

Pathogenesis and treatment of oral candidosis

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Oral infections caused by yeast of the genus *Candida* and particularly *Candida albicans* (oral candidosis) have been recognised throughout recorded history. However, since the 1980s a clear surge of interest and associated research into these infections have occurred. This has largely been due to an increased incidence of oral candidosis over this period, primarily because of the escalation in HIV-infection and the AIDS epidemic. In addition, changes in medical practice leading to a greater use of invasive clinical procedures and a more widespread use of immunosuppressive therapies have also contributed to the problem. Whilst oral candidosis has previously been considered to be a disease mainly of the elderly and very young, its occurrence throughout the general population is now recognised. *Candida* are true 'opportunistic pathogens' and only instigate oral infection when there is an underlying predisposing condition in the host. Treatment of these infections has continued (and in some regards continues) to be problematic because of the potential toxicity of traditional antifungal agents against host cells. The problem has been compounded by the emergence of *Candida* species other than *C. albicans* that have inherent resistance against traditional antifungals. The aim of this review is to give the reader a contemporary overview of oral candidosis, the organisms involved, and the management strategies that are currently employed or could be utilised in the future.

Keywords: oral candidosis; *Candida*

Received: 3 November 2010; Revised: 3 January 2011; Accepted: 4 January 2011; Published: 28 January 2011

The *Candida* genus is comprised of over 150 species of asporogenous 'yeast-like' fungi. Members of this genus are ubiquitously distributed, persisting as saprophytes in soil and aquatic environments, as well as colonising several animal reservoirs (1–3). The majority of *Candida* species are unable to grow at 37°C and are, therefore, not normally associated with human colonisation (4). However several species do persist as commensal microorganisms within humans and these can act as opportunistic pathogens in debilitated individuals (Table 1). *Candida albicans* is the species most frequently associated with normal oral carriage in humans, occurring in the mouths of up to 80% of healthy individuals (13).

A change from the harmless commensal existence of *Candida* to a pathogenic state can occur following alteration of the oral cavity environment to one that favours the growth of *Candida*. The causes of such changes are the so-called predisposing factors for *Candida* infection (candidosis) and most often these relate to a weakening of host immune defences (Table 2).

Infections caused by *Candida* are most frequently superficial, occurring on moist mucosal surfaces in individuals suffering with a mild debilitation. In severely immunocompromised patients, infections can be systemic

and are significant because of their associated high mortality. To highlight this, in intensive care unit patients the mortality rate for individuals with systemic candidosis is approximately 30–50% (24).

Recent decades have seen a significant increase in the incidence of all forms of candidosis and this reflects changes in medical practice with a greater use of invasive surgical procedures, a more widespread use of immunosuppressive therapies as well as broad-spectrum antibiotics. Key to the increase in oral candidosis has, however, been the escalation of HIV-infection and AIDs (25).

The most prevalent *Candida* species involved in human infection is *C. albicans*. In oral candidosis, *C. albicans* generally accounts for around 50% of cases (26, 27) and whilst a similar prevalence of *C. albicans* occurs in systemic candidosis, in recent years higher incidences of non-*C. albicans* *Candida* (NCAC) species have been reported (28, 29). The reasons for the increasing incidence of NCAC species in human infection are multifactorial and undoubtedly improved diagnostic methods, changes in medical practices such as the more widespread use of invasive medical procedures (e.g. use of indwelling catheters, organ transplants) and immunosuppressive therapy may all have facilitated increased rates (30).

Table 1. *Candida* species recovered from the human mouth

<i>Candida</i> species	References
<i>Candida albicans</i>	(5)
<i>Candida glabrata</i>	(6)
<i>Candida tropicalis</i>	(7)
<i>Candida krusei</i>	(8)
<i>Candida lusitanae</i>	(9)
<i>Candida dubliniensis</i>	(10)
<i>Candida kefyr</i>	(11)
<i>Candida guilliermondii</i>	(12)
<i>Candida parapsilosis</i>	(5)
<i>Candida lipolytica</i>	(12)

