Introduction to the second edition

The material has been revised extensively but our goal has been the same – to present, in a concise manner, the most important clinical, diagnostic and therapeutic aspects of fungal disease. In each chapter the clinical manifestations and management sections have been updated, and where appropriate, new emerging pathogens have been included. New sections include the molecular diagnosis of fungal infections and mycological aspects of the indoor environment. Medical mycology lends itself to illustration and we have included additional illustrative material in this edition. Throughout we have attempted to illustrates salient features of infection and to give an idea of the range of causative organisms including some illustrative photographs of macroscopic and microscopic morphology. Recent references have been added and the list of online resources has been updated. We have made every effort to ensure that our drug and dosage recommendations are accurate and in agreement with current guidelines. It should be noted that the formulations and usages of the different drugs described do not necessarily have the specific approval of the regulatory authorities of all countries. Because dosage regimens can be modified in the light of new clinical research findings, readers are advised to check the manufacturers' prescribing information to see whether changes have been made in the recommended dosages, or whether additional contraindications for use have been introduced.

Introduction to the first edition

The main aim of this Pocket Guide is to summarize the major features of fungal infections of humans and to provide visual information for each pathogen and the infections they cause in a convenient and practical format.

In this guide we have provided a succinct account of the clinical manifestations, laboratory diagnosis and management of fungal infections found in Europe, American and Australasian practice. The guide covers problems encountered both in hospitals and general practice and is designed to facilitate rapid information retrieval with representative colour illustrations.

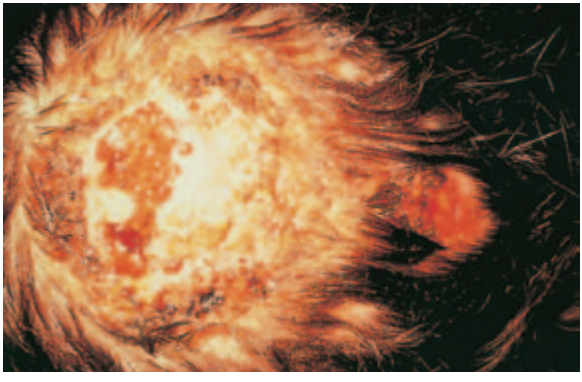
Our reading list of established literature has been carefully selected to permit efficient access to specific aspects of fungal infection. The list of World Wide Web sites allows access to an even greater wealth of information and illustrative material.

Acknowledgements

Again, we would like to thank David W. Warnock and Colin K. Campbell for kindly agreeing that the slides from the *Slide Atlas of Fungal Infection* could be used in this publication. Many of the illustrations were originally derived from collections of slides held at the Mycology Reference Laboratories in Bristol and Glasgow and we wish to thank friends and colleagues for their generosity in making this resource available to us. We also gratefully acknowledge additional sources of illustrations: firstly, the *Medical Mycology Atlas*, compiled by Stefano Andreoni, Claudio Farina and Gianlugi Lombardi, with kind permission of Gilead Sciences; secondly, Kaminski's Digital Image Library of Medical Mycology, with kind permission of David Ellis and Rolan Hermanis, Women's and Children's Hospital, North Adelaide, South Australia; and last but not least, pictures made available by colleagues in Finland, the UK, and from around the world. Many thanks for these.

Tinea capitis

Tinea capitis due to *Trichophyton tonsurans*.



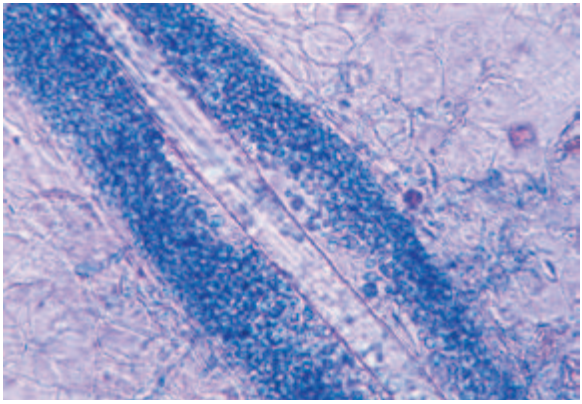
Kerion due to *Trichophyton verrucosum*.

Definition

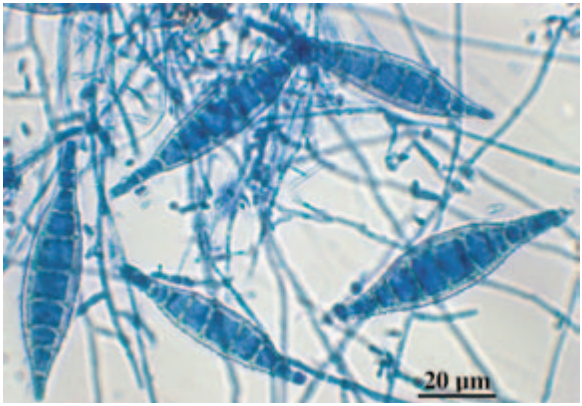
Tinea capitis describes infection of the scalp and hair with a dermatophyte.

Geographical distribution

World-wide, but more common in Africa, Asia and southern and eastern Europe, occurring mainly in prepubescent children. Increasing incidence.



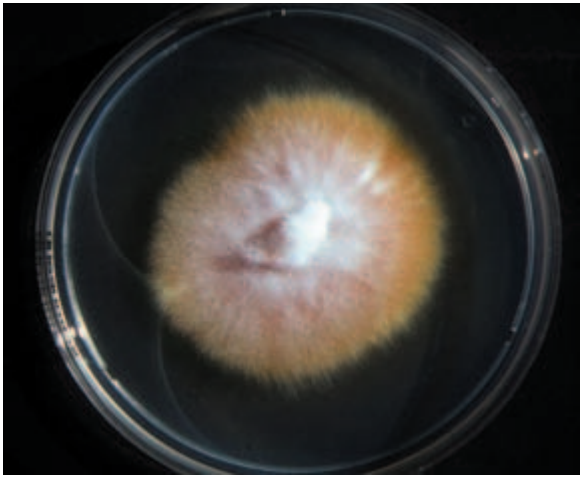
Hair infected by *Microsporum gyseum* showing large-spored ectothrix invasion.



Macroconidia of *Microsporum canis*.

Causal organisms and habitat

- Several *Trichophyton* spp. and *Microsporum* spp.
- Zoophilic *M. canis* (cats and dogs) is common in western Europe.
- Anthropophilic *T. violaceum* is predominant in eastern and southern Europe and north Africa.
- Anthropophilic *T. tonsurans* is increasing in prevalence, especially in North America.



Microsporum canis in culture.

- Anthropophilic species can be contagious and endemic.
- *T. schoenleinii* causes favus.

Clinical manifestations

- Mild scaling lesions to widespread alopecia.
- Kerion: highly inflammatory, suppurating lesion caused by zoophilic dermatophytes.
- Black dot appearance seen with ectothrix hair invasion.
- Favus is a distinctive infection with grey, crusting lesions.
- Asymptomatic carrier state recognized, may promote spread of infection.
  - *T. tonsurans* and *T. violaceum* – most commonly implicated in the carrier state.
  - Minimal inflammatory response.
  - Low spore numbers.
  - Topical treatment appears to help prevent spread of infection.
  - Fomites also implicated in spread.

Essential investigations

Microscopy

Direct microscopic examination of hair roots and skin softened

with KOH reveals hyphae, arthrospores and distinctive patterns of hair invasion: ectothrix – large or small arthrospores form a sheath around the hair shaft; endothrix – large or small arthrospores form within the hair shaft; ectoendothrix – spores form around and within the hair shaft; and favus – hyphae and air spaces form within the hairs.

Fluorescence under Wood's light may reveal hairs infected with *Microsporum* spp; not effective for revealing *T. tonsurans*.

Culture

Culture at 28°C for at least 1 week is essential to identify the organism.

Management

Mycological confirmation is essential before commencing oral treatment. Treat with these alternatives:

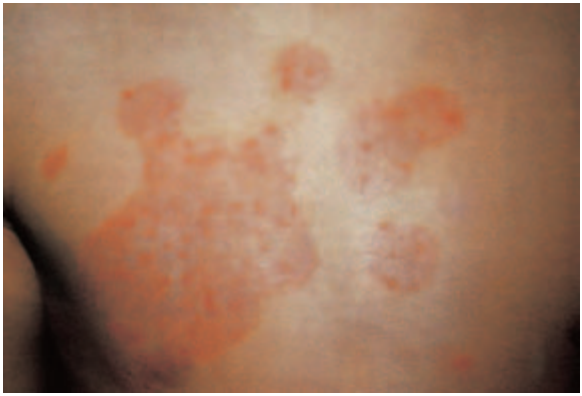
- griseofulvin 10 mg/kg for up to 3 months, absorption and bioavailability vary with dietary fat intake, rapidly eliminated from body when discontinued; some side effects
- itraconazole 100 mg/day for 4–6 weeks in adults, depending on causative species; note potential drug interactions
- itraconazole pulse therapy for children, oral solution, 5 mg/kg/day for 1 week per month for 3–4 months
- terbinafine 250 mg/day for 4–6 weeks, higher dose and longer duration if *Microsporum canis* is present; only mild and transient side effects
- fluconazole, oral suspension, daily or weekly regimens, good absorption, optimum dose to be determined.

Topical treatment of lesions with an azole, such as 2% ketoconazole shampoo, or 1% selenium sulphide shampoo, may reduce spread.

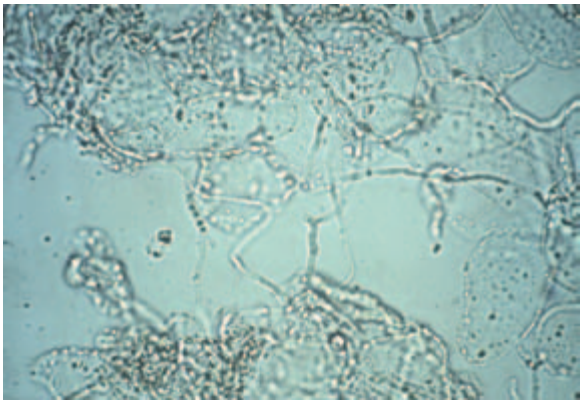
Recent studies suggest that a child does not need to be kept from school during treatment.

Regular epidemiological surveillance of causative fungal organisms in the community and their antifungal susceptibility is an essential component in management of tinea capitis.

Tinea corporis



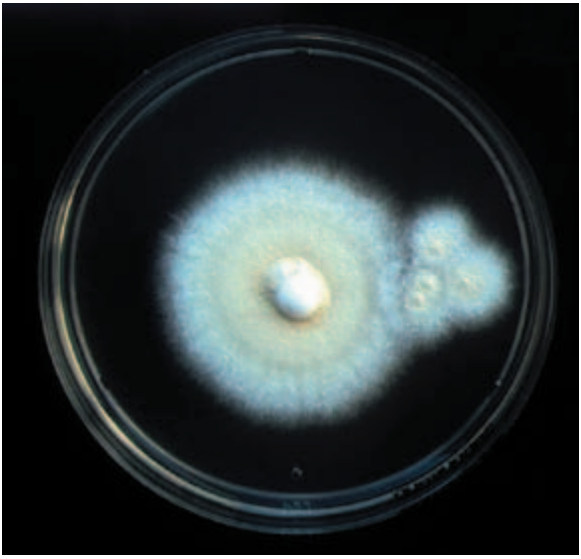
Tinea corporis due to *Trichophyton mentagrophytes*.



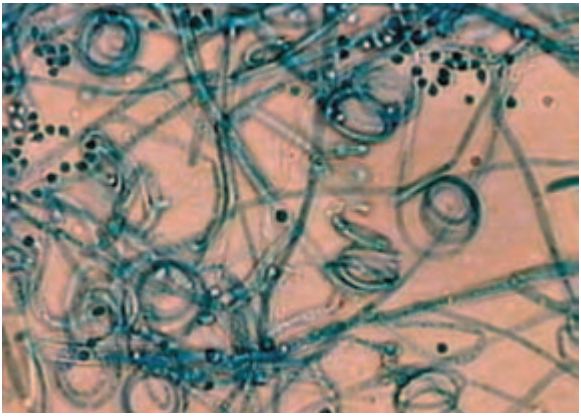
Infected skin scrapings softened in KOH.

Definition

Infection of the skin of the trunk, legs and arms with a dermatophyte.



Culture of *Trichophyton mentagrophytes*.



Microscopic morphology of *Trichophyton mentagrophytes* showing spiral hyphae.

Geographical distribution

World-wide, but more prevalent in tropical and subtropical regions.

Causal organisms and habitat

- Many *Trichophyton* spp., *Microsporum* spp. and *Epidermophyton floccosum*.
- Often zoophilic, occasionally geophilic organisms.
- Infection frequently contracted from a household pet.
- May follow infection of another body site.
- Person to person transmission may occur in contact sports.
- *M. canis* from cats and dogs most frequent.
- *T. verrucosum* from cattle in rural areas.

Clinical manifestations

- Usually affects exposed body sites.
- Exact nature depends on infecting organism; infections due to zoophilic species are often more inflammatory and may be pustular.
- Typically, there are itching, dry, circular, scaling lesions.
- Fungus more active at margin therefore more erythematous.

Essential investigations

Microscopy

Skin scrapings should be collected from the raised border. Direct microscopy of skin scrapings softened with KOH reveals branching hyphae with or without arthrospores. The use of an optical brightner such as Calcofluor white which is viewed under a fluorescence microscope enhances the microscopic detection of fungal elements.

Adhesive tape strippings may be used if little material can be scraped.

Culture

Isolation of the dermatophyte at 28°C allows identification.

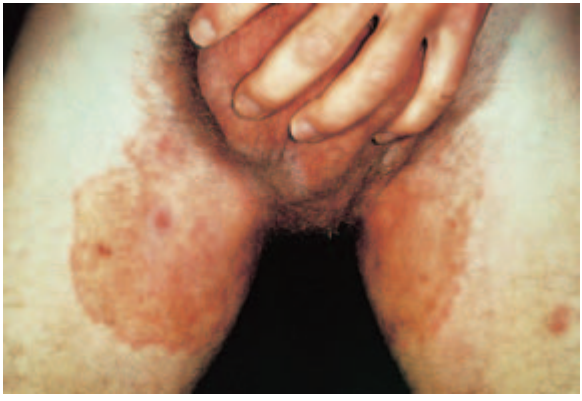
Management

This condition seldom resolves if untreated. However, it often responds to topical treatment with an azole (clotrimazole, econazole, miconazole, sulconazole), naftifine or terbinafine morning and evening for 2–4 weeks.

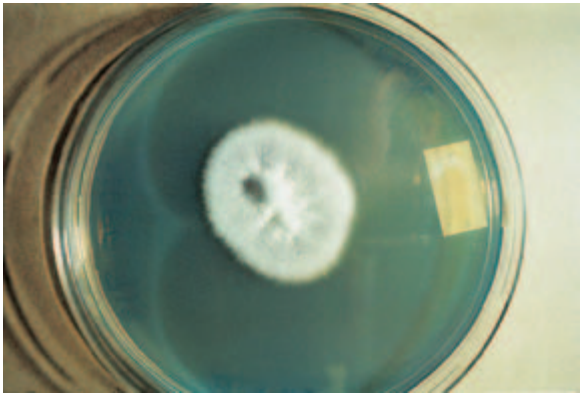
Oral therapy is indicated if the lesions are extensive or refractory. Treat with these alternatives:

- itraconazole 200 mg/day for 1 week
- terbinafine 250 mg/day for 2–4 weeks
- griseofulvin 10 mg/kg for 4 weeks.

Tinea cruris



Tinea cruris due to *Trichophyton rubrum*.



Colonial appearance of *Trichophyton rubrum*.

Definition

Infection of the skin of the groin and pubic region with a dermatophyte.

Microscopic morphology of *Epidermophyton floccosum*.

Geographical distribution

World-wide.

Causal organisms and habitat

- Anthropophilic dermatophytes *Epidermophyton floccosum* and *Trichophyton rubrum* are most common.
- Maceration and occlusion of groin skin gives rise to infection.
- Often transferred from another infected body site.
- Highly contagious via contaminated towels, floors, etc.

Clinical manifestations

- One or more rapidly spreading erythematous lesions with central clearing on the inside of the thighs, intense pruritis.
- Lesions with raised erythematous border and brown scaling.
- Infection may extend locally and spread to other body sites.

Essential investigations

Microscopy

Direct microscopy of skin scrapings softened with KOH reveals branching hyphae with or without arthrospores.

Culture

Isolation of the dermatophyte at 28°C allows identification.

Management

This condition seldom resolves if untreated. However, it often responds to topical treatment with an azole (clotrimazole, econazole, miconazole, sulconazole), naftifine or terbinafine morning and evening for 2–4 weeks.

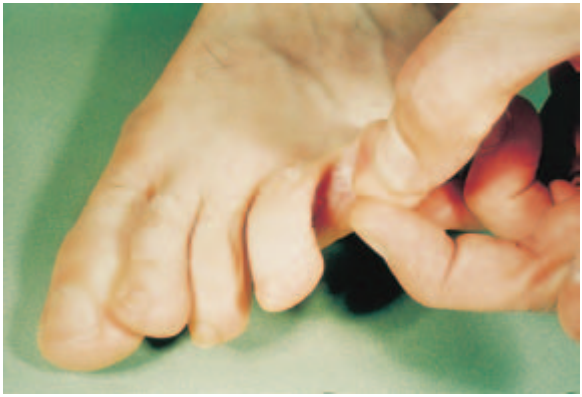
Oral therapy, if indicated, includes these alternatives:

- itraconazole 200 mg/day for 1 week
- terbinafine 250 mg/day for 2–4 weeks
- griseofulvin 10 mg/kg for 4 weeks.

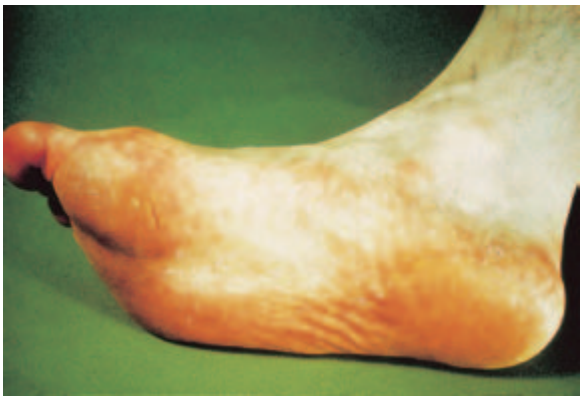
Hygiene measures such as thorough drying and using separate towels for the groin area should prevent spread.

There is a recurrence in 20–25% of patients.

Tinea pedis



Interdigital tinea pedis due to *Trichophyton rubrum*.



Moccasin form of tinea pedis.

Definition

Dermatophyte infection of the feet.

Geographical distribution

World-wide, but more common in countries where there is ready access to communal sports or bathing facilities.

Causal organisms and habitat

- *Trichophyton rubrum* is the most common cause.
- *Epidermophyton floccosum* and *T. mentagrophytes* var. *interdigitale* are also seen.
- Common condition often contracted by walking barefoot on contaminated floors.
- Extensive sweating and occlusive footwear predispose to the condition.
- Infection with the moulds *Scytalidium dimidiatum* (*Hendersonula toruloidea*) and *S. hyalinum* is clinically indistinguishable.

Clinical manifestations

Three types are recognized:
- acute or chronic interdigital infection: itching, peeling, maceration and fissuring of toe webs
- chronic hyperkeratotic (moccasin or dry type): fine, white scaling limited to heels, soles and lateral borders of feet
- vesicular (inflammatory) infection: vesicle formation on soles, instep and interdigital cleft.

Secondary bacterial or yeast infection is also possible.

Essential investigations

Microscopy

Direct microscopy of skin scrapings softened with KOH reveals branching hyphae with or without arthrospores.

Culture

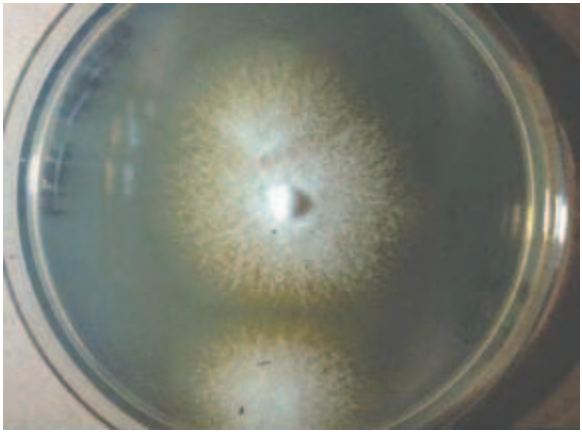
Isolation of the dermatophyte at 28°C allows identification.

Management

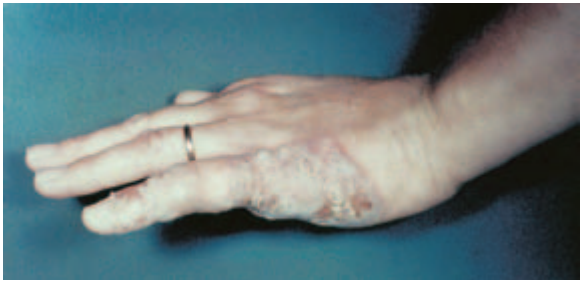
This condition seldom resolves if untreated. However, it often responds to topical treatment with an azole (clotrimazole, econazole, miconazole, sulconazole), naftifine or terbinafine morning and evening for 2–4 weeks.

Oral therapy, if indicated, includes these alternatives:
- itraconazole 200–400 mg/day for 1 week
- terbinafine 250 mg/day for 2–6 weeks.

Tinea manuum



Colony of *Trichophyton erinacei* showing white granular surface and bright yellow pigment diffusing into the agar.



Tinea manuum due to *Trichophyton erinacei*.

Definition

Fungal infection of the hand, or hands.

Geographical distribution

World-wide.

Causal organisms and habitat

- Most common anthropophilic dermatophytes are *Trichophyton mentagrophytes* var. *interdigitale*, *T. rubrum* and *Epidermophyton floccosum*.
- Most common zoophilic dermatophytes are *Microsporum canis* (cats and dogs), *T. verrucosum* (cattle), *T. mentagrophytes* var. *mentagrophytes* (rodents) and *T. erinacae* (hedgehogs).
- Occasional infections due to geophilic *M. gypseum* and *M. fulvum*.
- Acquisition by contact with infected person, animal, soil or fomites, or by autoinoculation from another infected body site.
- Profuse sweating and eczema predispose to infection.

Clinical manifestations

- Usually unilateral, predominantly affecting right hand.
- Two forms: dyshidrotic (eczematoid) and hyperkeratotic:
  - dyshidrotic: annular or segmental vesicles with scaling borders containing clear, viscous fluid on palms, palmar aspect of fingers and sides of the hand, characterized by intense pruritis and burning
  - hyperkeratotic: adjacent vesicles desquamate to form an erythematous, scaling lesion with a circular or irregular thick, white, squamous margin with extensions towards the centre. Chronic cases may cover the entire palm and fingers with fissuring in the palmar creases.

Essential investigations

Microscopy

Direct microscopic examination of vesicle tops and skin scales.

Culture

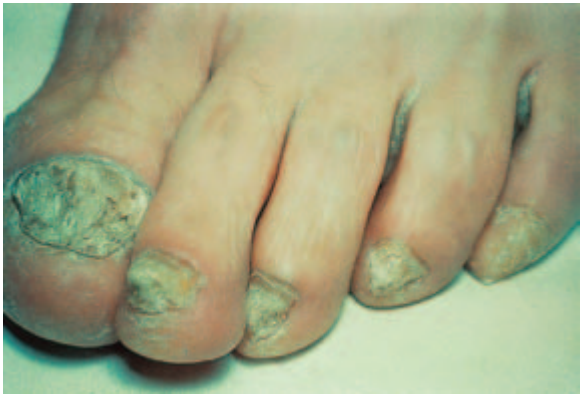
Isolation in culture at 28°C for at least 1 week will permit species identification.

Management

Topical treatment with imidazole or allylamine is often effective:

- itraconazole 200–400 mg/day for 1 week
- oral terbinafine 250 mg/day for 2–6 weeks.

Tinea unguium

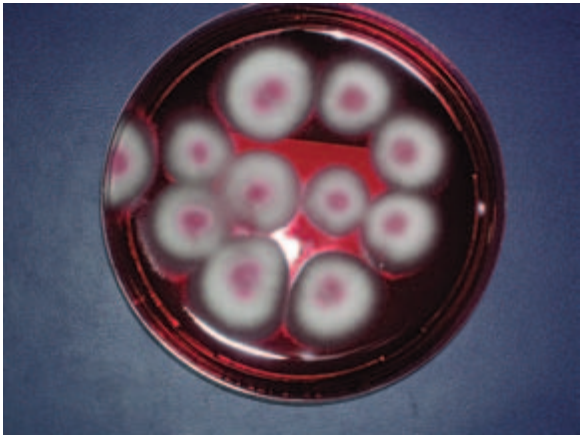


Tinea unguium due to *Trichophyton rubrum*.

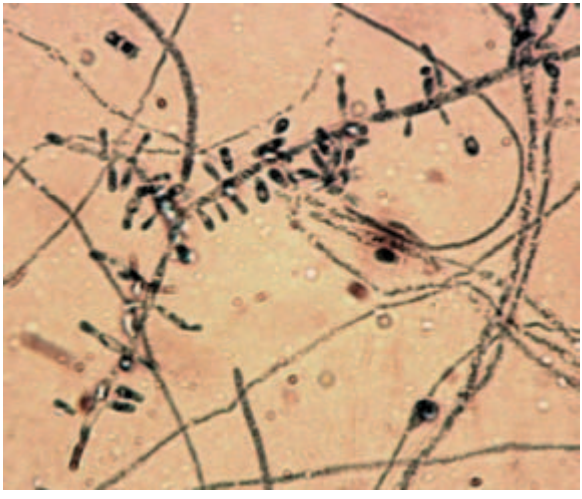
Superficial white onchomycosis.

Definition

Dermatophyte infection of the fingernails or toenails. Onychomycosis is also used to describe the condition but has a broader definition encompassing nail infections with yeasts and non-dermatophyte moulds in addition to dermatophytes.



Culture of *Trichophyton rubrum* on dermatophyte test medium.



Microscopic morphology of *Trichophyton rubrum*.

Geographical distribution

World-wide.

Causal organisms and habitat

- Most commonly caused by anthropophilic species *Trichophyton mentagrophytes* var. *interdigitale* and *T. rubrum*.
- May be rare infections of fingernails with zoophilic species.
- Affects up to 8% of adult population.

Clinical manifestations

- Toenails more often infected than fingernails.
- Infection often follows infection of another body site.
- First and fifth toenails most commonly infected, probably due to traumatic damage by ill-fitting footwear.
- White or yellow irregular lesion appears first at free end of nail and spreads slowly to cause entire nail to become thickened, opaque and yellow in colour, and it may crumble.
- Superficial white onychomycosis is seen predominantly in patients with AIDS where crumbling white lesions, most often due to *T. mentagrophytes* var. *interdigitale*, appear on the nail surface.

Essential investigations

Microscopy

Microscopy of material from KOH softened nails is essential.

Culture

Culture at 28°C will allow identification of the infecting species.

Culture of material on plates with and without cycloheximide will allow differentiation of dermatophyte and non-dermatophyte mould infections.

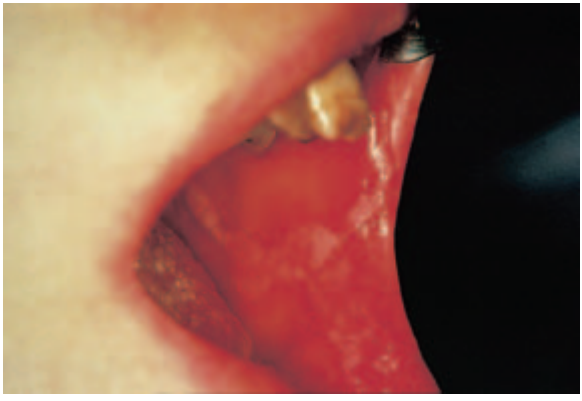
Subungual material may be most productive and a nail drill or scalpel may be used.

