Oral candidosis and the therapeutic use of antifungal agents in dentistry

MJ McCullough,* NW Savage†

Abstract

This paper reviews the current concepts of mycology and candidal infections as they relate to the oral cavity. Proposed classification for the presentation of oral candidosis is outlined as are examples of these topical infections, such as erythematous, pseudomembranous and hyperplastic candidosis, as well as angular chelitis and median rhomboid glossitis. The diagnosis and principles of management of oral candidosis are discussed, the therapeutic agents available for the management of these infections are presented and a treatment protocol for the management of patients with oral candidosis is given.

Key words: Candida, antifungal agents, dentistry.

Abbreviations and acronyms: PAS = periodic acid Schiff reagent.

Aust Dent J 2005;50 Suppl 2:S36-S39

INTRODUCTION

Mycology

Fungi are eukaryotic micro-organisms, the most important to dentistry belonging to the genus *Candida*. Human infections caused by the yeast *Candida albicans* and several related species (spp.) range from relatively trivial conditions such as oral and genital thrush to fatal, systemic super-infections in patients who are already seriously ill with other diseases.[1] The genus *Candida* is characterized as including white asporgenous (imperfect) yeasts capable of forming pseudohyphae. Within the genus, species are characterized primarily on colonial morphology, carbon utilization and fermentation. There are seven *Candida* species of major medical importance. By far the most important of these is *C. albicans* which is isolated most frequently (over 80 per cent) and believed to more virulent in humans.[2] The other *Candida* spp. encountered in human infections are *C. tropicalis, C. glabrata, C. parapsilosis, C. stellatoidea, C. krusei* and *C. kyfer*.[3]

Candida albicans is a dimorphic yeast and is believed to be an obligate associate of warm-blooded animals. It is an imperfect yeast having no sexual cycle and is diploid, having lost the ability to undergo meiosis and to form haplophase yeast. It has been postulated that most people usually carry a single strain of *Candida* at different body sites and they usually retain this same strain for a long period of time.[4] However, it has been shown that a small proportion of individuals may harbour more than one strain or species of *Candida* at the same time. This occurs more commonly in hospitalized and immunocompromised patients.[5] The commensal existence of *Candida* intra-orally occurs in at least 50 per cent of individuals and, if sensitive enough tests were developed, possibly greater than 90 per cent of healthy individuals.[6] The most investigated virulence factors for *C. albicans* are those which relate to the cell wall, adhesion and extracellular proteolytic enzyme production.[3]

*Associate Professor, Oral Medicine, School of Dental Science, The University of Melbourne.
†Associate Professor, Oral Pathology, Dental School, The University of Queensland.

Clinical presentation of oral candidosis

Various classification schemes have been proposed for the clinical variants of oral candidosis (Table 1). The classifications utilized in this paper remove the terms 'acute' and 'chronic' as the temporal aspects of the clinical presentation have little bearing on the causality or treatment of the condition.[7]

Erythematous candidosis

Two forms of this condition can be recognized: symptomatic and asymptomatic. The first may be associated with a burning sensation in the mouth or on the tongue. The tongue may be bright red, similar to that seen with a low serum B12, folate and iron. Diagnosis may be difficult but should be considered in the differential diagnosis of a sore tongue, especially in a frail older patient with dentures who has received antibiotic therapy or who is on inhaled steroids.

The asymptomatic form is much more common and is characterized by localized chronic erythema of tissues covered by dentures and is often referred to as denture-induced stomatitis (Fig 1). Lesions usually occur on the palate and upper jaw but may also affect mandibular tissue. It is quite common with incidence rates of up to 65 per cent reported. Trauma from an ill-fitting denture (usually a full maxillary, acrylic denture) is a major contributing factor, because this provides a suitable environment for candidal proliferation.[8]

Pseudomembranous candidosis

Extensive white pseudomembranes consisting of desquamated epithelial cells, fibrin and fungal hyphae. These white patches occur on the surface of the labial and buccal mucosa, hard and soft palate, tongue, periodontal tissues and oropharynx (Fig 2). The membrane can usually be scraped off with a swab to expose an underlying erythematous mucosa. In infants,