Oral candidosis is not a single infection and generally four primary oral forms are described based on clinical presentation (Fig. 1). Pseudomembranous candidosis (oral thrush) presents as creamy white lesions on the oral mucosa and a diagnostic feature of this infection is that these plaques can be removed by gentle scraping leaving behind an underlying erythematous mucosal surface (31, 32). Histological examination of recovered pseudomembranes reveals desquamated epithelial cells together with yeast and filamentous forms of *Candida*. The infection has traditionally been regarded as an acute condition often affecting newborn babies where there is an immature immune system. In older individuals, acute pseudomembranous candidosis often occurs when there is a nutritional limitation, local immune suppression (e.g. steroid inhaler administration for the treatment of asthma), or an underlying disease most notably HIV-infection and AIDS (26, 33, 34).

In the case of AIDS, or other instances where the individual is immunocompromised long-term, chronic pseudomembranous candidosis can develop and whilst antifungal therapy can temporarily resolve the condition, recurrent infection is frequent. Of additional concern with chronic forms of pseudomembranous candidosis is the subsequent progression of infection to oesophageal involvement, which in turn can lead to difficulties in swallowing and chest pains.

In addition to pseudomembranous candidosis, another acute form of *Candida* infection is acute erythematous candidosis. This form of oral candidosis frequently occurs after receipt of a broad-spectrum antibiotic, which, by lowering the oral bacterial population, facilitates subsequent overgrowth of *Candida* by alleviating competitive pressures. The infection can occur on the buccal mucosa, but most frequently presents as reddened lesions on the dorsum of the tongue and also the palate (32, 35). Erythematous candidosis is the only form of oral candidosis that is consistently painful. Where antibiotic treatment has been associated with predisposition, cessation of

Table 2. Host-related factors associated with oral candidosis

Predisposing host factor	Reference
Local host factors	
• Denture wearing	(14)
• Steroid inhaler use	(15, 16)
• Reduced salivary flow	(17)
• High sugar diet	(18)
Systemic host factors	
• Extremes of age	(19)
• Endocrine disorders (e.g. diabetes)	(20)
• Immunosuppression	(21)
• Receipt of broad spectrum antibiotics	(22)
• Nutritional deficiencies	(23)

treatment leads to spontaneous resolution of the lesions once the bacterial population of the mouth recovers to pretreatment levels (22).

Chronic forms of erythematous candidosis can also occur and traditionally these infections encompassed the atrophic lesions associated with angular cheilitis and denture stomatitis. However, both infections are also linked to bacterial colonisation and, therefore, these are now often categorised under *Candida*-associated lesions (see later). Chronic erythematous candidosis is prevalent in HIV-positive individuals and AIDS patients, and depending on the study can represent over a third of the *Candida* lesions encountered (36).

Chronic hyperplastic candidosis (occasionally referred to as candidal leukoplakia) can present on any oral mucosal surface and appears either as smooth (homogenous) or nodular white lesions (37). Unlike the lesions of pseudomembranous candidosis, those of chronic hyperplastic candidosis cannot be removed by gentle scraping. Most frequently, chronic hyperplastic candidosis occurs bilaterally in the commissural regions of the buccal mucosa with highest prevalence in middle-aged men who are smokers (38). A characteristic feature of this form of oral candidosis is the penetration of the oral epithelium by *C. albicans* hyphae, which are detected in biopsy sections following Periodic Acid-Schiff (PAS) or equivalent staining methods (Fig. 2). Histological examination is indeed the diagnostic tool for this infection and in addition to the presence of *Candida* hyphae, an inflammatory cell infiltrate is invariably present within the lamina propria together with marked variations in epithelial thickness (39). An important feature of chronic hyperplastic candidosis is its possible association with malignant transformation (40). A confirmed link between *Candida* and the development of oral cancer remains to be established, although it has been shown *in vitro* that yeast can generate the carcinogenic nitrosamine,

