Investigating patients with oropharyngeal candidiasis

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

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The advent of orally active azole antifungal agents and access to over-the-counter antifungal agents have made the treatment of oral thrush and other common fungal infections relatively easy in most cases. However, because such treatments are effective, clinicians may be less likely to consider significant disorders that may be heralded by these infections. What issues should we consider when patients present with suspected oral candidiasis, and how should we investigate these patients?

Is it candidiasis?

Classical oropharyngeal (pseudomembranous) candidiasis presenting as 'thrush' is usually a straightforward diagnosis (Figure 1), with white-to-cream patches in the mouth and throat that may be gently scraped back to show a raw, bleeding surface. *Candida* infection is likely to be the cause of such symptoms in patients receiving oral or inhaled corticosteroids, broad spectrum antibiotics, chemotherapy or radiotherapy, and in those who have HIV or are otherwise constitutionally unwell.

Not all candidiasis looks like this. The infection can manifest as:

- angular cheilitis, with painful fissures at the angles of the mouth
- an erythematous (sometimes atrophic or 'bald') type, with flat, red and painful areas
- candida leucoplakia, with white plaques that cannot be scraped off the surface epithelium.[1]

What else looks like candidiasis?

Other white lesions of the oral mucosa that may be mistaken for candidiasis include: smoker's leucoplakia, friction-induced leucoplakia and, in immunocompromised patients, Epstein-Barr virus-related hairy leucoplakia (Figure 2).[1]

What are the pathogenic species of Candida?

All the pathogenic species of *Candida* occur as commensals in healthy people. Candidiasis follows increased colonisation of *Candida* and altered host factors. Important pathogenic species of *Candida* besides *C. albicans* include *C. tropicalis*,

IN SUMMARY

- **Classical oropharyngeal candidiasis is usually a straightforward diagnosis, but *Candida* infection may also manifest as angular cheilitis, erythematous mucositis or candida leucoplakia.**
- **Candidiasis follows increased colonisation of *Candida* and altered host factors.**
- **Initial evaluation of patients with candidiasis may include exclusion of neutropenia, significant lymphopenia, diabetes and HIV infection.**
- **Subsequent evaluation may include examination for lymphadenopathy, splenomegaly or hepatomegaly and measurement of CD4 T-cell counts and iron, vitamin B_{12} and folate status.**
- **Popularisation of mystical entities like the 'candida hypersensitivity syndrome' has engendered confusion and been associated with the development of non-orthodox laboratory tests and the inappropriate use of antifungal agents.**

C. parapsilosis, *C. glabrata* and *C. krusei*; these are slightly more common in deeper tissue *Candida* infections.[2,3]

Why do patients develop thrush?

T-cells and neutrophils provide the central defence mechanism against *Candida* infections. Acute HIV infection with a marked initial reduction in CD4 T-cell count is often associated with oropharyngeal candidiasis. Progressive decline in CD4 T-cell numbers below 400/μL is associated with oral thrush, and below 50/μL with oesophageal candidiasis.[2]

Local or systemic immunosuppression, immunodeficiency and diabetes with secondary impairment of neutrophil function are common correlates of candidiasis. Other risk factors for candidiasis include impaired salivary gland function, use of certain drugs (e.g. inhaled corticosteroids), smoking and nutritional deficiencies.

Systemic candidiasis can affect the retina, kidney, spleen, liver and, occasionally, heart valves. Entry portals created by trauma, surgery and catheters expose vulnerable patients who are highly colonised with *Candida* to the risk of a systemic infection.[2,4,5]

How should patients be evaluated?

An isolated episode of oral thrush in a vulnerable patient may not be a harbinger of a more sinister process. However, in the absence of conventional risk factors or when episodes recur or persist despite reasonable therapy, further clinical evaluation may be appropriate.

Initial evaluation

Initial evaluation should be targeted to the patient's background and include:

- exclusion of neutropenia and significant lymphopenia by full blood count
- exclusion of diabetes by fasting glucose
- consideration of exclusion of HIV infection by serology.

Subsequent evaluation

Subsequent evaluation should include:

- examination for lymphadenopathy, splenomegaly or hepatomegaly
- consideration of CT imaging of the chest and abdomen for thymoma or lymphoma
- confirmation that the illness is due to *Candida* by microscopy, culture and, occasionally, biopsy
- measurement of CD4 T-cell counts (and usually also CD8 T-cell, B-cell and natural killer cell subset counts)
- measurement of iron, vitamin B_{12} and folate status (looking for nutritional deficiencies)
- investigation of renal and liver function by serum biochemistry
- investigation of other immune abnormalities that might imply an underlying lymphoma or similar process by serum IgG, IgA, IgM measurement and serum and urine electrophoresis.

How should recurrent or persistent candidiasis be investigated?

In patients suspected of having recurrent candidiasis, it may be reasonable to verify the infection and investigate for immunodeficiency. In addition, examination of other sites, including the nails, for *Candida* infection is important.

Chronic mucocutaneous candidiasis is a syndrome of recurrent or persistent candidiasis, clustering in families and sometimes associated with autoimmune disorders (commonly endocrine disorders). Investigations in such patients will show the following:

- absence of T-cell responsiveness to *Candida* on intradermal skin tests (performed like the Mantoux test but with *Candida* antigen)
- reduced or absent *in vitro* T-cell responses to *Candida* antigen
- often, autoantibodies.