Table 1. Classification schemes for oral candidosis

Early Classification	Revised* (1990)	Proposed** (2005)
Acute pseudomembranous	Acute pseudomembranous	pseudomembranous
Acute atrophic	Acute erythematous	erythematous
Chronic hyperplastic	Chronic nodular Chronic plaque-like	hyperplastic
Chronic atrophic (Denture stomatitis)	Chronic erythematous (Denture-associated candidosis)	erythematous (Denture-induced stomatitis)
–	Chronic pseudomembranous	pseudomembranous
Angular cheilitis	Candida-associated cheilitis	Angular cheilitis
Median rhomboid glossitis	–	Median rhomboid glossitis

*Samarnayake LP, Yaacob HB. Classification of oral candidosis. In: Samaranayake LP, MacFarlane TW. Oral Candidosis. London: Wright, 1990:124-132.
**The proposed classification removes the terms 'acute' and 'chronic' as the temporal aspects of the clinical presentation have little bearing on the causality or treatment of the condition.

the infection is usually superficial and easy to manage, but in debilitated patients it may be widespread with angular cheilosis and oesophageal involvement. This form of candidiasis is common amongst patients who are immunocompromised, in particular: those taking anti-mitotic drugs and/or corticosteroids; those patients with HIV infection; extremes of age; those with uncontrolled diabetes mellitus;[9] patients who have taken long-term broad spectrum antibiotics and psychotropic drugs; and patients who are terminally ill.[10]

Median rhomboid glossitis (central papillary atrophy)

A chronic symmetrical area on the tongue anterior to the circumvallate papillae (Fig 3). It is made up of atrophic filiform papillae. The exact cause is not fully understood, however biopsy of this area usually yields *Candida* hyphae in over 85 per cent of cases. It tends to be associated with smoking and the use of inhaled steroids.

Hyperplastic candidosis

Hyperplastic candidosis occurs in several different forms. The first of these is a form of oral candidosis occurring as a well demarcated white patch anywhere on the oral mucosa but frequently on the post-commissural cheek mucosa in patients over 35 years of age who smoke tobacco (Fig 4). These white patches cannot be wiped off. It is important to recognize this condition because hyperplastic candidosis has a higher incidence of dysplasia and malignant transformation than an otherwise similar white keratotic patch of the oral mucosa which is not infected with *Candida*.[11] (See below '*Postulated role in oral carcinogenesis*'.)

A further presentation of hyperplastic candidosis is as part of a more widespread mucocutaneous candidosis. There are a number of forms of mucocutaneous candidiasis but all have skin as well as mucosal involvement and the oral component is first noticed early in life, usually when the patient is younger than 10 years. The oral lesions often precede skin and nail involvement.

Finally, a form of hyperplastic candidosis can be seen in the posterior hard palate, immediately posterior to

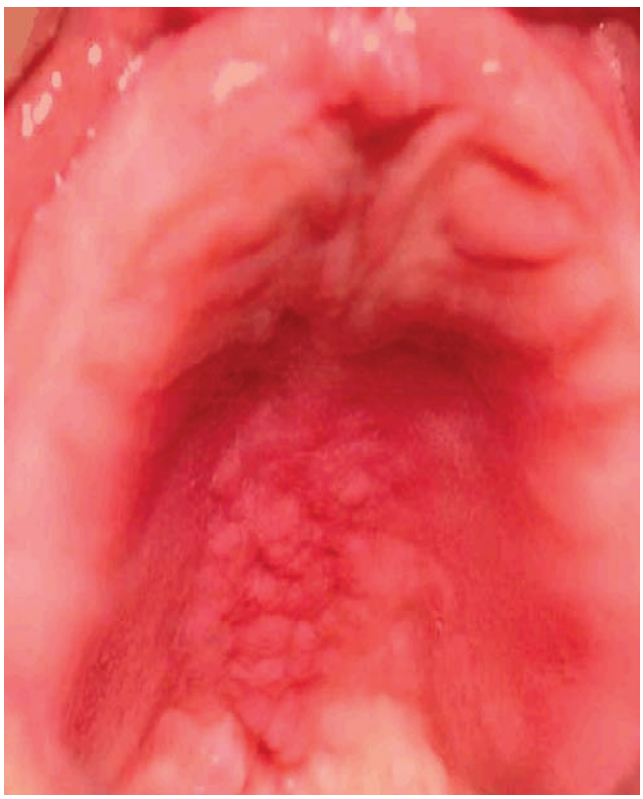

Fig 1. Erythematous candidosis, showing localized erythema of tissues covered by dentures, often referred to as denture-induced stomatitis.

