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Oral Candidosis in the Paediatric Patient

Abstract: Oral candidosis can present in childhood with recognizable mucosal changes. It may be associated with predisposing factors or suggest underlying systemic disease such as poorly controlled diabetes or an immunosuppressed state. Investigations are often required and management includes addressing predisposing factors in addition to prescribing topical or systemic antifungal therapy.

CPD/Clinical Relevance: It is important for general dental practitioners to recognize oral mucosal changes related to candidal infection and refer to secondary care for further assessment when appropriate.

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Candida albicans is the most common candida species isolated from the oral cavity in both healthy and diseased states.¹ However, there has been an increase in the incidence of non-*albicans* species such as *C. glabrata*, *C. tropicalis* and *C. krusei* in recent years.²

It is important to differentiate between candida as a commensal and candida infection (candidosis). Commensal oral carriage of candida can occur in up to 80% of healthy individuals.³ Progression from harmless commensal to pathogenic organism is often due to predisposing host factors which often relate to a weakening

of host immune defences.³ In the paediatric setting it is important to consider these predisposing factors as oral candidosis may reflect an undiagnosed systemic condition.

Predisposing factors

Factors that predispose to oral candidosis relate primarily to the host. The virulence factors unique to *Candida albicans* which allow it to colonize the oral mucosal surface so effectively are listed in Table 1.

The factors relevant in the paediatric setting include:

Local factors

- Reduced salivary flow;
- Use of inhaled steroids;
- Dental appliances.

Systemic factors

- Diabetes mellitus;
- Immunosuppression;
- Nutritional deficiencies.

Iatrogenic factors

- Use of broad spectrum antibiotics;
- Corticosteroid use;
- Radiotherapy;
- Chemotherapy.

Classification

Oral candidosis can be classified as primary, confined to the oral cavity alone,

and secondary, where lesions affect both oral and extra-oral sites (Table 2).⁴

Features of the main types are discussed below.

Pseudomembranous candidosis

This condition is often referred to as 'oral thrush' and is a common form of oral candidosis in newborns and the elderly. It presents as creamy white plaques, often said to resemble milk curds, which most commonly affect the soft palate, tongue and buccal mucosa (Figure 2). A feature of pseudomembranous candidosis is that these plaques can be removed with gauze, leaving an erythematous, and sometimes bleeding, mucosal surface.³ It affects up to 5% of newborns, at any time during the first few weeks of life, as a result of a newborn's immature immune system and vertical transmission during the passage through the birth canal.⁵

Predisposing factors include the use of inhaled or topical corticosteroid or immunosuppression, most notably human immunodeficiency virus (HIV) infection. It normally presents acutely with minimal symptoms but, in cases of long-term immunosuppression, a chronic pseudomembranous candidosis can develop with an associated risk of

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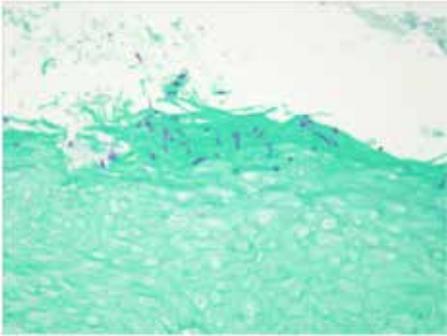


Figure 1. Oral mucosa showing candidal hyphae.



Figure 2. Pseudomembranous candidosis of palate.

oesophageal and respiratory involvement.⁶

Acute and chronic erythematous candidosis

Acute erythematous candidosis most commonly occurs acutely after the use of broad spectrum antibacterials when the normal bacterial flora of the mouth is altered allowing fungal overgrowth. Sites affected include the buccal mucosa, dorsal tongue and palate. It resolves spontaneously after the antibacterials are discontinued. Other causes include the use of inhaled corticosteroids. It is reported that erythematous candidosis is the only form of candidosis that is consistently painful.³

Chronic erythematous candidosis is most commonly seen in patients with removable appliances, such as dentures or orthodontic appliances (Figure 3). This presents as areas of erythema in relation to the fitting surfaces of the appliances, particularly if these are not removed regularly and/or if oral and appliance hygiene are poor.

