, comprising candidal elements, desquamated epithelial cells, fibrin, inflammatory cells and debris, affecting any oral mucosal site. The friable pseudomembrane can be rubbed off, revealing an underlying erythematous or bleeding surface. Nonspecific soreness or a burning sensation are variable.

Erythematous candidosis

Widespread erythema usually of the dorsal surface of the tongue or of the palate. Palatal erythematous candidosis is most frequently denture related. There may be some burning sensation.

Angular cheilitis

Manifests as erythematous fissures or macerations affecting both mucosa and skin at the corner of the mouth. Reduced intermaxillary dimension with associated maceration of the angular skin, and nutritional deficiencies are predisposing factors. *Staphylococci* and *streptococci* are aetiological co-factors.

Hyperplastic candidosis

A white patch that cannot be rubbed off that can affect any oral mucosal site, but most frequently the retro-commissural labial mucosa. The affected epithelium is hyperplastic, acanthotic, and may be dysplastic.

CLINICAL SPECTRUM OF ORAL CANDIDOSIS

There are several clinical patterns of oral candidosis (Table 1) but all have similar histopathological features. The superficial layers of the oral epithelium are penetrated by candidal elements with the formation of intraepithelial microabscesses, and with a chronic inflammatory cell infiltrate in the underlying lamina propria.² In hyperplastic candidosis, the oral epithelium is hyperplastic and acanthotic.¹⁸

Oral candidosis has been said to occur in acute and chronic forms, and there are those who include median rhomboid glossitis and so-called linear gingival erythema in the spectrum of *Candida*-associated oral lesions.^{17,19} In agreement with McCullough and Savage,⁷ the present authors are of the opinion that the terms 'acute' and 'chronic' are redundant and in median rhomboid glossitis, the fungal infection may be adventitious.¹¹

AETIOPATHOGENESIS

The genus *Candida* comprises about 200 yeast species, with *C. albicans* accounting for most of candidal infections. However, in recent times, the prevalence of other candidal species in the mouth such as *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. dubliniensis* and *C. parapsilosis* appear to have been on the increase as pathogens. It has been reported that candidal species occur as commensals on the normal oral and oro-pharyngeal epithelium of up to 60% of immunocompetent, non-hospitalized subjects who are free of clinically detectable oral candidosis.^{1,2,16,20}

C. albicans exists in the mouth in three different morphological forms: the yeast cell, also termed blastospore or blastoconidium, the septate filamentous form termed the pseudohypha, and the non-septate filamentous form, the hypha.^{1,2,14} The yeast cell is commensal, avirulent, does not invade the oral epithelium, and in a healthy host, induces regulatory immune responses mediated by keratinocytes and epithelial immunocytes releasing into the local microenvironment a number of biological agents which induce protective immune responses, preventing the development of clinical infection.^{9,14}

Table 2: Common risk factors for oral candidosis.^{14,16,30}**Microenvironmental factors:**

- lower pH
- increased carbohydrate concentration
- increased temperature
- nitrogen or carbon starvation
- products of inflammation and tissue breakdown
- suppressed commensal bacterial population

Local factors:

- microtrauma
- poor oral plaque control and generalized neglected oral self-care
- poorly fitting dentures
- reduced salivary flow
- radiotherapy to the head and neck
- oral cancer
- oral immunopathogenic diseases (i.e. lichen planus, mucosal pemphigoid)

Systemic factors:**Physiological:**

- old age
- infancy
- pregnancy

Nutritional:

- malnutrition
- avitaminosis
- iron deficiency

Medications:

- glucocorticosteroids
- other immunosuppressive drugs
- cytotoxic chemotherapy
- broad spectrum antibiotics

Illnesses:

- cell-mediated immunodeficiencies
- malignancies
- diabetes mellitus
- hypothyroidism
- hypoparathyroidism
- prolonged hospitalisation

The transition from the commensal yeast form to the potentially pathogenic filamentous forms occurs in response to local micro-environmental stress signals on a background of systemic and local predisposing factors (Table 2).^{2,14} This transition is associated with the production of virulence factors that promote the adhesion of the fungus to the epithelium, colonization, proliferation, and then invasion of the oral epithelium with evasion of protective immune responses by the fungus.¹⁴