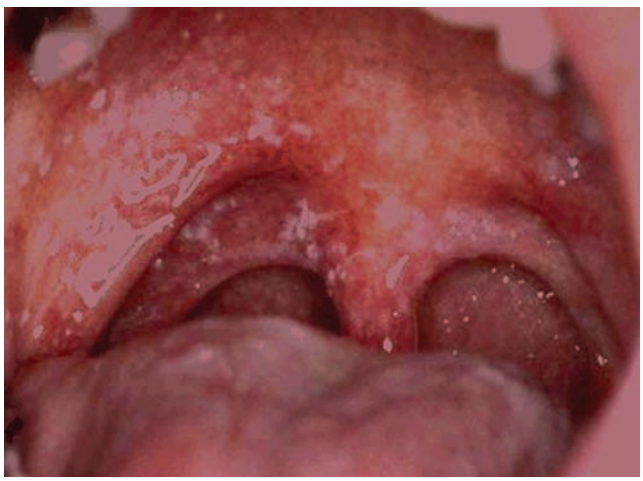

Fig 2. Pseudomembranous candidosis with extensive white pseudomembranous plaques consisting of desquamated epithelial cells, fibrin and fungal hyphae.

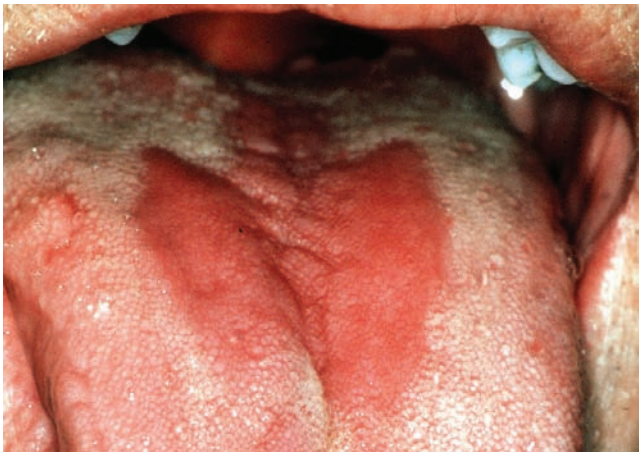

Fig 3. Median rhomboid glossitis, a somewhat symmetrical area on the tongue, anterior to the circumvallate papillae.

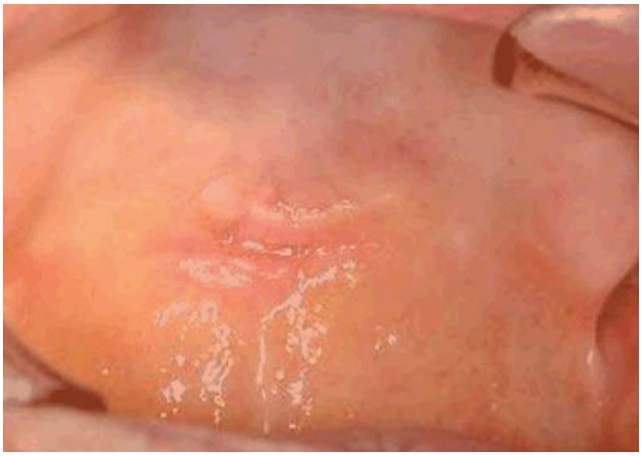

Fig 5. Hyperplastic candidosis presenting immediately posterior to full upper dentures.

full upper dentures in patients who incorrectly use steroid inhalers (Fig 5). These lesions are very difficult to treat without changing the use of the steroid inhaler.

Angular chelitis

An erythematous fissuring at one or both corners of the mouth, usually associated with an intra-oral candidal infection. Other organisms implicated are *staphylococci* and *streptococci*. Facial wrinkling at the corners of the mouth and along the nasolabial fold leads to a chronically moist environment that predisposes to this lesion. Other factors implicated are iron deficiency, anaemia and vitamin B12 deficiency.