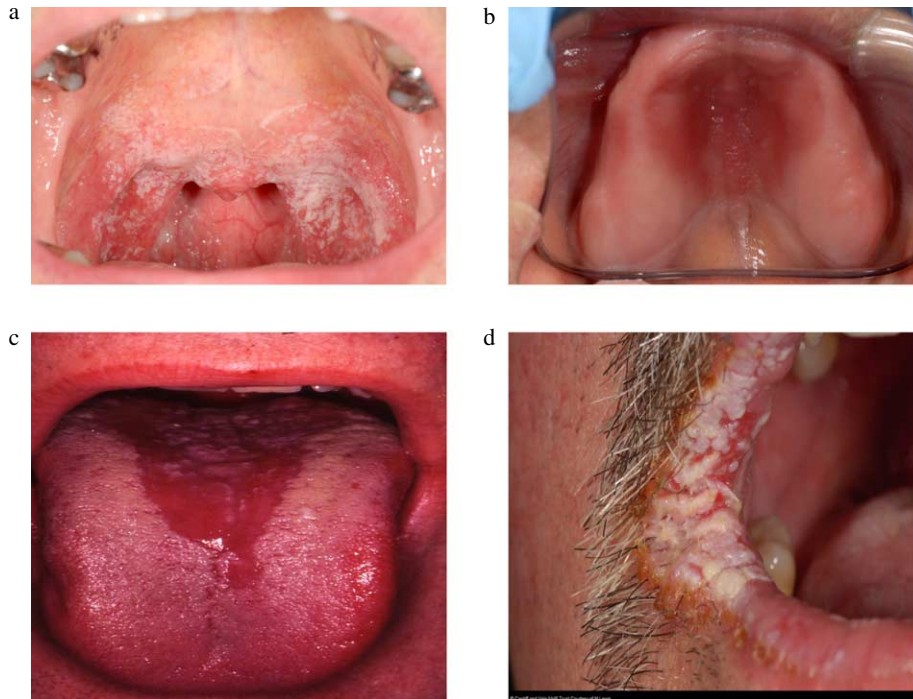


Fig. 1. Clinical presentation of the primary forms of oral candidosis. (a) acute pseudomembranous candidosis; (b) chronic erythematous candidosis; (c) acute erythematous candidosis; and (d) chronic hyperplastic candidosis.

N-nitrosobenzylmethylamine from suitable precursor molecules (41).

Secondary forms of oral candidosis can also occur and are frequently described as *Candida*-associated lesions. Angular cheilitis is a condition where lesions manifest at the angles of the mouth and microbiological sampling of these sites frequently reveal the presence of *C. albicans*, often in combination with the bacterium *Staphylococcus aureus* (42). The exact role of *Candida* in this infection remains unclear, but it is worth noting that angular cheilitis often occurs in patients with existing forms of

intraoral candidosis and where the *Candida* load is already high.

Median rhomboid glossitis is a chronic condition that presents as a diamond-shaped lesion at the posterior midline on the dorsum of the tongue (31). High levels of *Candida* can be recovered from these lesions, which are often associated with individuals who frequently use steroid inhalers or who are tobacco smokers (43).

The most prevalent oral infection involving *Candida* is *Candida*-associated denture stomatitis, which occurs in up to 65% of denture wearers, often asymptotically (44). As this name suggests, denture wearing is the major predisposing factor, particularly in cases where the denture is not adequately cleansed or is retained overnight in the oral cavity. Under these conditions, the stagnant area above the upper fitting surface of the denture provides an ideal environment for the growth of *Candida*, which is adept at adhering to acrylic used as the base material for the denture (45). Furthermore, the limited flow of saliva at this location means that loosely adherent *Candida* may not be efficiently removed from the site, as would be the case at other oral locations. In situations where there is an ill-fitting denture, frictional irritation can damage the normally protective mucosal barrier, allowing infiltration of *Candida* into the tissue thereby promoting infection.

