Candidiasis

Synonyms: candidosis

This article gives an overview of candidal infections, with detailed information on oral, oesophageal, skin and invasive candidal infections.

See separate articles Systemic Mycoses, Fungal Lung Infections, Fungal Nail Infections and Vaginal and Vulval Candidiasis. Illustrations of skin and mouth candidal infections are available on DermNet NZ.[1]

Candida spp. are yeast-like fungi which can form true hyphae and pseudohyphae. They may be part of the normal body flora, or may become an invasive pathogen. Candidal infection varies from a benign local mucosal membrane infection to disseminated disease; it can involve any organ. Severe disease is associated with an immunodeficiency - eg, malignancy, HIV infection or immunosuppressive therapy.

Epidemiology and risk factors[1] [2]

- Up to 60% of healthy people are asymptomatic carriers of *Candida* spp. (as a commensal in the gastrointestinal tract).[3]
- Candidal infection is the most common cause of invasive fungal infections in hospital patients.
- An estimate of systemic candidal infection prevalence can be obtained from azole consumption. One European study covered 15 countries from 2005-2009 and showed a trend of increasing azole use in all countries except France.[4]
- Non-*albicans* strains of *Candida* spp.are reported to be increasing but no increase in fungal bloodstream infections due to non-*C. albicans* has been found in the ten years up to 2011.[4]

Risk factors

Risk factors for candidal infection are:

- Broad-spectrum antibiotics.
- Central venous catheters or parenteral nutrition.
- Immunocompromise:[5]
    - T-cell disorders, which tend to cause mucocutaneous candidal infections.
    - Neutrophil disorders, which tend to cause invasive candidiasis.
- Corticosteroid treatment or Cushing's disease.
- Diabetes mellitus.
- Renal replacement therapy.
- Implanted prostheses.
- Radiotherapy.
- Intensive care or prolonged ventilation.
- Gastrointestinal (GI) tract surgery.

Other risk factors for mucocutaneous candidiasis are:

- Pregnancy or high-oestrogen contraceptive pill.
- Iron deficiency.
- Underlying skin disease - eg, psoriasis, dermatitis.
- General debility - eg, cancer or malnutrition.
- Local factors - heat, moisture, skin maceration, topical corticosteroids.
- Extremes of age.

Aetiology[4] [6]

Superficial (mucocutaneous) infections:

- *C. albicans* is the usual cause. It is commonly a commensal in the mouth and GI tract and is often found in the vagina.
- Less common species causing superficial infection include *Candida glabrata*, *Candida dubliniensis* and *Candida parapsilosis*. There is evidence that the first two species are more common now in oral infection in patients with HIV and *C. glabrata* in vaginal candidosis. There has been a shift from *C. albicans* towards other candidal species recently.

Invasive infection:

- *C. albicans* is the most common cause.
- Other species may be isolated, particularly in cases of endocarditis - for example, *C. parapsilosis*.
- *Candida tropicalis* has been implicated in infections of patients with neutropenia.
- Non-*albicans Candida* spp. are now more frequent causes of systemic infection and are important to recognise, as their antifungal susceptibility may differ from *C. albicans*.
- Portals of entry include the GI tract (common), the skin and the urinary tract (rare).

Oral candidiasis[3]

Types of oral candidiasis

- **Pseudomembranous oral candidiasis (oral thrush)**:
    - Curd-like white patches in the mouth. The white pseudomembrane can be easily removed, leaving an underlying red base that is usually painless (in contrast with leukoplakia, which cannot be rubbed off).
    - Most common in neonates.

- **Acute erythematous oral candidiasis (acute atrophic oral candidiasis)**:
    - Marked erythema and soreness, especially on the the tongue.
    - It often follows oral thrush.
    - It is common after oral antibiotics.

- **Chronic erythematous oral candidiasis (denture stomatitis or chronic atrophic oral candidiasis)**:
    - Redness of the denture-bearing area - rarely, also soreness.
    - It is common in denture users.

- **Chronic plaque-like oral candidiasis (chronic hyperplastic oral candidiasis)**:
    - Persistent firm, white plaques on the cheek or tongue, that are not easily removed.
    - It is most common in smokers and men aged >30 years.

- **Median rhomboid glossitis**:
    - A central, red, area of papillary atrophy of the tongue.
    - It usually occurs in smokers or those using corticosteroid inhalers.
    - It can cause recurrent/chronic candidiasis.

- **Angular cheilitis**:
    - Redness, fissuring and soreness at the angle of the mouth.
    - It can be due either to *Candida* spp. or to bacterial infection (mainly *Staphylococcus aureus*).
    - Contributing factors are older age, ill-fitting dentures, immunocompromise, vitamin B12 deficiency or iron-deficiency anaemia.