Postulated role in oral carcinogenesis

Oral yeast carriage has been shown to correlate with the presence and degree of oral epithelial dysplasia.[12,13]

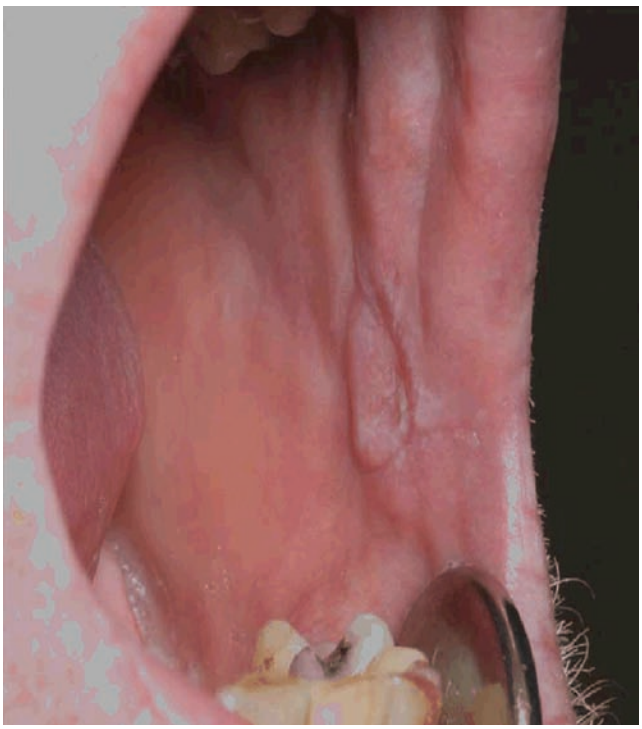

Fig 4. Hyperplastic candidosis presenting as a well demarcated white patch on the retro-commissural cheek mucosa.

There would appear to be an interaction between oral carriage of yeast and oral epithelial dysplasia, however it remains unclear how yeast infection, or the simple presence of increased amounts of *Candida* in the oral cavity, influences the development and progression of dysplasia.[13] There exists the possibility that the primary pathosis is dysplasia, or frank carcinoma, which has become secondarily infected with *Candida*. This possibility needs to be suspected, particularly if lesions do not respond to simple treatment for candidosis.

Therapeutic use of antifungal agents

Diagnosis: smear, culture, biopsy

Correct diagnosis should be based on history and thorough examination.[14] It should be treated based on clinical features[7] but confirmation by one of following methods should be undertaken if initial therapy is unsuccessful.[15]

Direct examination of a smear

The affected area is scraped with a spatula and the smear spread onto a glass slide. The slide is air dried, fixed in alcohol and stained with periodic acid Schiff reagent (PAS), after which examination by light microscopy is undertaken for the presence of yeast and hyphae. The dorsum of the tongue, a reservoir for oral yeast, should be smeared at the same time, along with the fitting surface of the denture, if one is worn.

Culture

Whole saliva, or a 10ml mouth-swill of sterile water, is collected and the presence and number of candidal colonies noted after culture on Sabouraud's agar.

Biopsy

Biopsy is particularly useful for the diagnosis of hyperplastic candidosis. Histopathological examination will reveal epithelial parakeratosis with polymorphonuclear leukocytes in the superficial layers. PAS stained slides will show the presence of candidal hyphae in this area. As this form may mimic other lesions, such as squamous cell carcinoma, a biopsy is recommended in addition to empirical therapy.

Principles of management: denture adequacy and hygiene; medical considerations (B12, folate, iron deficiency; diabetes; medication; immune deficiency)

Confirm the diagnosis. Investigate/eliminate underlying causes: (1) check adequacy of dentures; (2) exclude deficiency states (e.g., iron, folate or vitamin B12 deficiency); (3) exclude diabetes mellitus; (4) check drug history (e.g., antimicrobials, corticosteroids); and (5) check medical history (e.g., immune deficiency). Treat with appropriate antifungal agents (see below).

Available pharmacological agents: agents, dosage, interaction etc

A number of effective antifungal agents are available[16] including: (1) Amphotericin lozenges (10mg) used alone, four times daily, if dentate – if dentures are worn, also use nystatin or miconazole; (2) Nystatin ointment (100 000U/g) used on fitting surfaces of dentures and corners of the mouth; (3) Miconazole oral gel (20mg/mL) used four times daily in a dose of half a measuring spoonful dropped onto the tongue and swished around the mouth for as long as possible before swallowing. Alternatively, place on the fitting surface of the denture four times daily. Care should be taken with the use of miconazole as it can potentiate the effect of warfarin. Itraconazole, fluconazole and ketoconazole should be reserved for debilitated or immunocompromised patients.

Recommended treatment protocol

Recognize predisposing factors and eliminate as many as possible. Particular attention should be paid to denture hygiene and, if the dentures are inadequate, they should be replaced. Possible underlying systemic disorders (see above) should be investigated if local factors such as dentures are not contributing.