Chronic hyperplastic candidosis

This does not typically occur in the paediatric setting. It presents as a

persistent white lesion which may have associated erythema and which is not removable (Figure 4). It most commonly affects the commissures, though any site can be involved.

Angular cheilitis

Angular cheilitis is classified as a candida-associated lesion, as other factors are involved in its occurrence. It presents with painful erythema at the corners of the mouth (Figure 5). Both candida and the bacterium *Staphylococcus aureus* have been implicated⁷ and there is usually a high candida load intra-orally.³

Angular cheilitis can also present as a result of iron deficiency anaemia. It is commonly seen in cases of orofacial granulomatosis or as an oral manifestation of Crohn's disease.⁸

Median rhomboid glossitis

Median rhomboid glossitis is a candida-associated lesion characterized by an area of papillary atrophy with either a rhomboid or elliptical shape present in the midline of the dorsal tongue posteriorly (Figure 6). Usually it is a flat smooth lesion, although it can be raised and lobulated. It may be seen in children who use corticosteroid inhalers or those who are immunosuppressed.

Host factors in the paediatric setting

Asthma

It is evident that the use of corticosteroid inhalers in asthma promotes oral carriage of candida which may develop into clinical infection in susceptible individuals. This usually presents as areas of erythema or, less commonly, pseudomembranous candidosis (oral thrush). Only 10–20% of the corticosteroid from an inhaler reaches the lungs, while the remainder is left in the oropharynx.⁹ Lesions can often be found in areas where the aerosol is deposited.¹⁰ Despite this, the presence of oral thrush is an uncommon finding in children using inhaled corticosteroids.¹¹ The generalized immunosuppressive and anti-inflammatory effects of steroids are thought to be a factor in

- Cell wall proteins (adhesins) that interact with mucosal epithelial cells and increase adherence;
- Ability to produce hyphae (Figure 1) which allows deeper invasion of the oral mucosa;
- Phenotype switching which allows a change of morphology and evasion of host immune mechanisms;
- Secretion of proteolytic and lipolytic enzymes which assist with mucosal invasion and destruction of secretory IgA.

Table 1. *Candida albicans* virulence factors.¹

Primary Oral Candidosis	Secondary Oral Candidosis
<p>The primary triad Pseudomembranous Erythematous (acute or chronic) Chronic hyperplastic</p> <p>Candida-associated lesions Denture-related stomatitis Angular cheilitis Median rhomboid glossitis Linear gingival erythema</p>	<p>Familial chronic mucocutaneous Diffuse chronic mucocutaneous Candidosis endocrinopathy syndrome Familial mucocutaneous Severe combined immunodeficiency Di George syndrome Chronic granulomatous disease Acquired immunodeficiency syndrome</p>

Table 2. Classification of oral candidosis.⁴

the pathogenesis of candidosis.¹² Other factors which have been considered include the possibility that patients using inhaled corticosteroids have higher salivary glucose levels, which can promote proliferation and adhesion of candida to oral mucosal cells.¹³

Removable appliances

There are limited publications on the association of wearing orthodontic appliances and oral candidosis. In a review of two studies of removable appliances and three studies of fixed appliances, no subjects developed clinical oral candidosis. However, in all of the long-term studies included in this review, there was evidence of an increase in candidal carriage with both removable, or fixed, appliance orthodontic treatment.¹⁴

Clinical lesions of oral candidosis are more likely to occur in children who had a pacifier habit.¹⁵ It is possible that microscopic breaches in the oral epithelium caused by trauma from persistent sucking may predispose to candidal colonization.¹⁶ Other factors involved include the reduction in the flushing effect of saliva on the oral mucosa and the provision of surfaces for biofilm formation in both fixed and removable appliances.¹⁴

