Candidiasis

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Key Points

- Candidiasis refers to infections caused by *Candida* species.
- The most common encountered infections include oral candidiasis, superficial cutaneous candidiasis, candida balanitis, vaginal candidiasis, candida paronychia, candida onychomycosis and chronic mucocutaneous candidiasis.
- Therapy should always include removal of underlying predisposing factors with encouragement for dental and mouth hygiene, keeping dry skin folds, avoidance of detergents that flare up chronic paronychia and reduction of the *Candida* reservoir in the mouth and gut.
- Topical agents used in the treatment of candidiasis include amphotericin B, nystatin, natamycin, miconazole, ketoconazole, econazole, omoconazole, tioconazole and clotrimazole.
- Systemic agents used include itraconazole and fluconazole.

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Definition and Epidemiology

The term candidiasis refers to infections caused mainly by the classic opportunistic pathogen *Candida albicans* or occasionally by other species of *Candida*, such as *C. tropicalis*, *C. guilliermondii*, *C. parapsilosis*, *C. krusei*, *C. stellatoidea*, *C. pseudotropicalis* and *C. glabrata*. These various yeast species differ in their potential to invade and colonize epithelial and epidermal sites, *C. albicans* being the species with the greatest such potential. Infections of the skin, nails and mucous membranes are the most often encountered candida infections.

Basic Concepts of Pathogenesis

C. albicans, which is part of the normal human flora, is a dimorphic organism, developing in different morphological forms, such as yeasts, hyphae and pseudohyphae. This development is dependent on local conditions. *Different predisposing factors exist, which lead to different types of candidiasis*. Immunosuppression or leukopenia usually leads to systemic candidiasis, which is rare; endocrinopathies (hypoparathyroidism, hypothyroidism, diabetes mellitus), iron or zinc deficiencies and inherited defects of immunity lead to chronic mucocutaneous candidiasis, which is also rare; and diabetes, pregnancy,

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antibiotic therapy, high humidity, immersion in water and oral contraceptive drugs lead to *localized cutaneous candidiasis*, which *is the commonest type of disease*. These predisposing factors are extremely important in the management of candidiasis patients, since the reversal of these factors is of great significance and part of the treatment protocol.

Clinical Presentation

Oral Candidiasis

This disease is most commonly seen in infants and the elderly (associated with denture plates). The lesions may be situated on the mucosal surfaces of the tongue or at the corner of the mouth. *One or more whitish*, *sharply defined*, *adherent plaques are the characteristic signs of the condition*. If these plaques are wiped off, an underlying erythematous base is seen. Erosions or ulcerations are occasional complications.

In some cases, patients present with erythema, soreness, marked pain, atrophic mucous membranes and lack of whitish plaques (acute atrophic oral candidiasis).

Hyperplastic plaques on the cheek or the tongue that are not easily removed and develop especially in men who are smokers and over the age of 30 constitute a condition known as candida leukoplakia (chronic hyperplastic candidiasis).

Median rhomboid glossitis is another condition associated with candidiasis and presents with erythema of the tongue surface in the absence of papillae, pain and tenderness.

Chronic atrophic candidiasis (denture stomatitis) affects nearly 25 % of all denture wearers and sometimes children with orthodontic appliances. The condition is characterized by bright red of dusky erythema of the palate and gums, with atrophy of the epithelium and sometimes oedema.

Angular cheilitis (perleche) occurs at the corner of the mouth and it is not always associated with *Candida*. The area is moist, red and fissured, and the symptoms include pain.

Superficial Cutaneous Candidiasis (Candidal Intertrigo)

Any occluded skinfold, especially in hot and humid weather, may become moist and macerated, favouring the development of candidiasis. *Erythema and moist exudation deep in the fold are the characteristic symptoms at the beginning*. Erythema with well-defined borders though not razor sharp as in tinea cruris, subcorneal pustule, satellite pustular or papular lesions, itching and soreness make up the typical clinical pictures as the condition progresses.