The acronym APECED refers to a rare syndrome of autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy (mainly affecting the teeth). Among the conditions associated with

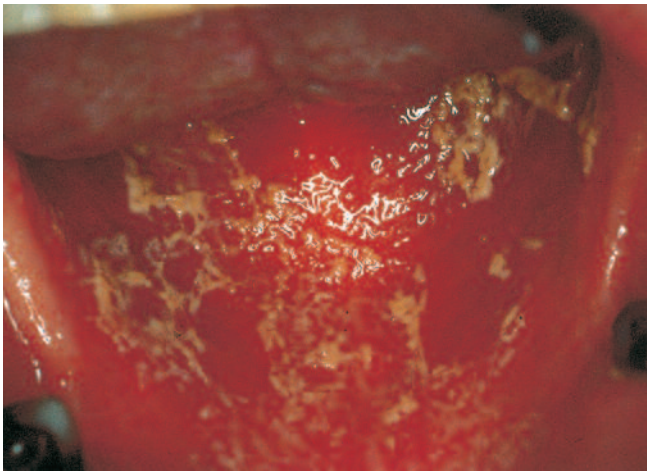

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Figure 1. Membranous oral candidiasis.

Figure 2. Consider oral hairy leucoplakia in the differential diagnosis of oropharyngeal candidiasis.

this syndrome are organ-specific autoimmune diseases, IgA deficiency and coeliac disease. The most common autoimmune endocrine disorders seen in this syndrome are hypoparathyroidism, hypoadrenalism, hypothyroidism, gonadal failure and type 1 diabetes mellitus. Haematologic autoimmune syndromes, vitiligo and alopecia are also recognised in APECED.

Other associations that can occur with chronic mucocutaneous candidiasis include thymoma and keratitis and, less often, other T-cell immunodeficiency disorders.[2,4,5]

Is measurement of antibodies to Candida spp. useful?

Measurement of antibodies to *Candida* spp. is not useful clinically, neither is measurement of *Candida* antigens. Candidaemia and other fungaemia may be identified in immunocompromised hosts by blood culture. In addition, new polymerase chain reaction (PCR) methods are becoming established for early diagnosis of infection in difficult sites and in immuncompromised hosts before cultures have become positive.

What is the 'candida hypersensitivity syndrome'?

The 'candida hypersensitivity syndrome' is not a real disease entity but has been popularised as a source of many symptoms that may benefit from dietary modification. The so-called 'anti-candida' or 'yeast-free' diet has many similarities to the elimination diet and challenge regimen often used to investigate polysymptomatic patients with food intolerances. Symptoms of classical food intolerance are common. They may result from amines, salicylates, monosodium glutamate, colours and preservatives, and may manifest as irritable bowel symptoms, vulvodynia, fatigue, headaches, 'fuzzy heads' and migraines and aggravate urticaria and angioedema. These symptoms are not caused by *Candida*.

Which tests for Candida are unproven or controversial?

Some patients may have been told that they have candidiasis or another fungal infection following a 'live blood analysis' 'Live blood analysis' is an unusual diagnostic procedure whereby a blood sample is taken and a blood film of sorts is projected on to a wall. Some visible shadows may then be labelled as 'yeast forms'. This test has no clinical use but is offered at various alternative medical clinics, and often by naturopaths.

A useful website that provides information on other controversial, unproven tests or charlatanism is Quackwatch's site (www.quackwatch.org).

Will amphotericin lozenges or nystatin drops be effective?

In most cases topical antifungal agents such as amphotericin lozenges (Fungilin) or nystatin drops (Nilstat Oral Drops, Mycostatin Oral Drops, N-Statin Oral Drops) will be effective in treating oropharyngeal candidiasis, except in some immunocompromised patients. If these agents are ineffective, other causes of the white plaques should be considered (see above).

Orally active systemic azole antifungals should be used when topical medicines fail. A major factor likely to interfere with the therapeutic success of some of these systemic agents (ketoconazole [Nizoral] and itraconazole [Sporanox]) is failure to maintain an acidic gastric pH, which is necessary for absorption. This is not so critical for the absorption of fluconazole (Diflucan). The table lists topical and oral systemic antifungal agents available in Australia for oropharyngeal candidiasis.

Summary

The advent of new antifungal agents has greatly simplified the management of candidiasis. Popularisation of mystical entities like the 'candida hypersensitivity syndrome' has engendered confusion, and this has been associated with the development of non-orthodox laboratory tests as well as inappropriate use of antifungal agents.

AIDS-related candidiasis is readily diagnosed and managed with the use of antifungal agents. Recognition of other T-cell disorders and the autoimmune associations with mucocutaneous candidiasis is probably being neglected because the initial clinical management has been aided by the development of potent orally active antifungal agents. MT

Table. Topical and systemic antifungal agents for oropharyngeal candidiasis

Topical antifungals

Amphotericin lozenges (Fungilin)
Miconazole (Daktarin Oral Gel)
Nystatin drops (Nilstat Oral Drops, Mycostatin Oral Drops, N-Statin Oral Drops)
Nystatin pastilles (Mycostatin Pastilles)

Oral systemic antifungals

Fluconazole (Diflucan)
Itraconazole (Sporanox)
Ketoconazole (Nizoral)
Voriconazole (Vfend)

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