Oral Candidosis

Grant T. McIntyre

Abstract: Oral candidoses are frequently encountered in the practice of dentistry. Although most oral candidoses are symptomless, they can indicate the presence of an underlying systemic disease, and the persistence of oral candidosis following appropriate conventional management may be one of the first signs of undiagnosed immunosuppression. The opportunistic pathogen Candida albicans is the most commonly isolated species from oral candidal lesions; however, the non-albicans Candida spp. are also implicated in the aetiology of oral candidoses. The effective management of oral candidosis is dependent on an accurate diagnosis, identification and elimination of any predisposing factors (where possible), and the prescription of either topical or systemic antifungal agents. Oral candidosis may have significant implications for the general health of immunosuppressed patients, particularly when caused by the non-albicans spp. and, in cases of severe immunosuppression, systemic candidosis can be life-threatening. This article outlines the clinical presentation and appropriate management for the commonly presenting oral candidal conditions.

Clinical Relevance: Dental professionals should be aware of the clinical signs of intraoral candidosis, the appropriate special investigations that may be required in order to derive a definitive diagnosis, the significance of immunosuppression in oral candidosis and the appropriate methods of management of the condition.

Organisms Involved in Oral Candidosis

Although C. albicans is frequently identified in the aetiopathogenesis of candidosis, other candidal species can be isolated from oral candidoses in the immunocompromised patient, and in such individuals the course of oral candidosis can be protracted and resistant to normal management protocols.

PREDISPOsing FACTORS

A number of predisposing factors have been identified, all with the common feature of producing a change in the host–commensal balance (altered oral homeostasis), allowing the proliferation of the candidal organisms that results in candidosis. C. albicans normally co-exists with Lactobacillus acidophilus in the vegetative (yeast or blastospore) state; however, it can readily change to the elongated cellular form (pseudo-hyphae) or chlamydospore forms. C. albicans has weak pathogenicity and when an imbalance occurs in the host–commensal relationship this commensal organism has the opportunity to become pathogenic. The production of an endotoxin – an extracellular proteolytic enzyme – is responsible for most of the adverse effects of the intraoral mucous membrane.
in oral candidosis.

Predisposing localized and systemic factors can be classified as natural factors, dietary factors, mechanical factors, iatrogenic factors or grouped according to physiological factors, trauma, dietary factors, endocrine factors, malignancy, immune defects, xerostomia, disturbed oral flora and ‘other’ factors. Table 1 summarizes the predisposing factors in oral candidosis.

The physiological factors – the extremes of age – predispose to oral candidosis, as they are associated with an impaired host response.

Mechanical irritation (from acrylic dentures and orthodontic appliances) may result in the breakdown of the integrity of the mucous membrane, destroying its intrinsic antimicrobial resistance, while the close contact of the acrylic and mucous membrane prevents salivary antimicrobial substances (lysozyme, lactoferrin, the lactoperoxidase system and salivary glycoproteins) coming into contact with the invading microorganisms.

Some dietary factors such as a high carbohydrate intake provide Candida spp. with ideal metabolites, whereas the deficiency states (iron, vitamin B₁₂, folate) may reflect the poor resistance of the intraoral and perioral tissues to growth and dissemination of fungi. Some dietary factors such as a high carbohydrate intake provide Candida spp. with ideal metabolites, whereas the deficiency states (iron, vitamin B₁₂, folate) may reflect the poor resistance of the intraoral and perioral tissues to growth and dissemination of fungi.