Candida have also been associated with linear gingival erythema, which, whilst rare, is occasionally seen in HIV-infected patients (46, 47). The precise role of *Candida* in

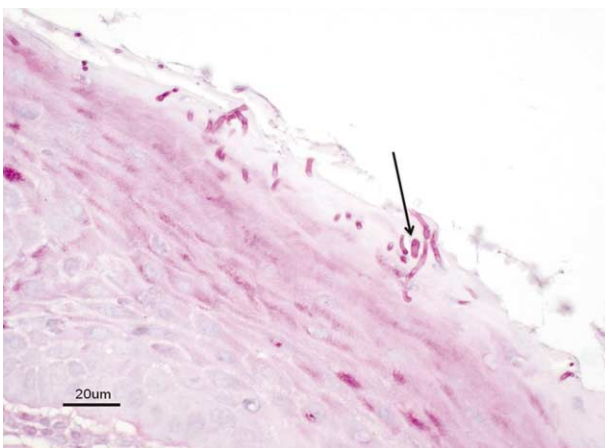


Fig. 2. Periodic Acid Schiff stained biopsy section of chronic hyperplastic candidosis. Typical invading hypha indicated by arrow.

this condition remains to be confirmed, which may in part be due to the frequent use of systemic antifungal agents in HIV patients.

In a discussion on the oral forms of candidosis, mention needs to be made of chronic mucocutaneous candidosis (CMC), characterised by the widespread occurrence of superficial candidosis of the skin, nails, and mucosal membranes (including those of the oral cavity) of infected individuals (48, 49). CMC is primarily associated with disorders resulting in the incorrect functioning of T-lymphocytes (48).

Candida virulence factors

Given the high prevalence of *Candida* as a harmless commensal in humans, it is not surprising that no single primary virulence factor has been identified with the organism. However, a number of putative virulence factors (Table 3) have been proposed that in the event of host debilitation contribute to tissue damage and persistence of the organism within the host.

The ability of *Candida* to adhere to host surfaces is a prerequisite for both successful commensal carriage as well as persistence during active infection. Within the oral cavity, removal of loosely attached *Candida* by the physical flushing action of salivary flow or the process of sloughing off of epithelial cells from mucosal surfaces are important factors in host defence against *Candida* overgrowth. An enhanced ability to overcome these removal mechanisms can therefore be regarded as a virulence attribute.

Adherence of *Candida* to human epithelial cells is initiated through weak and reversible interactions involving hydrophobic and electrostatic forces (50). The nature of these forces are in part governed by the local environment in the oral cavity; however, studies have shown that strain variation does occur in terms of cell surface hydrophobicity that may give certain isolates greater pathogenic potential (51).

Specific adhesion between *Candida* and receptors on host tissues results in a stronger covalent attachment. *Candida* genes of the ALS (agglutinin-like sequence) family (52) and also HWPI (hyphal wall protein) (53) encodes for cell wall associated glycoproteins that promote adhesion of *C. albicans* to epithelial surfaces. In addition, specific interaction of *Candida* with oral bacteria has also been demonstrated that could encourage biofilm formation on dentures and in dental plaque (54).

Biofilms can be defined as microbial communities that are often (but not necessarily) attached to a solid surface; invariably the biofilm microorganisms are encased within an extracellular polysaccharide matrix that has been generated by the organisms themselves. *Candida* species are adept at forming biofilms (55, 56) and this has been linked to both increased expression of virulence factors (57) as well as reduced susceptibility to antimicrobial agents (58). *Candida* biofilms in human disease are widely recognised and occur on tissue surfaces as well as the biomaterials of medical devices. *Candida* biofilms on artificial voice box prostheses have been identified as a major cause of their failure. Urinary tract infections caused by *Candida* biofilms in catheterised patients are recognised, whilst biofilms at other sites including on prosthetic heart valves, intravascular catheters, and replacement joints have also been linked with infection (59). Candidal biofilms in haemodialysis and peritoneal dialysis catheters are a common occurrence and associated with an infection rate of up to 20% in patients undergoing treatment (55).