The outcome of this sequence of events is tissue damage with the induction of an immuno-inflammatory response, thus establishing symptomatic clinical infection in the mouth. The effectiveness of the host immune response and the fitness of the invading candidal micro-organism, together with other systemic factors (Table 2) will determine the degree of severity of the infection.¹⁴ However, what factors determine the particular presentation of oral candidosis is unknown.¹⁸ Nevertheless, it has been suggested that differences in local cell-mediated immunity and variations in the virulence of different strains of *C. albicans* are important determinants.¹⁸

Candidal filamentous elements, but not yeasts, have the capacity to invade the epithelium. Only those species and strains of *Candida* that produce sufficiently potent virulence factors in response to environmental signals will invade the deeper layers of the oral epithelium, causing damage. An inflammatory reaction is induced in the underlying lamina propria, and a clinically apparent oral infection is seen.²¹⁻²⁴

Superficial invasion of the oral epithelium by candidal hyphae is seldom sufficient to bring about clinical evidence of inflammation.^{22,24} The deep invasion of candidal hyphae in the epithelium, however, results in an inflammatory reaction which is protective in nature, and is mediated by Th1 and/or Th17 lymphocytes. Together with their associated cytokines these cells recruit and activate neutrophils and macrophages that are the principle effector cells against the *candida*, causing the clinically apparent inflammation.¹⁴

If invasion of the epithelium with consequent clinical infection is to occur, the candidal hyphae have to penetrate the epithelial layers at a rate faster than the rate of maturation

and desquamation of the epithelial cells, otherwise the fungal elements will be shed together with the shedding keratinocytes.¹⁴

Oral keratinocytes and dendritic immunocytes are said to have the capacity, through pattern-recognition receptors, to distinguish between the molecular structures of commensal yeast and of filamentous pathogenic forms of *candida*. The commensal yeasts will activate signalling pathways mediating an overall state of immune tolerance without generating an inflammatory response; but the filamentous forms which become invasive will activate signalling pathways mediating protective immuno-inflammatory responses.⁸

Table 3: Some antifungal preparations available in South Africa for the treatment of oral candidosis.^{6,11,12,34,37,42}

Class	Active ingredient	Trade names	Formulation	Administration	Possible side effects
Topical					
Polyene derivatives	Nystatin	^a Nystacid® ^b Candacide® ^c Canstat®	Suspension (100 000 IU/mL)	1-2 mL 4-5x/day, 7-14 days Swish and expectorate	Unpleasant taste, occasional nausea and vomiting
	Amphotericin B	^c Fungizone®	Lozenges 10 mg <i>(discontinued in South Africa)</i>	Dissolve and swish 1 lozenge in the mouth 4-5x/day, 14-21 days	Unpleasant taste, occasional nausea and vomiting
Azoles: Imidazole derivatives	Clotrimazole	^d Canesten Troche®	Lozenges (10 mg)	Dissolve and swish 1 lozenge in the mouth 4-5x/day, 14 days	Raised liver enzymes, nausea, vomiting, oral irritation
	Miconazole	^e Daktarin®	Oral gel (20 mg/g - 2%)	Apply 2.5 mL 4-5x/day 14-21 days	Diarrhoea, headache, nausea, vomiting
Systemic per mouth					
Azoles: Triazole derivatives	Fluconazole	^f Diflucan®	Suspension (50 mg/5 mL; 200 mg/5 mL)	50-200 mg/day, 7-14 days Swish and swallow	Nausea, vomiting, abdominal pain, diarrhoea, headache, skin rash
		^f Diflucan®	Tabs (200 mg)	200 mg/day, 7-14 days Swallow	
		^f Diflucan®; ^b Florix®; ^g Difluzole®; ^h Mycocrest®; ⁱ Fluzol®; ^j Austell-Floconazole®; ^k Gulf-Fluconazole®; ^l Cipla- Fluconazole®; ^m Aspen-Fluconazole®; ⁿ Mylan-fluconazole®	Capsules (50, 150, 200 mg)	50-200 mg /once a day, 7-14 days Swallow	
	Itraconazole	^e Sporanox®	Oral solution (10 mg/mL)	100-200 mg/day, 7-14 days Swish and swallow	Skin rash, GIT effects, headache
^e Sporanox®; ^m Adco-Sporozole®; ⁿ Mylan- Itraconazole®; ^o Trisporal®		Capsule (100 mg)	100-200 mg/day Swallow		
	Posaconazole	^o Noxafil®	Oral suspension (40 mg/mL)	200 mg loading dose, 100mg/day 13 days Swish and swallow	Dizziness, headaches, fatigue, somnolence
Azoles: Imidazole derivatives	Ketoconazole	^e Nizoral® ^q Ketazol® ^r Sandoz-Ketoconazole®	Tabs (200 mg)	200-400 mg daily Swallow	Hepatotoxic!