Endocrine disturbances, the presence of malignancy and immune defects (e.g. AIDS) are associated with an inferior host response, particularly cell-mediated immunity. Furthermore, areas of ulcerated mucous membrane associated with oral carcinomata predispose to oral candidosis. The therapeutic use of chemotherapy and radiotherapy in malignancy are associated with an increased risk of oral candidosis: the mechanisms are complex, but involve these therapies having a direct effect on the rate of cellular turnover in the oral mucous membrane and reducing the salivary flow, respectively. Oral candidosis may be one of the earliest signs of AIDS, and in HIV-infected patients candidoses can affect multiple intraoral sites. Xerostomia results in reduced flow and quality of saliva and predisposes to oral candidosis. The reduced effectiveness of the antimicrobial properties of saliva (lysozyme, lactoferrin, the lactoperoxidase system, and salivary glycoprotein) favours the proliferation of Candida spp. Broad-spectrum antibiotics, steroid aerosols and smoking interfere with the normal balance of the oral microbial flora by removing the competition between the various microorganisms for adherence and nutrition which, in health, limits the growth and dissemination of fungi. Hospitalization may predispose individuals to oral candidosis; patients in hospita may encounter microorganisms to which they cannot mount an effective immune response, either because of reduced immunocompetence as a result of illness or due to the exposure to previously unmet potential pathogens. Following the discovery of a predisposing factor in a patient diagnosed with oral candidosis, its rectification should form an integral component of the overall patient management: the failure either to identify or manage predisposing factors will prevent the expedient resolution of oral candidosis, and will most likely result in recurrence. Where it is not possible to eliminate predisposing factors, such as in the long-term use of inhaled steroids or where malignancy is present, the prophylactic prescription of an antifungal agent may prevent recurrence.

Immunocompromization is the single most important predisposing factor that should be considered in patients with oral candidosis, owing to the potential for significant general health sequelae and, in severe cases of immunosuppression, the patient’s immune response may become overwhelmed by systemic candidosis, leading to a life-threatening situation. The prophylactic prescription of an antifungal may not only improve life quality, but also life expectancy for the severely immunocompromised patient.

### Classification of Oral Candidal Conditions

The first classification of oral candidosis was proposed by Lehner in 1966. Lehner recognized two major subdivisions:

- Acute, including pseudomembranous and atrophic candidosis; and
- Chronic, including atrophic and hyperplastic candidiasis.

The currently accepted classification

<table>
<thead>
<tr>
<th>Primary oral candidoses (group 1)</th>
<th>Secondary oral candidoses (group 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute: Pseudomembranous, erythematous</td>
<td>Oral manifestations of systemic mucocutaneous candidosis (due to diseases such as thymic aplasia and candidosis endocrinopathy syndrome)</td>
</tr>
<tr>
<td>Chronic: Pseudomembranous, erythematous, hyperplastic (plaque-like and nodular)</td>
<td>Candido-associated lesions: Candida-associated denture-induced stomatitis, angular cheilitis, median rhomboid glossitis</td>
</tr>
</tbody>
</table>

### Table 1. Predisposing factors in oral candidosis.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>Age (old and young), pregnancy</td>
</tr>
<tr>
<td>Trauma</td>
<td>Ill-fitting dentures and orthodontic appliances</td>
</tr>
<tr>
<td>Dietary factors</td>
<td>High carbohydrate intake, deficiency states (iron, vitamin B₁₂, folate)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes mellitus, Addison’s disease, Hypothyroidism</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Agranulocytosis, leukaeasions</td>
</tr>
<tr>
<td>Immune defects</td>
<td>AIDS</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>Drug-induced, Sjögren’s syndrome, radiation-induced</td>
</tr>
<tr>
<td>Disturbed oral flora</td>
<td>Antibiotics (especially broad spectrum), steroids</td>
</tr>
<tr>
<td>‘Other’ factors</td>
<td>Smoking, hospitalization</td>
</tr>
</tbody>
</table>

Table 2. Classification of oral candidosis (after Holmstrup and Axéll).
is based upon clinically relevant terminology and accounts for the limitations of Lehner’s original classification (see Table 2). As pseudomembranous candidosis can be present for an extended period of time, particularly in immunocompromised patients or in those using inhaled steroids, ‘pseudomembranous’ should be prefixed with ‘acute’ or ‘chronic’ as appropriate.6

The term ‘erythematous’ represents a more valid term than ‘atrophic’ for lesions that appear more ‘red’ than the surrounding mucous membrane, as redness of the mucous membrane may be due to either atrophy or increased vascularity.