Reduced salivary flow

Increased oral carriage of candida occurs in patients whose salivary flow rates are reduced. This is due to the reduced flushing action of saliva which contains lactoferrin, lysozyme, lactoperoxidase and IgA which act to minimize colonization of the oral mucosa by inhibiting candidal adhesion to epithelial cells and assisting in phagocytosis of candida.¹⁷

Causes of reduced salivary flow rate in children include the use of xerogenic medications and diabetes mellitus. In asthmatics, the use of B₂ agonists and corticosteroid inhalers may also reduce salivary flow rate.¹⁸

Salivary flow rate may also be diminished in Sjögren's syndrome, following radiation therapy or during cytotoxic therapy. Radiotherapy to the head and neck will cause alterations to the oral mucosa after 10 Gy, with often permanent damage to the salivary glands after 30 Gy.¹⁹ The outcome is best in those

patients whose radiation field does not involve the parotids. Dry mouth due to chemotherapy is usually temporary and tends to resolve within 48 hours.²⁰

Sjögren's syndrome is a chronic autoimmune disease characterized by lymphocytic infiltration and destruction of exocrine glands. Involvement of the salivary and lacrimal glands leads to both dry eyes and dry mouth. It is more common in women than in men (9:1) with an onset usually between the ages of 40–50. It is a rare condition in children, and when diagnosed usually presents as recurrent swellings of the parotid glands.²¹ Dry mouth and dry eye symptoms were reported less frequently.

Congenital salivary gland disease in the form of hypoplasia or aplasia is rare. It can affect one, several or all of the salivary glands and may be associated with other congenital facial malformations such as Treacher Collins syndrome or hemifacial microsomia.²¹

Diabetes mellitus

A review of oral candidosis in diabetes mellitus²² notes varying rates of oral carriage of candida in diabetics from 18–80% reported in the literature. Salivary flow rate and pH of saliva of diabetic patients are generally lower than in non-diabetic controls,²³ with hyposalivation more common in poorly controlled diabetics.²⁴

Other factors involved in predisposing diabetics to oral candidosis include defective candidal activity of neutrophils and potentially higher salivary glucose levels, which may alter the cell surface receptors involved in the adherence of candida.²⁵

Nutritional deficiencies

Numerous nutritional factors have been considered with regards to oral candidosis, including iron and vitamin deficiencies and carbohydrate rich diets.

A number of mechanisms have been proposed for oral candidosis in iron deficiency:¹⁷

- Epithelial abnormalities;
- Depression of cell-mediated immunity;



Figure 3. Chronic erythematous candidosis affecting the hard palate.



Figure 4. Chronic hyperplastic candidosis right commissure.



Figure 5. Bilateral angular cheilitis.



Figure 6. Median rhomboid glossitis.

- Defective phagocytosis;
- Inadequate antibody production.

Folate and B₁₂ have been implicated in the pathogenesis of oral candida infections.²⁶ It is proposed that such deficiencies could affect the integrity of the oral mucosa, making candida colonization more likely, which would also be compounded by a generalized deficiency state.

There is limited evidence to support higher rates of the candida carriage in malnourished children compared to otherwise healthy children, with conflicting results in some studies.²⁶

Antimicrobial use

The use of broad-spectrum antimicrobials, in particular tetracyclines and, to a lesser degree, metronidazole and ampicillin, are associated with oral candidosis.²⁷ In the paediatric setting tetracyclines can be used in the treatment

of acne vulgaris which most commonly presents in puberty.²⁸ Of note, tetracycline can cause permanent staining of the dentition if prescribed prior to the age of 8 years, when permanent teeth are still undergoing mineralization.²⁹

The oral lesion typical of candida overgrowth related to antibiotic use is acute erythematous candidosis.