Management

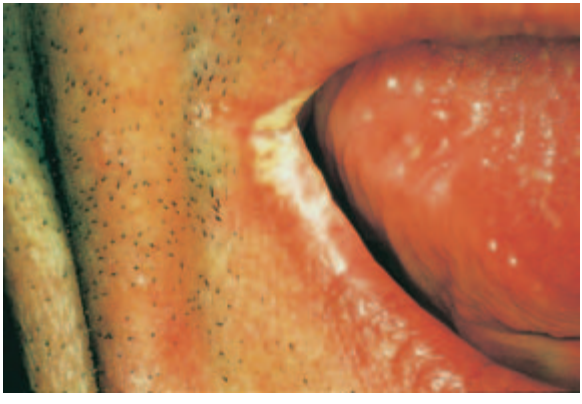
This condition is difficult to treat, requiring prolonged courses. Topical treatment may be effective for superficial white onychomycosis or where there is very limited distal nail involvement otherwise an oral therapy is indicated.

- Topical: amorolfine at weekly intervals or tioconazole twice daily for 6 months for fingernails and 9–12 months for toenails.
- Oral: itraconazole 2 or 3 pulse treatment 400 mg/day for 1 week in 4, or continuous 200 mg/day for 3 months.
- Oral griseofulvin for 4–8 months, but low success rate in toenail infections.
- Oral terbinafine 250 mg/day for 6–12 weeks for fingernails, 12 weeks or longer for toenails.
- Oral fluconazole 150–450 mg once weekly for 6–9 months in toenail infections, 3 months for fingernails.

Oral candidosis



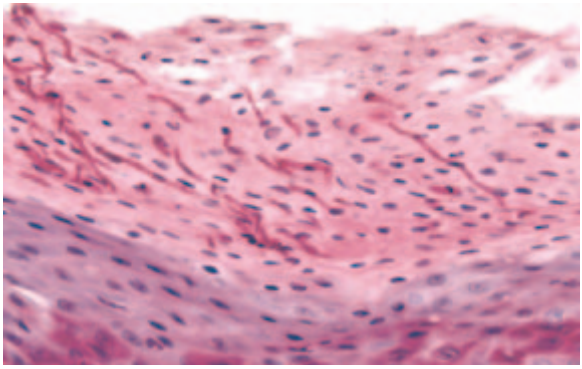
Pseudomembranous oral candidosis.



Angular chelitis.

Definition

Oral candidosis is an opportunistic infection of the oral cavity with yeasts of the genus *Candida*. It can be classified into a number of distinct clinical forms.



Histopathological appearance of oral candidosis.

Geographical distribution

World-wide.

Causal organisms and habitat

- *Candida albicans* is most frequent cause (60–80% cases).
- At least eight other pathogenic species.
- Opportunistic infection, often endogenous in origin.
- Infection follows humoral or cell-mediated immunological impairment, debilitation or occlusion of oral surfaces.

Clinical manifestations

- Acute pseudomembranous candidosis (thrush): white raised lesions on buccal mucosa, gums or tongue (infants, the elderly, HIV-infected, diabetics, cancer patients and steroid users).
- Erythematous candidosis: erythema, oedema
  - acute atrophic candidosis: antibiotic stomatitis
  - chronic atrophic candidosis: denture stomatitis and glossitis.
- Chronic hyperplastic candidosis (oral leukoplakia): possibly premalignant, translucent or dense, opaque white plaques on cheeks, commissures and tongue. Often associated with smoking and systemic cofactors such as vitamin deficiency and generalized immune deficiency. Lesions are symptomless.

- Angular cheilitis: soreness, erythema and fissuring at corners of mouth often associated with ill-fitting dentures; has been reported in up to 20% of HIV-infected persons.
- Chronic mucocutaneous candidosis: oral manifestation of candidosis in patients with congenital immunological or endocrinological disorders (see p. 34).

Essential investigations

Microscopy and culture

Microscopy of oral smear reveals filaments and/or yeasts. Culture at 37°C yields the organism in 24–48 hours. All yeasts should be identified to species level, and antifungal susceptibility tests performed if appropriate.

Management

Treat uncomplicated oral candidosis with topical nystatin, amphotericin B or azole for 2 weeks and scrupulous oral hygiene measures.

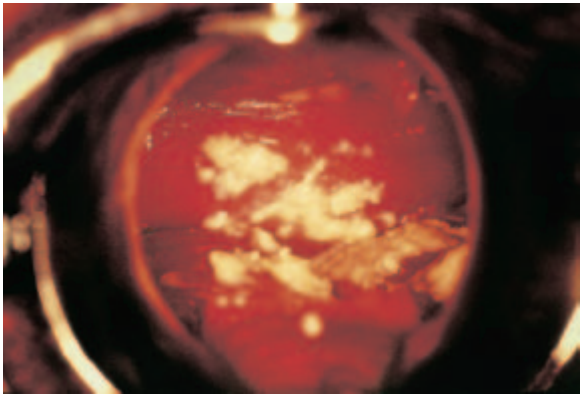
- Dental hygiene.
- Brushing.
- Diet: carbohydrate reduction.
- Trauma: denture replacement.

Treat immunocompromised patients with these alternatives:

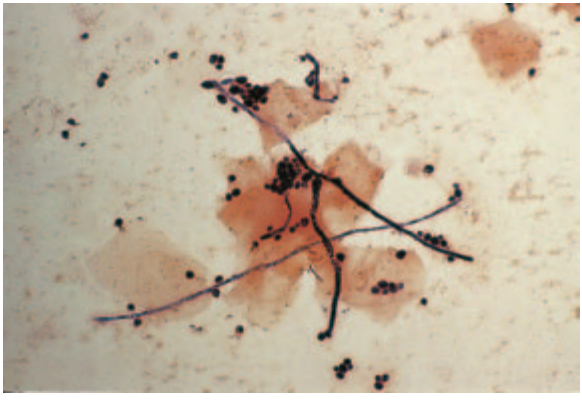
- fluconazole 100–200 mg/day for 2 weeks or 400–800 mg/day for recalcitrant infections
- itraconazole 200–400 mg/day for 1–2 weeks
- parenteral amphotericin B 0.5–0.7 mg/kg/day for 1 week.

In immunocompromised patients, primary or secondary prophylaxis with fluconazole or itraconazole may be appropriate, in particular in patients with acute leukaemia, bone marrow transplant recipients and AIDS patients.

Vaginal candidosis



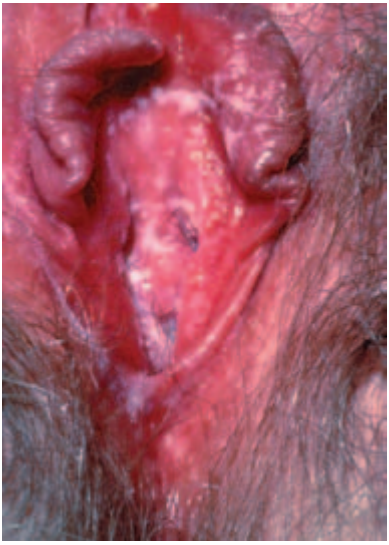
White plaques on vaginal membrane.



Gram stained *Candida albicans* in a vaginal smear.

Definition

Infection of the vagina and/or vulva with species belonging to the genus *Candida*. Often referred to as vaginal 'thrush'.



Vaginal candidosis caused by *Candida albicans*.

Geographical distribution

World-wide.

Causal organisms and habitat

- *Candida albicans* accounts for more than 80% of infections.
- Infections with *C. glabrata* are often refractory to treatment.
- *Candida* spp. can be present in the absence of disease.
- Pregnancy may precipitate chronic or recurrent infections.
- More common amongst women with diabetes mellitus.
- Antibiotic treatment predisposes to yeast overgrowth.
- Treatment of male partner does not seem to prevent recurrence.

Clinical manifestations

- Intense vulval and vaginal pruritis and burning with thick, white, curdy vaginal discharge and adherent white plaques on vulval, vaginal or cervical epithelium.

- Dysuria and dyspareunia are common.
- Perianal intertrigo with pustular or vesicular lesions may occur.
- Tends to occur in the week prior to menstruation.

Essential investigations

Microscopy

Microscopy of a high vaginal swab reveals yeasts with or without filaments in 40% of cases. Calcofluor white staining increases sensitivity.

Culture

Culture at 37°C yields yeast colonies in 90% of cases. All yeasts should be identified to species level. Susceptibility testing is appropriate in cases of recurrent or recalcitrant infection.

Management

Acute vaginal candidosis

- Treat with topical nystatin tablets for 14 nights.

Alternatively, treat with a topical azole such as clotrimazole, miconazole, econazole, ketoconazole creams and pessaries for 6 nights.

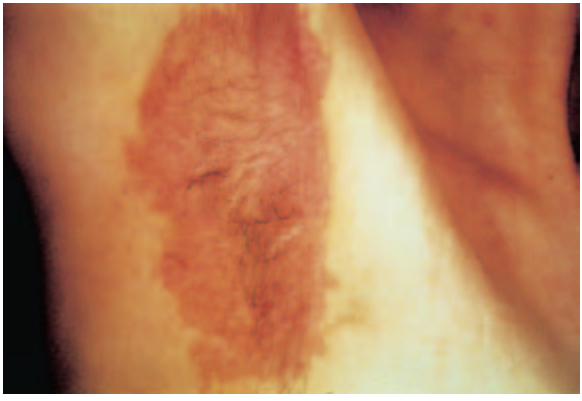
Oral treatments include:

- fluconazole, single dose 150 mg
- itraconazole, two doses 200 mg 8 hours apart.

Recurrent vaginal candidosis

- Intermittent prophylaxis recommended.
- Topical clotrimazole 500 mg as single dose at 2- or 4-week intervals.
- Oral fluconazole 150 mg at 1-week intervals.
- Following 3–6 months treatment, discontinue and reassess.

Cutaneous candidosis

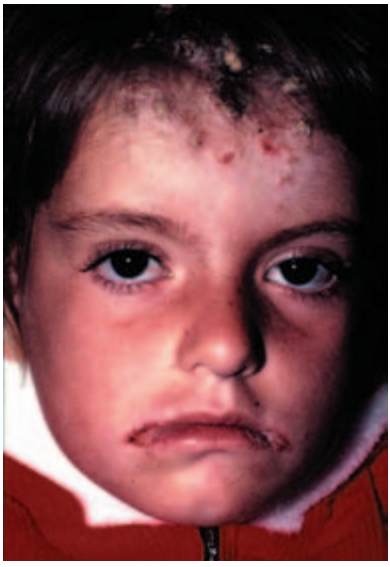


Candida albicans infection of axilla.

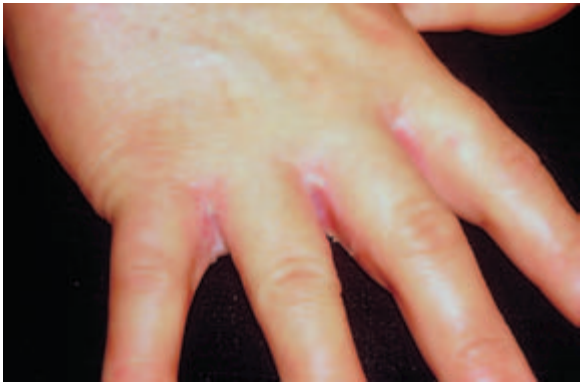
Chronic mucocutaneous candidosis.

Definition

Cutaneous candidosis is a yeast infection of the skin caused by members of the genus *Candida*. Infection of the proximal nail fold known as *Candida* paronychia may lead to nail infection.



Candida granuloma of the forehead and angular cheilitis associated with chronic mucocutaneous candidosis due to congenital defects in cell-mediated immunity.



Interdigital candidosis caused by *Candida albicans*.

Geographical distribution

World-wide.

Causal organisms and habitat

- Most commonly caused by *Candida albicans* then *C. tropicalis*; other species are occasionally implicated.
- Normal flora of the skin, mouth, intestinal tract and vagina.
- Disruption of the epidermal barrier function can lead to overgrowth and infection.

Clinical manifestations

- Affects intertriginous areas, e.g. the groin, axillae and submammary folds.
- Erythematous, inflamed and painful skin.
- Predisposing factors include: corticosteroid, hormonal or antibiotic therapy, diabetes mellitus, obesity, maceration, friction, occlusion, immunosuppression, dermatitis, pregnancy, infancy or old age.
- *Candida* folliculitis may occur in occluded areas.
- *Candida* paronychia, infection of the proximal nail fold or cuticle, characterized by erythema, oedema and purulent discharge, may lead to nail infection.
- Chronic mucocutaneous candidosis (CMC) is a severe, often widespread, erythematous or granulomatous infection of the mucous membranes, skin and nails seen in patients with congenital defects in their cell mediated immunity.

Classification

Group 1

Familial CMC: autosomal recessive inheritance. *Candida* lesions are usually oral, although other sites may be involved. Associated with iron deficiency, since iron supplementation may enhance response to antifungal therapy.

Group 2

Diffuse CMC: sporadic disorder. Severe and extensive lesions of oral cavity and skin, especially scalp, face, neck and upper chest. Prone to other opportunistic infections.

Group 3

Candidosis–endocrinopathy syndrome: typical presentation is mild but persistent oral candidosis. Associated with hypoparathyroidism, hypoadrenocorticism, hypothyroidism, diabetes or other endocrinopathies.

Group 4

Late onset CMC: commonly found in males. Usually severe, affecting both oral and other sites on the body.

Essential investigations

Microscopy and culture

Microscopy of skin scrapings or swabs revealing yeasts with or without filaments is crucial in confirming infective status. Culture at 37°C yields yeast colonies after 24–48 hours.

Management

Oral agents are indicated for folliculitis, nail involvement, extensive lesions and in the immunocompromised:

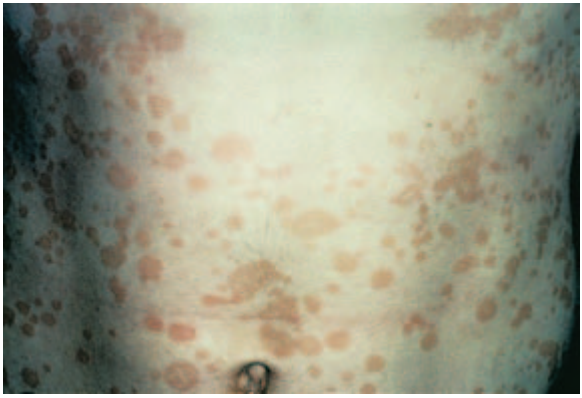
- itraconazole 200 mg/day or fluconazole 100 mg/day.

Control or eradication of the predisposing factor.

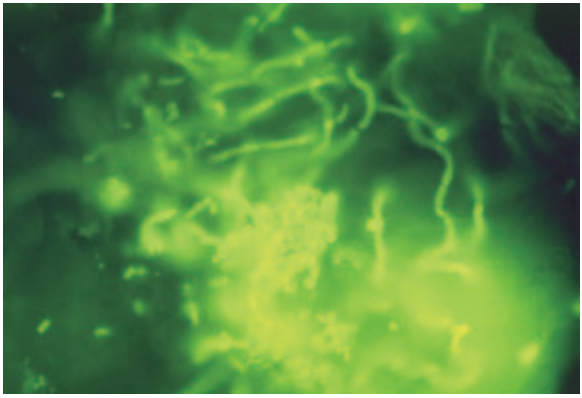
Topical therapy with azole agents, nystatin and naftifine, should be used twice daily until 1–2 weeks after clearing.

Additional steroid or antibacterial therapy may be indicated.

Malassezia infections



Pityriasis versicolor.

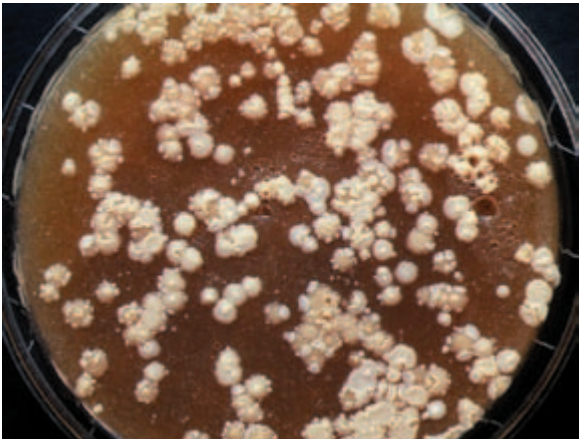


Microscopic appearance of *Malassezia furfur* in skin with calcofluor staining.

PITYRIASIS VERSICOLOR

Definition

Common, mild, often recurrent infection of the stratum corneum due to *Malassezia* yeasts.



Culture of *Malassezia furfur* on a lipid rich medium.

Geographical distribution

World-wide, but it is more prevalent in tropical and subtropical regions.

In temperate climates, it is most common during the summer months.

Causal organisms and habitat

- Caused by *Malassezia* spp.:
  - *M. furfur* (previously called *Pityrosporum ovale* or *P. orbiculare*)
  - *M. globosa* (main species associated with pityriasis versicolor)
  - *M. obtuse*
  - *M. restricta*
  - *M. slooffiae*
  - *M. sypodialis* (second most common species associated with pityriasis versicolor)
  - *M. dermatis* (specifically associated with atopic dermatitis).
- Budding yeast cells and numerous filaments.
- Normal skin of head and trunk.
- Sebaceous areas.
- Most common in adults 20–40 years of age.

- Occurs more frequently in tropical climates, and the summer months.
- Human to human transmission possible.

Clinical manifestations

- Patches of fine, brown scaling on upper trunk, neck, upper arms and abdomen.
- Light-skinned patients: lesions initially pink then pale brown.
- Dark-skinned patients: skin loses colour, becomes depigmented.
- Most cases produce pale yellow fluorescence under Wood's light.

Essential investigations

Microscopy

Microscopy reveals oval, budding yeasts and short filaments.

Culture

A lipid supplement is required. When cultured at 32–34°C, small, yellow-cream colonies develop within 1 week.

Management

Good response to topical treatment with selenium sulphide (2%) shampoo, or ketoconazole shampoo or terbinafine.

Variable response to oral treatment with:

- ketoconazole 200 mg/day for 1 week
- ketoconazole 400 mg, once per week for 2 weeks
- ketoconazole 400 mg, 3 doses 12 hours apart
- itraconazole 200 mg/day for 1 week, also as prophylaxis 200 mg b.i.d., one day per month
- fluconazole 300 mg, once per week for 2 weeks
- fluconazole 300 mg, single dose repeated 2 weeks later
- fluconazole 150 mg, once per week for 4 weeks.

MALASSEZIA (*PITYROSPORUM*) FOLLICULITIS

Clinical manifestations

There are three main forms:

- Folliculitis on back or upper chest of young adults: scattered, itching follicular papules or pustules. These often appear after sun exposure.
- Associated with seborrhoeic dermatitis: numerous small follicular papules appear over upper and lower chest and back. There may be a florid rash, particularly marked on the back.
- In AIDS: multiple pustules on trunk and face, associated with severe seborrhoeic dermatitis.

Management

For extensive or recalcitrant lesions treat with:

- oral ketoconazole 200 mg/day for 1–2 weeks or oral itraconazole.

Otherwise,

- topical imidazoles or
- selenium sulphide.

SEBORRHOEIC DERMATITIS

Causal organisms and habitat

- Occurs most commonly on lipid-rich areas of skin.
- Strong association with large numbers of *Malassezia* yeasts, although role is controversial.
- Affects 2–5% of population.
- More frequent in men than in women.
- Occurs most frequently in winter.

Clinical manifestations

- Dandruff: affects 5–10% of population; considered to be initial form of seborrhoeic dermatitis.
- Erythematous rash with scaling on scalp, face, ears, chest and upper part of back:

- scaling of eyelid margins and around nasal folds, greasy appearance
- in AIDS, onset is early sign of CD4 suppression
- mycological investigation not required.

- Occurs in some patients with neurological disorders, e.g. Parkinson's disease.

Management

Topical agents:

- Zinc pyrithione.
- Mild corticosteroid cream.
- Azoles.
  - Ketoconazole shampoo is very effective in seborrhoeic dermatitis and dandruff. It should be applied twice per week for 2–4 weeks, then used at 1- or 2-week intervals to prevent recurrence.
  - Bifonazole.
  - Miconazole.
  - Combining an azole with hydrocortisone is effective.
- Allylamines: terbinafine.
- Benzylamines: butenafine.
- Hydroxypyridones: ciclopirox.
- Non-corticosteroid immunomodulators: tacrolimus.

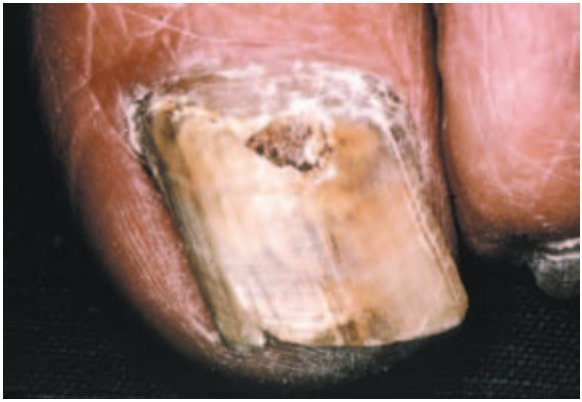
Oral antifungals:

- Ketoconazole.
- Itraconazole.
- Terbinafine.

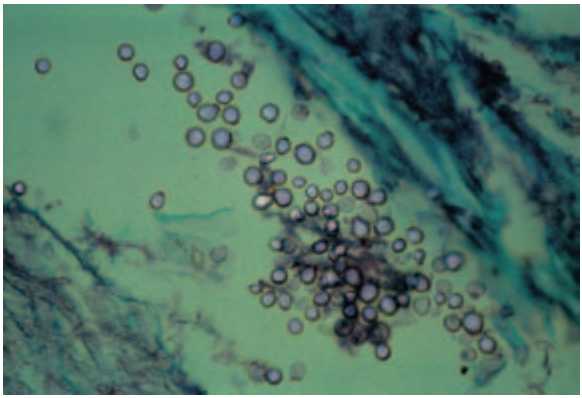
Short-term therapy: limited value.

Oral prophylaxis: itraconazole – 200 mg/day for the first 2 days of each month; very little relapse after 9 months.

Mould infections of nails



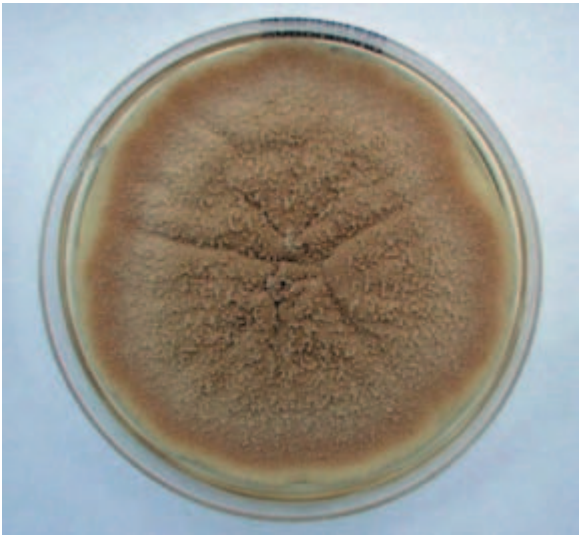
Nail showing onychomycosis due to *Scopulariopsis brevicaulis*.



KOH preparation of a nail infected with *Scopulariopsis brevicaulis*.

Definition

The term onychomycosis is used to describe infection of the nails with fungi. In addition to the dermatophytes and *Candida* spp. there are a group of filamentous moulds that can invade nail tissue.



Culture of *Scopulariopsis brevicaulis*.

Geographical distribution

World-wide.

Causal organisms and habitat

- Saprophytic moulds account for about 5% of nail infections.
- *Scopulariopsis brevicaulis* is implicated most frequently and can infect otherwise healthy nails.
- *Acremonium* spp., *Aspergillus* spp. (particularly *A. sydowii* or *A. versicolor*), *Fusarium* spp., *Penicillium* spp., and more recently *Onychocola canadensis*, are also encountered.
- *Scytalidium dimidiatum* (previously *Hendersonula toruloidea*) and *S. hyalinum* are encountered in patients of tropical origin.

Clinical manifestations

- Non-dermatophyte moulds usually only infect diseased or traumatized nails.
- Frequently only one nail is affected; toenails more commonly than fingernails; seen in males more often than females, especially those over 50 years of age.
- No specific clinical features; the nail becomes lustreless and thickened. Small pits and streaks may appear in the nail plate, which is at first white, then yellow, brown, green or black.

Essential investigations

Microscopy and culture

The fungus must be seen on direct microscopic examination and grown in pure culture from most tissue samples. Cycloheximide-free medium should be used or mould growth will be suppressed. Examination of histopathological sections may be helpful.

Management

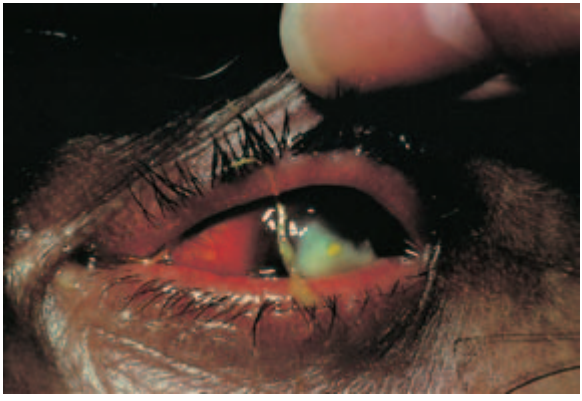
There is no consistent treatment of proven efficacy, with often a poor response; however, chemical avulsion may be helpful.

- Oral treatment (occasionally individual cases respond to):
  - itraconazole 200 mg b.i.d. for 3–4 months or longer
  - itraconazole pulse treatment (1 week treatment alternated with 3 weeks without treatment)
  - terbinafine 250 mg/day for 3–4 months.
- Topical (may eradicate localized distal disease):
  - amorolfine, once or twice weekly for 6–12 months
  - tioconazole, applied twice daily
  - terbinafine and ciclopirox after chemical dissolution with 40% urea ointment.

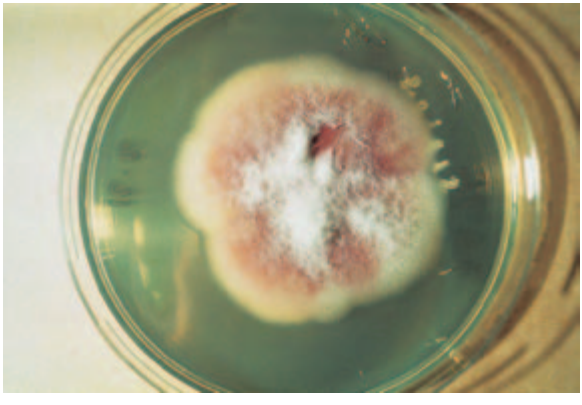
- Combination:
  - amorolfine nail lacquer plus terbinafine: superior to monotherapy with terbinafine
  - topical amorolfine and itraconazole: toenail disease – superior response compared to itraconazole alone.

Treatment may have to be continued for 6 months or more.