As angular cheilitis and denture stomatitis and median rhomboid glossitis may have a combined bacterial and fungal aetiology, they are more appropriately classified as Candida-associated lesions.

PSEUDOMEMBRANOUS CANDIDOSIS

This condition (see Figure 1) is also known colloquially as ‘thrush’. The clinical lesions of pseudomembranous candidosis are very characteristic. Non-adherent creamy white patches or flecks are easily wiped from an underlying erythematous and bleeding mucous membrane. Commonly affected areas are the soft palate, oropharynx, tongue, cheek and gingivae. Surprisingly, pain is rarely reported.

The pseudomembrane consists of a mesh of fungal hyphae containing entangled desquamated epithelial cells, fibrin, keratin, necrotic tissue and bacteria. Although pseudomembranous candidosis is usually termed ‘acute’ in view of the short duration of the condition, in immunocompromised individuals the condition is often of a chronic, protracted nature, and can last for months (and even years).

Diagnosis

The diagnosis of pseudomembranous candidosis can usually be based on the clinical findings, although a swab of the lesion should be sent for culture and sensitivity, and a phosphate-buffered saline rinse may indicate the fungal load present within the patient’s mouth (Table 3). A smear may also be helpful in the diagnosis of pseudomembranous candidosis; however, biopsy is not usually necessary. The identification of the causative candidal species and any resistance to proposed antifungal agents will allow the clinician to provide effective patient management.

Management

Pseudomembranous candidosis in the immunocompetent patient is usually managed using topical agents alone, although use of systemic agents may be associated with increased compliance because nystatin pastilles and amphotericin B lozenges have an unpleasant taste (Table 4). In patients with AIDS, systemic antifungals are more effective than topical agents.

Patients who do not experience resolution of pseudomembranous candidosis within two weeks of the institution of antifungal therapy should be referred for investigation of possible underlying disease. Pseudomembranous candidosis in the immunosuppressed (e.g. AIDS) should be managed in specialist centres.

ERYTHEMATOUS CANDIDOSIS

Erythematous candidosis may be termed ‘acute’ or ‘chronic’, depending on the time factor in the course of the condition. The acute form was formerly known as ‘acute atrophic candidosis’, ‘antibiotic sore tongue’ or ‘glossodynia’ and is now known as erythematous candidosis. It often results from treatment with broad-spectrum antibiotics, steroid preparations (e.g. asthma inhalers), and short-course topical antibiotics. The tongue is most often affected, although any area of the oral mucous membrane is susceptible. Erythematous candidosis resulting from

<table>
<thead>
<tr>
<th>Condition</th>
<th>Swab</th>
<th>Smear</th>
<th>Oral rinse</th>
<th>Biopsy</th>
<th>Blood tests*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomembranous</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Erythematous</td>
<td>+</td>
<td>+(-)</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hyperplastic</td>
<td>+</td>
<td>+(-)</td>
<td>+</td>
<td>+(-)</td>
<td>+</td>
</tr>
<tr>
<td>Candida-associated denture-induced stomatitis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Angular cheilitis</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+(-)</td>
</tr>
<tr>
<td>Median rhomboid glossitis</td>
<td>+</td>
<td>+</td>
<td>+(-)</td>
<td>+</td>
<td>+(-)</td>
</tr>
</tbody>
</table>

*Blood tests include iron, vitamin B12, folate, glucose
+: Useful; –: not useful; +(-) may be useful

Table 3. Appropriate laboratory investigations for oral candidosis.
the prescription of broad-spectrum antibiotics is the only oral candidosis where pain is a common symptom.