A possible mechanism for candidal overgrowth following broad-spectrum antimicrobial use involves a reduction in the normal oral bacteria which would otherwise inhibit the adherence of candida to the oral mucosa and also compete with candida for nutrients.²⁷

Malignancy

The most common cancers in children are lymphoblastic and myeloid leukaemia, retinoblastoma, neuroblastoma and Ewing sarcoma. These are commonly

treated with cytotoxic therapy alone or combined with radiotherapy.³⁰

Oral candidosis in these patients is multifactorial in origin and often relates to treatment:

- Mucositis as a result of cytotoxic and radiotherapy;
- Use of broad spectrum antimicrobials and corticosteroids;
- Reduced salivary flow caused by both cytotoxic and radiotherapy.

Oral candidal lesions in these patients typically presents as a chronic erythematous candidosis or as a pseudomembranous candidosis.³¹

The oral mucosa is also affected by complications that arise from chronic graft versus host disease, which can occur following haematopoietic cell transplantation (HCT) used in the treatment of haematologic malignancies.¹⁹ Inflammatory infiltration of the salivary gland leads to reduced salivary flow which can subsequently lead to increased carriage of oral candida.

Human immunodeficiency virus (HIV)

Candida lesions commonly associated with HIV infection in children include pseudomembranous candidosis, erythematous candidosis and angular cheilitis.³²

Interestingly, oral candidosis may be the first manifestation of HIV and is the most commonly reported lesion in HIV-infected children.³³

The use of anti-retroviral therapy (ART) has significantly reduced HIV-related oral manifestations. Lower rates of candida-related oral lesions have been reported in children on ART compared to those not on this treatment.³³

Diagnosis and management

It is essential that a thorough medical and dental history is carried out with a focus on the numerous predisposing factors in oral candidosis. The clinical examination will often lead to a diagnosis due to the typical appearance of lesions resulting from oral candidosis. In both the diagnosis and management of oral candidosis in children, a multidisciplinary approach may be

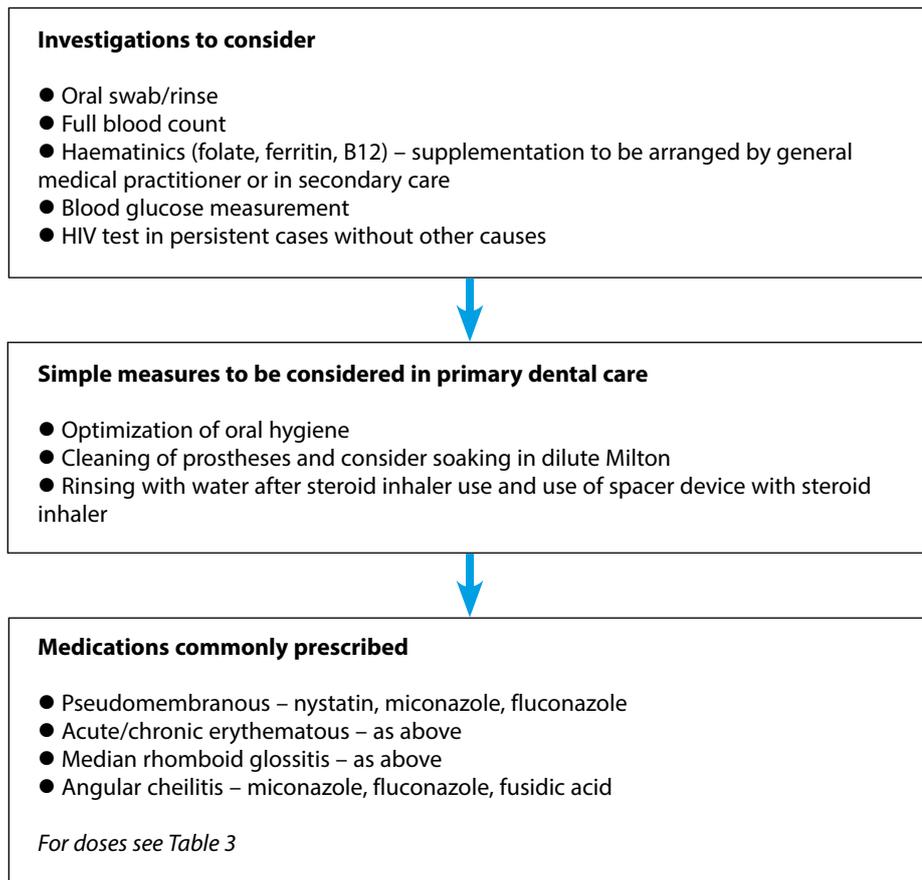


Figure 7. Investigation and management of oral candidosis in children.