*For all topical agents, the residue must remain in the mouth and not rinsed away with water; # As almost all the azoles have potential to interact with other medications, before prescribing any of the azole derivatives the clinician should consult the MIMS

*All preparations in liquid form should be swished vigorously in the mouth for at least 90 seconds.

^aAspen Pharmacare, Woodmead, South Africa; ^bBe-Tabs Pharmaceuticals (Sun Pharma), Centurion, South Africa; ^cBristol-Myers Squibb, Sandton, South Africa; ^dBayer, Isando, South Africa; ^eJanssen Pharmaceutica, Sandton, South Africa; ^fPfizer South Africa, Sandton, South Africa; ^gCipla SA, Bellville, South Africa; ^hZydus Healthcare SA, Potchefstroom, South Africa; ⁱSandoz SA, Pinetown, South Africa; ^jAustell Laboratories, Johannesburg, South Africa; ^kGulf Drug Company, Mount Edgecombe, South Africa; ^lMylan South Africa, Modderfontein, South Africa; ^mAdcock Ingram, Bryanston, South Africa; ⁿSanofi Aventis South Africa, Midrand, South Africa; ^oMSD/Schering-Plough South Africa, Midrand, South Africa

The transition of *candida* from a commensal to a pathogenic form causing clinical infection is associated to a great extent with any reduction in the inherent fitness of the immune system. To a lesser extent the transition is influenced by changes in the microenvironment in response to antibiotic treatment, xerostomia, malignancy, systemic chemotherapy, pregnancy, or diabetes with possible secondary reduction in the fitness of the immune system.^{8,11,19}

To add to the complexity of the pathogenesis of oral candidosis, it is now evident that in the mouth, *candida* usually resides in mixed fungal-bacterial biofilms encapsulated in, and protected by, a matrix of glycoproteins and polysaccharides. Within this biofilm, the bacterial-fungal interactions influence the morphogenetic status, virulence, proliferation and survival of *candida*.¹ Nutrient availability, saliva composition and flow dynamics, and the level of oral cleanliness are some of the local factors that determine the density, thickness and the biological properties of the mixed biofilm.¹

TREATMENT OF ORAL CANDIDOSIS

A thorough medical and dental history, and a comprehensive oral examination are essential to identify the presence of predisposing factors for oral candidosis (Table 2). Where possible, such predisposing factors must be eliminated or modified, otherwise the benefits of anti-fungal treatment may be transient.^{17,19} Regardless of any systemic risk factor, guidance should be provided with regards to improving nutrition and oral health care, cessation of cigarette smoking, and reduction of sugar intake.^{11,19} Removable dentures of patients with oral candidosis must be well-fitting, thoroughly cleaned both physically and chemically, proper dentogingival plaque control should be effected and the patient be instructed to use an appropriate antimicrobial mouthwash.^{25,26}

Owing to its effective antimicrobial activity against a broad spectrum of micro-organisms, including *candida* species, chlorhexidine gluconate is frequently used adjunctively in the treatment of oral candidosis, as a twice daily 0.2% mouthwash, and in a 2% solution as an overnight denture disinfectant.²⁷⁻²⁹

As it is evident that *candida* proliferates and survives within protective biofilms that are relatively resistant to drug penetration, it is imperative to mechanically disrupt the integrity of the biofilm as soon as oral candidosis is diagnosed. This will interfere with the fungal-supportive ecosystem and will permit the antifungal agent to come into contact with the fungus more readily.³⁰ Therefore, when brushing the teeth, the gingiva, the dorsum of the tongue and the buccal mucosa should also be gently brushed.