Diagnosis of oral candidiasis

- Swabs/culture and serology are generally not useful because candidal organisms are commonly found in healthy people.
- Swabs may be relevant for suspected drug resistance - eg, in HIV-positive patients.

Management of oral candidiasis

When to admit or refer [3]

- Admit to hospital if there are systemic symptoms, the patient is unwell or if there are oesophageal symptoms (dysphagia or retrosternal pain) - particularly if there is immunocompromise.
- Obtain specialist advice if there is:
    - Widespread candidiasis.
    - No response to treatment (below).
    - Recurrent episodes (may be immunocompromised).
    - Breakthrough candidiasis on preventive treatment (may be drug-resistant).
    - Chronic plaque-like oral candidiasis not responding to treatment (needs biopsy).
- Symptomatic oral candidal infection is rare in healthy adults - if present, consider investigating for underlying illness - eg, immunocompromise.

Treatment - children [3]

- Use topical treatment for ≥7 days or until 2 days after symptoms clear.
- First choice is miconazole gel but beware drug interactions and liver dysfunction.
- Otherwise, use nystatin suspension (no significant contra-indications).
- Infants - note that miconazole gel is not licensed for age <4 months; however:
    - Some doctors feel this is an unnecessary limitation (it arose from concerns about choking if the gel is administered incorrectly to young babies).
    - The correct method of use is to smear 1 ml of miconazole oral gel round the mouth and gums with a finger after feeds four times a day.
- After 7 days, change to nystatin suspension if not responding to miconazole gel.
- Specialist treatment for refractory infections includes fluconazole given by mouth or itraconazole for fluconazole-resistant cases. [7]

Treatment - immunocompetent adults [3]

- Mild or localised oral candidiasis:
    - Use topical treatment for 7 days and continue until 2 days after symptoms clear.
    - Options are oral miconazole gel or nystatin suspension. **Note**: miconazole cautions re drug interactions and liver disease.
- Extensive or severe oral candidiasis:
    - Exclude risk factors - for example:
        - Diabetes
        - Dentures
        - Inhaled steroids
    - Oral fluconazole 50 mg/day for 7 days.
- Candidiasis persisting after 7 days of treatment:
    - If not responding to miconazole, change to nystatin.
    - If taking fluconazole, continue treatment for another week.

Treatment - adults taking immunosuppressive treatment [3]

- Obtain specialist advice if the patient is taking ciclosporin, tacrolimus, or chemotherapy.

- Patients taking oral corticosteroids or disease-modifying antirheumatic drugs:
    - Mild/localised oral candidiasis - topical treatment.
    - Extensive/severe oral candidiasis - fluconazole 50-100 mg/day for 7 days.
    - Follow-up after 7 days.
    - Have a low threshold for admission/specialist advice; also consider if FBC is indicated.

Treatment - HIV-positive adults [3] [8]

- Have a low threshold for hospital admission.
- Obtain specialist advice before treatment if:
    - There is severe/extensive oral candidiasis.
    - Previous fluconazole treatment was ineffective.
    - The patient is already taking antifungal prophylaxis.

- Otherwise, use oral fluconazole 100 mg/day for 7-14 days, reviewing after 7 days.
- Highly active antiretroviral therapy (HAART) is also part of the treatment and antifungal prophylaxis may help to prevent recurrence. [9]

Prevention of oral candidiasis

- Patients taking oral/inhaled steroids - good inhaler technique, spacer device, rinse mouth with water after use.
- Denture wearers - thorough cleaning of dentures, leave them out at night, ensure they fit correctly.
- Smoking cessation.

Oesophageal candidiasis

Presentation

- Dysphagia, pain on on swallowing food or fluids and/or retrosternal pain, usually with oropharyngeal candidiasis.
- This combination of symptoms is predictive of oesophageal candidiasis.
- It is most often associated with treatment of haematopoietic or lymphatic malignancies.
- In HIV-positive patients, it is an AIDS-defining illness.

Diagnosis

- A therapeutic trial of fluconazole for patients is useful; most patients will respond within 7 days of treatment.
- Definitive diagnosis is by endoscopy.

Management of oesophageal candidiasis

- Consider admission to hospital - oesophageal candidiasis is a life-threatening infection. [2]
- Treat for 14-21 days; the following treatment options are suggested:
    - First-line treatment options:
        - Oral fluconazole (200-400 mg daily).
        - Intravenous (IV) fluconazole, an echinocandin - eg, caspofungin, or amphotericin. [10]

    - Second-line drugs are oral itraconazole oral solution, IV posaconazole or IV voriconazole.

- For AIDS patients, HAART is advised to prevent recurrence.

Candidal vulvovaginitis

See separate article Vaginal and Vulval Candidiasis.

