

# Deep mycoses

## Introduction

Deep or systemic mycoses can be subdivided into

1. Cosmopolitan deep mycoses, such as aspergillosis, candidosis and cryptococcosis. They are caused by fungi that occur worldwide.
2. Exotic deep mycoses, including coccidioidomycosis and histoplasmosis and infection with *Penicillium marneffe*, the pathogens of which have a limited geographical distribution.

## Exotic deep mycoses

The exosaprophytic moulds that cause exotic deep mycoses have the lungs as their portal of entry.

They are dimorphic, i.e. they occur in two forms. In the environment they are filamentous, while in vivo they exhibit another morphology that of yeasts. These moulds are capable of causing disease in patients without predisposing factors. The severity of the condition varies according to the inoculum and the patient's immune status. In patients without predisposing factors dissemination is rare and associated with a very large inoculum. In at risk patients (AIDS) dissemination always occurs even if only a small number of spores are inhaled. Dissemination leads to the secondary form in which numerous deep foci are possible and cutaneous lesions are also often observed.

The laboratory diagnosis is based on the specific morphology which the pathogen exhibits in vivo and on the culture of the saprophytic phase. Manipulation of the cultures is dangerous! There are reliable serological tests which are of diagnostic and prognostic value. For therapy as an alternative to amphotericin B use is increasingly, and successfully, being made of the azoles (itraconazole), particularly for the secondary chronic forms or relapse prevention (cfr. cryptococcosis).

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## Classic or American histoplasmosis

Histoplasmosis is also known as “**Cave disease**”, “**Darling’s disease**”, “**Ohio valley disease**”, “**reticuloendotheliosis**,” “**spelunker’s lung**” or “**caver’s disease**”. This mycosis occurs primarily in the southeast of the USA, but is not exclusively North American. Native cases also occur in South America, Africa and Asia. Apart from a handful of Romanian and Italian cases those found in Europe have been imported.

### Causative agent

The causative agent *Histoplasma capsulatum* var. *capsulatum*, is an exsaprophytic mould that is isolated in the USA from various biotopes such as chicken manure, soil under starling roosts, seagull breeding sites and bat guano in caves (cave disease or speleologist’s disease).

The filamentous phase is found in the environment or in culture at 25°C characterised by round spores with a thick wall, surrounded by protrusions (chlamydospores) and small round spores with a smooth wall. In vivo, in the parasitic phase; small, ovoid yeasts of 3-4 µm are found in the cells of the RES (histiocytes, monocytes).

### Clinical aspects

‘The syphilis of the fungus world’, meaning that histoplasmosis is one of the “Great Imitators”. Histoplasmosis has been described as an illustration of the large variety of clinical forms.

In most cases, after contact with a low dose, an asymptomatic infection (99%) is seen or a self-limiting flu syndrome occurs (1%). At high inoculum or with temporary suppression of immunity an acute pulmonary disease can occur. After recovery calcifications in the lung and lymph nodes are seen in 1/3 of cases after 1-2 years.