In terms of oral candidosis, biofilms on an oral prosthesis, most commonly a denture, are a major predisposing factor to chronic oral candidosis. *Candida* readily adhere to the polymethylacrylate material of dentures, and also exploit micro fissures and cracks within the material to facilitate retention (60). Biofilm formation on denture surfaces is further promoted by

Table 3. Putative virulence factors of *Candida albicans*

Virulence factor	Effect
Adherence <ul style="list-style-type: none"> Cell surface hydrophobicity Expression of cell surface adhesins 	Promotes retention in the mouth <ul style="list-style-type: none"> Non-specific adherence Specific adherence
Evasion of host defences <ul style="list-style-type: none"> Phenotypic switching Hyphal development Secreted aspartyl proteinase production Binding of complement 	Promotes retention in the mouth <ul style="list-style-type: none"> Antigenic modification Reduces phagocytosis Secretory IgA destruction Antigenic masking
Invasion and destruction of host tissue <ul style="list-style-type: none"> Hyphal development Hydrolytic enzyme production 	Enhances pathogenicity <ul style="list-style-type: none"> Promotes invasion of oral epithelium Host cell and extracellular matrix damage

poor oral hygiene and retention of dentures in the mouth whilst sleeping.

Several *Candida* species are described as polymorphogenic (61) and whilst in nutrient rich culture media at 37°C, yeast growth would appear to be prevalent, filamentous growth can occur and indeed is frequently seen in clinical situations. Both *C. albicans* and *Candida dubliniensis* are species associated with the generation of true hyphae (62). True hyphae are distinct from pseudohyphae (which are effectively elongated yeast cells), as the former lack constriction at yeast/hyphal junctions and also possess septa within the filaments (Fig. 3). The pathogenic significance of being able to produce hyphae could relate to the greater resistance of hyphae to phagocytosis compared with yeast, enhanced adherence to host surfaces, and the ability of hyphae to invade epithelial layers resulting in tissue damage (Fig. 2). Hyphal production is also linked with enhanced expression of several putative virulence genes, some of which are not involved in the morphogenic process itself (63). It should be noted that both filamentous and yeast forms are encountered in the oral cavity of healthy individuals, highlighting the importance of host factors in controlling *Candida* and the fact that no single predominant virulence factor is associated with the organism (64).

A phenomenon referred to as 'high frequency phenotypic switching' is evident *in vitro* for certain strains of *C. albicans* when cultured on appropriate agar media. Colonies generated by isolates that are 'high frequency switchers' exhibit variation in terms of colour, shape, and translucency. The cause of these colony switch variants relates to cell morphology and differential gene expression by the variants (56, 61). The so-called white-opaque switching is associated with mating in *C. albicans* as well as the up-regulation of biofilm genes (65, 66). High frequency switching strains have been proposed to have greater virulence, as replication of this property *in vivo*

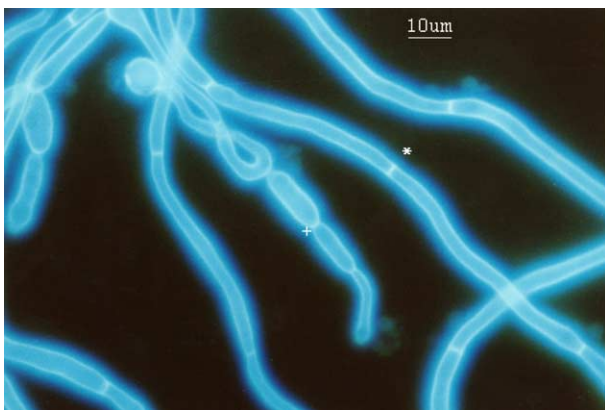


Fig. 3. Calcofluor white stained *Candida albicans* showing true hyphae (*) and pseudohyphae (+).

might aid in evading recognition by adaptive immune responses as well as promoting biofilm formation.

Candida produces several extracellular enzymes that could have a locally damaging effect on host structures (67). Significant attention has been given to the secreted aspartyl proteinases (SAPs) of *Candida*. *C. albicans* possesses at least 10 different genes that encode for SAPs, and the resulting proteins are in turn designated SAPs 1–10. SAPs 1–8 are released extracellularly, whilst SAPs 9 and 10 are thought to be membrane bound. SAP enzymes belong to the same class of proteinases as the HIV aspartyl proteinase as well as human pepsin and renin. All *Candida* SAPs are inhibited by the agent pepstatin A. *Candida* SAPs have optimal activity at acidic pH (pH 2–7 activity range), although distinct differences in pH optima are evident with SAPs 1–3 being most active at the lower end of the pH scale and SAPs 4–6 at higher pH. This heterogeneity in activity optima of the SAPs could benefit *Candida* in its survival under different environmental conditions. Of the *Candida* SAPs, the most widely studied are SAPs 1–6. From research it has been shown that SAP 2 is induced when *C. albicans* is cultured in media containing proteins as the only nitrogen source (68). SAP 1 and SAP 3 are specifically expressed during switching of *C. albicans*, whilst SAPs 4–6 are involved in promoting hyphal growth (69). *C. albicans* proteinases have keratinolytic activity that can both serve to facilitate initial penetration of keratinised cells as well as providing a valuable source of nitrogen during colonisation (70, 71).