Diagnosis

The clinical diagnosis of erythematous candidosis may be confirmed by microbiological analysis of the organisms cultured from a swab of the lesion, and a phosphate-buffered saline rinse may indicate the intraoral fungal load (see Table 3). A biopsy provides no additional diagnostic value.

Management

Cessation of treatment with the offending antibiotic medication usually leads to spontaneous resolution: however, this may not be possible and topical antifungals may be necessary prophylactically if the causative therapy is to be continued (Table 4).

Patients using inhaled steroid prescriptions should be advised to rinse their mouth after inhalation to ensure speedy resolution of erythematous candidosis. Moreover, routine oral rinsing after inhalation should be suggested as a preventive measure to all people using inhaled steroid prescriptions.

HYPERPLASTIC CANDIDOSIS

This chronic condition is also known as candidal leukoplakia and is characterized by irregular whitish raised plaque-like lesions on the buccal mucous membrane near to the commissures (see Figures 2 and 3). The tongue is rarely involved. The patient and referring dentist are often concerned about potential malignancy (Figure 3). Lesions are usually bilateral, do not have a surface that is easily removed, and can be extensive. Most patients are smokers. Other candidal lesions may also be present, possibly angular cheilitis.

Diagnosis

Biopsy may be considered appropriate in certain cases to exclude neoplasia (Table 3) and to diagnose hyperplastic candidosis definitively. Microbiological investigation in the form of swabs can help in clarifying the presence of Candida in the lesions, and a phosphate-buffered saline rinse may be confirmatory of the intraoral presence of the organism and indicate the fungal load. Haematological investigations are also important to assess any underlying predisposing factors such as deficiency of iron, vitamin B₁₂ or folate (Table 3).

Management

The condition is managed by rectification of any predisposing factors (e.g. smoking), provision of an appropriate antifungal (either topically or systemically) and by institution of a low-carbohydrate diet (see Table 4).

Sometimes the protracted nature of hyperplastic candidosis necessitates
combined and lengthy treatment. Follow up is imperative to ensure complete resolution, and for persistent lesions cryosurgery or surgical excision should be considered unless precluded by the size of the lesion.

**Candida-associated denture-induced stomatitis**

This condition is classified as a Candida-associated lesion, as it may result from a combined bacterial/fungal etiology. Patients affected by Candida-associated, denture-induced stomatitis are not usually aware of its presence. Curiously, in full-denture wearers, the maxillary denture-bearing area is more often affected than the mandibular denture-bearing area.

Newton classified this condition into three distinct clinical categories:

- **Type 1**: pinpoint erythema.
- **Type 2**: diffuse areas of erythema and oedema of palatal mucosa. The affected area is sharply demarcated from surrounding normal mucosa. Angular cheilitis can accompany this condition (Figure 4).
- **Type 3**: nodular, hyperplastic areas of mucosa with interspersed normal areas of mucosa.

**Diagnosis**

The appropriate investigations for Candida-associated, denture-induced stomatitis are outlined in Table 3. A swab of the lesions, the fitting surface(s) of dentures and orthodontic appliances should be sent for culture and sensitivity, while a phosphate-buffered saline oral rinse will indicate the intraoral fungal load.

Blood tests form an essential part of the management of this condition, in order to identify any predisposing factors, which include the deficiency states (iron, vitamin B₁₂, folate) and possible undiagnosed diabetes mellitus. A biopsy specimen provides no additional diagnostic information.

**Management**

The management of the condition should follow the following lines:

1. Correction of any predisposing factors.
2. Improved appliance hygiene: immersion of the appliance in a 1% hypochlorite solution for acrylic appliances, or 2% chlorhexidine solution for metal-based dentures, whilst sleeping.
3. Advice regarding a low-carbohydrate diet.
4. Prescription of antifungals. Miconazole oral gel should be applied to the fitting surface of the appliance and the denture-bearing area four times daily (the antifungal is most effective while the patient is sleeping due to the reduced salivary flow). Miconazole is available over the counter as well as on prescription, but should be avoided by patients concurrently being prescribed oral anticoagulants. A 2% chlorhexidine mouthwash can also be of benefit due to its antifungal action.
5. Systemic antifungal agents (see Table 4) may be considered for patients whose compliance may be expected to be poor (such as elderly people in care), immunocompromised patients and for patients with Newton's Type 3 Candida-associated denture-induced stomatitis (in addition to the application of miconazole oral gel to the palate and the fitting surface of the denture).