Keratomycosis



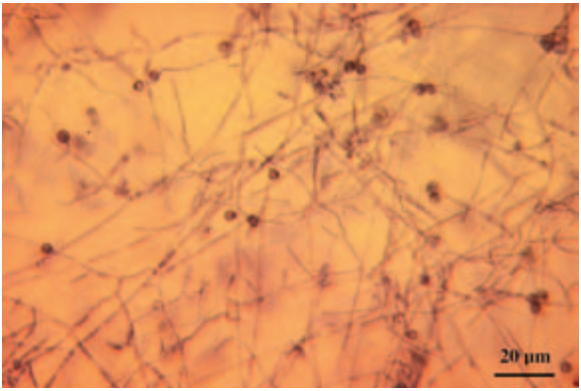
Corneal ulcer due to *Aspergillus glaucus*.



Culture of *Fusarium oxysporum*.

Definition

Keratomycosis is also referred to as mycotic keratitis and describes fungal infection of the cornea. Infection usually follows traumatic implantation of spores.



Hyphal elements and conidia of *Pseudallescheria boydii* in corneal scrapings.

Geographical distribution

World-wide, but it is more common in the tropics and subtropical regions.

Causal organisms and habitat

- Mainly due to saprophytic moulds (more than 60 species implicated).
- Most common are *Fusarium* spp., *Aspergillus* spp., *Curvularia* spp. and *Penicillium* spp. *Candida* spp. are also implicated.
- Infection follows traumatic injury either by direct implantation or subsequent infection of superficial abrasion.
- Topical antibiotics or steroids are predisposing factors.

Clinical manifestations

- Manifestations similar regardless of organism, although *Fusarium* spp. can produce toxins which increase local damage.
- Insidious in onset: increasing pain, ocular redness, photophobia and blurred vision.
- Slit lamp examination reveals: corneal ulcer with ragged white border, deep infiltrates, often discrete satellite lesions.

Essential investigations

Microscopy

Microscopy of corneal scrapings reveals fungal elements.

Culture

Culture at 28°C for 2 weeks to isolate causal organism. Significance increases with repeated isolation.

Management

Removal of infected tissue, discontinuation of steroids and topical or oral antifungal agent.

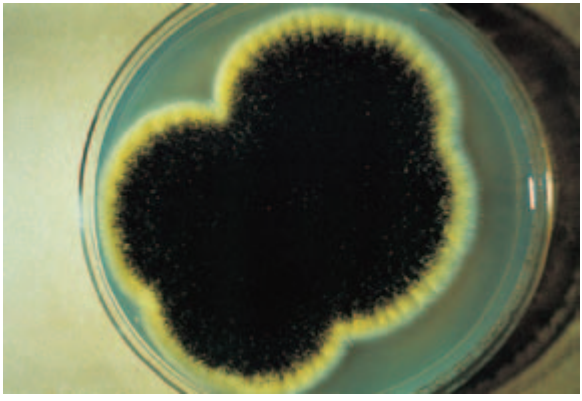
Treat with topical solutions such as 5% natamycin, 0.15% amphotericin B or 1% azole (econazole and miconazole). Topical treatment should be applied at hourly intervals for the first week. Thereafter it should be applied at similar intervals when the patient is awake.

Oral: fluconazole for yeasts – good corneal penetration, 200–800 mg/day, itraconazole for moulds, 200 mg twice daily. Voriconazole demonstrates good ocular penetration and is active against moulds and yeasts. Six weeks of treatment is necessary for yeast and 12 weeks for mould infections. Poor response in *Fusarium* infections, *Aspergillus* more responsive.

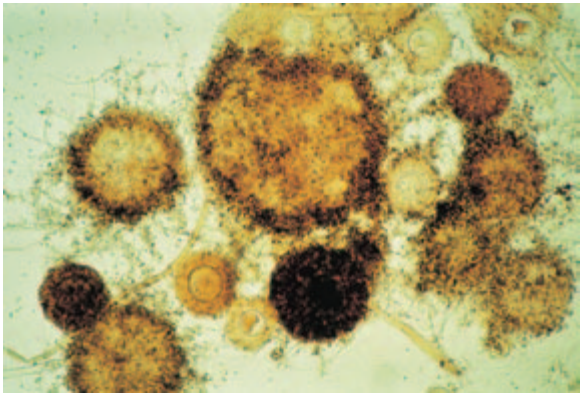
Prolonged treatment with careful follow-up is essential.

Surgical intervention indicated in cases of treatment failure.

Otomycosis



Culture of *Aspergillus niger*.



Aspergillus niger sporing heads from infected ear debris.

Definition

The term otomycosis describes infections of the ear canal.

Geographical distribution

World-wide, but more common in warm climates.

Causal organisms and habitat

- Ubiquitous saprophytic moulds, particularly *Aspergillus* spp., are implicated most frequently. *Scedosporium* spp., *Penicillium* spp., *Absidia* spp., *Rhizopus* spp., *Acremonium* spp. and *Scopulariopsis* spp. have also been reported.
- *Candida* spp. are also frequently isolated, particularly *C. albicans* and *C. tropicalis*.
- In temperate regions it is most frequent during the summer.
- Often there is pre-existing aural disease.
- Topical antibiotics and steroids are predisposing factors.
- High humidity and waxy secretions favour mould growth.

Clinical manifestations

- Discomfort and irritation around the ear canal; there may be some hearing loss, tinnitus and giddiness.
- Discharge may be present; with mixed bacterial infections pain and suppuration are common.
- In advanced cases the mould can occupy much of the lumen of the canal and may be visible as a woolly mycelial mat.

Essential investigations

Microscopy and culture

Microscopic examination of debris from the ear canal will reveal branching hyphae, budding cells or both.

Sporing heads may be seen in *Aspergillus* spp. infections.

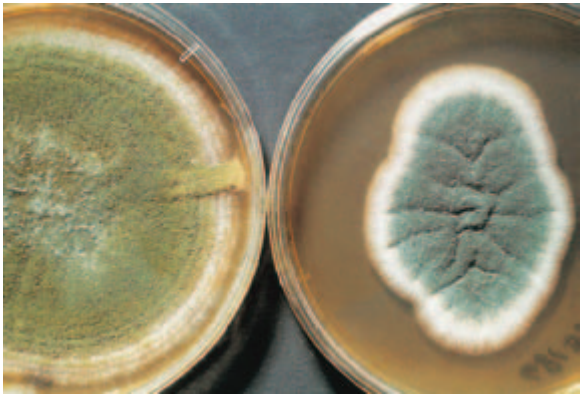
Isolation in culture at 28°C allows identification of the infecting organism.

Management

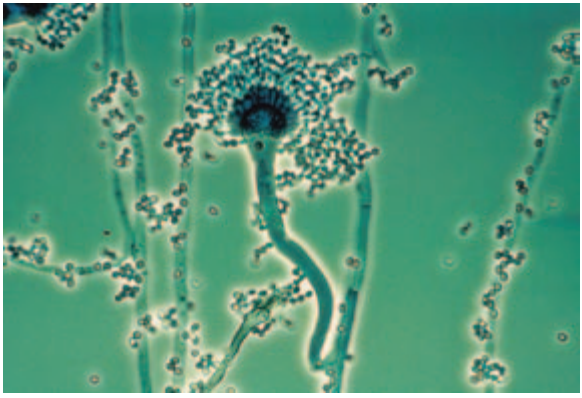
Treatment commences with thorough cleaning followed by the application of an antifungal.

- Topical natamycin or nystatin morning and evening for 2–3 weeks. Local application of an imidazole cream, such as clotrimazole or econazole nitrate, also gives good results.
- Insertion of a regularly replaced gauze pack soaked in amphotericin B, natamycin or an azole for 1 week.
- Most patients respond to treatment.
- Complications are rare, but include recurrence of perforation of tympanic membrane.

Aspergillosis



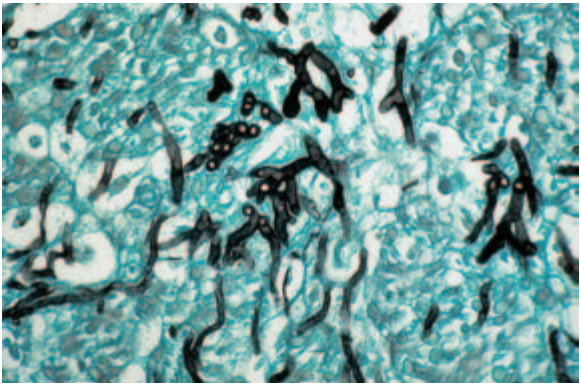
Aspergillus flavus and *Aspergillus fumigatus* in culture.



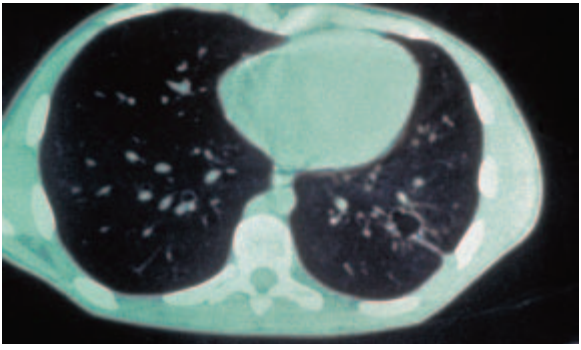
Aspergillus fumigatus sporing head.

Definition

The term aspergillosis describes infections caused by moulds belonging to the genus *Aspergillus.* These can range from localized infections to life-threatening systemic infections. Disease may also result from an allergic reaction to inhaled spores.



Histopathological appearance of *Aspergillus* lung infection.



CT scan of lung showing invasive aspergillosis.

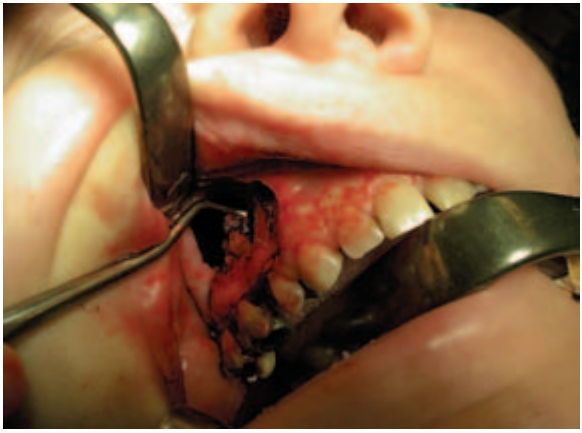
Geographical distribution

World-wide.

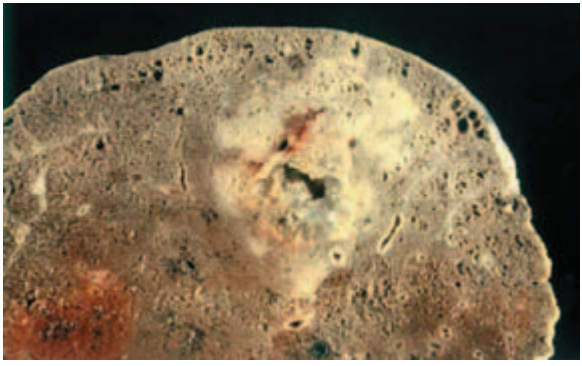
Causal organisms and habitat

Aspergillus species are found:

- in soil, air, plants and decomposing organic matter
- in dust and on food in homes
- in hospital environments, especially ceiling voids, foods, plants, fabrics and in association with demolition or construction work, or defective ventilation.



Aspergilloma in the maxillary sinus.



Invasive aspergillosis of the lung.

Clinical manifestations

Allergic aspergillosis

- Uncommon, but most often seen in atopic individuals.
- Bronchial allergic reaction.
- Mucus plugs form in bronchi, leading to atelectasis.
- Often progresses to bronchiectasis and fibrosis.
- Results from type I and III reaction to *Aspergillus* antigens.
- Fever, intractable asthma, productive cough, malaise, weight loss.

- Expectoration of brown eosinophilic mucus plugs containing *Aspergillus* is common.
- Variable radiographic findings.

Aspergilloma (fungus ball)

- Occurs in patients with residual lung cavities following tuberculosis, sarcoidosis, bronchiectasis, pneumoconiosis and ankylosing spondylitis.
- Patients often asymptomatic.
- Chronic cough.
- Malaise, resulting in weight loss.
- Haemoptysis in 50–80% of cases, in 25% can be life threatening.
- Upper lung lobes:
  - oval or round mass with radiolucent halo or air crescent on radiographs
  - CT will delineate lesion.
- Spontaneous lysis in 10% of cases.

Chronic necrotizing aspergillosis of the lung

- Indolent condition seen in middle-aged or older patients with underlying lung disease.
- Seen associated with alcoholism or diabetes in particular.
- Often similar in clinical presentation to aspergilloma.
- Most frequent symptoms are fever, a productive cough, malaise and weight loss.
- Radiological changes:
  - chronic upper lobe infiltrate associated with pleural thickening
  - cavitation is common.

Acute invasive pulmonary aspergillosis

- Occurs in compromised patients and is often fatal.
- Patients at risk include neutropenic cancer patients, transplant recipients, patients with GVHD, AIDS patients, children with CGD. It may be a focal or diffuse infection, with haematogenous dissemination a frequent complication.
- In neutropenic patients, symptoms include unremitting fever that fails to respond to broad-spectrum antibiotics, pleuritic chest pain and coughing. Typical CT chest signs are small nodular lesions, larger peripheral lesions and a halo sign

around nodular lesions. However, signs of diffuse infection are much less distinctive.

Tracheobronchitis and obstructing bronchial aspergillosis

- Tracheobronchitis:
  - AIDS and lung transplant recipients
  - dyspnoea and wheezing
  - CT scan ineffective
  - diagnosis established by bronchoscopy.
- Obstructing bronchial aspergillosis:
  - non-invasive
  - seen most often in AIDS
  - cough, fever, wheezing
  - expectoration of large mucus plugs
  - if untreated, can become invasive
  - diagnosis established by bronchoscopy.

Sinusitis

- Most common form of fungal sinusitis.
- Five patterns of infection:
  - allergic sinusitis
  - acute invasive sinusitis
  - chronic necrotizing sinusitis
  - aspergilloma (fungal ball) of the paranasal sinuses
  - paranasal granuloma.

Cerebral aspergillosis

- Follows haematogenous dissemination from lungs.
- 10–20% brain involvement.
- Seldom diagnosed during life.
- *Aspergillus* common cause of brain abscesses in bone marrow transplant recipients.
- Disease progression gradual in onset.
- CT helpful in locating lesions, but findings are non-specific.

Ocular aspergillosis

Three forms:

- corneal infection
- endophthalmitis
- orbital infection.

Endocarditis

- Mainly associated with heart transplantation.
- Complication of parenteral drug abuse.
- Similar symptoms to bacterial endocarditis:
  - fever, weight loss, fatigue, loss of appetite
  - murmurs in 50–90% of patients.

Cutaneous aspergillosis

Two forms in immunocompromised patients:

- primary infection at catheter insertion sites due to contaminated splints
- haematogenous spread to skin in about 5% of patients with invasive aspergillosis.

Aspergillosis in AIDS

- Seen in about 4% of patients.
- Lung most common site.
- Bronchoscopic examination helpful.

Essential investigations

Microscopy

Sputum examination is helpful in ABPA, but of limited use in invasive disease.

However, BAL is sometimes helpful in invasive disease.

Histopathology is the most reliable diagnostic method, though a similar appearance is seen with *Fusarium* and *Scedosporium*.

Culture

Culture provides the definitive diagnostic method, although interpretation is difficult.

Isolation may come from sputum and BAL.

Aspergillus is seldom isolated from blood, urine or CSF, but can often be isolated from sinus washings or biopsies.

Clinical tests

CT and MRI scans have enhanced the early diagnosis of invasive aspergillosis as lesions are often visible earlier than on a chest X-ray. Diagnostic signs include a halo presentation and the appearance of crescent-shaped air pockets.

Serology

- Precipitin testing is useful in ABPA and aspergilloma.

- Antigen testing is useful in invasive disease, such as ELISA for galactomannan (Bio-Rad Platelia *Aspergillus*).
- Fungitell,™ a diagnostic kit for the detection of β-1,3-D-glucan in serum, is under evaluation (Associates of Cape Cod).
- PCR may be used for the detection of fungal genomic sequences (experimental) (see p. 170).

Management

Allergic aspergillosis

Mild disease does not require treatment, but when treatment is indicated, prednisolone is drug of choice:

- 1.0 mg/kg/day
- when radiographs clear 0.5 mg/kg/day for 2 weeks
- 0.5 mg/kg at 48-hour intervals for 3–6 months
- itraconazole 200 mg/day for 16 weeks.

Aspergilloma

- Surgical removal of the lesion is necessary.
- Endobronchial instillation or percutaneous instillation of amphotericin B 10–20 mg in 10–20 mL distilled water instilled two or three times per week for about 6 weeks.
- Some responses to oral itraconazole.

Chronic necrotizing aspergillosis

- Itraconazole 200–400 mg/day.
- Surgical resection of necrotic lung with local and parenteral amphotericin B.

Sinusitis

- Allergic:
  - prednisolone
  - surgical debridement to remove polyps and allergic mucin
  - amphotericin B solution
  - itraconazole oral solution (single cases)
  - frequent recurrence.
- Non-invasive:
  - surgical resection.
- Invasive:
  - surgical debridement
  - amphotericin B 1 mg/kg/day

- AmBisome 3–5 mg/kg/day.
- Itraconazole 400–600 mg/day.

Paranasal granuloma

Surgical debridement and itraconazole 200–400 mg/day.

Acute invasive pulmonary aspergillosis

- Prompt treatment is necessary.
- Variable response rate:
  - 10% in BMT recipients
  - 30% in neutropenic patients.
- Amphotericin B 1.0–1.5 mg/kg/day.
- AmBisome 3–5 mg/kg/day or higher.
- Amphocil (Amphotec) 3–4 mg/kg/day or up to 6 mg/kg/day.
- Abelcet 5 mg/kg/day.
- Itraconazole 400–600 mg/day for 4 days then 200 mg twice daily.
- Cancidas (caspofungin) 70 mg/day for salvage therapy in adults in invasive infection either refractory to ≥ 7 days of other therapies or intolerant to other therapies.
- Voriconazole 6 mg/kg IV b.i.d. on day 1 followed by 4 mg/kg b.i.d. until patient stabilizes, then 200 mg b.i.d. orally.

Cerebral

- Poor prognosis.
- AmBisome 3–5 mg/kg and higher.
- Voriconazole 6 mg/kg IV b.i.d. on day 1 followed by 4 mg/kg b.i.d. until patient stabilizes, then 200 mg b.i.d. orally.

Cutaneous

- Amphotericin B 1.0 mg/kg/day.
- Surgical debridement at catheter insertion sites.

Prophylaxis

- Itraconazole oral solution 400 mg/day (may need to monitor see p. 165).
- Amphotericin B 0.5 mg/kg/day.

Empirical

- Amphotericin B 1 mg/kg/day.
- AmBisome 3 mg/kg/day.
- Cancidas (caspofungin): 70 mg loading dose followed by 50 mg/day or 70 my/day in patients > 70 kg.

Pneumocystis carinii pneumonia

Definition

Infection with *Pneumocystis carinii* usually presents as a pneumonitis (PCP). It occurs in immunosuppressed or debilitated patients and is the commonest cause of pneumonia in AIDS.

Geographical distribution

World-wide.

Causal organism and habitat

Pneumocystis carinii shares morphological and structural features with both fungi and protozoa.

Clinical manifestations

- The lung is the primary site of infection.
- Tachypnoea may be the only sign.
- Cysts are formed in linings and other tissues, especially kidneys; spread is probably haematogenous.
- AIDS is the defining illness in 30% of cases.

Essential investigations

- *P. carinii* cannot be isolated in culture; diagnosis is by detection of cysts or 'trophozoites'.
- Immunofluorescence staining with specific monoclonal antibodies.
- The yeast forms of *P. carinii* may resemble *Histoplasma capsulatum* but they do not bud and are usually extracellular. Diagnostic molecular methods are available.

Management

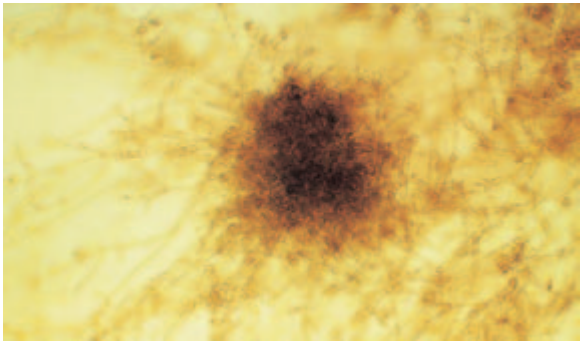
P. carinii lacks ergosterol in its cell membrane and responds better to antibacterial and antiprotozoal than antifungal agents.

Co-trimazole 120 mg/kg/day in divided doses for 2–3 weeks. An alternative is pentamidine isethionate 4 mg/kg/day for 2–3 weeks.

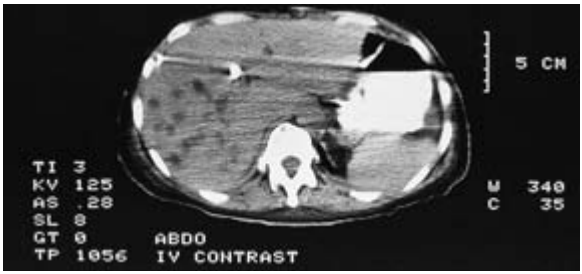
Very high mortality despite treatment.

Prophylaxis is indicated in some patient groups.

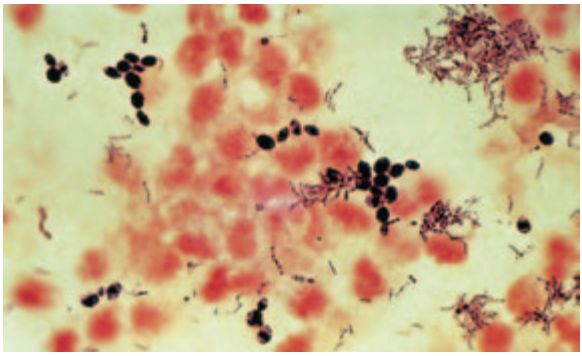
Deep candidosis



Microscopic appearance of *Candida albicans* in cerebrospinal fluid.



Radiographic appearance of hepatosplenic candidosis.



Microscopic appearance of urine infected with *Candida glabrata*.

Gross pathology of liver infected with *Candida albicans*.

Definition

Acute or chronic deep-seated infection due to organisms belonging to the genus *Candida*. Infections are seen in surgical, debilitated or immunocompromised patients and may be confined to one organ or become systemic.

Geographical distribution

World-wide.

Causal organisms and habitat

- *Candida albicans* remains most frequent cause.
- Other species, particularly *C. tropicalis*, *C. parapsilosis* and *C. glabrata* increasing in prevalence. Many others implicated less frequently.
- *Candida* spp. are part of normal flora of skin, mouth, intestinal tract and vagina thus breaches of epidermal barrier function can lead to infection.
- Most deep-seated infections are endogenous in origin.
- Outbreaks due to transmission on hands of healthcare workers reported in neonatal, surgical intensive care and burns units.
- Risk factors include surgery; neutropenia or other immunosuppression; intensive care; trauma; malnutrition; extensive antibiotic therapy; adrenal corticosteroids; catheterization; prematurity and low birth-weight; and IV drug abuse.

• Candidaemia increasing in incidence; recorded as the fourth most common bloodstream infection.

Clinical manifestations

Acute disseminated candidosis

• Disseminated infection occurs more frequently than single organ infection.
• Non-specific clinical signs and symptoms; infection should be suspected in any patient with one or more predisposing factors who develops a fever unresponsive to broad-spectrum antibiotics.
• Endophthalmitis occurs in 5–50% of patients with disseminated candidosis but rarely seen in neutropenic patients who develop the disease.
• Characteristic macronodular skin lesions occur in up to 10% of patients.
• Can involve any organ, typically infection extends to three or four organs, most commonly the kidneys (80%), heart, gastrointestinal tract and lung.
• Pattern of invasion suggests initial entry into the systemic circulation.

Chronic disseminated candidosis

• Previously known as hepatosplenic candidosis, frequently involves the liver and spleen, often seen in leukaemic patients who have recovered their neutrophil counts.
• Pattern of infection suggests initial invasion via the portal circulation from the GI tract.

Congenital candidosis

• Rare condition which can result in fetal or neonatal death.
• Ascending maternal infections linked to symptomatic vaginal candidosis (the incidence of which increases to 25% during pregnancy), the presence of intrauterine devices, cervical sutures, antibiotic use and premature rupture of the membranes.
• Occasionally yeasts may be transferred to the fetus via invasive procedures such as amniocentesis.

Oesophagitis
- Symptoms include oesophadynia and dysphagia.
- Occurs in AIDS patients or following cancer chemotherapy.
- Most commonly seen in patients with oral candidosis.

Gastrointestinal candidosis
- Often asymptomatic.
- Pre-existing mucosal ulceration may be superinfected:
  - perforation can lead to dissemination
  - intestinal candidosis in patient groups other than those undergoing cancer chemotherapy or those with AIDS remains controversial.

Urinary tract and renal candidosis
- Symptoms include fever, rigors, and lumbar and abdominal pain.
- Ascending renal *Candida* infections may be due to catheterization or instrumentation of the bladder or local spread of infection from the perianal area.
- Yeasts may be filtered from the blood, thereby infecting the kidney; 80% of patients with disseminated candidosis develop renal candidosis.
- Fungal ball may form in the kidney obstructing the renal pelvis, leading to anuria.

Pulmonary candidosis
- Uncommon infection in debilitated or neutropenic patients.
- Haematogenous spread or endobronchial inoculation.
- Non-specific clinical and radiological presentation.

CNS candidosis
- *Candida* meningitis is uncommon.
- Low birth-weight infants and neurosurgical patients.
- Haematogenous spread or direct inoculation.
- CSF findings indistinguishable from bacterial meningitis and include raised protein and decreased glucose concentrations.
- Brain abscess may be diagnosed by CT or MRI scan.
- Diffuse metastatic encephalitis is rarely diagnosed during life.

Endocarditis, myocarditis and pericarditis

- Symptoms indistinguishable from those of bacterial endocarditis and include fever, weight loss, fatigue, heart murmurs and enlarged spleen.
- Risk factors include damaged or prosthetic heart valves and IV drug abuse.
- Indolent onset often with a silent period of several weeks or months.
- Vegetations may be apparent on echocardiogram.
- Myocardial infection with abscess formation may be a consequence of endocarditis or arise as a result of haematogenous dissemination.
- Pericarditis with associated chest pain, pericardial friction rub and effusion is most frequently a complication of a superficial myocardial abscess.

Peritonitis

- *Candida* peritonitis associated with fever, abdominal pain and tenderness may be an infective complication of peritoneal dialysis or may occur as a result of gastrointestinal perforation or leaking intestinal anastomosis.

Endophthalmitis

- Painful condition resulting from haematogenous dissemination.
- Fluffy yellow-white exudates may be seen on the retina. These are due to the fungus and the consequent inflammatory reaction, which may explain their rarity in neutropenic patients.
- May be a consequence of IV heroin abuse.

Osteomyelitis, arthritis and myositis

- Characterized by localized pain but rarely fever.
- Usually arise as a consequence of haematogenous dissemination, less commonly traumatic implantation.

Catheter-associated candidaemia

- Intravenous catheters become infected with yeasts leading to positive blood cultures or candidaemia.
- Infection may clear on removal of the catheter or have progressed to disseminated candidosis.

Essential investigations

Microscopy and culture

Microscopy and culture of normally sterile body fluids reveals yeast cells with or without filament production, and growth of yeast colonies after 24–48 hours.

Isolates should be identified to species level and, where appropriate, antifungal susceptibility testing carried out.

Histopathology provides definitive evidence.

Blood culture may result in a diagnosis of candidaemia. This may be line-associated and transient, or indicative of disseminated disease.

Clinical tests

CT and MRI scans may be helpful in diagnosing chronic disseminated candidosis (a normal liver scan has a high negative predictive value) and determining the extent of brain involvement.

Fundoscopic examination may reveal opacities, whilst electrocardiograms may be useful in detecting heart valve vegetations.