In terms of virulence, SAP activity can therefore directly induce damage to host cells, facilitate hyphal growth for invasion of tissue, increase adherence following exposure of receptor sites, and also degrade host immunoglobulins and other defence proteins (55, 72–75).

Another group of hydrolytic enzymes produced by *Candida* species are the phospholipases (PLs) and seven distinct encoding genes have been identified in *C. albicans*. These genes have been given the designations *PLA*, *PLB1*, *PLB2*, *PLC1*, *PLC2*, *PLC3*, and *PLD1* (76). Through the hydrolysis of ester linkages of phospholipids, PLs can effectively degrade the membrane of host cells leading to cell lysis and death. By this process, both adherence of *Candida* to receptor sites and its subsequent penetration of damaged tissue can be facilitated.

The role of extracellular lipase and esterase production by *Candida* in pathogenic processes is less well understood (77). Both lipases and esterases share the ability to hydrolyse the ester bonds in glycerides, although the latter only act on soluble substrate molecules. A total of 10 *Candida* lipase (*LIP1–10*) genes have been identified in *C. albicans* and sequence-related genes found in *C. tropicalis*, *C. parapsilosis*, and *C. krusei* (78). Lipases of *C. albicans* have recently been shown to exhibit cytotoxic

effects on host cells (79) and *LIP* gene expression detected in oral candidosis (80).

Haemolysins are substances that lyse red blood cells and their production by *Candida* is considered an important attribute in promoting survival within the host through an increased ability to sequester iron. Luo et al. (81) demonstrated α - and β -haemolysis by clinical isolates of *C. albicans*, *C. dubliniensis*, *C. kefyr*, *C. krusei*, *C. zeylanoides*, *C. glabrata*, *C. tropicalis*, and *C. lusitaniae*. *Candida* haemolysin production positively correlates with glucose concentration and that this could be a predisposing factor in candidosis of poorly controlled diabetics where higher blood and salivary glucose levels occurs (76, 82).

Host response to oral candidosis

Immunocompetent individuals rarely suffer from oral candidosis even when *Candida* is present in the oral cavity. Prevention of mucosal infection by *Candida* is mediated primarily by the functions of the innate immune response. In particular, neutrophils and macrophages are key to successful phagocytosis and killing of *Candida*. Professional phagocytes recognise *Candida* through pattern recognition receptors (PRRs), which interact with specific molecules (pathogen-associated molecular patterns; PAMPs) exposed on the surface of *Candida* (83). Following recognition, these cells release cytokines and chemokines to further modulate the immune response. Dendritic cells (DCs) are professional antigen presenting cells that provide a sentinel role in mucosal tissue. Interaction of DCs with *Candida* leads to DC activation and phagocytosis. Following phagocytosis, DCs migrate to the lymph nodes where the *Candida* antigen is processed and presented on the surface of the DC to naïve CD4⁺ T-cells (84–88). Interaction between DCs and T-cells cause the latter to differentiate into mature effective T-cells (89). The type of T-cell generated is thought to be under direction of the DC and examples of effective T-cells include T-helper 1 (Th1), T-helper 2 (Th2), T-helper 17 (Th17), and regulatory T-cells (Tregs). Previously it was generally accepted that a Th1 elicited response was a protective one, whilst Th2 responses were implicated in infection. More recently, evidence suggests that a Th17 response is predominant in protection of mucosal surfaces (90).