**Angular Cheilitis**

Angular cheilitis presents as erythema and crusting of the skin at the commissures of the lips (Figure 5). As a mixed bacterial/fungal aetiology may be present, it should be classified as a Candida-associated lesion. Edentulous elderly people are most commonly affected by angular cheilitis. In most cases of angular cheilitis, simultaneous intraoral candidosis is evident. A multifactorial aetiology has been proposed for this disease and includes:

- infection by either Candida spp. or Staphylococcus spp. (sometimes both);
- deficiency states: notably iron, vitamin B₁₂ and folate deficiency (these may also be identified in the anaemias and latent anaemias);
- undiagnosed or poorly controlled diabetes mellitus;
- skin creasing due to advancing age;
- poor dentures with inadequate vertical component, allowing the skin at the commissures to crease.
Diagnosis

Haematological investigations are important to exclude deficiency disease (ferritin, vitamin B₁₂, folate); importantly, a blood glucose assay may highlight possible undiagnosed diabetes mellitus, which may be a significant predisposing factor.

Swabs of the commissures and the anterior nares, and any potential intraoral reservoir for organisms (commonly the fitting surface of dentures, the palate and areas of hyperplastic candidosis) should also be sampled. These samples are important to identify the causative organism as well as the nucleus of organisms, which may be ‘feeding’ the angular cheilitis.

A phosphate-buffered saline oral rinse should also be undertaken. This may detect the presence of Candida at intraoral sites not otherwise sampled.

Management

The management of angular cheilitis (see Table 4) will depend on the elimination of organisms from the reservoir of infection and the treatment of any systemic sources of microorganisms. The empirical application of miconazole gel four times daily to the lesions is helpful, as it is active against both Candida spp. and Staphylococcus spp., as well as other Gram-positive organisms; and therefore will eliminate many cases of infection. An alternative is fusidic acid (Fucidin), again applied four times daily to the lesions is helpful, as it is active against both Candida spp. and Staphylococcus spp., as well as other Gram-positive organisms; and therefore will eliminate many cases of infection. An alternative is fusidic acid (Fucidin), again applied four times daily to the lesions, but this is generally only prescribed on the basis of a confirmatory microbiological report exclusively identifying Staphylococcus spp. as the causative organism.

If microbiology reveals an intraoral source of infection (commonly the fitting surface of a denture and palate) this must also be treated appropriately. Similarly, if organisms are identified in the anterior nares, they must also be treated.

The concomitant prescription of topical and systemic antifungals for angular cheilitis (where intraoral and/or intranasal reservoirs have been identified) may be regarded as a ‘belt and braces’ approach but should ensure speedy resolution. Systemic antifungals are the treatment of choice for angular cheilitis in immunocompromised individuals, for lesions resistant to topical measures alone, and where compliance is likely to be poor.

The failure to identify or treat a reservoir of organisms will result in the angular cheilitis recurring. Sufferers should be discouraged from any habits that involve contact of nose and mouth in close succession. Fabrication of new full dentures should be delayed until angular cheilitis has resolved.

MEDIAN RHOMBOID GLOSSITIS

The usual clinical manifestation of median rhomboid glossitis is of a diamond-shaped depapillated erythematous patch on the midline of the tongue dorsum (Figure 6). It is classified as a Candida-associated lesion as a mixed microbiological flora may be implicated in the aetiology.