Candida Balanitis

Although *candida balanitis* (which *is seen mostly in uncircumcised men*) is usually acquired form a sexual partner with vulvovaginitis, the possible oral and anal origins of the disease should not be forgotten. In mild cases, erythema and tiny papules predominate and are seen after intercourse; in more severe cases, the entire glans can be involved, and soreness may prevent sexual intercourse as it becomes painful.

Vaginal Candidiasis

It has been estimated that 75 % of all adult women will suffer from vaginal candidiasis at some time during their lives. There are two types of the disease, the occasional and the recurrent. In the case of occasional vaginal candidiasis, *C. albicans* is the commonest causative yeast, accounting for over 80 % of isolates. The predisposing factors are antibiotics (which alter the normal vaginal flora), peak production of oestrogen before menstruation or use of high-oestrogen contraceptives (increase of glycogen, a nutrient source of *C. albicans*), pregnancy (increased levels of circulating oestrogen and progesterone raise the glycogen content of vaginal epithelial cells), immunosuppressive drugs of disease, increased sugar levels of the urine

and vaginal secretions and synthetic or tight-fitting clothes (they create a warm and moist environment). The condition presents with itching, soreness, erythema and a thick, creamy-white discharge. *Vaginal candidiasis is recurrent in 10–20 % of patients*, and the male partner may play a part in reinfection (50 % of male partners carry the same strain of *Candida* on the penis or in the mouth). Symptoms are the same as in occasional vulvovaginitis, and only in chronic cases does the vaginal mucosa become glazed and atrophic.

Candida Paronychia

This is a chronic condition found *mainly in those who frequently immerse their hands in water* (housewives, chefs, etc.) The nail fold is red and swollen, thick white pus may be discharged and the patient complains of pain. Nail dystrophy, with onycholysis and nail plate discoloration, is also found.

Candida Onychomycosis

C. albicans infection of the nail may be seen *secondary to chronic paronychia or onycholysis*. The nail plate is opaque, brownish-green in colour and altered in shape. There may be nail plate changes secondary to the inflammation of the nail fold.

Chronic Mucocutaneous Candidiasis

This is an immunodeficiency disease, which is characterized by persistent candidiasis of mucous membranes, skin and nails. The infection may vary from mild, localized, persistent lesions to a severe, generalized condition. The disease usually starts in infancy and is often associated with endocrinopathy (mainly Addison's disease and hypoparathyroidism). A few late-onset cases are associated with thymic tumours; candida granulomas may appear on the scalp and face.

Diagnosis

Diagnosis is based on the clinical examination and the history and is usually confirmed by laboratory examination (direct microscopy and culture).

Direct Microscopy

Skin scrapings are examined microscopically for yeasts, pseudohyphae or hyphae, after the addition of 10 % KOH solution to the slide preparation.

Culture

Swabs from suspected areas are cultured on Sabouraud's agar. *C. albicans* is a fast grower; colonies mature in 1–3 days (with the exception of nail-clipping cultures, which must be kept for at least 7 days). Other candida species may require longer time to mature.

Differential Diagnosis

Leukoplakia	Does not clear with prolonged anti-*Candida* therapy
Flexural psoriasis	Histology, microbiology
Bacterial intertrigo	Microbiology
Tinea	Microbiology, sharp edges
Seborrhoeic dermatitis	Microbiology
Hailey-Hailey disease	Histology
Flexural Darier's disease	Histology
Trichomonas vaginitis	Watery brown discharge, microbiology
Contact dermatitis of vagina	Microbiology, history
Herpes simplex of the penis	Anti-HSV antibodies positive (1gM), history
Psoriasis of the penis	Chronic psoriasis plaques in other body areas
Erythroplasia	Chronic, persistent more dusky colour
Napkin dermatitis	The skin deep in the fold is free of symptoms
Bacterial paronychia	Microbiology, acute onset

General Principles of Treatment

- Removal of underlying predisposing factors.
- Denture hygiene and frequent mouth toilet plus abstention form smoking will help those suffering from oral candidiasis.
- Infected skinfolds should be kept dry and if possible separated.
- Patients with chronic paronychia should keep their hands warm and dry.
- In most cases of candida infection, topical treatment alone is sufficient.
- Consideration should always be given to reduction of the *Candida* reservoir in the mouth and gut.