Serology

Serology is useful in immunocompetent individuals; high or rising antibody titres (1 : 8 or greater) are considered indicative of active infection; a raised antibody titre is the single most consistent finding in *Candida* endocarditis. Quantitative determination of anti-*Candida* mannan IgG is useful in various manifestations (Bio-Rad Platelia *Candida* antibody).

Detection of mannoprotein antigen (Bio-Rad Platelia *Candida* antigen) by ELISA is useful.

Fungitell,™ a diagnostic kit for the detection of β-1,3-D-glucan in serum, is under evaluation (Associates of Cape Cod).

Experimental PCR has been used to detect yeast genomic sequences (see p.170).

Management

Selection of therapy should be guided by the species of yeast isolated and antifungal susceptibility test results where appropriate.

Candida oesophagitis

Effective treatments for *Candida* oesophagitis include these alternatives:

- Caspofungin 50–70 mg q.d. for 7–14 days.
- Oral ketoconazole 200–400 mg/day for 1–2 weeks.
- Fluconazole 100–200 mg/day for 1–2 weeks.
- Itraconazole 200–400 mg/day for 2 weeks.

Deep and disseminated infection: Cancidas (Caspofungin)

Documented candidaemia should always be treated and lines should be removed or replaced where possible.

Disseminated infection and most deep forms of candidosis should be treated with:

- Amphotericin B 1 mg/kg/day for 4–6 weeks with or without the addition of flucytosine 100–200 mg/kg/day in four divided doses depending on the organism's susceptibility to this agent.
- Caspofungin 70 mg loading dose followed by a once daily 50 mg dose. No dose adjustment is needed for renal impairment; however, reduce maintenance dose to 35 mg/kg in a setting of moderate hepatic impairment.
- Depending on the infecting species, fluconazole 200–400 mg/day may also be effective.

Fluconazole is excreted unchanged in the urine so is useful for urinary tract infections; it also reaches high concentrations in the vitreous humour so may be useful in *Candida* endophthalmitis.

Lipid preparations of amphotericin B should be considered in patients who fail to respond, or develop side effects, to the conventional formulation. Voriconzole is licensed in this indication for difficult to treat infections – same dose as for invasive aspergillosis.

In cases of chronic disseminated candidosis:

- Liposomal amphotericin (AmBisome) 3–5 mg/kg/day is especially useful because it accumulates in the liver.

Candida endocarditis

Removal of infected valves is the treatment of choice for *Candida* endocarditis; antifungal cover with a combination of amphotericin B and flucytosine should be given prior to

surgery and should be continued for 2–3 months to help prevent relapse.

Prophylaxis

Prophylactic chemotherapy with either

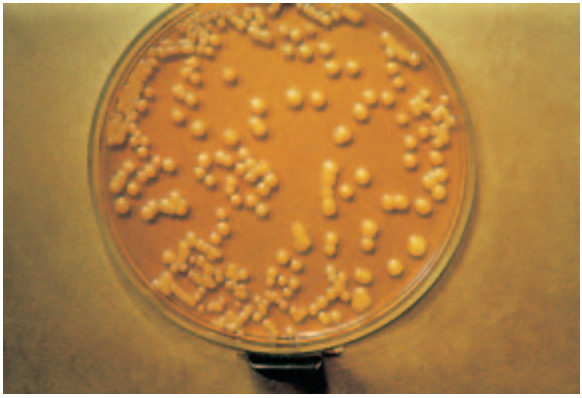
- fluconazole 100 mg/day or
- itraconazole 100–200 mg/day should be considered in patients at risk from invasive yeast infection.

Empirical: Cancidas (Caspofungin)

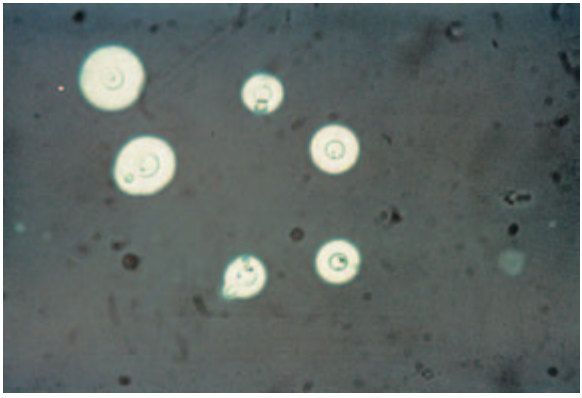
Empirical therapy with amphotericin B, one of its lipid formulations, or caspofungin should be considered in neutropenic patients with persistent fever despite 96-hour therapy with broad-spectrum antibiotics.

- Amphotericin B 1.0 mg/kg.
- AmBisome 1–3 mg/kg/day.
- Caspofungin: 70 mg on day 1 followed by 50 mg/day until resolution of fever.

Cryptococcosis



Appearance of *Cryptococcus neoformans* on Niger seed agar.



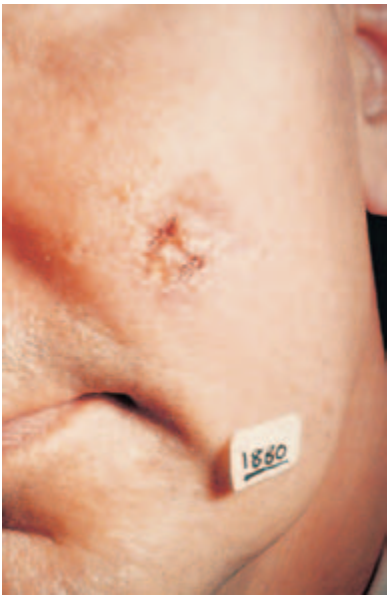
Indian ink preparation of *Cryptococcus neoformans*.

Definition

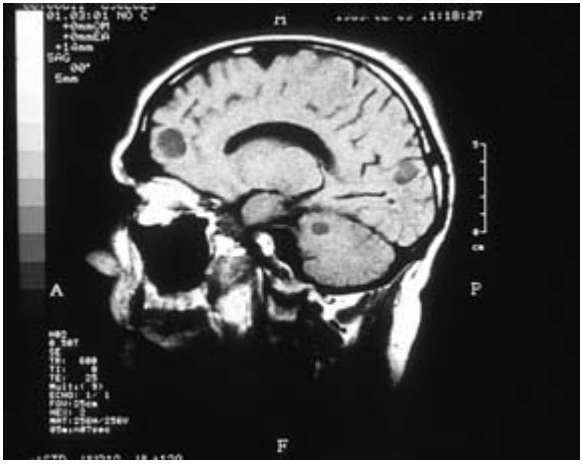
Infection with the encapsulated yeast *Cryptococcus neoformans*.

Most infections occur in immunocompromised patients, especially those with AIDS.

Meningitis is the most common clinical presentation.



Cutaneous cryptococcosis.



MRI showing multiple cryptococcomas in the brain.

Geographical distribution

World-wide, but there are differences in distribution of the causal species.

Causal organisms and habitat

- Encapsulated yeast.
- Two varieties:
  - *C. neoformans* var. *neoformans* serotypes A and D, which are encountered world-wide, often in pigeon guano.
  - *C. neoformans* var. *gattii* serotypes B and C are restricted to tropical and subtropical regions, often in association with the red gum tree.
- Sexual form is the filamentous mould *Filobasidiella neoformans*.

Clinical manifestations

- Infection is believed to follow inhalation of desiccated spores.
- Pulmonary infection is asymptomatic in 30% of normal individuals; others have a productive cough, chest pain, weight loss and fever.
- Radiology reveals well-defined, non-calcified, single or multiple nodular lesions.
- Pulmonary infection may occur and resolve weeks to months before disseminated infection becomes manifest in compromised patients.
- Immunocompromised patients often present with meningitis.
- T cell-mediated immunological defects are the main predisposing factor.
- Major cause of morbidity and death in AIDS patients.
- Abnormal CSF findings:
  - raised pressure, increased protein, lowered glucose
  - lymphocytic pleocytosis.
- Often insidious in onset.
- Cutaneous, osteomyelitic or endophthalmitic lesions may follow haematogenous spread of the organism.

- The prostate is a reservoir for relapse.
- Infection is usually with *C. neoformans* var. *neoformans* even in areas where *C. neoformans* var. *gattii* is found in the environment.

Essential investigations

Microscopy

Microscopic examination of CSF mounted in Indian ink reveals encapsulated yeast cells.

Culture

Culture of CSF, sputum, blood, urine, prostatic fluid; the sample should be centrifuged and the residue plated onto glucose peptone agar and incubated at 30–35°C for 2 weeks.

Positive blood cultures are found in 35–70% of AIDS patients.

Niger seed agar can be used to distinguish *Cryptococcus* spp. (brown colonies) from *Candida* spp. (white colonies).

Concanavalin medium can be used to distinguish *C. neoformans* var. *neoformans* (yellow) from *C. neoformans* var. *gattii* (blue).

Antigen test (LPA or ELISA) on CSF, serum, urine and BAL is a very reliable diagnostic test.

Ninety per cent of patients with cryptococcal meningitis have a positive LPA test, but titres are higher in AIDS patients.

Antibodies are detected in patients with early or localized infection and may be found as a good prognostic sign later on in resolving infections.

Management

Meningitis in normal hosts

- Amphotericin B 0.7–1.0 mg/kg/day, plus flucytosine 37.5 mg/kg every 6 h for 4 weeks, or for 6–10 weeks in patients with risk factors that correlate with a high frequency of relapse.
- Amphotericin B 0.7–1.0 mg/kg/day, plus flucytosine 100 mg/kg/day for 2 weeks, followed by fluconazole 400 mg/day for a minimum of 10 weeks, then fluconazole maintenance for 6–12 months.
- Lipid formulations of amphotericin B.

Meningitis in AIDS

- Amphotericin B 0.7–1.0 mg/kg/day plus flucytosine 100 mg/kg/day for 2–3 weeks, followed by fluconazole 400 mg/day for a minimum of 10 weeks, then fluconazole 200 mg/day for life, or until there has been a prolonged period of CD4 count recovery.
- Liposomal amphotericin B (AmBisome®) 4 mg/kg/day or itraconazole 200–400 mg/kg/day.
- Maintenance therapy with fluconazole 200 mg/day.
- Combination of fluconazole 400–800 mg/day plus flucytosine 100 mg/kg/day but high incidence of side effects.
- If CD4 T-lymphocyte count increases above 100–200 cells per μL following highly active antiretroviral therapy (HAART), maintenance treatment can be discontinued.

Pulmonary – normal hosts

- Usually none, observation only.
- Asymptomatic: if treatment considered, fluconazole 200–400 mg/day for 3–6 months.
- Symptomatic infection:
  - fluconazole 200–400 mg/day for 3–6 months
  - itraconazole 200–400 mg/day for 6–12 months
  - amphotericin B 0.4–0.7 mg/kg/day up to a total dose of 1000–2000 mg.

Pulmonary – progressive and/or HIV-infected patients

- Amphotericin B 0.7–1.0 mg/kg/day.
- Fluconazole 200–400 mg/kg/day for life.
- Itraconazole 200 mg b.d.

Extrapulmonary – non-meningeal

- Amphotericin B 0.3–0.6 mg/kg/day plus flucytosine 100–150 mg/kg/day.
- Fluconazole 400 mg/day for 3–6 months.
- Itraconazole 200 mg twice daily for 6–12 months.

Management of elevated intracranial pressure

- Percutaneous lumbar drainage.

Maintenance

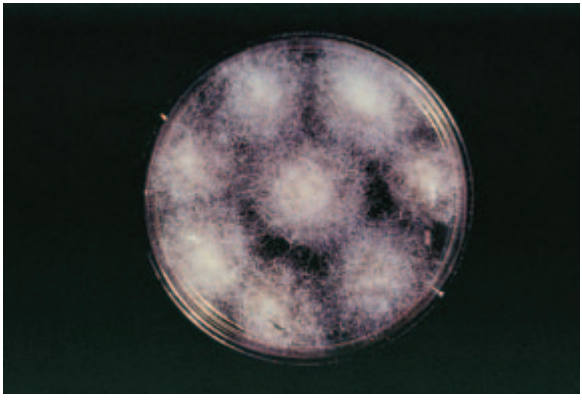
- Fluconazole 200–400 mg p.o. 4 times daily, for life.

- Itraconazole 200 mg p.o. 2 times daily, for life.
- Amphotericin B 1 mg/kg IV 1–3 times a week, for life.

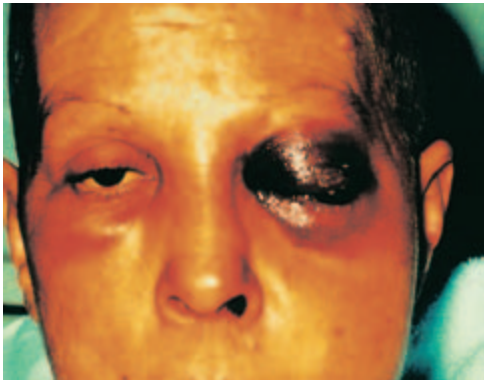
Monitoring of treatment

- Antigen titres should be monitored at 1, 2, 3 and 6 months following treatment but they should be interpreted with caution. A change of less than fourfold is not considered significant and a high titre is not necessarily indicative of active infection. Titres on CSF and serum should only be considered in conjunction with a clinical evaluation. Serum titres are usually lower than CSF titres.
- Successful treatment includes resolution of clinical symptoms and two consecutive negative cultures.
- It can be considered relapse rather than recalcitrant infection if the patient is free from clinical signs and symptoms and previously positive cultures are negative for a period of several months.
- Reinfection from an environmental source is also possible.

Mucormycosis



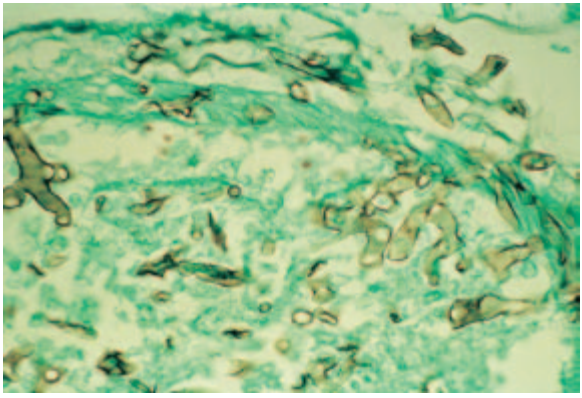
Culture of *Absidia corymbifera*.



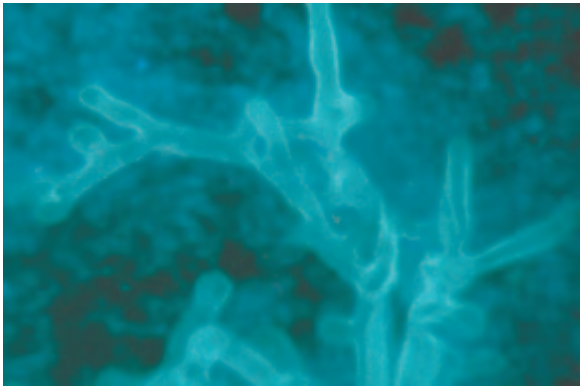
Rhinocerebral mucormycosis with infection of the orbit.

Definition

Mainly rhinocerebral, but also pulmonary, gastrointestinal, cutaneous or disseminated infection caused by moulds belonging to the order Mucorales.



Histopathological appearance of mucormycosis.



Calcofluor staining of a biopsy of brain tissue infected with a zygomycete showing broad, aseptate hyphae.

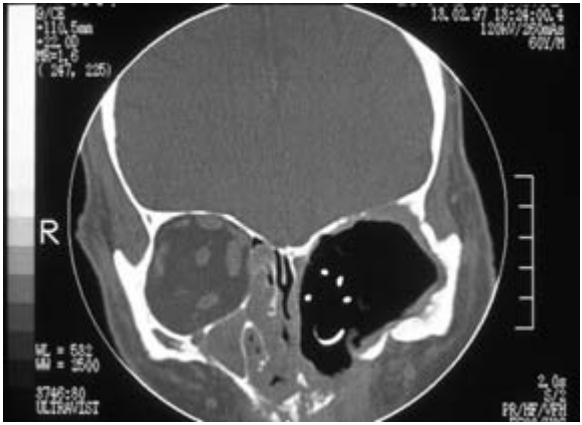
Geographical distribution

World-wide.

Causal organisms and habitat

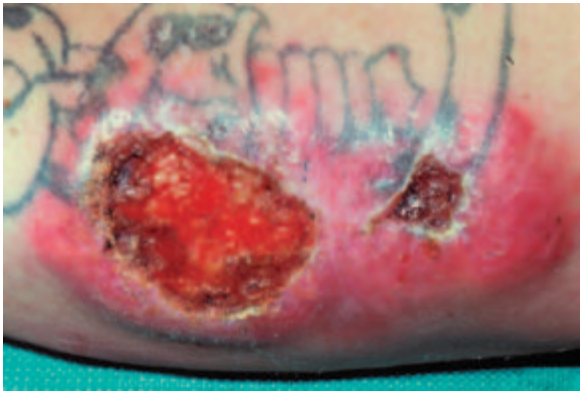
- *Rhizopus oryzae*.
- *Absidia corymbifera*.
- *Apophysomyces elegans*.

Microscopic morphology of *Rhizopus oryzae*.

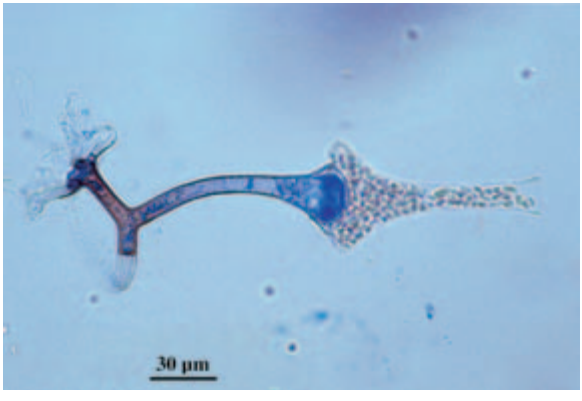


MRI of rhinocerebral mucormycosis caused by *Apophysomyces elegans*.

- *Cunninghamella bertholletiae*.
- *Rhizomucor pusillus*.
- *Rhizopus microsporus* group.
- *Saksenaea vasiformis*.
- Ubiquitous in environment – in soil, food and on decomposing organic matter:
  - spores inhaled
  - less frequently, traumatic inoculation into skin.



An ulcerated erythematous plaque from which *Saksenaea vasiformis* was isolated.



Microscopic morphology of *Saksenaea vasiformis* showing a typical trumpet-shaped sporangiophore.

Clinical manifestations

- Opportunistic infection.
- Clinical forms associated with particular underlying disorders.
- Predilection for vascular invasion:
  - thrombosis
  - infarction
  - tissue necrosis.

- Classic feature is rapid onset of necrosis and fever.
- Rapid progression and death if not treated aggressively.

Rhinocerebral mucormycosis

- Starts in paranasal sinuses.
- Spreads to orbit, face, palate and/or brain.
- Most commonly seen associated with uncontrolled diabetes.
- Often fatal if left untreated.
- Initial symptoms include unilateral headache, nasal or sinus congestion, serosanguinous nasal discharge and fever:
  - spreads into palate and forms black necrotic lesion
  - nasal septum or palatal perforation frequent.
- Consequences of spread into orbit:
  - periorbital or perinasal swelling occurs
  - induration and discoloration
  - ptosis and/or proptosis
  - loss of vision
  - drainage of black pus
  - angioinvasive spread to brain is common.
- CT and MRI useful in defining extent of bone and soft-tissue destruction.

Pulmonary mucormycosis

- Most cases in neutropenic cancer patients.
- Aspiration or inhalation of infectious material.
- Non-specific symptoms include fever and cough.
- Seldom diagnosed during life.
- Haematogenous spread during dissemination.
- Fatal within 2–3 weeks.

Gastrointestinal mucormycosis

- Uncommon.
- Malnourished infants or children.
- Stomach, colon and ileum.
- Seldom diagnosed during life.
- Varied symptoms, typically non-specific abdominal pain and haematemesis.
- Peritonitis if intestinal perforation occurs.

Cutaneous mucormycosis

- Associated with burns: spread to underlying tissue.

- Severe underlying necrosis develops.
- In diabetics: cutaneous lesions at injection site.
- Associated with contaminated surgical dressings or splints.

Disseminated mucormycosis
- Develops from other manifestations.
- Usually in neutropenic patients with pulmonary infection.
- Brain is most common site of spread.
- Metastatic lesions found in spleen, heart and other organs.
- Seldom diagnosed during life.
- Occasional cutaneous lesions permit early diagnosis.

Cerebral infection alone
- Follows haematogenous dissemination.
- Distinct from rhinocerebral mucormycosis.
- Focal neurological signs.
- Difficult diagnosis:
  - neutropenic patient
  - IV drug abusers
  - confusion, obtunded or somnolent
  - CT and MRI useful but non-specific
  - CSF investigations unhelpful.

Essential investigations

Microscopy and culture

The presence of broad, mostly non-septate hyphae with right-angled branching in specimens from necrotic lesions, sputum or BAL is highly significant. Tissue samples for culture should be chopped into small pieces but not homogenised as this will result in non-viable hyphal fragments. It is not usual to fail to isolate the causative fungus from necrotic tissue.

Nasal, palatal and sputum cultures are seldom helpful.

Interpretation should be cautious, but isolation should not be ignored if the patient is diabetic or immunosuppressed.

Management

Rhinocerebral

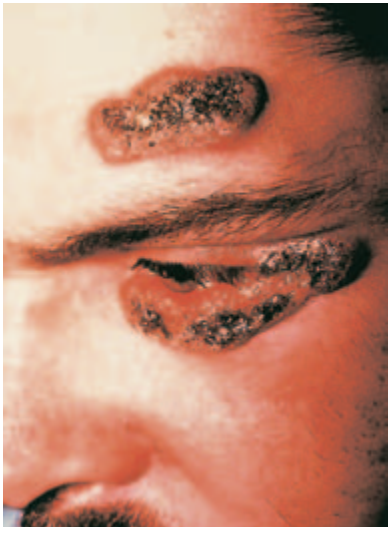
- Control the underlying disorders, including prompt correction of acidosis. Also, remove infected necrotic tissue.

- Amphotericin B 1.0–1.5 mg/kg/day, continued for 8–10 weeks, until reaching a total dose of 2 g.
  - Liposomal amphotericin B 5 mg/kg or higher.
- Surgical resection in pulmonary disease.
- Aggressive surgical debridement of necrotic lesions in cutaneous mucormycosis.

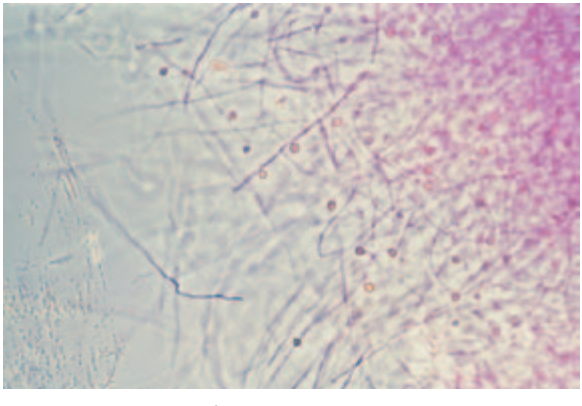
Pulmonary

- Removal of predisposing conditions.
- Restitution of neutrophils – spontaneously or with colony-stimulating factors – and reduction of glucocorticosteroid dose.
- Amphotericin B: rapid escalation to 1.0–1.5 mg/kg/day.
- Liposomal amphotericin B 3–5 mg/kg/day or higher.
- Following stabilization, resection of lung tissue.

Blastomycosis



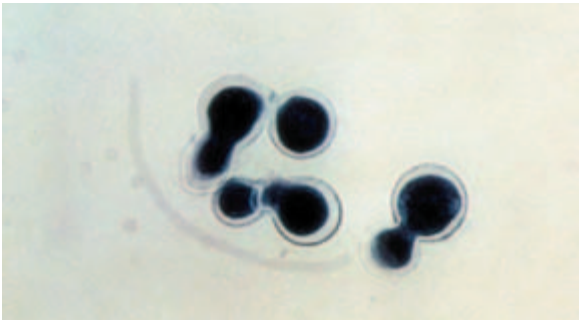
Cutaneous blastomycosis.



Microscopic appearance of *Blastomyces dermatitidis*.

Definition

Pulmonary infection caused by *Blastomyces dermatitidis* in



Yeast cells of *Blastomyces dermatitidis* in pus.

normal individuals but it often spreads to involve other organs, particularly skin and bones.

Geographical distribution

Midwestern and southeastern regions of North America; it also occurs in Central and South America and parts of Africa.

Causal organism and habitat

- *Blastomyces dermatitidis*.
- Exists in nature as mycelium; in tissue as large, round budding cells.
- Soil is natural habitat; greatest survival in moist soil containing organic debris or in rotting wood.
- Associated with outdoor occupations or recreational interest.
- Sporadic disease in endemic areas but may also cause outbreaks after a point-source exposure.
- Endemic regions not easily delineated.
- Much more common in men, although women and children are infected during outbreaks.
- Risk factors have not been identified.

Clinical manifestations

Pulmonary blastomycosis

- Infection follows inhalation.
- Lungs are initial site of infection.

- Asymptomatic infection common (50%).
- Incubation period 30–45 days.
- Pulmonary lesions often not detected until infection has spread to other sites.
- Acute disease: flu-like illness: fever, chills, productive cough, myalgia, arthralgia, pleuritic chest pain.
- Radiological findings are non-specific; include lobar or segmental consolidation, often in lower lobes.
- Most patients recover after 2–12 weeks of symptoms.
- Patients who fail to recover develop chronic pulmonary infection or disseminated disease.

Cutaneous blastomycosis

- Cutaneous lesions occur in over 70% of cases with disseminated disease.
- Painless raised verrucous lesions with irregular borders.
- Ulcerative lesions formed by drainage of subcutaneous abscesses.
- Face, upper limbs, neck and scalp are most frequently involved.

Osteoarticular blastomycosis

- Occurs in about 30% of patients with disseminated disease.
- Spine, ribs, long bones most common sites of infection.
- Lesions often remain asymptomatic until infection spreads into contiguous joints, or into adjacent soft tissue causing abscess formation.
- Radiological findings non-specific; well-defined osteolytic or osteoblastic lesions cannot be distinguished from other fungal or bacterial infections.
- Arthritis occurs in up to 10% of patients; in knee, ankle, elbow or wrist.

Genitourinary blastomycosis

- Prostate involved in 15–35% of men with disseminated blastomycosis.
- Epididymitis presents as scrotal swelling.

Blastomycosis in special hosts

- Occasionally associated with impaired T cell-mediated immunological function.
- Occasionally seen in AIDS.

Essential investigations

Microscopy

Large round cells with thick refractile walls and broad-based single buds seen in pus, sputum, bronchial washings and urine.

Culture

Culture provides the definitive diagnosis. Mycelial colonies with small round conidia are seen after 1–4 weeks at 25–30°C. Exoantigen testing can confirm the identification. Identification can also be confirmed by demonstration of thermal dimorphism on subculture on brain–heart infusion agar at 37°C; under these growth conditions large yeast cells with broad-based buds are evident.

Serology

Complement fixation is insensitive and non-specific. Immunodiffusion is more specific but negative reactions occur in many patients with the disease.

Management

Many patients who are asymptomatic recover without treatment but may develop serious complications later; therefore monitor for signs of reactivation.

All patients with symptomatic infection require treatment.

- Oral itraconazole 200–400 mg/day for at least 6 months for non-immunocompromised patients with indolent forms of the disease. The lower dose is often sufficient. Continue for at least 3 months after the lesions have resolved.