Diagnosis

The diagnosis is usually clinically based; however, a swab and a phosphate-buffered saline oral rinse should be carried out, as a mixed aetiological flora may be identified. Biopsy is unnecessary, unless diagnostic uncertainty still exists following the microbiological investigations and the lesion fails to respond to antifungal agents.

Management

Treatment requires the prescription of topical or systemic antifungals. However, Nystatin and amphotericin B are not palatable, and compliance may be poor, in which case systemic antifungals may be more effective (Table 4). Advice regarding cessation of smoking is an integral part of the management of patients with median rhomboid glossitis, in order to prevent successive recurrences.

OTHER CONDITIONS

These include cheilocandidosis, mucocutaneous candidosis and chronic oral multifocal candidosis. The reader is referred to a specialist text for further information.

LABORATORY INVESTIGATIONS FOR ORAL CANDIDOSIS

The most appropriate laboratory investigations are outlined in Table 3.

Swabs, first moistened with sterile saline and then rubbed along the surface of the lesions, should be promptly submitted to the microbiological laboratory with a request for culture and sensitivity. These allow the identification of the causative candidal species, which in most cases is C. albicans. However, the identification of non-albicans Candida spp. is of considerable relevance in the management of oral candidosis – especially in the immunocompromised patient – as non-albicans organisms may not respond to common topical and systemic antifungals.

A smear of the lesion may duplicate the information provided by a swab but in cases of diagnostic uncertainty, may be indicated.

A phosphate-buffered saline oral rinse will determine the presence of Candida within the oral cavity; and
high candidal counts correspond with high fungal loads in the diseased areas of mucous membrane. Biopsy is generally unnecessary for the diagnosis of oral candidosis, except where potential malignancy is one of the provisional diagnoses. Blood investigations should be instigated where appropriate, in order to identify any deficiency states and undiagnosed or poorly controlled diabetes mellitus, which may indicate poor tissue resistance to candidal infection.

Acknowledgements
I thank Dr D. Felix of Glasgow Dental Hospital and School for providing the clinical photographs in the preparation of the images.

Further Reading

Book Review

This multi-author text aims to provide an up-to-date account of the pathogenesis and management of oral cancer. It embraces the basic science, pathology and clinical aspects of this disease.

No fewer than 29 authors have contributed to this book, which comprises 17 chapters and runs to some 405 pages in length. Ten of the contributors work at the Tata Memorial Centre and thus it is not surprising that the text is biased somewhat towards the issue of oral cancer in South Asia.

The first chapter addresses the epidemiology and possible prevention of oral cancer, introducing the subject matter effectively, whilst chapter two provides an overview of the molecular biology of the disease. This is an intrinsically complex topic and, in parts, the grammatical style of the text does not encourage the reader’s grasp of the subject matter.

The following three chapters outline immunological aspects of oral cancer and the departments of Dental Illustration at Glasgow Dental Hospital and School and Media Services at the University of Dundee for their help in the preparation of the images.

The text continues with chapters on serological markers in head and neck malignancy, the possible aetiological role of viruses and a chapter devoted to chemoprevention.

Six chapters address therapeutic modalities of oral cancer and, as well as summarizing the more traditional approaches, the potential use of photodynamic therapy, immunotherapy and gene therapy are also discussed.

The book concludes with a discussion of novel diagnostic techniques and finally summarizes certain of the more recent observations in the field of oral malignancy, considering their possible future applications in the management of this disease.

The work is extensively referenced, but a number of the illustrations lack clarity and are difficult to interpret. There is a widespread and unnecessary use of abbreviations throughout the text. A number of these abbreviations are not in common usage and this may be a source of irritation to the reader.

In summary, this book is very broad in its scope and perhaps, as a result, represents somewhat of a compromise, lacking a particularly authoritative approach. However, it should appeal to both clinicians and basic scientists who either have an interest in, or are involved with, the management of patients with oral cancer. The publication contains a very considerable amount of information and at a cost of £25, notwithstanding some of the above criticisms, it represents good value for money.

John Hamburger
Birmingham Dental School