Candidal skin infections[11]

Presentation

- Soreness and itching.
- The appearance of the affected skin is variable; there may be:
    - Red, moist skin area with a ragged, peeling edge and possibly pustules or papules at the margin. There may be satellite lesions (pustules or erythema) surrounding the margin.
    - Pustules which are thin-walled with a red base.
    - Yellow-white scale on the surface (looks like curds).
    - In the foot or hand web spaces - maceration (moist damaged skin) with a thick horny layer.

There are different forms of cutaneous candidiasis:

- Intertrigo (skin fold infection).
- Candidal nail infections - chronic paronychia or onychomycosis (see separate article Fungal Nail Infections).
- Napkin dermatitis.
- Balanitis.
- Chronic mucocutaneous candidiasis:[12]
    - A rare condition, usually beginning in childhood, with persistent and prolonged candidal infections of the skin and mucous membranes.
    - May be due to genetic predisposition, endocrinopathies, T-cell disorders or low immunoglobulin levels.
- Candidal folliculitis.
- Generalised cutaneous candidiasis (rare): a widespread rash, worse in skin folds and extremities, with pruritus.
- Skin lesions in patients with invasive candidiasis - see 'Invasive candidal infections', below.

When to investigate

Swabs are not usually required but take standard bacteriology swabs for microscopy and culture if:

- The diagnosis is unclear, or bacterial infection is suspected.
- There is no improvement after initial treatment.
- The patient is immunocompromised.
- Systemic treatment is considered.

Look for an underlying cause if there is widespread or recurrent candidiasis (see 'Risk factors', above).

Treatment[7]

- Usually, topical imidazole cream - eg, clotrimazole, econazole, ketoconazole, or miconazole.
- Topical terbinafine is an alternative.[7]
- If there is problematic itch or inflammation, consider adding a mild corticosteroid cream for 7-14 days.
- Oral fluconazole 50 mg/day for 2-4 weeks if:
    - Topical treatment is ineffective.
    - There is widespread infection.
    - The patient is immunocompromised (depending on the severity of infection and the level of immunocompromise).
- Review after 2 weeks of fluconazole treatment.
- Itraconazole may be used if fluconazole does not work.
- If not improving, obtain specialist advice.
- Chronic mucocutaneous candidiasis is a difficult condition to treat. Systemic antifungals are the mainstay of treatment; fluconazole and itraconazole are first-line options. Oral ketoconazole was withdrawn in 2013 because of concerns about liver damage.[13]

Invasive candidal infections[2] [4]

- The term invasive candidiasis encompasses a variety of severe candidal infections:
    - The most common form is candidaemia (about 60% of cases).[6]
    - Any internal organ can be affected (see 'Disseminated candidiasis (deep organ infection)', below).

- Usually there is underlying risk factor - eg, immunocompromise, intensive care, implants or indwelling catheters.
- Invasive candidiasis is life-threatening. Systemic candidiasis has an estimated mortality rate of about 70-80%.

Diagnosis[2] [14]

- Prompt diagnosis is important but often difficult.
- Have a low index of suspicion and prompt treatment in at-risk patients - eg, in neutropenic patients, start antifungal therapy if there are >4 days of persistent fever despite antibiotics.
- Cultures:
    - Blood cultures should be taken but lack sensitivity (probably <50%) and usually become positive late.
    - Culture of body fluids or tissues as appropriate.
    - Various rapid tests are available to identify *Candida* spp. from cultures.
    - Antifungal susceptibility tests are important in view of the increasing problem of resistance.[15]

- Ultrasound and/or CT scans are useful in abdominal or renal tract infections. Again, radiological signs may appear late.
- Echocardiography for suspected cardiac involvement.
- Tissue biopsy and culture - if feasible.
- Endoscopy for suspected upper GI infections.
- Serological tests:
    - These detect components of the fungal cell wall or antibodies directed against these antigens (eg, mannan or anti-mannan). Several tests are now commercially available although their sensitivity and specificity are variable.[16]
    - Molecular-based tests for detection of candidal DNA are under development.

Candidaemia

Presentation

- Risk factors, including prolonged IV catheterisation.
- Fever/chills unresponsive to broad-spectrum antibiotics.
- May have macronodular skin lesions, candidal endophthalmitis, multiorgan infection or, rarely, septic shock.
- Characteristic skin lesions may be present in some patients with candidaemia or disseminated candidiasis. These are erythematous, firm, non-tender macronodular lesions with discrete borders. Biopsy of these lesions shows yeast cells, hyphae, or pseudohyphae, with cultures positive for *Candida* spp. in approximately 50% of cases.

Treatment[2] [4]

Current treatment guidelines recommend:

- First-line treatment:
    - Non-neutropenic patients - IV fluconazole or an echinocandin (echinocandins are preferred for severe illness, recent azole exposure or likely *C. glabrata*).
    - Neutropenic patients - an echinocandin, a lipid formulation of amphotericin or voriconazole. Fluconazole can be used in less ill patients with no recent azole exposure.