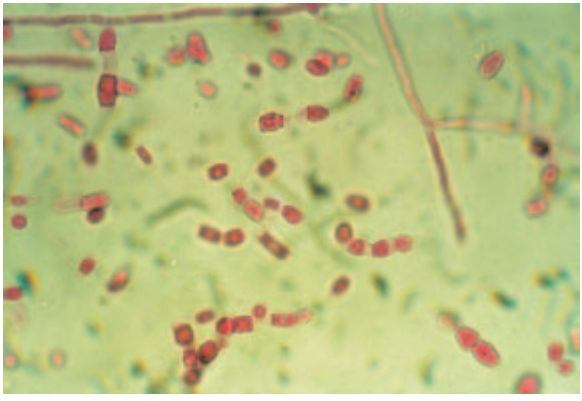
Patients with osteomyelitis may require treatment for up to 12 months:

- Fluconazole is useful where itraconazole is not absorbed; 400–800 mg/day for 6–9 months.
- Ketoconazole is also effective; 400–800 mg/day for 6 months.

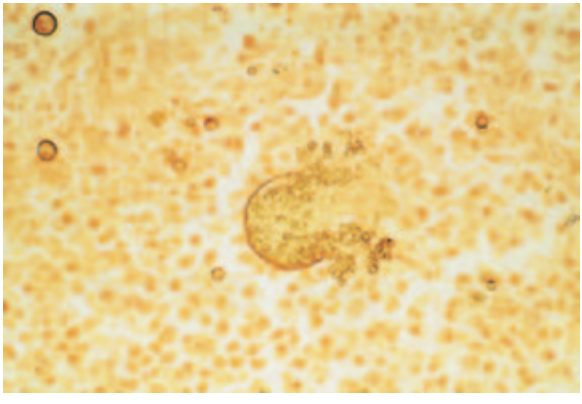
In cases of life-threatening infection or where CNS is involved:

- Amphotericin B 0.7–1.0 mg/kg/day, to a total dose of 1.5–2.5 g. This may be used in immunocompromised patients or itraconazole failures. Switch to itraconazole after initial amphotericin B response.

Coccidioidomycosis



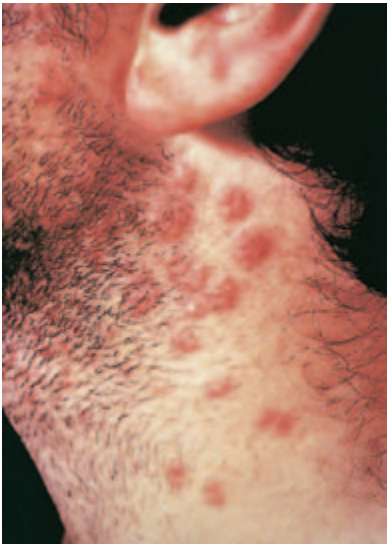
Microscopic appearance of *Coccidioides immitis* arthrospores.



Histopathological appearance of *Coccidioides immitis* spherules in tissue.

Definition

A mild, transient pulmonary infection caused by the dimorphic fungus *Coccidioides immitis* (or the recently described phenotypically and clinically indistinguishable *Coccidioides posadasii*). It can proceed to a progressive infection of the lungs or more generalized infection in immunosuppressed patients.



Erythema multiforma in a patient with primary pulmonary coccidioidomycosis.

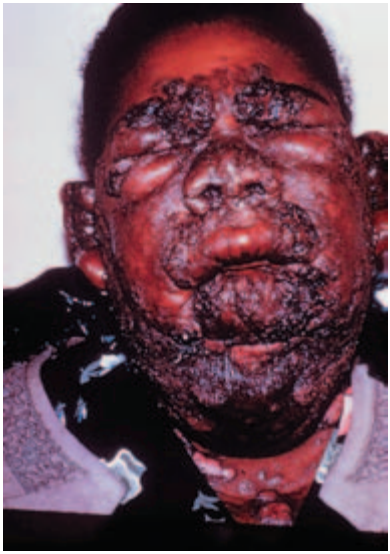
Geographical distribution

Most cases occur in the southwestern USA, and in parts of Central and South America.

Infection diagnosed outside these regions occurs in individuals exposed in endemic regions.

Causal organisms and habitat

- *Coccidioides immitis*, found in soil only in California, cannot be distinguished phenotypically from *Coccidioides posadasii*, which is found elsewhere.
- Both exist in nature as mycelium, which fragments into arthrospores that are readily disseminated on air currents.
- Inhalation leads to the formation of large, round, thick-walled spherules containing endospores in tissue.
- Restricted geographical distribution: hot, arid regions of southwestern USA, parts of Central and South America.
- Dust storms often spread the organism far outside its endemic regions.



Chronic cutaneous coccidioidomycosis showing granulomatous lesions on face, neck and chin.

Clinical manifestations

Primary pulmonary coccidioidomycosis

- About 60% of newly infected persons develop no symptoms following inhalation of arthrospores. The remainder develop symptoms after 1–4 weeks.
- Higher levels of exposure increase the likelihood of acute symptomatic disease.
- Most patients develop a mild or moderate flu-like illness that resolves without treatment.
- Up to 50% of patients develop a mild, diffuse, erythematous or maculopapular rash.
- Erythema nodosum or erythematous multiforme seen in 30% of cases, more common in women.
- Segmental pneumonia is most common radiological finding.
- About 20% of cases develop enlarged hilar lymph nodes or a pleural effusion.
- Single or multiple nodules, thick- or thin-walled cavities, as well as enlarged mediastinal lymph nodes can occur.

Chronic pulmonary coccidioidomycosis

- Small number of patients with primary disease are left with benign residual lesions.
- Most patients are asymptomatic but haemoptysis may occur in up to 25% of cases.
- Residual cavities can enlarge and rupture.
- In the immunocompromised, acute pulmonary disease can be fatal.
- In the immunocompetent, illness can mimic tuberculosis.

Disseminated coccidioidomycosis

- Fewer than 1% of patients develop disseminated disease.
- Almost any organ of the body can be involved.
- Progressive and fatal.
- Men five times more affected than women; ratio is reversed if women are pregnant.
- Higher risk of dissemination in persons of African or Filipino descent.
- Disease usually develops within 12 months of initial infection.
- Disease can develop much later due to reactivation of quiescent lesions.
- Cutaneous, soft tissue, bone, joint and meningeal disease are most common.
- In the immunosuppressed, widespread dissemination often occurs.
- Meningitis most serious complication; occurs in 30–50% of patients with disseminated disease; often results in hydrocephalus; fatal if not treated.

Coccidioidomycosis in AIDS

- Most cases recently acquired in endemic areas.
- Pulmonary disease most common presentation; chest radiographs show diffuse, reticulonodular infiltrates; more than 70% of patients die within 1 month despite treatment.

Essential investigations

Microscopy

Large, thick-walled endospore containing spherules can be seen on direct microscopy of pus, sputum or joint fluid but less commonly in blood.

Culture

C. immitis or *C. posadasii* isolated from sputum, joint fluid, CSF sediment, pus and other specimens.

Identifiable mycelial colonies can be seen after incubation at 25–30°C for 2–7 days. Exoantigen test can confirm identification.

Skin tests

Skin tests do not distinguish between present or past infection.

Conversion from a negative to a positive result suggests recent infection.

False-negative results are common in anergic patients with disseminated disease.

Serology

Detection of specific IgM is useful in diagnosing acute infection; it appears within 4 weeks from onset of infection and disappears after 2–6 months.

IgM can be detected by latex agglutination (LA), test-tube precipitation (TP), or immunodiffusion (ID).

Specific IgG is useful for detecting later stages of coccidioidomycosis; titres rise with the progression of the disease.

IgG can be detected using complement fixation (CF) or ID. Rising CF titre is indicative of progressive disease.

Management

Primary pulmonary coccidioidomycosis

This condition is normally self-limited and recovers without antifungal treatment, although patients should have follow-up visits to document resolution or identify any possible complications at an early stage.

However, a few patients require treatment to prevent progression.

Treatment is indicated in non-immunocompromised patients with persistent symptoms, persistent debilitation, extensive or progressive pulmonary involvement, persistent hilar or mediastinal lymph node enlargement, rising or elevated antibody titre, or negative skin tests.

- Treatment of choice: amphotericin B 0.5–0.7 mg/kg/day.
- Once stabilized, 0.8–1.0 mg/kg every 48 hours. Achieve total dose of 0.5–1.5 g.

For milder infections: itraconazole 200 mg b.i.d. or fluconazole 400 mg/day for 2–6 months.

Chronic pulmonary coccidioidomycosis

Enlarging cavities require surgical resection plus:

- amphotericin B 0.5–0.7 mg/kg/day for 4 weeks, commencing 2 weeks before surgery.

For chronic progressive pneumonia:

- amphotericin B 0.5–0.7 mg/kg/day
- fluconazole 200–400 mg/day is an effective alternative, but has a high relapse rate.

Disseminated coccidioidomycosis

For non-meningeal disease:

- Amphotericin B 1.0–1.5 mg/kg/day. Continue treatment until 2.5–3.0 g total dose reached. However, there is poor response, with relapses common.
- Itraconazole 400 mg/day.
- Ketoconazole 400 mg/day.
- Fluconazole 400–800 mg/day effective in cutaneous, soft-tissue, bone or joint lesions.

Surgical debridement is necessary for osteomyelitis.

For AIDS patients:

- Amphotericin B 1.0–1.5 mg/kg/day. Continue until total dose of 1.0 g reached, then switch to itraconazole 400 mg/day or fluconazole 400 mg/day if there is improvement.

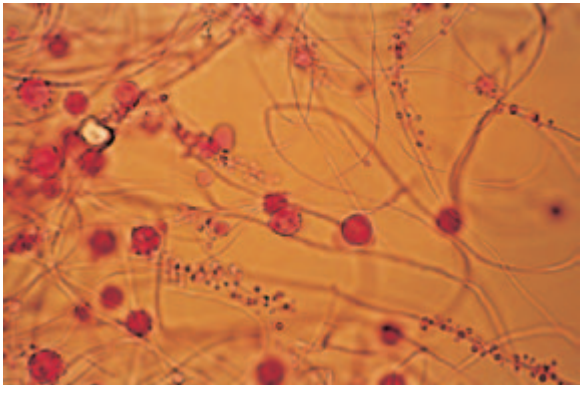
Meningitis

- Fluconazole 400–800 mg/day is drug of choice; improvement in up to 80% of patients. Response rate in AIDS is lower.

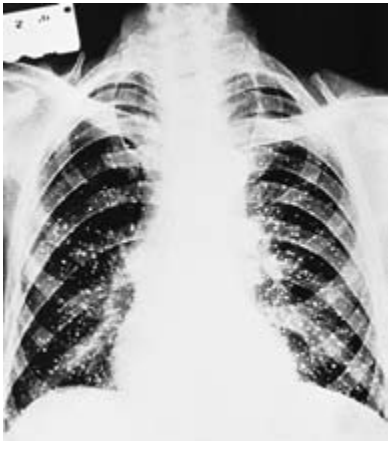
However, fluconazole does not eradicate meningeal infection; the drug must be continued for life to prevent relapse.

Treatment with itraconazole 400 mg/day is under evaluation.

Histoplasmosis



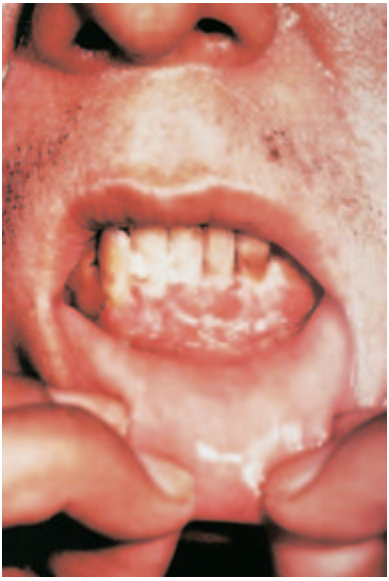
Histoplasma capsulatum conidia.



Radiographic appearance of chronic pulmonary histoplasmosis.

Definition

A mild and transient pulmonary infection in normal individuals caused by the dimorphic fungus *Histoplasma capsulatum*. Can proceed to a chronic infection of the lungs or more widespread infection in predisposed patients.



Mucosal ulcer in a patient with histoplasmosis.

Geographical distribution

Most prevalent in central North America, Central and South America. Other endemic areas include Africa, Australia, India and Malaysia.

Causal organism and habitat

- *H. capsulatum* exists as mycelium in nature; in tissue it forms small round budding cells.
- Two varieties recognized in human infection: *capsulatum* and *duboisii*.
- Found in soil enriched with bird or bat droppings.
- Large numbers of spores dispersed into atmosphere.
- Large numbers of individuals can become infected in a point-source outbreak.
- *H. capsulatum* var. *duboisii* confined to central Africa.

Clinical manifestations

Acute pulmonary histoplasmosis

- Normal individuals who inhale large numbers of spores develop acute symptomatic and often severe infection after 1–3 week incubation period.
- Non-specific flu-like illness in symptomatic patients, resolves without treatment.
- Common symptoms include fever, chills, headache, myalgia, loss of appetite, cough and chest pain. In addition:
  - 10% of patients present with aseptic arthritis or arthralgia associated with erythema multiforme or nodosum
  - normal chest radiographs in most patients
  - hilar lymph node enlargement often evident
  - infiltrates heal over several-month period to form a histoplasmoma, which sometimes enlarges.
- Reinfection results in similar illness but distinct differences:
  - milder and occurs over much shorter incubation period
  - radiological signs different from newly infected individuals
  - no mediastinal lymph node enlargement; pleural effusions not seen.

Chronic pulmonary histoplasmosis

- Slowly progressive illness seen in middle-aged men with underlying chronic obstructive lung disease.
- A transient, segmental pneumonia that frequently progresses to fibrosis and cavitation with significant lung destruction.
- If left untreated, death can result from progressive lung failure.
- In patients with pneumonia, symptoms include a productive cough, fever, chills, weight loss, malaise, night sweats and pleuritic chest pain:
  - on radiography, interstitial infiltrates can be seen in apical segments of upper lung lobes.
- In patients with chronic fibrosis and cavitation there may be cough and sputum production. In addition:
  - haemoptysis in 30% of patients
  - fever, chest pain, fatigue and weight loss
  - radiographs reveal progressive cavitation and fibrosis
  - lesions more common in right upper lobe

- pleural thickening adjacent to lesions found in 50% of patients.

Disseminated histoplasmosis

- Progressive, often fatal, associated with T cell-mediated immunological defects.
- Treatment essential.
- In infants and immunosuppressed, symptoms include high fever, chills, prostration, malaise, loss of appetite and weight loss. Also:
  - liver and spleen enlarged
  - liver function tests abnormal
  - anaemia common.
- In non-immunosuppressed patients:
  - indolent, chronic course
  - hepatic infection common
  - adrenal gland destruction common
  - mucosal lesions seen in more than 60% of patients.
- Meningitis is a chronic complication:
  - occurs in 10–25% of patients with indolent disseminated infection
  - most patients have an abnormal CSF
  - *H. capsulatum* often isolated
  - occasional endocarditis and mucosal ulcerations in gastrointestinal tract.

African histoplasmosis

- Due to *Histoplasma capsulatum* var. *duboisii*.
- Indolent in onset.
- Skin and bones are predominant sites.
- Involvement of liver, spleen and other organs causes fatal wasting illness.
- Cutaneous lesions common.
- Both nodules and papules often enlarge and ulcerate.
- Osteomyelitis occurs in about 30% of patients:
  - spine, ribs, cranial bones, sternum and long bones most common sites
  - lesions often painless
  - spread into joints causes arthritis
  - spread into adjacent soft tissue causes purulent subcutaneous abscesses.

Histoplasmosis in AIDS patients

- AIDS defining illness; occurs in 2–5% of patients with AIDS.
- Acute infection or reactivation of an old latent infection.
- Most patients with AIDS present with disseminated histoplasmosis.
- Non-specific symptoms, such as fever or weight loss.
- Up to 25% of patients have enlarged liver and spleen.
- Up to 25% of patients have anaemia, leucopenia and thrombocytopenia.

Essential investigations

Microscopy

All material must be examined as stained smears. Small, oval budding cells are often seen within macrophages. There is a possibility of confusion with *Candida glabrata*, *Penicillium marneffei* and the small non-encapsulated cells of *Cryptococcus neoformans*.

Culture

Culture provides the definitive diagnosis, although unequivocal identification of culture requires conversion to yeast form, or exoantigen testing. The cultures should be incubated at 25–30°C for 4–6 weeks.

Serology

Immunodiffusion (ID) and complement fixation (CF) are positive in about 80% of patients. CF is more sensitive than ID, but ID is more specific.

False-negative reactions occur in immunosuppressed individuals with disseminated disease.

The detection of antigen in blood and urine is the most useful test for disseminated disease in AIDS.

Management

Acute pulmonary histoplasmosis

There is usually spontaneous improvement in this condition. However, treatment is indicated where there is no resolution of symptoms after 2–3 weeks. In this case, treat with:

- amphotericin B 0.7 mg/kg/day followed by oral itraconazole 400 mg/day for 6–12 weeks
- amphotericin B 0.7 mg/kg/day to a total dose of at least 35 mg/kg
- oral itraconazole 400 mg/day for 6–12 weeks.

Chronic pulmonary histoplasmosis

If cavitation is not present and the symptoms are mild, delay treatment if healing is apparent. In cases where the symptoms progress, treat with:

- oral itraconazole 400 mg/day for 12–24 months.

If itraconazole is contraindicated, treat with:

- amphotericin B 0.7 mg/kg/day to a total dose of at least 35 mg/kg.

Follow-up patients for at least 12 months after discontinuation of treatment.

Disseminated histoplasmosis

For non-immunosuppressed patients, treat with:

- oral itraconazole 400 mg/day for 6–18 months or
- amphotericin B 0.7 mg/kg/day for 10 weeks; but for infants 1.0 mg/kg for at least 6 weeks.

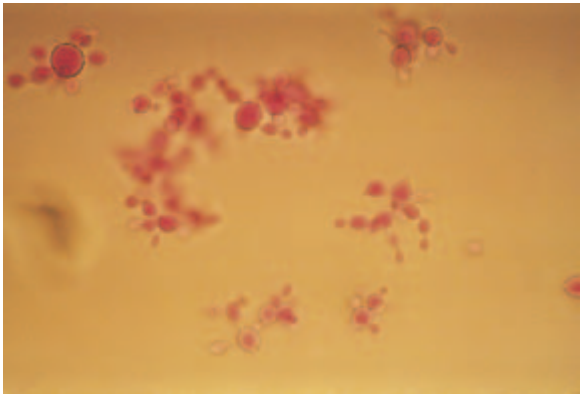
For AIDS patients and patients with African histoplasmosis, treat with:

- itraconazole 200 mg 3 times daily for 3 days then twice daily for 12 weeks
- amphotericin B 0.7 mg/kg/day followed by oral itraconazole 400 mg/day for 12 weeks or
- IV itraconazole 400 mg/day followed by oral itraconazole 400 mg/day for 12 weeks or
- fluconazole 800 mg/day.

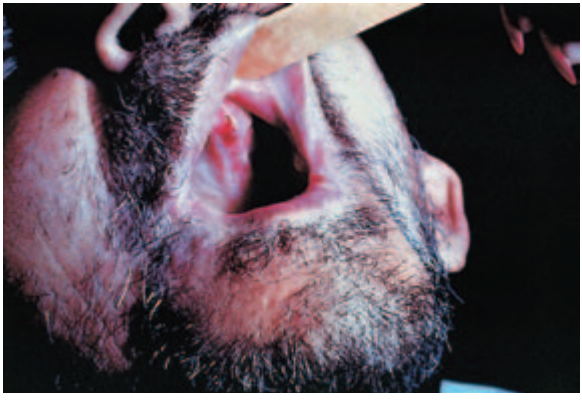
Relapse is common; therefore a maintenance treatment should be given:

- itraconazole 200 mg once or twice daily for life
- amphotericin B 50 mg IV once weekly
- fluconazole 400–800 mg/day if oral therapy required and itraconazole not tolerated (relapse more common).

Paracoccidioidomycosis



Microscopic appearance of *Paracoccidioides brasiliensis*.



Oral lesions in a patient with paracoccidioidomycosis.

Definition

A benign and transient pulmonary infection caused by *Paracoccidioides brasiliensis*.

Later reactivation results in chronic infection of the lungs or other organs, in particular the skin and oral mucous membranes.

Cutaneous lesions in a patient with paracoccidioidomycosis.

Geographical distribution

Most cases are in South and Central America.

Infection occurs among individuals who have visited an endemic region.

Causal organism and habitat

- *P. brasiliensis* is dimorphic; it grows in nature as mycelium.
- Large oval or globose cells with characteristic multiple buds encircling the mother cell in tissue.

Clinical manifestations

Chronic pulmonary paracoccidioidomycosis

- Symptomatic disease most prevalent between ages of 30 and 50 years. Most cases in men – associated with outdoor occupations.
- Lungs are normal site of infection and symptoms include productive cough, fever, night sweats, malaise, haemoptysis and weight loss.
- Spread through lymphatics to regional lymph nodes and then mucosa, skin and other organs.
- Normal presentation: chronic progressive infection as a result of reactivation of old quiescent lesions.

- Indolent in onset, appearing long after an individual has left an endemic region.
- Characteristic radiological findings, but not diagnostic.
- Multiple bilateral interstitial infiltrates often found.
- Hilar lymph node enlargement found in 50% of cases.
- Lesions must be distinguished from histoplasmosis and tuberculosis.

Mucocutaneous paracoccidioidomycosis

- Ulcerative mucocutaneous lesions are most obvious presentation.
- Mouth and nose most common sites.
- Perforation of palate or nasal septum may occur.
- Lymphadenopathies common in patients with buccal cavities.

Disseminated paracoccidioidomycosis

- Haematogenous and lymphatic spread can lead to widespread infection.
- Nodular or ulcerated lesions of small or large intestine, hepatic and splenic lesions, adrenal gland destruction.

Essential investigations

Microscopy

Distinctive, large, multiple budding cells, characteristically with one larger cell surrounded by small buds are seen in pus, sputum and crusts from granulomatous lesions.

Culture

Culture provides the definitive diagnosis. The cultures should be incubated at 25–30°C for 2–3 weeks and thereafter retained for 4 weeks. Small, white to tan irregularly shaped colonies may produce characteristic cracking of the agar and sometimes a brown pigment. Rarely on nutritionally poor media, small pear-shaped microconidia may eventually be formed. As the mycelial form is not distinctive, demonstration of thermal dimorphism should be attempted.

Subculture on blood agar at 37°C will induce yeast cell formation. Large round to oval structures, some producing a characteristic mother cell surrounded by smaller buds or chains of cells.

Serology

Complement fixation is positive in more than 90% of cases.

There is a cross-reaction with blastomycosis, histoplasmosis and sporotrichosis.

Immunodiffusion is positive in 80–90% of cases with the active disease.

Titres decline following successful treatment.

Management

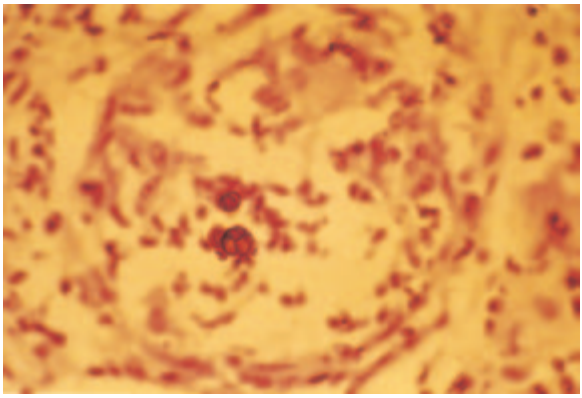
Long-term treatment is needed and relapse is common. Treat with:

- oral itraconazole 200 mg/day initially then 100 mg/day for 6 months
- ketoconazole 400 mg/day initially then 200 mg/day for 12 months is an alternative, but is less well tolerated.

If itraconazole and ketoconazole are contraindicated fluconazole up to 600 mg/day for at least 12 months may be used, but relapse is more common..

Chromoblastomycosis

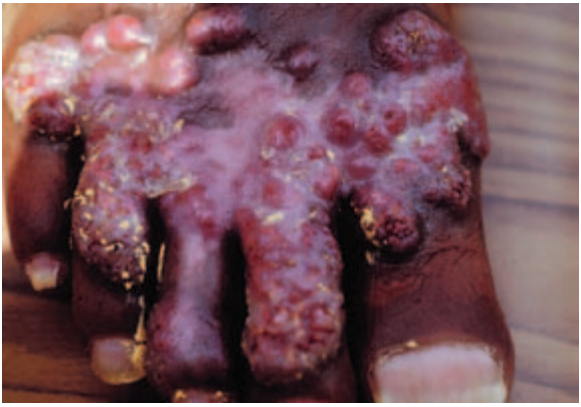
Chromoblastomycosis.



Histopathological appearance of chromoblastomycosis.

Definition

Chromoblastomycosis (chromomycosis) is a chronic, localized infection of the skin and subcutaneous tissue of the limbs, characterized by raised, crusted lesions.



Chronic verrucose chromoblastomycosis of the foot.

Geographical distribution

Most common in tropical and subtropical regions, with most cases occurring in South and Central America.

Causal organisms and habitat

- Caused by brown-pigmented (dematiaceous) fungi, most commonly *Fonsecaea pedrosoi*, but including *Phialophora verrucosa*, *Fonsecaea compacta*, *Cladophialophora* (*Cladosporium*) *carrionii* and *Rhinocladiella aquaspersa*.
- Widespread in the environment in soil, wood and plant material.
- Infection follows traumatic inoculation of fungus into skin.
- Disease is most prevalent among individuals with outdoor occupations.
- Rare in children, most common in males aged 30–60 years.

Clinical manifestations

- Common sites: lower legs, feet, hands, arms, back and neck.
- Initial lesion is a small, pink, painless papule. However, lesion increases in size over a period of years if left untreated and becomes a large hyperkeratotic plaque.
- Lymphatic spread with satellite lesions around original lesion.

- Advanced disease:
  - some lesions become pedunculated
  - bacterial superinfection
  - lymph stasis and elephantiasis in some patients
  - haematogenous dissemination extremely rare even in the immunocompromised.

Essential investigations

Microscopy

Microscopy reveals clusters of small, round, thick-walled, brown sclerotic cells in tissue sections or wet preparations of pus, scrapings or biopsies.

Culture

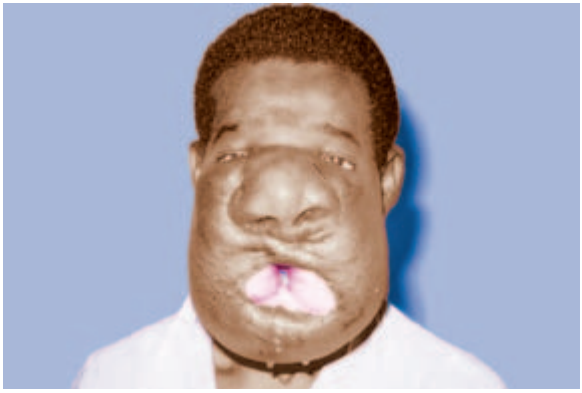
Culture provides a definitive diagnosis. Olive green–brownish black mycelial colonies appear after 1–2 weeks at 25–30°C. Cultures should be retained for 4 weeks before discarding. Any moulds that are isolated can usually be identified by their characteristic spore formation.

Management

This condition is difficult to treat; spontaneous resolution is rare.

- Oral itraconazole 200–400 mg/day for 12–36 months.
- Terbinafine 500 mg/day for 12 months.
- Local application of heat is beneficial, and surgery or cryosurgery for small lesions.
- Voriconazole shows good *in vitro* activity against dematiaceous fungi.

Subcutaneous zygomycosis



Rhinofacial conidiobolomycosis.

Microscopic appearance of *Conidiobolus coronatus* spores.