Candidal microorganisms are eukaryotic cells having organelles identical to those of human cells. Therefore, there are not many classes of anticandidal pharmacotherapeutic agents that are both effective and non-toxic.^{19,30} In general, oral candidosis is treated with topical agents which may be either fungicidal or fungistatic. It is preferable to start treatment with topical agents as their side effects and interactions with other drugs are less significant than are those of systemically administered antifungals (Table 3). Frequently used topical antifungal agents include the polyenes, amphotericin B and nystatin, and the azole, miconazole.^{12,31,32}

Polyenes interact with the ergosterol component of the fungal cell membrane, increasing its permeability, allowing leakage of the cytoplasmic content and consequent death of the fungal cell. Polyenes are poorly absorbed by the gastrointestinal tract making them safe for use, with little side effect (Table 3). However the unpleasant taste, and the multiple dosage regimen tend to make for poor patient compliance.^{27,33-35} Patients who do take these drugs are inclined to quickly swallow or spit them out, before there has been sufficient contact time for therapeutic effectiveness,³⁴ so the patient should be warned about the bad taste, and motivated to use the preparation correctly.

Azoles inhibit the biosynthesis of ergosterol with functional alterations of the fungal cell wall and consequent inhibition of cell multiplication, or cell death.³⁶ Fluconazole and itraconazole given systemically orally are well absorbed in the gastrointestinal tract, and some of the fluconazole is secreted in the saliva giving it an additional topical effect.²⁷ Azoles also inhibit several hepatic cytochrome P450 (CYP) microsomal enzymes, including CYP2C9 which is an enzyme involved in the metabolic breakdown of warfarin, so that the blood concentration of warfarin rises, increasing the potential for bleeding. Even topically applied miconazole oral gel, believed to be only negligibly absorbed in the gastrointestinal track, may result in an increase in the blood concentration of warfarin.^{37,38}

As many other drugs, including diazepam and ritonavir, are metabolized in the liver by the cytochrome P450 enzyme system, the risk of hazardous interactions with azoles, which inhibit the action of the enzyme system, is significant. The prudent clinician should consult the Monthly Index of Medical Specialities Desk Reference (MIMS), before prescribing azoles.^{37,39} Therefore, nystatin and amphotericin B which are not absorbed in the bowel and thus do not have any significant drug interactions, are to be preferred for the treatment of oral candidosis in patients who are taking other drugs (Table 3).⁴⁰

As a general rule, any topical agent used in the mouth should be left *in situ* for as long as possible and accordingly the patient must be instructed not to eat, drink, rinse the mouth or brush the teeth for 40-45 minutes after each dose.⁴¹ Any of the topical antifungal agents listed in Table 3 should be equally effective for first line treatment, if correctly used.

If the oral candidosis does not respond to a course of a topical antifungal, the agent should be changed. If treatment is still unsuccessful, the patient should be referred to a specialist in oral medicine for evaluation and for possible treatment with a systemic antifungal agent.⁶ Systemic antifungal agents used for the treatment of moderate, severe or refractory oral candidosis include fluconazole, itraconazole, posaconazole and ketoconazole. These agents should preferably be given in a liquid form as the local effect, if the patient is instructed to swish-and-swallow, appears to be additionally beneficial. Fluconazole should be used as the first choice systemic antifungal agent.¹³

SUMMARY

About 60% of healthy subjects have *candida* in their mouths as commensals. In the great majority of subjects, oral mucosal immunity mediates tolerance of yeast forms, limits colonisation by the potentially pathogenic filamentous forms and generates immuno-inflammatory

protection against invasion. Topical antifungal agents are the first line of treatment of oral candidosis. As a general rule, any topical agent used in the mouth should be left *in situ* for as long as possible, and accordingly the patient must be instructed not to eat, drink, rinse the mouth or brush the teeth for 40-45 minutes after each dose. If topical treatment proves to be ineffective, then a systemic agent should be prescribed.

Conflict of interest: None declared

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