Recommended Therapies

(a) Topical therapeutic agents
(b) Systemic therapeutic agents
(c) Treatment of clinical forms

Antifungal drugs belonging to the polyene and azole families are the ones used in the treatment of *Candida* infections. A morpholine antifungal agent, amorolfine, is also active.

Topical Therapeutic Agents

These drugs are used in the forms of creams, solutions, suspensions, vaginal suppositories, lacquers, shampoos and powders.

The members of the polyene family used are topical amphotericin B, nystatin and natamycin, while the azole family provides the imidazole derivatives miconazole, ketoconazole, econazole, omoconazole, tioconazole and clotrimazole for use in these conditions.

Amorolfine is also used in the form of cream of nail lacquer.

The use of topical preparations is effective in the majority of *Candida* infections, but their use is restricted by the extent of the area involved. Factors that should be considered when choosing topical agents include the lack of side effects of these drugs, when administered topically; the minimal development of resistance, except in the case of nystatin; and their lack of interaction with other classes of drugs.

The topical formulations (except amorolfine nail lacquer) should be used one to three times daily, and their application should continue at least for 1 week after clinical resolution of the disease, to allow reconstitution of the stratum corneum.

The type of formulation selected for treatment depends on the site and the symptoms of the disease (for dry lesions, lotions of creams are preferable, for wet lesions powders, for oral lesions suspensions, for vaginal lesions pessaries and for nail lesions lacquers).

Topical Treatment at a Glance

- The use of topical preparations is effective in the majority of Candida infections, but their use is restricted by the extent of the area involved.
- Use lotions or creams for dry lesions, powders for wet lesions, suspensions for oral lesions, pessaries for vaginal lesions and lacquers for nail lesions.
- The main treatment agents for oral candidiasis are topical nystatin suspension and miconazole oral gel.
- Amorolfine and ciclopirox nail lacquers for 12 months are the main treatment for mild nail candidiasis.

Systemic Antifungal Agents

For systemic candidiasis or extensive skin disease, in immunosuppressed patients and when there are frequent relapses after topical treatment of high patient compliance is needed, the triazoles i*traconazole* and *fluconazole and* the imidazole *ketoconazole are used for systemic treatment*. The major disadvantages of these drugs are the potential toxicity (ketoconazole) and the development of both clinical and microbiologically proved resistance (fluconazole). Another serious disadvantage of these antifungals is their interaction with other drugs.

The chief side effects of ketoconazole are nausea, pruritus, transient elevations in liver enzymes and significant liver toxicity, which can lead to death.

The incidence of adverse events is higher during long-term itraconazole therapy (16.2 %) than during short-term administration (7.0 %). The side effects observed with itraconazole are not severe and mainly take the form of gastrointestinal disturbances (nausea, epigastralgia and diarrhoea).

The most frequent side effects of fluconazole are gastrointestinal symptoms and rash.

Use of the azoles is not recommended in pregnancy. Azole resistance is substantial problem. It is found in AIDS patients, in intensive care units and in leukaemia patients. It is manifested in two ways. The first is replacement of susceptible *Candida* isolates with resistant *Candida* spp., such as *C. glabrata* and *C. krusei*. The second is in situ development of resistance in a certain isolate. The problem of the resistance is focused chiefly on fluconazole, although cross-resistance to the other azoles in common.