RHINOFACIAL CONIDIOBOLOMYCOSIS (ENTOMOPHTHORAMYCOSIS)

Definition

Chronic localized subcutaneous fungal infection caused by a

member of the order Entomophthorales. Originates in nasal mucosa and spreads to adjacent subcutaneous tissue of the face, causing severe disfigurement.

Geographical distribution

It is most common in West Africa, in particular Nigeria and in Southeast Asia.

Causal organisms and habitat

- *Conidiobolus coronatus* (*Entomophthora coronata*) or *Conidiobolus incongruous*.
- Found in soil and decomposing vegetation in tropical rainforests.
- Insect pathogen.

Clinical manifestations

- More common in men than in women or children.
- Associated with living or working in tropical rainforests.
- Infection usually originates in nasal mucosa – inferior turbinates.
- Autoinoculation from soiled hands.
- Common symptoms include nasal obstruction, often unilateral, and nasal discharge.
- Progression of disease is slow but relentless.
- Tissue swelling becomes pronounced – affects forehead, nose, cheeks, upper lip.
- No bone involvement.
- Lesions have distinct margin.
- Skin stretched but not broken.
- Dissemination rare.

Essential investigations

Microscopy

Broad, non-septate, thin-walled mycelial fragments are seen in mucosal smears. Hyphae are visualized best with haematoxylin and eosin staining.

Culture

Culture is difficult to obtain. Use a wide range of media. Incubate at 25–35°C. White to buff spreading colonies, waxy at first, becoming powdery with age, typically produce characteristic balistospores which can be seen on the underside of the lid of the petri dish. Some can be seen as a large primary spore producing multiple secondary spores on short stalks, others produce hair-like appendages and some germinate by hyphal outgrowth.

Management

This is difficult to treat.

- Good response to oral itraconazole 200–400 mg/day.
- Ketoconazole 200–400 mg/day.

Continue treatment for at least 1 month after clearance of lesions.

- Saturated potassium iodide 1 mL three times daily, increase up to 4–6 mL three times daily. Continue for at least 1 month after resolution of lesions.

BASIDIOBOLOMYCOSIS (ENTOMOPHTHORAMYCOSIS)

Definition

This is a chronic subcutaneous infection of trunk and limbs.

Geographical distribution

Most common in East and West Africa and Southeast Asia.

Causal organism and habitat

- *Basidiobolus ranarum* (*B. meristosporus*, *B. haptosporus*).
- Decomposing vegetation, soil.
- Intestines of frogs, toads, lizards and other small reptiles.

Clinical manifestations

- More common in children and adolescents than in adults.

- Transmission probably by traumatic inoculation, possibly following the use of leaves for personal hygiene after bowel movements.
- Common sites: buttocks, thighs, perineum, arms, legs and neck.
- Disfiguring.
- Firm, painless nodular subcutaneous lesions spread locally.
- Lymphatic obstruction can result in elephantiasis.

Essential investigations

Microscopy

In histopathological sections wide, irregular, non-septate filaments or hyphal fragments can be seen. Hyphae are visualized best with haematoxylin and eosin staining.

Culture

Culture specimens on glucose peptone agar at 30°C. Identifiable colonies should be obtained in less than 1 week. Flat, spreading, yellow-grey to buff, wrinkled or radially folded, waxy surface with short aerial mycelium. Characteristic ballistospores forcibly discharged to the lid of the petri dish. Secondary spores may be formed on the end of swollen hyphae emerging from the germinated spore or ballistospores may develop endospores.

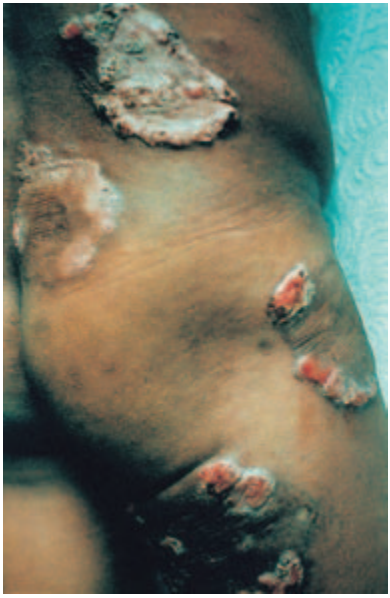
Management

- Topical application of saturated potassium iodide solution is a possible treatment.
- However, co-trimoxazole is sometimes more effective: two tablets, three times daily.

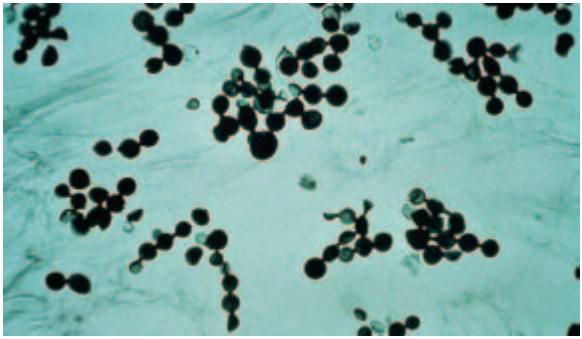
In either case, continue treatment for at least 1 month after resolution of the lesions.

- Oral ketoconazole 400 mg/day is sometimes useful.

Lobomycosis



Lobomycosis.



Histopathological appearance of *Lacazia loboi* in tissue.

Definition

Lobomycosis (keloidal blastomycosis) is a rare, chronic

infection of skin and subcutaneous tissue due to *Loboa loboi* (now known as *Lacazia loboi*).

Geographical distribution

Most cases occur in the Amazon region of central Brazil and in Surinam.

Causal organism and habitat

- *Lacazia loboi*.
- All attempts to isolate in culture have failed.
- Round or elliptical yeast-like cells in tissue.
- Natural habitat unknown but likely to be vegetation, soil and water.
- Water has an important role in infection, which is also seen in dolphins.
- Infection related to a traumatic incident.
- Disease more common in men than in women or children.
- Most prevalent in those 30–40 years of age.

Clinical manifestations

- Most common sites: legs, arms, face, ears, buttocks.
- Initial lesion: papule or a small nodule, slowly proliferates to form extensive keloidal or verrucous lesions in dermis.
- Autoinoculation leads to further lesions.
- Disease symptomless in most cases.
- Insidious progression.

Essential investigations

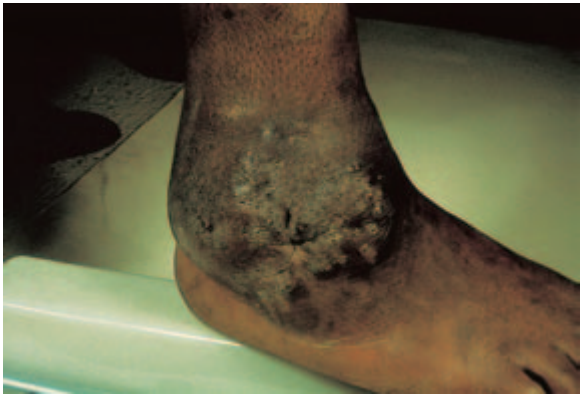
Microscopy

Microscopy reveals large numbers of large, round or oval thick-walled cells (over 10 μm in diameter). The cells produce multiple buds that resemble the tissue form of *Paracoccidioides brasiliensis*. The cells often form in unbranched chains.

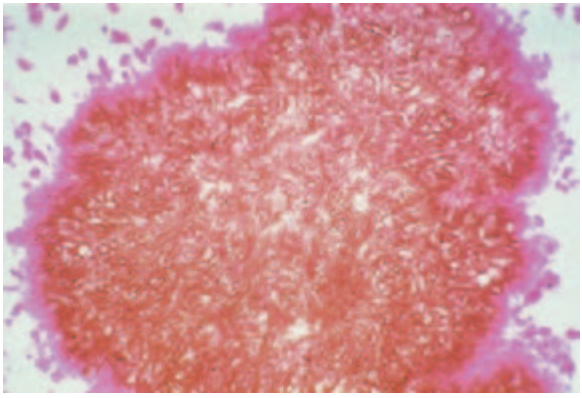
Management

Antifungal treatment is often ineffective. However, oral clofazamine has given promising results. The treatment of choice is surgical excision if the lesions are not too extensive. Cryosurgery and electrosurgery may be curative for small lesions.

Mycetoma



Mycetoma of foot.



Microscopic appearance of *Madurella grisea* grain.

Definition

Chronic localized destructive infection of the skin, subcutaneous tissue and bone of feet or hands.

May be caused by various species of fungi (eumycetoma) or actinomycetes (actinomycetoma).

Geographical distribution

It is found in arid tropical and subtropical regions of Africa and Central and South America. It is endemic in countries surrounding the Saharan and Arabian deserts, India and the Far East.

Causal organisms

- Fungi and actinomycetes, isolated from soil and vegetation.
- Five species of fungi are common causes of eumycetoma: *Madurella mycetomatis*, *M. grisea*, *Scedosporium apiospermum*, *Leptosphaeria senegalensis* and *Pyrenochaeta romeroi*. At least 24 different fungal species have been implicated on occasion.
- Three species of actinomycetes are associated with most cases of actinomycetoma: *Actinomadura madurae*, *Streptomyces somaliensis* and *Nocardia brasiliensis*.

Clinical manifestations

- Infection follows traumatic implantation into skin or subcutaneous tissue.
- Mycetomas most common on feet (70% of cases), followed by hands (10% of cases). Other sites include back, neck and back of head.
- Clinical features of disease are similar, regardless of organism.
- Initial lesions are small, firm painless nodules.
- Eumycetomas follow a slower, less destructive course than actinomycetomas:
  - eumycetomas remain localized: swelling and destruction of adjacent anatomical structures occurs late in course of disease
  - actinomycetomas have less well-defined margins and merge with surrounding tissue. Progression is more rapid. Involvement of bone is earlier and more extensive.
- Lesions present as swellings covered with hypo- or hyperpigmented skin.
- Lesions develop single or multiple sinus tracts.
- Sinus tracts discharge pus containing grains onto skin surface.

- Infection spreads to adjacent tissue, including bone.
- Movement of joints may be impaired.
- Radiology useful in determining extent of bone involvement.
- Cavities in bone vary in size.
- Spread to adjacent tissue is common.
- Bacterial superinfection is common.

Essential investigations

Microscopy

Direct microscopy will confirm diagnosis. Actinomycotic grains contain very fine filaments whereas fungal grains contain short hyphae, which are sometimes pigmented:

- black grains: suggest a fungal infection
- minute white grains: *Nocardia*
- large white grains: fungal or actinomycotic
- small red grains: actinomycotic or fungal
- yellowish-white grains: actinomycotic or fungal.

Culture

Culture grains on glucose peptone agar at 25–30°C and at 37°C for up to 6 weeks. Agents of eumycetoma may be identified by the spores they produce, with the exception of *M. grisea* which does not sporulate. Molecular methods can be used for identification purposes. Actinomycetes can be identified by phenotypic (morphological and biochemical) or molecular methods.

Management

It is essential to distinguish eumycetoma from actinomycetoma.

In cases of actinomycetoma:

- streptomycin sulphate 1000 mg/day intramuscular injection
- streptomycin and co-trimoxazole, two tablets in the morning and two in the evening
- infection due to *A. madurae* and *S. somaliensis*, combine streptomycin with dapsone, 200 mg/day.

If there is no response:

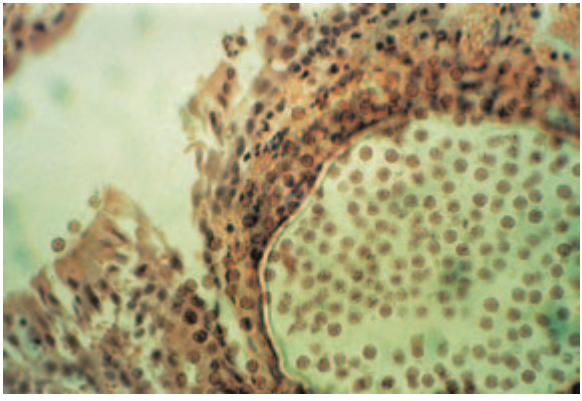
- streptomycin plus rifampicin 600 mg/day

- streptomycin plus sulphadoxine–pyrimethane in the form of one Fansidar tablet twice a week. Each tablet contains 500 mg sulphadoxine and 25 mg pyrimethamine.

In cases of eumycetoma:

- early surgery can be curative for small lesions
- variable responses to antifungal therapy possibly due to lack of penetration of drug into the mycetoma
- *in vitro* testing of the causative agent may help to direct therapy although correlation not always good
- antifungal therapy for at least 6 months may cure lesions or help to reduce size of lesion prior to surgery
- amputation if bone involvement
- relapse common if not all infected tissue removed
- antifungal therapy may reduce relapse rate when used following surgical excision
- long-term treatment with ketoconazole 400 mg/day or itraconazole 400 mg/day successful in some cases
- voriconazole may be useful in the treatment of mycetoma due to *Scedosporium apiospermum* and some of the other hyaline and dematiaceous moulds
- high-dose terbinafine (up to 1000 mg/day) has been used with some success.

Rhinosporidiosis



Histopathological appearance of rhinosporidiosis showing thick-walled sporangium.

Definition

Granulomatous infection of the nasal and other mucosa.

Geographical distribution

Most common in India and Sri Lanka. However, there have been sporadic cases in East Africa, Central America and Southeast Asia.

Causal organism and habitat

- *Rhinosporidium seeberi* has long been considered as a fungus but may in fact be a protistan parasite.
- Attempts to isolate in culture have failed.
- In tissue, forms abundant, large, thick-walled 'sporangia'.
- Large numbers of 'endospores' produced within 'sporangium'.
- Not known how infection is acquired, however, pools of stagnant water may be an important source.
- Increased numbers of infections following dust storms.

- Disease most prevalent in rural districts.
- Males more commonly affected than females; most common in age group 15–40 years.

Clinical manifestations

- Nose most common site, with large sessile or pedunculated lesions in one or both nostrils.
- Insidious infection.
- Rhinoscopic examination reveals papular or nodular, smooth-surfaced, pink, red or purple lesions that become pedunculated.
- If located low in nostril, polyps may protrude and hang onto the upper lip.
- Ocular infection involving the conjunctiva may also occur.
- General health is not usually impaired.
- If left untreated, polyp will continue to enlarge.

Essential investigations

Microscopy

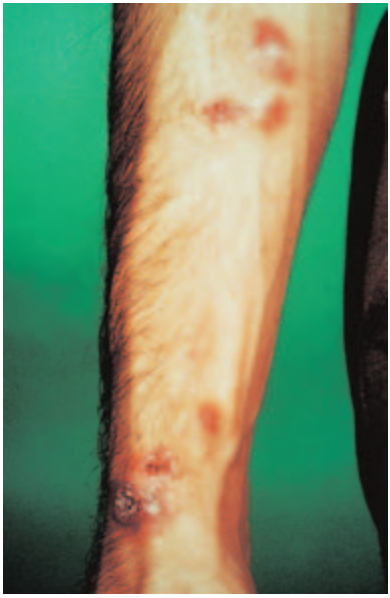
Microscopy of tissue sections or wet preparations of tissue or discharge show large round or oval sporangia up to 350 μm in diameter. The 'sporangium' may be filled with 'endospores'.

R. seeberi has never been isolated in culture.

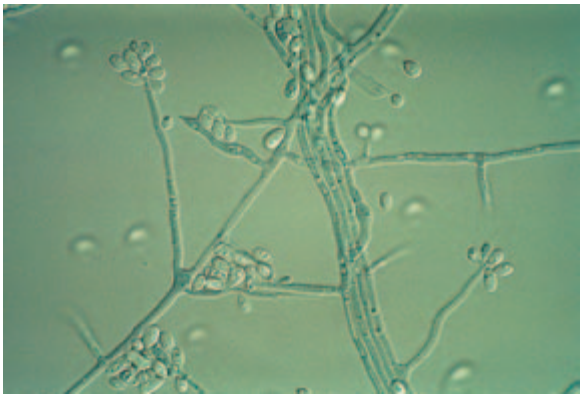
Management

Surgical excision of the lesions is treatment of choice, especially electrosurgery. Response to some drug treatment reported (dapsone, amphotericin B, griseofulvin). Recurrence is common.

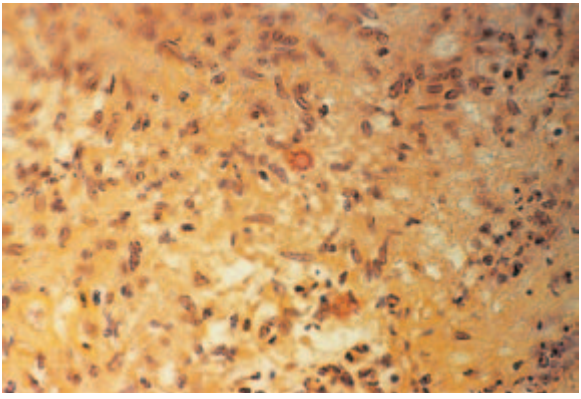
Sporotrichosis



Sporotrichosis.



Sporothrix schenckii conidia.



Histopathological appearance of sporotrichosis showing asteroid bodies.

Definition

Subacute or chronic cutaneous or subcutaneous infection caused by the thermally dimorphic fungus *Sporothrix schenckii*. Commonly shows lymphatic spread. Occasionally, infection of lungs, joints and bones occurs in predisposed individuals.

Geographical distribution

World-wide, although it is most common in warm, temperate or tropical climatic regions. Most cases are from the USA but it is also endemic in Central and South America, Africa and Australia.

Causal organism and habitat

- *Sporothrix schenckii*.
- Soil, on plants, on plant materials.
- Mycelium in nature, small budding cells in tissue.
- More common in adults and most prevalent where there is contact with soil, plants, or plant materials.
- Most cases sporadic.
- Epidemics sometimes occur in endemic regions.

Clinical manifestations

Cutaneous sporotrichosis

- Follows traumatic implantation of fungus into skin or subcutaneous tissue.
- Minor trauma sufficient to introduce organism.
- Affects exposed sites, in particular hands and fingers.
- Initial lesion appears 1–4 weeks after traumatic incident as a small, firm, painless nodule. After this:
  - skin becomes violaceous
  - nodule becomes soft to form persistent discharging ulcer with irregular edge
  - ulcer becomes oedematous and crusted
  - further nodules develop along course of lymphatic channels, and become ulcerated.
- No lymphatic spread in about 25% of cutaneous infections.
- Disseminated cutaneous forms occur occasionally.

Extracutaneous sporotrichosis

- Most commonly where there is underlying disease.
- Most common sites: lungs, joints and bones – resulting in arthritis.
- Chronic pulmonary disease uncommon.
- Meningitis and ocular disease are uncommon manifestations.
- HIV-infected patients are much more likely to present with haematogenously disseminated disease.

Essential investigations

Microscopy

The organism is seldom seen in pus or tissue. Detection of oval-shaped cells or asteroid bodies confirms diagnosis.

Culture

Culture provides the definitive diagnosis. Use several media, including glucose peptone agar. On this, mycelial colonies appear in 3–5 days at 25–30°C. Initially the colony is moist and off-white, often forming a black or brown pigment after 10 days. Characteristic rosettes of small, tear drop-shaped

spores are formed at the end of conidiophores. Later-formed conidia are formed along the sides of hyphae and are darkly pigmented. The rarer pathogen *Sporothrix cyanescens* produces a purple pigment.

Confirmation of identification requires conversion to yeast form on blood agar at 37°C. Microscopy of smooth, cream-coloured colonies reveals long to oval budding yeast cells.

Management

Cutaneous and lymphocutaneous forms

Treat with:

- Oral itraconazole 100–200 mg/day for 3–6 months.

Continue treatment for several months after the lesions have cleared.

- Alternatively, give fluconazole 400 mg/day minimum for 6 months if itraconazole is not tolerated or not absorbed.

Supersaturated solution of potassium iodide is useful where antifungals are not available.

Local application of heat may be used in cases of drug intolerance.

Extracutaneous forms

These are difficult to treat. For osteoarticular forms potassium iodide is ineffective. Therefore:

- itraconazole 400 mg/day for more than 12 months is the drug of choice
- alternatively, if itraconazole is contraindicated, fluconazole 400–800 mg/day can be given.

For pulmonary forms:

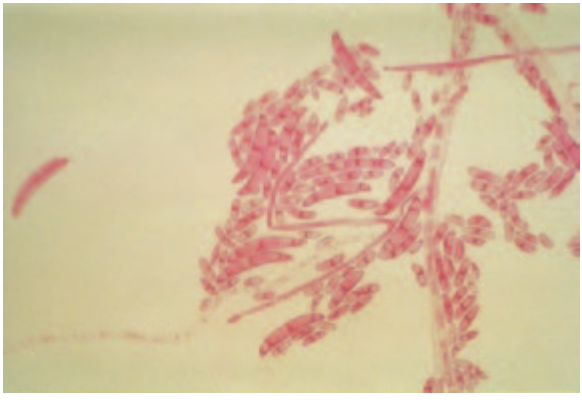
- amphotericin B 1.0 mg/kg/day. When there are signs of improvement, substitute with itraconazole 400 mg/day.

For disseminated forms:

- amphotericin B 1.0 mg/kg/day until 1–2 g have been administered. Less acute forms can be treated with itraconazole 400 mg/day
- in AIDS itraconazole treatment must be maintained for life.

Hyalohyphomycosis

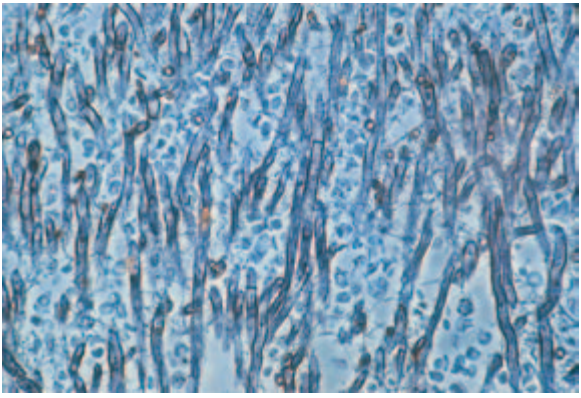
Fusarium solani culture.



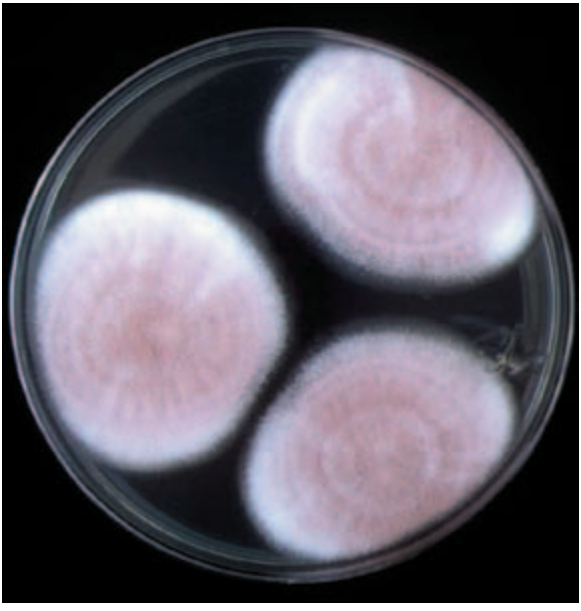
Microscopic appearance of *Fusarium solani*.

Definition

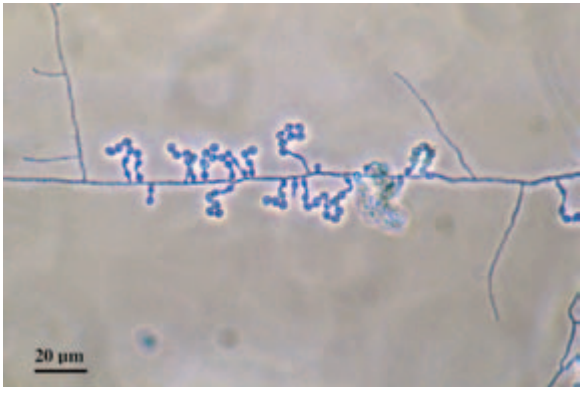
Hyalohyphomycosis is the term used to describe infections with moulds that appear as hyaline (colourless), septate filaments in host tissues.



Histopathological appearance of *Scedosporium apiospermum* in a heart valve.



Culture of *Paecilomyces lilacinus*.



Microscopic morphology of *Scedosporium prolificans*.

Geographical distribution

World-wide as environmental saprobes or plant pathogens.

Causal organisms and habitat

- More than 40 species from more than 20 genera implicated.
- Infections caused by environmental moulds and plant pathogens that produce large numbers of spores suited to air or water dispersal.
- Diseases sufficiently common to warrant own disease name are not included in this group. Best known example of hyalohyphomycosis is aspergillosis.
- Two most commonly isolated agents: *Fusarium* spp. and *Scedosporium* spp.
- Infections with *Scedosporium apiospermum* sometimes referred to as pseudallescheriosis after the sexual form of the fungus *Pseudallescheria boydii*.
- *Scedosporium prolificans* emerging as a pathogen in immunocompromised patients.
- Other emerging pathogens: *Acremonium* spp., *Paecilomyces* spp., *Scopulariopsis* spp., with many others isolated rarely.

Clinical manifestations

- Localized infection following traumatic inoculation in immunocompetent hosts.
- May occur in patients on continuous peritoneal dialysis.
- These agents can cause sinusitis, which may be the presenting feature of disseminated disease in an immunocompromised host.
- Inhalation thought to be the major route of acquisition of disseminated infection.
- Manifestations of pulmonary or disseminated hyalohyphomycosis often mimic those of invasive aspergillosis.
- Disseminated infections most commonly encountered in neutropenic patients.
- Neutropenic fever unresponsive to broad-spectrum antibiotics – most common presenting feature.
- Skin lesions may be present in up to 70% of *Fusarium* infection cases.
- Vascular invasion may result in thrombosis and tissue necrosis.
- Infection with *Fusarium* spp. or *Scopulariopsis* spp. may arise from an infected nail in neutropenic patients.
- Infection with *Scedosporium* spp. may follow aspiration of contaminated fresh water during near-drowning accidents.
- Dissemination to the brain is a common consequence of *Scedosporium* pneumonia.
- Fungus ball formation may be caused by *Scedosporium* in patients with pre-existing lung cavities.
- *Scedosporium* spp. are frequently seen colonizing the lungs of patients with cystic fibrosis and can go on to become invasive.

Essential investigations

Microscopy

On microscopy, the hyphal tissue form cannot be distinguished from other agents of hyalohyphomycosis or aspergillosis unless terminal annelloconidia are seen, indicating infection with *Scedosporium* spp., or occasionally *Fusarium* spores may be formed in tissues.

Culture

The infecting organism may be isolated from biopsies of cutaneous lesions. These should be chopped into small portions but not homogenised as this could result in non-viable mycelial fragments.

Culture is essential to make a definitive diagnosis. Blood culture is frequently positive in cases of infection with *Fusarium* and *Acremonium* spp. Culture of tissue, sputum, bronchoalveolar lavage specimens and other body fluids, etc. should be attempted on glucose peptone agar at 30°C and 37°C. Once a mould colony has been isolated microscopic examination of the spores and their method of formation can reveal the identification.

As many of these moulds are encountered as contaminants care should be taken to establish the clinical significance of isolates for which there is not positive direct microscopy.

CT scans are invaluable in determining the extent of paranasal sinus infection and determining whether lung and/or brain lesions are solitary or multifocal.

Management

Many of the agents of hyalohyphomycosis are refractory to treatment with currently available agents so it is important wherever possible to make a definitive diagnosis.

Aggressive surgical debridement of infected tissue is the treatment of choice in patients with localized lesions. However, the therapeutic outcome in disseminated disease is often dependent on the immune status of the host.

Cytokine therapy may be used in addition to antifungal therapy in an attempt to reduce the depth and duration of neutropenia.