Treatment and management of oral candidosis

A priority in the treatment of oral candidosis is the alleviation of any identifiable predisposing factor. Acquiring a thorough medical history is, therefore, an essential component in the management process. An example of this are the recommendations made to patients suffering from chronic erythematous candidosis in order to improve oral hygiene through adequate denture cleansing. Such recommendations would include the regular and frequent use of a denture cleanser with anti-candidal properties

such as 1% sodium hypochlorite preparations, together with the removal of dentures overnight. Chlorhexidine (0.2%) should be used if the denture has metal components since hypochlorite will otherwise cause discolouration. However, it should also be noted that discolouration of teeth and mucosal surfaces have been reported with the use of chlorhexidine (91).

Certain predisposing factors are, however, more difficult if not impossible to eradicate such as where there is an underlying disease (e.g. leukaemia or AIDS). In these cases, targeted antifungal therapy, as discussed later, plays an important role in the management strategy.

Both the physical and chemical reduction of *Candida* load in the oral cavity can be achieved by good oral hygiene practices including tooth brushing and the use of antimicrobial mouthwashes. Manual tooth brushing is limited to accessible oral surfaces, although powered or electrical tooth brushing may be more effective as cavitation within surrounding fluids could disrupt *Candida* biofilms at otherwise inaccessible sites (92). Several mouthwashes exhibit anti-candidal activity including triclosan, chlorhexidine gluconate, and essential oil formulations. The latter tend to contain natural plant extracts such as thymol, eucalyptol, and bioflavonoids and these can have a direct anti-candidal activity *in vitro* through cell membrane disruption and enzyme inhibition (93, 94).

When compared with antibacterial agents, the availability of antifungal agents is significantly lower. The reason for this relates to the relatively recent recognition of the significance of human fungal infections and also the fact that fungal organisms are eukaryotic and share many features with mammalian cells making selection of suitable targets for antifungal agents problematic. Classification of antifungal agents is based on the target of activity, and in the treatment of candidosis the two classes most commonly used are the polyenes and the azoles (Table 4).

Polyenes include the drugs amphotericin B and nystatin and their mode of action is through direct binding to the sterol ergosterol found within fungal cell membranes. Polyene binding to ergosterol induces leakage of cytoplasmic contents leading to fungal cell death (95). The equivalent mammalian sterol is cholesterol, which has a lower binding affinity for polyenes and this makes host cells less susceptible to their toxic effects. Nevertheless, at higher therapeutic concentrations polyenes do exhibit a degree of toxicity in humans. The use of polyenes is limited further as they are poorly absorbed through the gut and, therefore, topical application in the form of lozenges and oral suspensions are the principle means of administration in oral infection. Polyenes are frequently used in the treatment of chronic erythematous candidosis, and oral suspension of amphotericin B may be employed

Table 4. Antifungals used in the management of candidosis

Antifungal	Mode of action	Administration	Frequently recommended treatment
Polyenes	Binds to ergosterol and disrupts fungal cell membrane		
• Nystatin		Topical	CEC
• Amphotericin B		Topical	CEC
Azoles	Inhibits ergosterol biosynthesis		
• Fluconazole		Systemic	PMC, AEC, CHC
• Miconazole		Topical	CEC
• Ketoconazole		Topical/systemic	PMC, AEC, CHC
• Clotrimazole		Topical	CEC
• Itraconazole		Systemic	PMC, AEC, CHC
• Voriconazole		Systemic	
• Posaconazole		Systemic	
5-flucytosine	Inhibition of DNA/protein synthesis	Systemic, often in combined therapy with amphotericin	
Echinocandins	Inhibits β 1, 3 D-glucan synthesis	Intravenous	
• Caspofungin			
• Micafungin			
• Anidulafungin			

Abbreviations: CEC, chronic erythematous candidosis; PMC, pseudomembranous candidosis; AEC, acute erythematous candidosis; CHC, chronic erythematous candidosis.

Nystatin is used as an ointment or oral suspension.

Amphotericin B is used as a lozenge.

Miconazole is used as an oral gel and cream.

Clotrimazole is used as a cream and pessary.

Other antifungals are available and more frequently used in hospitalised patients.

in treating refractory oral candidosis frequently seen in HIV-infected and AIDs patients.