- Second-line treatments and species-specific treatments:
    - Remove central venous catheters if possible in non-neutropenic patients; consider catheter removal in neutropenic patients but it can be retained if the patient is on an echinocandin.
    - Fundoscopy (dilated) within the first week (ocular lesions (mostly chorioretinitis) occur in 16% of candidaemias and can have late presentation).
    - Blood cultures to assess for clearance of candidal infection.
    - If there are no complications, continue treatment for 2 weeks after the patient is clinically well, there is resolution of neutropenia and clearance from the bloodstream.

Disseminated candidiasis (deep organ infection) [4]

General points

- Any internal organ, or multiple organs, may be affected (listed below).
- It presents with fever unresponsive to broad-spectrum antibiotics and features of sepsis; there may be septic shock.
- Characteristic skin lesions may be present (see under 'Candidaemia', above).
- Blood cultures may be negative in about 50% of cases.

Treatment of disseminated candidiasis

This involves:

- Systemic antifungal therapy (prolonged treatment in many cases): specific recommendations for different organ infections are detailed in current guidelines. [4]
- Removal of the source of infection or of the precipitating factors, if feasible (eg, remove indwelling devices, treatment of immunocompromise).
- Surgical debridement may be appropriate.

Types of disseminated candidiasis

The following deep organ candidal infections can occur.

Cardiovascular system: [17]

- Endocarditis.
- Myocarditis.
- Pericarditis.
- Suppurative thrombophlebitis.
- Candidal infection of pacemakers, implantable cardiac defibrillators and ventricular assist devices.

Respiratory system: [2]

- *Candida* spp. isolated from respiratory secretions - this rarely indicates invasive candidiasis; candidal infection is common in respiratory secretions and cultures from them.
- Candidal pneumonia, lung abscess or tracheobronchitis - these are rare.
- Laryngeal candidiasis - is uncommon and mainly associated with malignancies.

Abdominal organs:

- Candidal peritonitis - may be a complication of peritoneal dialysis. [18]
- Chronic disseminated candidiasis (hepatosplenic candidiasis):
    - This is a form of systemic candidiasis, occurring in patients with a haematological malignancy and neutropenia. It develops during the recovery phase of a neutropenic episode.
    - Clinical features are fever (unresponsive to broad-spectrum antibiotics), abdominal pain, tender hepatosplenomegaly, vomiting, dysphagia and jaundice.
    - It may be a form of inflammatory immune reconstitution syndrome.

- Non-oesophageal GI candidiasis:
    - This most commonly involves the stomach or small intestine.

- Candidal cholecystitis (rare).

Renal tract:

- Asymptomatic cystitis:
    - *Candida* spp. are found in up to 10% of urine cultures; treatment is not usually indicated, except in high-risk patients - eg, low birth-weight neonates, neutropenia, or urological procedures.
- Symptomatic cystitis.
- Pyelonephritis
- Urinary fungus balls:
    - These are due to accumulation of fungal material in the renal pelvis; the balls can occur anywhere in the urinary collecting system.
    - May cause intermittent urinary tract obstruction with anuria and renal insufficiency.
- Candidal prostatitis and epididymo-orchitis (rare).

CNS candidiasis:

- Meningitis.
- Granulomatous vasculitis.
- Diffuse cerebritis with microabscesses.
- Mycotic aneurysms.

Ocular candidiasis: [19]

- Chorioretinitis.
- Vitritis.
- Endophthalmitis.

Candidal osteo-articular infection:

- Septic arthritis.
- Osteomyelitis (including sternal osteomyelitis following sternotomy).
- Infection of prosthetic device.
- Costochondritis (rare).
- Myositis (rare).

Obstetric and neonatal candidal infections

Neonatal invasive candidiasis: [20] [21]

- This is an important cause of mortality and morbidity in very low birth-weight (VLBW) infants; those who are extremely preterm or low birth-weight are most at risk.
- Outbreaks of infection in neonatal units have recently been reported. [22]
- *C. albicans* and *C. parapsilosis* are the most common species found in neonates.
- The usual treatment agents are amphotericin and fluconazole. Other azoles such as voriconazole and the echinocandins are being studied and may have a role to play.
- There is some evidence to support the use of prophylactic oral, topical or systemic antifungal agents in VLBW infants in the neonatal intensive care unit. [23]

Chorioamnionitis (rare): [24]

- May cause fetal death.
- May result in cutaneous congenital candidiasis - a very rare disease comprising a generalised rash at, or shortly after, birth and usually without other signs or symptoms, which is always secondary to candidal chorioamnionitis; it is is essentially benign and self-limiting.

Placental infection is rare. In vitro fertilisation is a risk factor.[25]

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