Administer topical antifungal agents, e.g., amphotericin lozenges – alone if the patient does not wear dentures, or in conjunction with nystatin ointment or miconazole if dentures are worn – for a period of three weeks. The ointment should be liberally applied to the fitting surface of the denture four times daily. At night, dentures should be removed and cleaned thoroughly and soaked twice weekly in a diluted solution (approximately 1:20) of either sodium hypochlorite (common bleach) or white vinegar. This latter step is most important as the denture will act as a reservoir of infection if not treated in this way.

If there are still signs of infection after three weeks, ensure that the patient is complying with the prescribed regimen, that the diagnosis is correct and that any predisposing factor has not been overlooked. If necessary, prescribe another course of medication.

Occasionally, it is necessary to prescribe another form of antifungal, e.g., change to miconazole oral gel. Systemic antifungal agents should be reserved for candidal infections in debilitated or immunocompromised patients.

Treatment of immunocompromised patients with oral candidal infection using the drugs mentioned above will usually resolve or significantly diminish the signs and symptoms, but recurrences can be expected and regular reviews and repeated antifungal therapy are usually required.

When to refer recalcitrant oral lesions

Refer any patient who does not respond to the treatment outlined above to an oral medicine specialist or an oral and maxillofacial surgeon.

REFERENCES

1. Arkell S, Shinnick A. Update on oral candidosis. Nurs Times 2003;99:52-53.
2. McCullough MJ, Clemons KV, Stevens DA. Molecular epidemiology of the global and temporal diversity of Candida albicans. Clin Infect Dis 1999;29:1220-1225.
3. McCullough MJ, Ross BC, Reade PC. Candida albicans: a review of its history, taxonomy, epidemiology, virulence attributes, and methods of strain differentiation. Int J Oral Maxillofac Surg 1996;25:136-144.
4. Al-Karaawi ZM, Manfredi M, Waugh AC, et al. Molecular characterization of Candida spp. isolated from the oral cavities of patients from diverse clinical settings. Oral Microbiol Immunol 2002;17:44-49.
5. Odds FC. Candida albicans, the life and times of a pathogenic yeast. J Med Vet Mycol 1994;32(32Suppl1):1-8.
6. Borromeo GL, McCullough MJ, Reade PC. Quantitation and morphotyping of Candida albicans from healthy mouths and from mouths affected by erythematous candidosis. J Med Vet Mycol 1992;30:477-480.
7. Sherman RG, Prusinski L, Ravenel MC, Joralmon RA. Oral candidosis. Quintessence Int 2002;33:521-532.
8. Lamfon H, Al-Karaawi Z, McCullough M, Porter SR, Pratten J. Composition of in vitro denture plaque biofilms and susceptibility to antifungals. FEMS Microbiol Lett 2005;242:345-351.
9. Manfredi M, McCullough MJ, Al-Karaawi ZM, Hurel SJ, Porter SR. The isolation, identification and molecular analysis of Candida spp. isolated from the oral cavities of patients with diabetes mellitus. Oral Microbiol Immunol 2002;17:181-185.
10. McCullough MJ, Firth NA, Reade PC. Human immunodeficiency virus infection: a review of the mode of infection, pathogenesis, disease course, and the general and clinical manifestations. Aust Dent J 1997;42:30-37.
11. Sitheeque MA, Samaranayake LP. Chronic hyperplastic candidosis/candidiasis (candidal leukoplakia). Crit Rev Oral Biol Med 2003;14:253-267.
12. Barrett AW, Kingsmill VJ, Speight PM. The frequency of fungal infection in biopsies of oral mucosal lesions. Oral Dis 1998;4:26-31.
13. McCullough M, Jaber M, Barrett AW, Bain L, Speight PM, Porter SR. Oral yeast carriage correlates with presence of oral epithelial dysplasia. Oral Oncol 2002;38:391-393.
14. Akpan A, Morgan R. Oral candidiasis. Postgrad Med J 2002;78:455-459.
15. Pankhurst C. Oropharyngeal candidiasis. Clin Evid 2002:1248-1262.
16. Rich AM, Reade PC. Candidiasis, oral. E-MIMS Disease Index May 2003.

Address for correspondence/reprints:
Associate Professor Michael McCullough
School of Dental Science
The University of Melbourne
Parkville, Victoria 3010
Email: m.mccullough@unimelb.edu.au