Unlike the polyenes, azole antifungals are fungistatic rather than fungicidal (96). The mechanism of action is by inhibiting the enzyme lanosterol demethylase that is a cytochrome P-450 3-A dependent enzyme involved in the synthesis of ergosterol. Subsequent depletion of ergosterol in the fungal cell results in inhibition of fungal growth and impairment of membrane permeability. Since azoles are fungistatic, complete resolution of the infection will be aided by simultaneously addressing predisposing host factors. The two most frequently administered azole antifungals in the treatment of oral candidosis are fluconazole and itraconazole and these drugs have the advantage of being readily absorbed through the gut with the result that oral administration is an effective means of delivery (97). Furthermore, fluconazole is secreted in high levels in saliva making the agent particularly suitable for treating oral infection (98).

Unfortunately, in recent years *Candida* resistance to azole antifungals has been detected and this can arise through several mechanisms including the over produc-

tion of the lanosterol demethylase enzyme, an alteration in the demethylase enzyme structure that makes it less susceptible to azole inhibition, the use of multi-drug transporter pumps to remove azoles from the cell, and the incorporation of alternative sterols to ergosterol within the cell membrane (99). Several NCAC species are inherently more resistant to azoles than other species. For example, 35% and 75% of *C. glabrata* and *C. krusei* isolates exhibit resistance to fluconazole and this could be a reason why the prevalence of certain NCAC species in human disease has increased in recent years (29, 100).

As the need to expand antifungal options increases, newer azole drugs such as itraconazole have been used in the treatment of oral candidosis, whilst others including voriconazole and posaconazole are alternatives for invasive infections by *Candida*. Recently, the echinocandin class of antifungals have emerged as alternatives to the azoles and polyenes (101). Echinocandins act through inhibition of the D-glucan synthase, which is an enzyme required for the synthesis of the fungal cell wall. This enzyme is absent from mammalian cells thereby reducing potential host cell toxicity. Whilst echinocandins such as

caspofungin, micafungin, and anidulafungin are fungicidal against *Candida*, their use is somewhat limited by their large molecular size that dictates the need for intravenous administration. Echinocandins are again primarily used in the treatment of invasive fungal infections.

Successful treatment of candidosis can be hampered where there is an established biofilm. *Candida* biofilms exhibit significantly higher tolerance to both antimicrobial mouthwashes and also traditional antifungal agents. As a consequence, alternative strategies have been suggested to combat such infections. These have included the modification of biomaterials such as those used in denture prosthesis to inhibit adherence of *Candida*. Examples include the use of coatings with silanes, chlorhexidine, histatins, antifungals, as well as the incorporation of surface-modifying groups (102–105). Alternative strategies could exploit quorum-sensing agents to promote biofilm disruption with the agent farnesol already having been shown to induce instability in *Candida* biofilms (106). Other possible strategies could involve the use of probiotics (107), which would induce an added microbiological pressure on *Candida* within the oral cavity and may also promote local immune function. The potential benefits of probiotics in the management of *Candida* biofilms have already been reported for indwelling voice box prostheses (108), as well as in lowering the *Candida* prevalence in the oral cavity (109).

Summary

Whilst *Candida* species are frequent members of the commensal oral microflora of humans, they are opportunistic pathogens that under conditions of host debilitation can cause a spectrum of oral infection. Oral candidoses have been recognised throughout recorded history, although most attention has been given to the infections in the last few decades when the incidence increased greatly with the advent and escalation of the AIDs epidemic. *C. albicans* is the species most frequently implicated in oral candidosis, although other species are increasingly being encountered. Putative virulence factors of *Candida* include the ability to adhere to host surfaces, produce filamentous growth forms, and release hydrolytic enzymes capable of inducing damage to host cells. Effective management of oral candidosis demands correction of any identified predisposing factor together with the administration of appropriate antifungal agents. Given the increasing incidence of NCAC species in oral infection and the development of resistance against some of the traditionally used antifungals, there is a constant need for research into new and effective agents to treat oral candidosis.

Conflict of interest and funding

There is no conflict of interest in the present study for any of the authors.

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