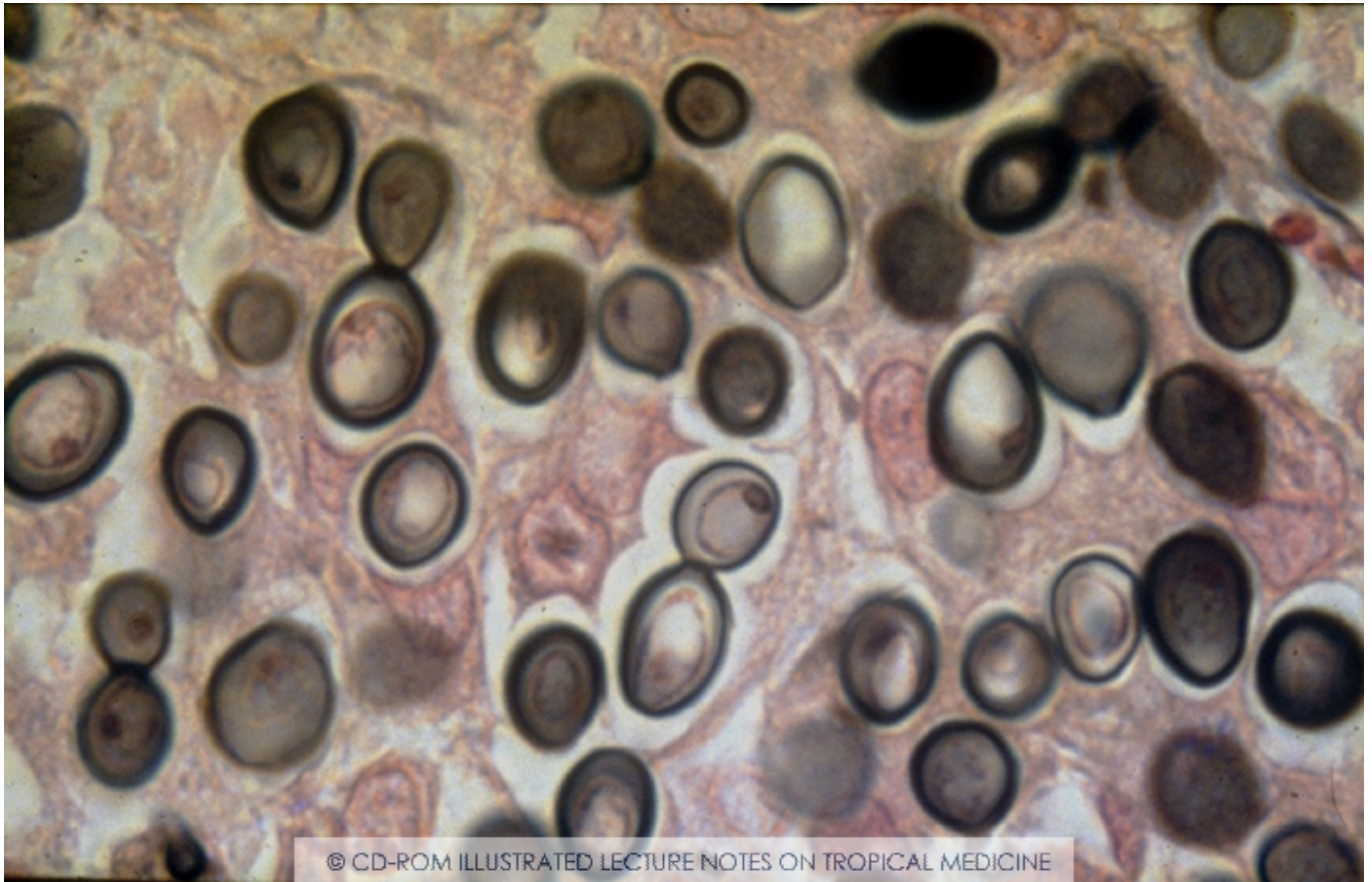
A chronic mild form is described in adults in the event of a temporary suppression of cellular immunity. This involves an endogenous re-activation, as in ex-colonial soldiers, 10-20 years

after they have returned from Africa, South America or Asia, or a re-infection in people still living in endemic areas.

Oropharyngeal and nasal lesions and lesions of the vocal chords closely resembling malignant cells (nodules, ulcerations) and which may be associated with dysphagia and dysphonia are seen. In 50% of cases the adrenal glands are also involved. Systemic histoplasmosis is described in AIDS patients, sometimes with very severe cutaneous and mucosal lesions, as well as a possible cerebral involvement (meningitis). It results in a systemic granulomatous disease with preferential lesions on lips and in the adrenals.



Chest X-ray, pulmonary histoplasmosis. Copyright ITM



*Histoplasma duboisii*, histoplasmosis. Microscopic smear. With special thanks to Mr De Vroey. Copyright ITM

## Diagnosis

The diagnosis of histoplasmosis is made by direct examination of the parasitic phase (yeast) in sputum, bone marrow or blood. *Histoplasma* can also be found in histological preparations in RES cells. The intradermal reaction with histoplasmin is of no diagnostic value. The serological tests (immunodiffusion and complement fixation) are based on the detection of specific antibodies or on the detection of specific antigens (RIA). Both variants of *H. capsulatum* are level 3 pathogens and should only be cultured in a laboratory with the appropriate security procedures.

## African histoplasmosis due to *H. capsulatum* var. *duboisii*

African histoplasmosis is geographically confined to Central Africa. Although it is established that the pathogen is also an exosaprophytic mould, the natural biotope remains unknown.

In the parasitic phase, *H. capsulatum* var. *duboisii* exhibits large, round spores of 10-15 µm. In the saprophytic phase, the two varieties are morphologically indistinguishable.