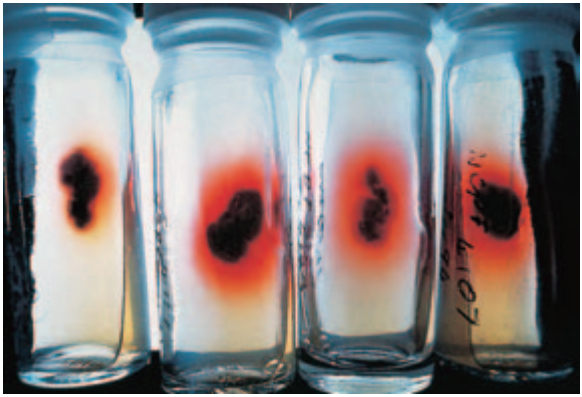
Treatment with high-dose amphotericin B may be effective in patients with *Fusarium* infection; use of a lipid preparation should be considered.

There is evidence that the new triazole, voriconazole, may be of benefit in some cases of *Fusarium* infection.

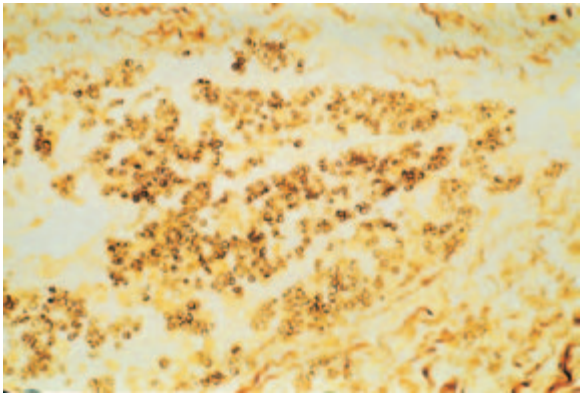
Scedosporium spp. are often resistant to amphotericin B *in vitro* and fail to respond to the drug *in vivo*.

Azole therapy with itraconazole 400 mg/day or voriconazole may be beneficial in cases of *Scedosporium* infection and there is anecdotal and laboratory evidence that an azole combined with terbinafine may have more activity than either drug alone.

Penicillium marneffei infection



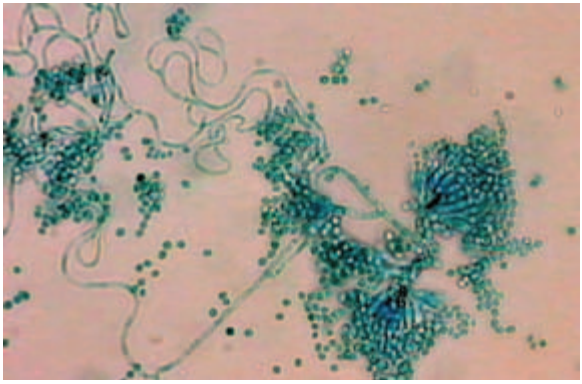
Penicillium marneffei culture.



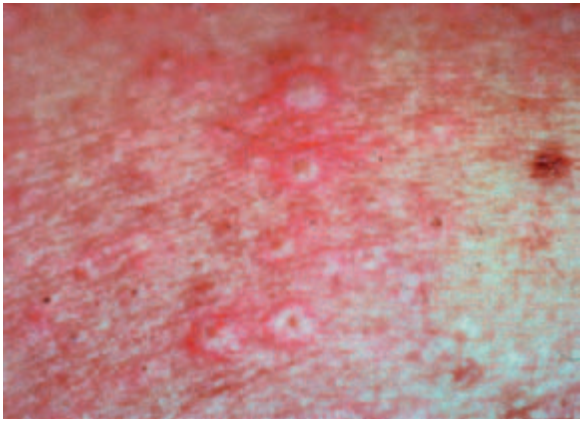
Histopathological appearance of *Penicillium marneffei* in the liver of an AIDS patient.

Definition

Penicillium marneffei is one of the most frequent opportunistic infections encountered in patients with AIDS who have resided



Microscopic morphology of *Penicillium marneffei*.



Papules caused by *Penicillium marneffei* in an HIV-positive patient.

in or visited Southeast Asia or southern China. However, the disease can also occur in otherwise healthy patients.

Geographical distribution

Northern Thailand and southern China.

Causal organism and habitat

- Dimorphic fungus: mycelium at 28°C; but in tissue and at

37°C on brain heart infusion agar forms round to elliptical cells which divide by fission.

- Frequently isolated from the internal organs of bamboo rats in the absence of overt infection.
- Natural habitat has not been identified, but probably soil; the organism has been isolated from the faeces and burrows of bamboo rats.
- The main risk factor appears to be occupational soil exposure.
- Doubling of cases during the rainy season.
- Third most common opportunistic infection among AIDS patients in northern Thailand.
- Increasingly diagnosed in patients with AIDS who have visited endemic areas.

Clinical manifestations

- Infection probably follows inhalation as the disease is usually primarily pulmonary.
- Most patients present with widespread dissemination.
- Often chronic progressive illness.
- Most common symptoms are fever, weight loss, debilitation, multiple papular skin lesions, generalized lymphadenitis and hepatosplenic enlargement.
- It is fatal if left untreated.

Essential investigations

Microscopy and culture

Round, oval or elliptical cells, often with prominent cross-walls seen in Wright-stained bone marrow smears or touch smears of skin lymph node biopsies.

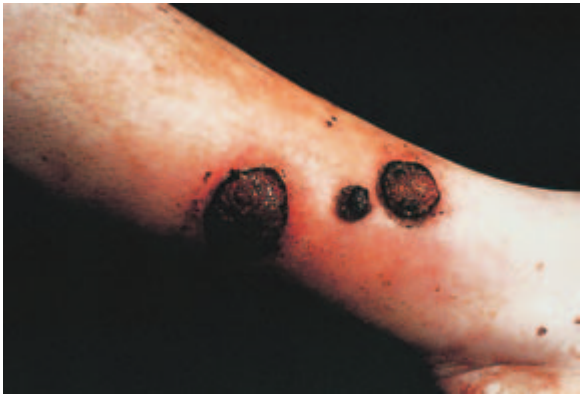
- Isolated from skin and lymph node biopsies, pus, bone marrow aspirates, sputum and BAL.
- Recovered from blood cultures in > 70% of AIDS cases.
- Mycelial cultures after 1 week at 25–30°C on glucose peptone agar; green, sometimes yellow, powdery mould with distinctive red diffusing pigment.
- Hazard category III.
- Yeast-like growth at 37°C on brain heart infusion agar, a feature that can be used to differentiate this pathogenic

species from other environmental *Penicillium* spp., which do not form yeast-like cells at 37°C.

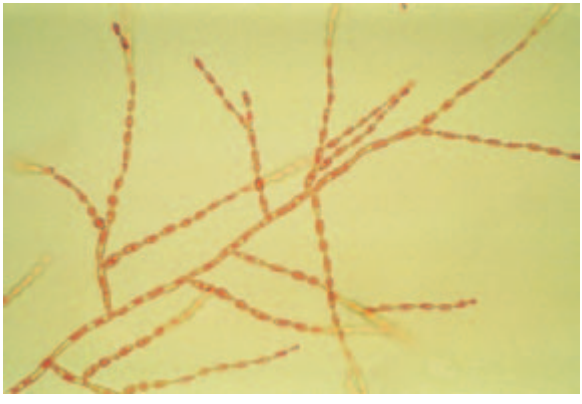
Management

- Amphotericin B 0.6–1.0 mg/kg/day for 6–8 weeks.
- Or, after 2 weeks switch to itraconazole 400 mg/day for a further 10 weeks if patient shows improvement.
- For mild infections itraconazole can be used from the outset but more than 8 weeks therapy may be required.
- Maintenance with oral itraconazole 200 mg/day in AIDS patients; relapse is common when discontinued.
- Primary prophylaxis with itraconazole 200 mg/day should be considered in HIV-infected patients in endemic areas.

Phaeohyphomycosis



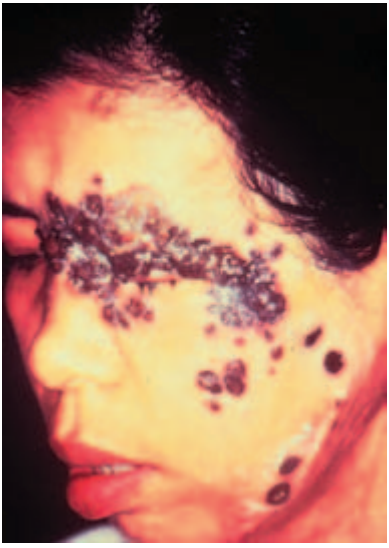
Cutaneous phaeohyphomycosis caused by an *Alternaria* spp.



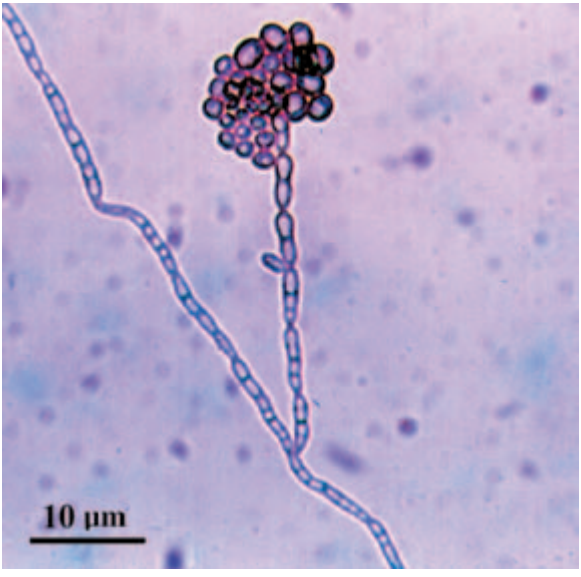
Microscopic appearance of *Cladophialophora bantiana*.

Definition

Phaeohyphomycosis is the term used to describe infections with darkly pigmented moulds that appear as septate filaments in host tissues.



Cutaneous phaeohyphomycosis caused by (*Wangiella*) *Exophiala dermatitidis*.



Microscopic morphology of (*Wangiella*) *Exophiala dermatitidis*.

Geographical distribution

World-wide, but invasive forms have been reported more frequently in temperate climates. Subcutaneous lesions are more common in tropical regions.

Causal organisms and habitat

- Agents of phaeohyphomycosis share a common feature of melanin in the cell wall producing a dark colour and possibly making them more resistant to damage by host phagocytic cells.
- More than 100 different species from at least 60 genera implicated and list increasing steadily.
- Infections caused by environmental moulds or plant pathogens that produce large numbers of spores suited to air or water dispersal.
- Infection often follows inhalation or traumatic implantation.
- Recognized aetiological agents include *Alternaria* spp., *Bipolaris* spp., *Cladophialophora bantiana*, *Curvularia* spp., *Exerohilum* spp., *Exophiala* spp., *Phialophora* spp. and *Ochroconis* spp., with many others encountered occasionally.
- *Exophiala jeanselmei* and *Exophiala* (*Wangiella*) *dermatitidis* implicated most frequently.
- *Cladophialophora bantiana* and *Exophiala dermatitidis* appear to be particularly neurotrophic.
- *C. bantiana* is categorised as Hazard Category III.

Clinical manifestations

- There are several different presentations depending on the route of acquisition.
- Superficial phaeohyphomycosis, known as tinea nigra, is caused by *Phaeoannellomyces werneckii* and only infects the stratum corneum.
- Another form known as black piedra caused by *Piedraia hortae* affects the hair shaft.
- Superficial infection due to *Scytalidium* spp. infecting skin and nail can become more invasive in the immunosuppressed.
- The most common lesions of phaeohyphomycosis are localized cutaneous or subcutaneous abscesses, granulomas or cysts that occur following traumatic implantation.

- Such lesions should not be confused with those of chromoblastomycosis (see p. 102) in which muriform cells are seen or black-grain eumycetoma (see p. 114), which is characterized by the formation of dark granules.
- Cutaneous or subcutaneous lesions of phaeohyphomycosis often follow minor trauma such as cuts, abrasions or splinters and there is little tendency for lymphatic or haematogenous dissemination. Draining sinus formation may occur in immunocompromised patients.
- Paranasal sinus infection may follow inhalation.
- In immunocompromised patients black, necrotic lesions may be visible.
- Cerebral infection may progress from paranasal sinus infection or may be due to haematogenous dissemination from the lungs.
- Infection of the brain is often indolent in onset.
- Infection of other deep sites including the heart may follow surgical procedures.
- Nosocomial outbreaks can follow contamination of medical equipment, fluids or drugs.
- Infection of long-term indwelling catheters, such as those required for CAPD, can occur.

Essential investigations

Microscopy

Microscopy of exudates or tissue sections reveals dark coloured, branching, septate hyphae often with yeast-like forms, pseudohyphae and moniliform hyphae. Sometimes a routine haematoxylin–eosin stain is insufficient to reveal the dark pigment as some fungal species produce little melanin *in vivo*. In such cases a Fontana–Masson stain may be useful to confirm the presence of melanin.

Culture

Culture is essential to isolate and identify the aetiological agent and in order to perform antifungal susceptibility testing. As many of these moulds can be isolated as contaminants care should be taken to establish the clinical significance of any isolates for which there is no positive direct microscopy.

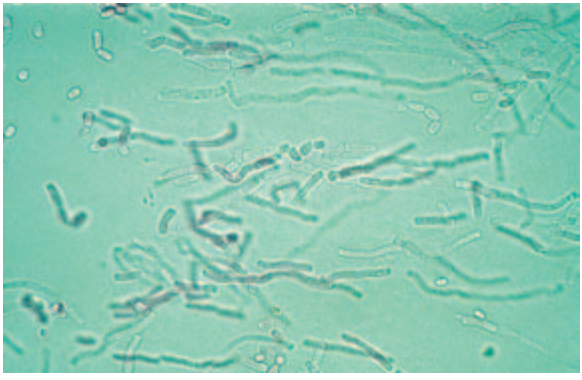
Prolonged incubation for up to 3 weeks at 30°C on glucose peptone agar may be required.

CT scans are invaluable in determining the extent of paranasal sinus infection and determining whether brain lesions are solitary or multifocal.

Management

- Surgical excision is often curative in cases of localized infection or sinusitis, whereas antifungal therapy alone with amphotericin B has often resulted in relapse.
- Repeated surgical debridement is also an important adjunct to antifungal therapy in cases of paranasal sinus infection and cerebral phaeohyphomycosis.
- Disseminated infections are associated with a high rate of mortality especially if there are multifocal brain lesions.
- Amphotericin B therapy is indicated, possibly with the addition of flucytosine.
- There is some evidence that itraconazole 100–400 mg/day has proved effective in cases of paranasal sinus infection.
- Experience with the newer azoles such as voriconazole and posaconazole is limited but there are anecdotal successes.
- If the causative agent is isolated then antifungal susceptibility testing may help to direct appropriate antifungal therapy, although the pharmacokinetic properties and tissue distributions of the agents should also be considered.

Uncommon yeast infections



Microscopic appearance of *Trichosporon asahii*.

Culture of *Trichosporon asahii*.

TRICHOSPORONOSIS

Definition

A deep-seated infection in immunocompromised hosts caused by *Trichosporon asahii* (previously known as *T. beigelii*,

T. cutaneum). Similar infection caused by *Blastoschizomyces capitatus* (formerly *T. capitatum*, *Geotrichum capitatum*).

Geographical distribution

World-wide.

Causal organisms and habitat

- *Trichosporon asahii* (may include several different *Trichosporon* spp.) and *Blastoschizomyces capitatus*.
- Soil, water and on plants.
- Mucosal and cutaneous surfaces.
- Endogenous reservoir in gastrointestinal tract.

Clinical manifestations

- Localized deep infections:
  - endophthalmitis
  - endocarditis
  - peritonitis
  - pulmonary (most frequently affected organ).
- Disseminated:
  - uncommon, seen in neutropenia, BMT recipients, solid organ recipients and AIDS
  - many similarities with systemic candidosis
  - cutaneous lesions in about one-third of patients
  - renal involvement in > 75% (haematuria, proteinuria, red cell casts)
  - chorioretinitis common.

Essential investigations

Microscopy

Microscopy will reveal branching hyphae, rectangular arthrospores and budding blastospores.

Culture

Culture of blood, urine and cutaneous lesions yields white to cream, heaped, folded, colonies. Identification on the basis of carbohydrate assimilation patterns and microscopic morphology. Most species produce urease.

Blood cultures and cutaneous lesion biopsies are often positive.

Serology

There is antigenic cross-reactivity with *Cryptococcus neoformans*.

Latex agglutination test for cryptococcosis positive in trichosporonosis.

Management

High mortality rate for disseminated infection.

Important to reduce or reverse the immunocompromised state.

For localized infection in non-neutropenic patients treat with

- amphotericin B 1.0 mg/kg/day; add flucytosine or fluconazole if blood culture remains positive.

In neutropenics amphotericin B is of little benefit and often shows reduced activity against *Trichosporon asahii* in *in vitro* susceptibility tests.

Some success with fluconazole 400–800 mg/day or itraconazole 400–600 mg/day or combinations of fluconazole and lipid forms of amphotericin B.

Antifungal susceptibility testing may help to guide treatment. The newer azoles voriconazole, posaconazole and ravuconazole all demonstrate good *in vitro* activity against *Trichosporon* spp. and *Blastoschizomyces capitatus*.

SYSTEMIC *MALASSEZIA* (*PITYROSPORUM*) INFECTION

Definition

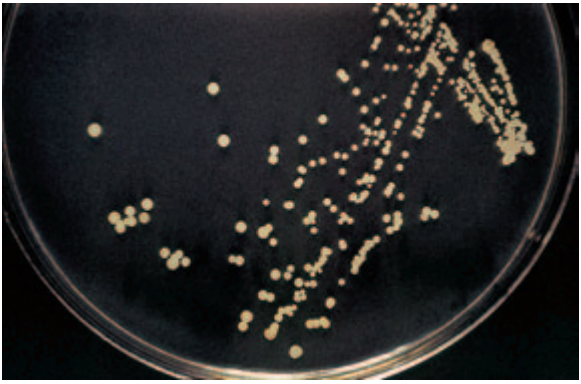
This is a serious systemic infection seen in low birth-weight infants, and debilitated adults and children receiving parenteral lipid nutrition through indwelling catheters.

Geographical distribution

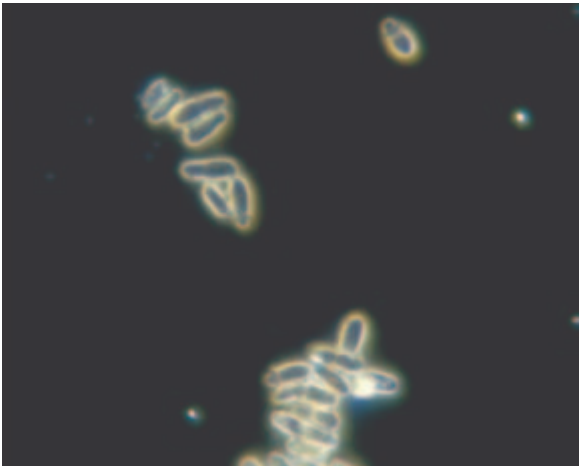
World-wide.

Causal organism and habitat

- *Malassezia furfur* (*Pityrosporum orbiculare*, *P. ovale*).
- Lipophilic.
- Part of normal cutaneous flora, especially areas of oily skin.



Culture of *Malassezia pachydermatis*.



Microscopic appearance of *Malassezia* spp. demonstrating budding on a broad base.

- *Malassezia pachydermatis* causes similar infections; it is most often found causing otitis externa in dogs.
- Well-recognized complication of total parenteral nutrition.
- Especially seen in preterm and infants less than 12 months old.
- Low virulence.

Clinical manifestations

- Fever and/or apnoea and brachycardia.
- Interstitial pneumonia and thrombocytopenia.
- Hepatosplenomegaly.
- No sign of infection at catheter insertion sites.
- Predominant pathological changes involve heart and lungs.

Essential investigations

Microscopy and culture

Culture can be taken from blood that has passed through the catheter, with isolation from the catheter tip.

Gram stain of the buffy coat may reveal small yeast cells with characteristic percurrent budding on a broad base.

Subculture onto lipid-containing media, after which identifiable colonies can be seen after 4–6 days at 32°C. Sometimes carryover of lipid in the blood culture allows minimal growth of the organism on subculture onto lipid-free medium.

Malassezia pachydermatis will often grow well on lipid-free medium; this is a helpful feature for its identification.

Microscopy reveals yeast cells with characteristic budding on a broad base.

Management

Remove the infected vascular catheter and discontinue the lipid supplements. Patients can be treated with parenteral fluconazole 5 mg/kg or amphotericin B 0.7 mg/kg/day. Antifungal therapy should be instituted if fungaemia persists or there is deep organ involvement.

More stable patients can be given fluconazole or itraconazole by mouth.

SYSTEMIC *SACCHAROMYCES* INFECTION

Definition

This is a serious systemic infection due to *Saccharomyces* spp., particularly *Saccharomyces cerevisiae* (brewer's and baker's yeast), which is seen most often in immunocompromised patients.

Geographical distribution

World-wide.

Causal organisms and habitat

- *Saccharomyces cerevisiae* isolated most frequently, *S. carlesbergensis* and other *Saccharomyces* spp. occasionally. These are ascomycete yeasts.
- Used in the baking and brewing industry.
- May be found as part of normal flora of gastrointestinal tract and mucosal surfaces.
- Opportunistic pathogens with very low virulence.

Clinical manifestations

- Fungaemia associated with intravenous catheters, broad-spectrum antibacterial use, hyperalimentation, surgery, immunosuppression.
- Fever and other features similar to those of systemic candidosis.
- Occasional cases of pneumonia, empyema, endocarditis, peritonitis and urinary tract infection.

Essential investigations

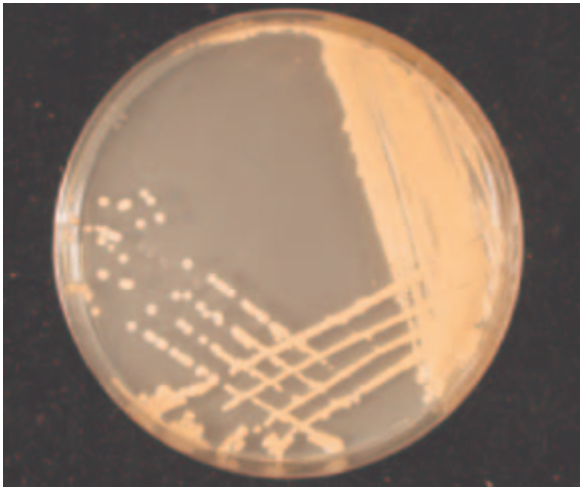
Microscopy and culture

Culture can be taken from blood that has passed through the catheter, with isolation from the catheter tip.

Subculture onto glucose peptone agar; colonies can be seen after 1–3 days at 30°C. Budding yeast cells seen sometimes with rudimentary pseudomycelium. Identification by analysis of carbohydrate assimilation patterns and microscopic morphology; about 60% of isolates produce ascospores.

Management

The role of antifungal therapy remains unproven. Remove the infected vascular catheter. Patients can be treated with parenteral fluconazole 5 mg/kg or amphotericin B 0.7 mg/kg/day although *in vitro* susceptibility is usually less than that seen with most *Candida* spp. Antifungal therapy



Culture of *Rhodotorula rubra* on glucose peptone agar showing pink colouration.

should be instituted if fungaemia persists or there is deep organ involvement.

More stable patients can be given fluconazole or itraconazole by mouth.

SYSTEMIC *RHODOTORULA* INFECTION

Definition

This is a serious systemic infection due to *Rhodotorula* spp. seen mainly in immunocompromised and surgical patients.

Geographical distribution

World-wide.

Causal organisms and habitat

- *Rhodotorula* spp. are encapsulated basidiomycetous yeasts belonging to the family Cryptococcaceae.
- *Rhodotorula rubra*, *R. glutinis* and *R. minuta* are the species most commonly encountered from infection.

- Can be found as part of the human commensal flora, especially as a contaminant of skin, nail and gastrointestinal tract, often associated with food, particularly dairy products and fruit.
- May be encountered as an airborne culture contaminant.
- Red, pink or orange colonies due to carotenoid pigment.

Clinical manifestations

- Fungaemia associated with intravenous catheters, broad-spectrum antibacterial use, hyperalimentation, surgery, immunosuppression.
- Fever and other features of systemic candidosis.
- Peritonitis in patients undergoing continuous ambulatory peritoneal dialysis.
- Endocarditis, vetriculitis, meningitis.

Essential investigations

Microscopy and culture

Culture can be taken from blood that has passed through the catheter, with isolation from the catheter tip.

Subculture onto glucose peptone agar reveals bright red, pink or orange-coloured mucoid colonies.

Microscopy reveals large, spherical or subspherical budding yeast cells, rarely with the formation of true or pseudohyphae. Identification by analysis of carbohydrate assimilation patterns, urease production and microscopic morphology.

Care should be taken to establish clinical significance of isolates from non-sterile sites.

Management

Remove the infected vascular catheter. Patients should also be treated with systemic antifungal therapy. As isolates often demonstrate reduced susceptibility or *in vitro* resistance to azole drugs and are not susceptible to caspofungin, amphotericin B 0.7–1.0 mg/kg/day is recommended and the addition of flucytosine may be helpful in some circumstances.

SYSTEMIC *HANSENULA* INFECTION

Definition

This is a serious systemic infection due to *Hansenula* spp. seen mainly in immunocompromised and surgical patients.

Geographical distribution

World-wide.

Causal organisms and habitat

- *Hansenula* spp. are environmental ascomycetous yeasts often found associated with organic substrates.
- *Hansenula anomola* (*Candida pelliculosa*) is the species most commonly encountered from infection.

Clinical manifestations

- Fungaemia associated with intravenous catheters, broad-spectrum antibacterial use, hyperalimentation, surgery, immunosuppression.
- Fever and other features of systemic candidosis.

Essential investigations

Microscopy and culture

Culture can be taken from blood that has passed through the catheter, with isolation from the catheter tip.

Subculture onto glucose peptone agar reveals cream-coloured colonies.

Microscopy reveals multilateral budding yeast cells with the ability to form hat-shaped ascospores.

Management

Remove the infected vascular catheter. Patients should also be treated with systemic antifungal therapy: amphotericin B 0.7–1.0 mg/kg/day has been used most often. Fluconazole has also proved effective although isolates should undergo susceptibility testing as some are azole resistant.

SPOROBOLOMYCES INFECTION

Definition

This is a rare infection due to *Sporobolomyces* spp.

Geographical distribution

World-wide.

Causal organisms and habitat

- *Sporobolomyces* spp. are commonly isolated from soil.
- *Sporobolomyces salmonicolor* is the species most commonly encountered from infection.
- Red, pink or orange colonies due to carotenoid pigment produce ballistospores.

Clinical manifestations

- Rare cause of infection, with differing presentations.

Essential investigations

Microscopy and culture

Culture of tissue or body fluids onto glucose peptone agar reveals bright red, pink or orange-coloured mucoid colonies that produce ballistospores which can be seen on the lid of the petri dish. This can be used to help differentiate this genus from the colonially similar *Rhodotorula* spp.

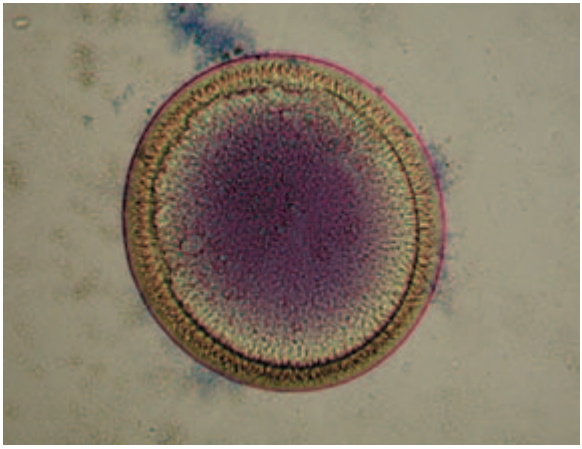
Microscopy reveals budding yeast cells with the formation of true or pseudohyphae. Identification by analysis of carbohydrate assimilation patterns; urease producers.