Some of the drugs with which ketoconazole interacts are agents decreasing gastric acidity: rifampicin, acyclovir, coumarins, cyclosporin, phenytoin, terfenadine and astemizole. Fluconazole is reported to interact with amphotericin B, coumarins, cyclosporin, phenytoin, oestradiol, cimetidine, astemizole, terfenadine, sulfonyl ureas, thiazides, etc.

Itraconazole interacts mainly with cyclosporin, food, digoxin, phenytoin, rifampicin, H2 antagonists, terfenadine and astemizole.

Systemic Treatment at a Glance

- Itraconazole or fluconazole should be used for systemic candidiasis or extensive skin disease.
- Fluconazole 50–100 mg daily for 1 week, or itraconazole 100 mg daily for 1–3 weeks are effective in persistent oral candidiasis.
- Recurrent vulvovaginitis is treated with a single dose of 150 mg fluconazole, given on day 21 of each menstrual cycle or clotrimazole as a 500 mg vaginal pessary once a week for 6–12 months.

Treatment of Clinical Forms

Oral Candidiasis and Perleche

The main treatment agents are topical nystatin suspension and miconazole oral gel. For more persistent disease, oral antifungals are used: ketoconazole 200 mg daily for 1–2 weeks, fluconazole 50–100 mg daily for 1 week or itraconazole 100 mg daily for 1–3 weeks. Fluconazole is reported to be effective with a single 150 mg dose. Perleche is treated with topical antifungal creams.

Cutaneous Candidiasis

Topical antifungal preparations are used, with excellent results. For widespread disease, oral antifungal drugs are used: itraconazole 200 mg daily for 1 week or fluconazole 50–100 mg for 1–3 weeks. A dose of 150 mg fluconazole once a week for 2 weeks has also proven to be very effective in the treatment of cutaneous candidiasis.

Candida Balanitis

Topical treatment has proven sufficient in treating this condition. Fluconazole in a single 150 mg dose is effective in more resistant cases

Vaginal Candidiasis

Topical treatment generally results in a good mycotic and clinical cure rate. Owing to common relapses and complaints from patients that intravaginal products are messy and often leak, oral treatment is prescribed. Cases of occasional vulvovaginitis are treated with fluconazole orally in a single dose of 150 mg, ketoconazole 200 mg daily for 5 days or itraconazole 400 mg in a single dose. Recurrent vulvovaginitis is treated with a single dose of 150 mg fluconazole, given on day 21 of each menstrual cycle for 6–12 months. Clotrimazole as a 500 mg vaginal pessary once a week has proven efficient in suppressing relapses of recurrent vaginitis.

Candida Paronychia

This condition requires prolonged topical treatment. The hands should be kept warm and dry.

Candida Onychomycosis

Topical treatment with the ordinary polyene or azole antifungal drugs *is not effective*, as these drugs are not absorbed from the nail plate. For mild candida onychomycosis of the hands involving not more than 60 % of the entire nail plate, amorolfine nail lacquer is used once a week

for 6 months. For more severe onychomycosis of the hands, itraconazole is used in a pulsed regimen of 400 mg daily for 1 week. This scheme is repeated for 3 months.

For mild onychomycosis of the feet, amorolfine nail lacquer is used once weekly for 12 months and for more severe cases itraconazole pulse therapy with 400 mg daily for 1 week. This scheme is repeated for 4 months.

Fluconazole is used in a dose of 150 mg weekly for 6 months for hand onychomycosis and for up to 9 months for foot onychomycosis.

Chronic Mucocutaneous Candidiasis

A combination of antifungal drugs and immunological reconstruction is needed in the treatment strategy for this condition. A restoration of T-cell function is attempted by using transfer factor of thymosin or by grafting compatible lymphocytes from blood or marrow or foetal thymic tissue.

The antifungal drugs most commonly used are ketoconazole, fluconazole and itraconazole, which are used for some years. The main problems encountered with the use of these drugs are the growing problems of infection with *Candida* that has become resistant and hepatotoxicity with long-term use of ketoconazole.

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