Drug	Dose	Directions for Use	Notes
Nystatin oral suspension	100,000 units/ml	1ml four times daily for 7 days	To take after food Suspension to be retained near lesion for 5 minutes before swallowing
Miconazole Gel	24 mg/ml	4 months–2 years: 2.5 ml twice daily 2–6 years: 5 ml twice daily Over 6 years: 5 ml four times daily	Retain near lesions before swallowing Continue use for 2 days after lesion has resolved To take after food
Fluconazole/ Fluconazole Oral Suspension	50 mg/50 mg/5 ml	6 months–12 years: 3–6 mg/kg on first day and then 3 mg/kg (max 100 mg) daily 12–18 years: 50 mg daily	Administer for maximum of 14 days

Table 3. Modified from British National Formulary.

required, often necessitating liaison with the general medical practitioner and/or referral to an oral medicine unit.

Use of oral swabs and/or rinse can be helpful to confirm a diagnosis, as may a smear or imprint if available.

However, as noted previously, isolation of candida from the oral mucosa does not equate to oral candidosis. Use of oral rinse allows a quantitative analysis of candida burden. Normal carriage in 50% of the population is less than 1,000 cfu/ml.⁸

Additionally, blood investigations include FBC, haematinic assessment and blood glucose assessment may be arranged and, in some cases of persistent oral candidosis in the absence of obvious predisposing causes, assessment of HIV status may be warranted.

A synopsis of investigations which would be carried out in secondary care, or by the general medical practitioner and management, is summarized in the flowchart (Figure 7).

The management of oral candidosis firstly involves rectifying any predisposing factors. In cases of corticosteroid inhaler use, advice on rinsing or toothbrushing, after use of the inhaler and the use of a spacer device with

it may prove helpful.¹²

Where a diagnosis of diabetes is involved, optimization of blood sugar control is necessary to assist with resolution of oral candidosis. Any causes of anaemia will need to be further assessed and managed accordingly and, in some cases, iron and vitamin supplementation may be necessary.

Good oral hygiene will reduce the candida load intra-orally and the use of a chlorhexidine gluconate mouthwash has anti-candidal activity.³ It should be noted that chlorhexidine renders Nystatin ineffective and these should not be used together.

The two classes of antifungal medications which can be prescribed are the polyenes and the azoles. Polyenes have a fungicidal action and include nystatin and amphotericin (Table 3). Azole medications are fungistatic and the most commonly prescribed in this group include fluconazole and miconazole (Table 3.) Primary care practitioners may consider prescription of topical preparations in an otherwise healthy child. Systemic medications are best managed in secondary care.

Certain medications can prove

helpful in specific candidal lesions. In cases of angular cheilitis, the use of miconazole gel or ointment or fusidic acid, either alone or in combination with hydrocortisone in cream or ointment form, can be used for a short period to reduce inflammation.

In cases of recalcitrant oral candidosis, the option of using antifungal treatment prophylactically can be considered. It should be noted that some oral candida species such as *C. glabrata* and *C. krusei* are innately less susceptible to azoles than other candida species and that *C. albicans* can develop resistance to azoles.³⁴

Conclusion

Although oral candidosis in children is uncommon, when it does occur it often presents with pathognomic signs and symptoms. In these cases it is important to consider both local and host factors relevant in the paediatric setting which may predispose to onset. If a general dental practitioner identifies features typical of oral candidosis, referral to an oral medicine unit should be considered if simple measures do not lead to resolution.

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