Care should be taken to establish clinical significance of isolates from non-sterile sites.

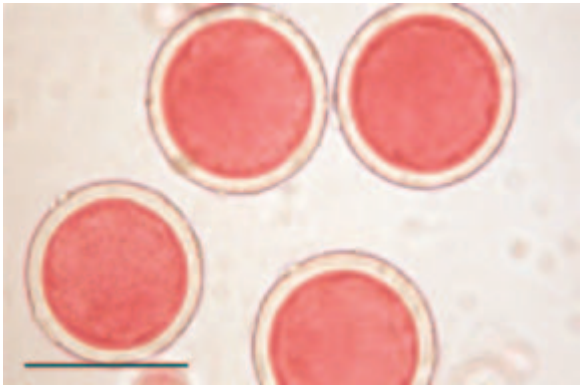
Management

Patients should be treated with systemic antifungal therapy. Amphotericin B and azole treatment have proved effective. Susceptibility testing of isolates may help to guide therapy.

Adiaspiromycosis



Adiaspore from KOH-digested water vole lung, stained with calcofluor.



Adiaspores of *Emmonsia crescens in vitro* (6 weeks, 37°C on BHBC media; bar = 100 μm).

Definition

Rare pulmonary infection of humans following inhalation of spores of the dimorphic fungus *Emmonsia*. Adiaspiromycosis

is most often encountered in rodents and is widespread amongst the rodent population in endemic areas. Inhaled conidia do not germinate or reproduce within host tissues but enlarge to form adiaspores.

Geographical distribution

Adiaspiromycosis is widespread in rodent populations in many temperate climates; the causative organism *Emmonsia* is a soil organism often associated with rodent burrows. There are endemic areas for *Emmonsia parva* (*Chrysosporium parvum*) in southwestern USA, Australia and Eastern Europe. *Emmonsia crescens* appears to be more widespread and is found in temperate zones.

Causal organisms and habitat

- *E. crescens* causes disease in humans and animals, and is widespread.
- *E. parva* has only been found causing disease in animals and has a restricted endemic area.
- *E. pasteuriana* has been reported from an HIV-infected patient and forms yeast cells (some swollen) in tissue.
- *Emmonsia* spp. exist in nature as mycelium, and in tissue as large, round adiaspores that resemble the spherules of coccidioidomycosis
- Soil is the natural habitat; greatest survival is in moist, cold soil.
- Found in many different temperate regions.
- Risk factors have not been identified.

Clinical manifestations

Pulmonary adiaspiromycosis

- Infection follows inhalation.
- Lungs are principal site of infection.
- Severity may be related to initial inoculum.
- Often asymptomatic.
- Cough, dyspnea, asthenia and fever.
- Once inhaled, spores do not germinate or reproduce but form adiaspores 50–500 μm in diameter, which are large

round structures resembling the spherules of coccidioidomycosis.
- Adiaspores often become surrounded by granulomatous tissue.

Disseminated adiaspiromycosis

- Disseminated lung disease may resemble miliary tuberculosis on radiography.
- There may be dissemination to other organs, including kidneys, skin and bone.

Essential investigations

Microscopy

Gross histopathological examination of heavily infected lung tissue may reveal white or grey nodules. Microscopy reveals large, round, multinucleate adiaspores 50–700 mm in diameter, with refractile walls up to 70 mm thick surrounded by granulomatous tissue.

Culture

Culture is difficult but provides the definitive diagnosis. Sputum and BAL specimens are rarely culture positive. Mycelial colonies of *Emmonsia* spp. are seen after 1–3 weeks at 25–30°C and produce small, thin-walled, single-celled conidia along the sides of hyphae or on short stalks. Identification can be confirmed by formation of adiaspores at 37°C by *E. parva* and *E. crescens*. The two can be differentiated by the inability of *E. crescens* to grow at 40°C. *E. pasteuriana* will grow at 40°C but is rarer and appears to form yeast cells only at 37°C and *in vivo*.

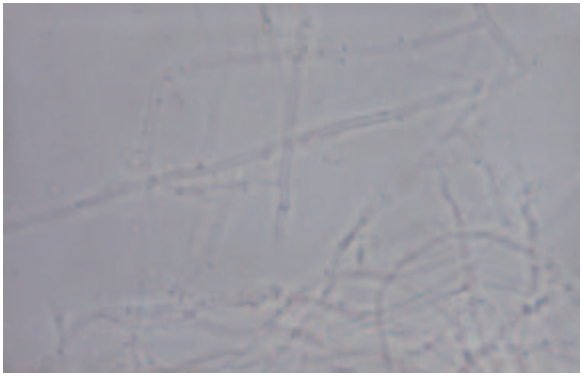
Management

Patients who are asymptomatic recover without treatment and some cases of overt infection may regress without treatment; however, there have been cases where infection has contributed to mortality.

The small number of recorded human cases (about 40 world-wide) makes any firm conclusions about antifungal therapy difficult. There have been successes with

amphotericin B and ketoconazole. When examined *in vitro* the mould form of *Emmonsia* and germinating adiaspores are susceptible to amphotericin B and to azole drugs including voriconazole.

Basidiomycosis



Spicules (small projections) seen on microscopic examination of the hyphae of *Schizophyllum commune*.

Fruiting body of the basidiomycete *Schizophyllum commune* seen on prolonged incubation (6 weeks) on a nutrient-rich medium.

Definition

Rare infections caused by the basidiomycete group of fungi, which incorporate the fungi with macroscopically visible fruiting bodies such as mushrooms, toadstools, bracket fungi and puffballs.

Geographical distribution

World-wide but most commonly encountered in temperate regions.

Causal organisms and habitat

- Various members of the basidiomycete group implicated on occasion.
- Environmental organisms associated with dead and decaying organic material; some are plant pathogens.
- Most common infection is due to *Filobasidiella neoformans*, which is the sexual form of *Cryptococcus neoformans*.
- Most common emerging infection is sinusitis due to *Shizophyllum commune*.
- Infections reported with *Coprinus* spp., *Hormographiella aspergillata* (the anamorph of *Coprinus cinereus*) and *Ustilago* spp.
- Basidiospores inhaled or introduced into the body via surgery.

Clinical manifestations

- Invasive or allergic sinusitis.
- Deep infection following inhalation or surgical introduction.

Essential investigations

Microscopy

Tissue appearance is of hyaline, septate hyphae and resembles invasive aspergillosis and hyalohyphomycosis.

Culture

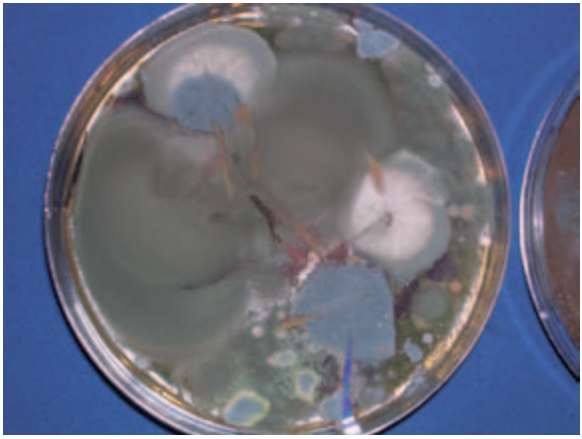
Isolation in culture on glucose peptone agar at 30°C yields

cream-coloured floccose colonies. Often on microscopy only hyphae are seen, sometimes producing arthroconidia; the presence of clamp connection may suggest the identification of a basidiomycete. In the case of infection with *Schizophyllum commune* hyphae may demonstrate the presence of short needle-like projections known as spicules (see p. 170). It is very difficult to induce the formation of fruiting bodies by which they can be fully identified; prolonged incubation (often several months) on a nutrient-rich medium under the influence of diurnal light and dark cycles may be successful with isolates of *S. commune.* Molecular identification methods may have to be employed.

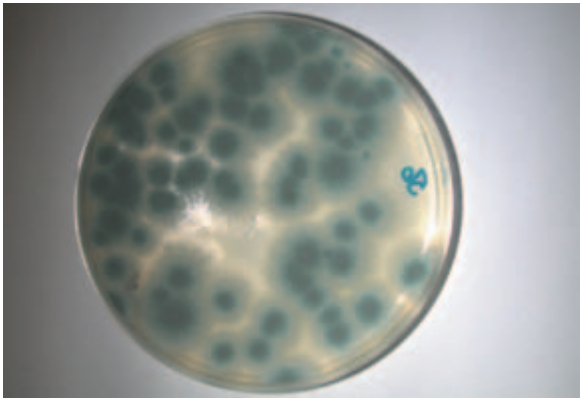
Management

Cases have been too few to recommend particular courses of treatment. There have been successes with amphotericin B and azoles. Choice of agent may be influenced by antifungal susceptibility testing.

Mycological aspects of the indoor environment



Aspergillus fumigatus and other environmental moulds growing on an agar plate.



Aspergillus fumigatus isolated from the air of a hospital ward using an impactor-type air sampler.

Macroconidia of *Alternaria alternate* a showing transverse and longitudinal septa.

SAS Super100 air sampler.

Non-controversial diseases caused by indoor moulds

Allergy to fungi:

- Affects only a portion of the population.
- Usually leads to asthma, but not believed to be a common cause of allergic rhinitis.

Atopy:

- A symptom complex of asthma, allergic rhinitis, atopic dermatitis, allergic gastroenteropathy.
- Mediated by IgE: induced by fungal spores and hyphal fragments.
- A clear but complex genetic predisposition.
- Fungal allergens react with specific IgE that occupy receptor sites on mast cells, thereby releasing inflammatory mediators.

Allergic fungal rhinosinusitis:

- Definition and diagnosis not clearly established.
- Typical presentation: recurrent hypertropic sinusitis in an atopic patient.
- Many different moulds implicated.
- Fungi may be cultured from nasal or sinus mucus.
- Positive wheal-and-flare skin test.
- Nasal polyposis is common.
- Total IgE may be elevated.
- Eosinophils and lymphocytes are present in mucosal inflammation (allergic mucin).
- Recurrences common despite surgery and corticosteroids.

Controversial diseases or conditions attributed to moulds

Moulds implicated:

- *Stachybotrys spp.*
- *Cladosporium spp.*
- *Penicillium spp.*
- *Aspergillus spp.*
- *Alternaria spp.*

Stachybotrys-alleged diseases or conditions:

- No human infection reported.
- No allergy reported.
- No case of hypersensitivity pneumonitis reported.
- No proven association with acute pulmonary haemorrhage.
- Building-related illness due to mycotoxicosis has never been proved in the medical literature.

Indoor activities contributing to indoor mould sources

- Plants.
- Pets.
- Damp building materials and fabric.
- Contaminated air conditioners and humidifiers.
- Inadequate ventilation.
- Inadequate/faulty air filtration.

Outdoor levels of airborne mould spores

These vary widely due to:

- Geographical location.
- Activities within the geographical location.
- Time of day.
- Degree of moisture.

Most common outdoor spore types

- Basidiospores.
- Conidia of *Cladosporium* spp.
- Ascospores.
- Conidia of *Alternaria* spp.
- Conidia of *Penicillium* spp.
- Conidia of *Aspergillus* spp.

Most common indoor species

- *Cladosporium.*
- *Penicillium.*
- *Aspergillus.*
- *Alternaria.*
- *Aureobasidium.*

Optimal sampling methods

- Air sampling.
- Material analysis.
- Tape lift.

- Surface sampling with contact plates or swabbing.
- Cell wall components: ELISA for glucan and galactomannan.
- Quantitative PCR (United States Environmental Protection Agency), although this should be quantitative.

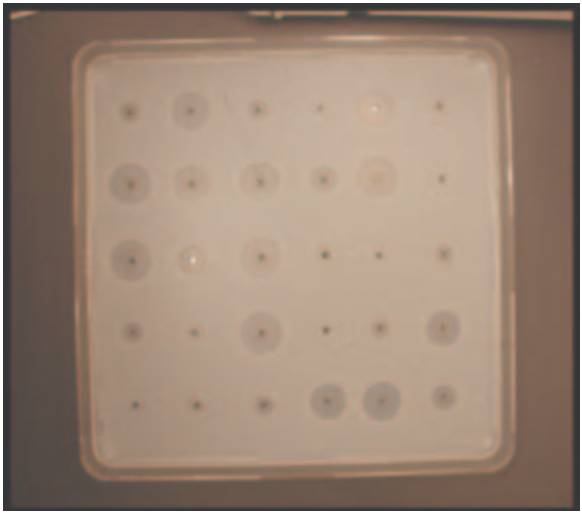
Optimal culture media

- Malt extract agar.
- DG18.
- Glucose peptone agar.

Standards, thresholds and guidelines

- No universally accepted standards or guidelines.
- Elevated indoor air spore counts (> 500 colony-forming units/m^3) of a single species should be regarded as hazardous.
- Heavy contamination of building fabric (100,000 colony-forming units/g) should be regarded as hazardous to health.
- No medical evidence that mycotoxins impact on human health other than by ingestion and occasional reports of contact allergy, although many indoor mould species produce potent mycotoxins, some of which are volatile.
- Moulds and bacteria with a high water activity indicate water damage and dampness, e.g. *Paecilomyces variotti*, *Apergillus versicolor*, *Stachybotrys spp.*, *Pseudomonas* spp.

Antifungal assays



Agar plate demonstrating zones of inhibition obtained by diffusion of antifungal agents during bioassay.

Equipment employed in high-performance liquid chromatography (HPLC) assay of antifungal agents.

Rationale for monitoring antifungal therapy

- To avoid toxicity.
- To ensure therapeutic levels.
- To monitor compliance.

Methods

- HPLC.
- Bioassay.
- Spectrophotometric methods.

Currently recommended antifungal drug monitoring

Flucytosine: to ensure toxic levels are not reached

- Good absorption and distribution following oral administration but mainly used IV.
- Toxic side effects on liver and bone marrow if levels exceed 100 mg/L for a prolonged period.
- Excreted via the kidneys so may accumulate when used in combination with amphotericin B, which can impair renal function.
- Need for monitoring: 2 hours post-oral, 30 minutes to 1 hour post-IV.

  Pre-dose range: 20–40 mg/L.
  Post-dose range: 60–90 mg/L.

Itraconazole: to ensure adequate levels are attained

- Variable and unpredictable bioavailability.
- Oral solution better absorbed than capsules.
- Capsule absorption affected by antacids, H_2 antagonists.
- Levels reduced with the concomitant administration of rifampicin, rifabutin, phenytoin, isoniazid, carbamazepine, nevirapine, phenobarbital.
- High levels not associated with additional side effects (liver toxicity).
- Often used as prophylaxis.
- Low levels (< 0.5 mg/L trough) associated with treatment failure and relapse.

- With oral formulations: 7–14 days to steady state.
  - Examine trough just before next administration.
  - Peak levels are attained 4 hours after an oral dose.
  - Trough should be maintained > 0.5 mg/L.

Amphotericin B: assay not required

- IV administration therefore no issue with absorption.
- Blood levels increase in proportion to the dose.
- Optimum levels for particular infections have not been established.
- High blood levels do not lead to greater renal impairment.
- Renal impairment does not lead to higher blood levels.

Fluconazole: assay not required

- 100% bioavailability.
- Levels increase directly in proportion to dose.
- Levels unchanged in AIDS patients and BMT recipients.
- Levels reduced with the concomitant administration of rifampicin.
- High levels not associated with side effects.
- Low levels associated with treatment failure resistance induction and relapse.

Voriconazole: assay may be helpful in some patients

- Inter-individual variability of voriconazole levels is high.
- Hepatic metabolism by cytochrome P450 isoenzymes.
- One of these, CYP2C19, exhibits genetic polymorphism.
- Up to 20% of the Asian population and 5% of other racial groups lack the enzyme and are therefore poor metabolizers.
- Normal serum level about 3.0 mg/L.
- May be two- to fourfold higher in poor metabolizers.
- Higher levels may be more likely to lead to visual disturbances – seen in as many as 30%.
- Levels >10 mg/L may be associated with liver toxicity.

Caspofungin: assay not indicated

- IV administration only, therefore absorption not an issue.
- Metabolized, not excreted unchanged.
- Low toxicity.

Terbinafine and griseofulvin: assay not usually indicated

Susceptibility tests

Rationale behind susceptibility testing of yeast and mould isolates

- Increasing incidence of invasive disease.
- New and emerging pathogens.
- Choice of therapeutic agents.
- Investigational agents.
- Standardized methods now available.
- Some evidence of *in vivo–in vitro* correlation.

Methods

The National Committee of Clinical Laboratory Standards (NCCLS) have published standardized methods for the susceptibility testing of yeast (M27-A2) and filamentous fungi (M38-A). These are broth dilution methods performed in tubes (macrodilution) or in microtitre plates (microdilution). The recently proposed EUCAST methods differ slightly from these. There is also an NCCLS method for antifungal disk diffusion susceptibility testing of yeasts (M 4-A).

There are several commercially available susceptibility testing systems, the results of which correlate well with the NCCLS methods.

Resistance

Clinical

Failure of therapy may be due to subtherapeutic drug levels at the site of the infection caused by the pharmacokinetics of the drug, drug interactions or poor patient compliance. Other reasons for clinical failure include overwhelming infection, site of infection, and immune status of the host.

In vitro

Failure of drug to suppress growth of the test organism under certain specific growth conditions may be a predictor of poor clinical outcome. Two forms of antifungal drug resistance are recognized: innate and emergent.

Innate/intrinsic/primary

The isolate was resistant to the drug before treatment started. This is predictable if one knows what the organism is and highlights the need for species identification.

Emergent/acquired/induced/secondary

The strain became resistant during treatment with the drug. This is the most difficult form of resistance because it is unpredictable.

Definitions

Minimum inhibitory concentration (MIC)

The lowest concentration of an antimicrobial agent that inhibits the growth of an organism *in vitro*.

Minimum fungicidal/lethal concentration (MFC or MLC)

The lowest concentration of an antimicrobial agent that produces > 99% or 99.9% kill of an organism *in vitro*.

Minimal effective concentration (MEC) (used for echinocandin agents)

The lowest concentration of an antimicrobial agent that causes marked cellular damage of an organism *in vitro* (microscopic observation).

NCCLS interpretative guidelines for some antifungal agents against yeast isolates

These are mainly based on experience with mucosal infections. They do not apply to isolates of *Candida krusei* which should be considered azole resistant.

	Fluconazole	Itraconazole	Flucytosine
Susceptible	< 8	< 0.125	< 4.0
Intermediate*	16–32	0.25–0.5	8.0–16
Resistant	> 64	> 1	> 32

* Susceptible: dose dependent.

Current status of antifungal drug resistance

Amphotericin B

- Both innate and emergent resistance to amphotericin B are rare, but we lack good methods of detection.
- Innate resistance:
  - *Aspergillus terreus.*
  - *Trichosporon* spp.
  - Some isolates of *Scedosporium apiospermum*.
  - *Scedosporium prolificans*.
  - Some isolates of *Candida lusitaniae*.

Flucytosine

- Innate and emergent resistance to flucytosine are relatively common, therefore it should not be used as monotherapy.

Azoles

- Innate resistance of certain yeast species and moulds to various azole agents is predictable and there is not necessarily cross-resistance amongst the azoles:
  - Innate fluconazole resistance in *Candida krusei*.
  - *Candida glabrata* often azole resistant.
  - *Candida tropicalis* sometimes azole resistant.
- Most zygomycete species are resistant.
- *Scedosporium prolificans* is resistant *in vitro*
- Emergent resistance is currently rare but has been documented in *C. glabrata* and *C. albicans.*

Echinocandins

- Innate resistance to the echinocandins is seen in fungi lacking β-1,3-D-glucan in the cell wall, which limits its spectrum of activity mainly to *Candida* spp. and *Aspergillus* spp.
- Resistance to the echinocandins can be induced *in vitro* but to date emergent resistance is rarely seen in clinical use.

Molecular methods

Molecular methods for the diagnosis of invasive fungal infection

- Methods for the detection of fungal genomic sequences in body fluids are under evaluation for the diagnosis of invasive aspergillosis, systemic candidosis and infections due to emerging mould pathogens.
- Currently there are no standardized methods with good levels of sensitivity, specificity and reproducibility.
- Panfungal, as well as species-specific primers are under investigation.
- Detection methods include nested polymerase chain reaction (PCR), PCR-ELISA, PCR-blot, real time PCR with light-cycler analysis and PCR-sequencing.
- Test specimens include whole blood, serum, CSF, bronchoalveolar lavage fluid and tissue samples.
- DNA extraction methods vary from physical freeze-thaw techniques to enzymatic extraction.
- Microsatellite arrays have been designed with sepsis chips that include *Candida albicans* and *Aspergillus fumigatus*.

Molecular methods for the identification of pathogenic fungi

- Molecular identification methods allow identification of non-sporing mould isolates and the differentiation of morphologically similar groups of yeasts and moulds.
- May be applied to tissue sections or blocks when culture of the organism has failed or when only formalin-fixed tissue sections are available.
- Amplification of the fungal DNA by PCR followed by species-specific probes or DNA sequencing.
- Various regions, including the D1–D2 region of the large ribosomal DNA and sections of the intergenic spacer region (ITS), can be sequenced and matched with stored databases or web-based data.
- Species-specific probes can also be applied and some of these are commercially available.

- Restriction fragment length polymorphisms (RFLPs) have been used.
- Microsatellite primers can be used to generate species-specific fingerprints.

Molecular methods for tracing the epidemiology of pathogenic fungi

- A multitude of different methods of molecular subtyping (DNA fingerprinting) have been investigated for their utility in assessing genetic relatedness within a species.
- May be useful for establishing the source in an outbreak situation.
- May help to distinguish relapse from reinfection.
- Can be used to trace the emergence of resistant strains.
- Can be used to trace the geographical and temporal passage of strains.
- Care required to distinguish true differences from microevolution.
- RFLPs lacks sensitivity.
- RFLP followed by a specific mitochondrial or ribosomal probe shows promise.
- Multilocus enzyme electrophoresis (MEE) has been evaluated.
- Multilocus sequence typing (MLST) shows enormous potential.

Selected reading: recently published texts and monographs

General texts and reviews

Anaissie EJ, McGinnis MR, Pfaller MA (eds) (2003). *Clinical Mycology.* Churchill Livingstone, New York.

Dismukes WE, Pappas PG, Sobel JD (eds) (2003). *Clinical Mycology*. Oxford University Press, Oxford.

Flannigan B, Sampson RA, Miller JD (eds) (2001). *Microorganisms in Home and Indoor Work Environments: Diversity, Health Impacts, Investigation and Control*. Taylor and Francis, London.

Gupta AK, Ryder JE, Nicol K, Cooper EA (2003). Superficial fungal infections: an update on pityriasis versicolor, seborrheic dermatitis, tinea capitis, and onychomycosis. *Clini Dermatol* 21: 417–25.

Hay RJ, Mertz W (eds) (2005). *Topley & Wilson's Microbiology and Microbial Infections*, 10th edn. Vol. 5: *Medical Mycology*. Arnold, London.

Kibbler CC, Mackenzie DWR, Odds FC (eds) (1996). *Principles and Practice of Clinical Mycology*. John Wiley, Chichester.

Midgely G, Clayton YM, Hay RJ (1997). *Diagnosis in Colour: Medical Mycology*. Mosby-Wolfe, Chicago.

Richardson MD, Warnock DW (2003). *Fungal Infection: Diagnosis and Management*, 3rd edn. Blackwell Publishing, Oxford.

San-Blas G, Calderone RA (eds) (2004). *Pathogenic Fungi: Host Interactions and Emerging Strategies for Control*. Caister Academic Press, Wymondham, Norfolk.

San-Blas G, Calderone RA (eds) (2004). *Pathogenic Fungi: Structural Biology and Taxonomy*. Caister Academic Press, Wymondham, Norfolk.

Monographs on particular aspects

Barnes RA, Warnock DW (eds) (2002). *Fungal Infection in the Intensive Care Unit*. Kluwer Academic, Norwell, MA.

Brakhage AA, Jahn B, Schmidt A (eds) (1999). *Aspergillus*

fumigatus: Biology, Clinical Aspects and Molecular Approaches to Pathogenicity. Karger, Basel.
Elewski B (1998). *Cutaneous Fungal Infections*, 2nd edn. Blackwell Science, Oxford.
Richardson MD, Elewski B (2000). *Fast Facts: Superficial Fungal Infections*. Health Press, Oxford.
Richardson MD, Jones BJ (2003). Therapeutic Guidelines in Systemic Fungal Infections, 3rd edn. Current Medical Literature, London.
Roberts DT, Evans EGV, Allen BR (1998). *Fungal Infection of the Nail*, 2nd edn. Mosby-Wolfe, Chicago.
Thomas PA (2003). Current perspectives on ophthalmic mycoses. *Clin Microbiol Rev* 16: 730–97.
Wray D, Bagg, J (1998). *Oral Candidosis*. Science Press, London.

Identification manuals

Campbell CK, Johnson EM, Philpot CM, Warnock DW (1996). *Identification of Pathogenic Fungi*. Public Health Laboratory Service, London.
De Hoog GS, Guarro J, Gene J, Figueras MJ (eds) (2000). *Atlas of Clinical Fungi*, 2nd edn. Centraalbureau voor Schimmelcultures, Baarn.
Kane J, Summerbell RC, Sigler L, Krajen S, Land G (1997). *Laboratory Handbook of Dermatophytes: A Clinical Guide and Laboratory Manual of Dermatophytes and Other Filamentous Fungi from Skin, Hair and Nails*. Star Publishing, Belmont, CA.
St-Germain G, Summerbell R (1996). *Identifying Filamentous Fungi: A Clinical Laboratory Handbook*. Star Publishing, Belmont, CA.
Sutton DA, Fothergill AW, Rinaldi MG (1998). *Guide to Clinically Significant Fungi*. Williams and Wilkins, Baltimore.

Mycological aspects of the indoor environment

Chapman JA, Terr AI, Jacobs RL, Charlesworth EN, Bardana EJ (2003). Toxic mould: phantom risk vs science. *Ann Allergy Asthma Immunol* 91: 222–32.
Flannigan B, Sampson RA, Miller JD (eds) (2001). *Microorganisms in Home and Indoor Work Environments: Diversity, Health Impacts, Investigation and Control*. Taylor and Francis, London.

WWW sites

Please note that this list is by no means exhaustive!

Fungal infections, general

http://www.clinical-mycology.com
http://www.mycology.adelaide.edu.au
http://fungus.utmb.edu/mycology
http://www.doctorfungus.org/
http://www.medicalmycology.org/
http://www.medsche.wisc.edu/medmicro/myco/mycology.html
http://www.fungalforum.com

Specific infections

http://www.aspergillus.man.ac.uk
http://www.genolist.pasteur.fr/CandidaDB
http://www.panix.com/~candida/
http://alces.med.umn.edu/Candida.html

Training

http://www.montana.edu/wwwmb/docs/Medicalmycology.html

Societies

http://www.asmusa.org/division/f/divf_main.htm (American Society for Microbiology, Division F: Medical Mycology)
http://www.isham.org (International Society for Human and Animal Mycology, and links to national societies)

Publishers

http://www.blackwellmedicine.com (medical mycology books and journals)
http://www.tandf.com (publishers of *Medical Mycology*, the journal of the International Society for Human and Animal Mycology)
http://www.prous.es/product/journal/mic.html (*Current Topics in Medical Mycology* journal)
http://www.RevIberoamMicol.com (ejournal: *Revista Iberoamerica de Micologia*)

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