Patients with this chronic mycosis always exhibit polymorphous cutaneous lesions, bone and lymph node involvement and ultimately random deep localisations. When the disease follows an acute course (e.g. in AIDS patients), the yeast cells remain small and the infection is usually ascribed mistakenly to the variety *capsulatum*. In experimental infections also, cells exceeding the variety *capsulatum* in size are found only after a long time.

### Histoplasmosis treatment

In the majority of immunocompetent individuals, histoplasmosis resolves without any treatment.

Antifungal medications are used to treat severe cases of acute histoplasmosis and all cases of chronic and disseminated disease. Typical treatment of severe disease first involves treatment with amphotericin B, followed by oral itraconazole. Alternatives to itraconazole are posaconazole, voriconazole, and fluconazole.

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## *Talaromyces marneffe* (Previously known as *Penicillium marneffe*)

This mycosis only occurs in Southeast Asia and is usually associated with suppression of cellular immunity. The pathogen *T. marneffe* was first isolated from bamboo rats in Vietnam



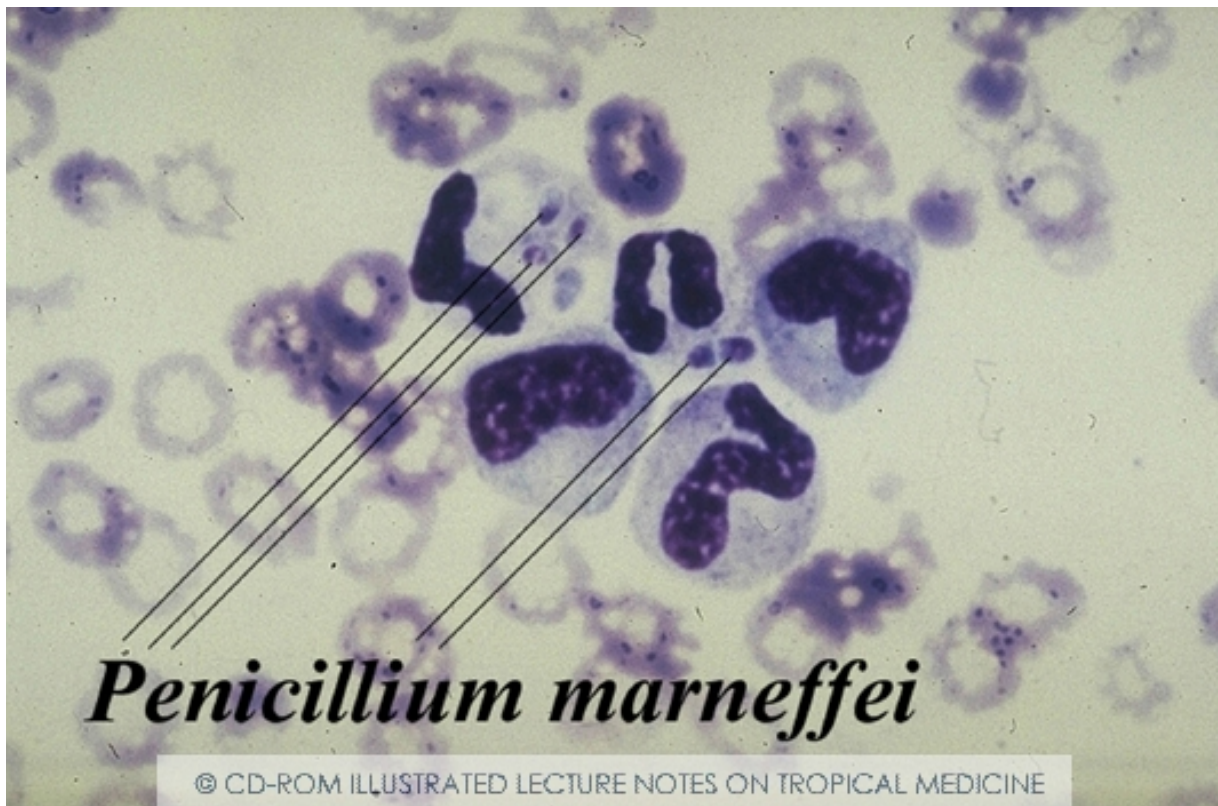
and has since been found in patients with a disseminated often fatal mycosis. The disease is an AIDS indicator.

## Causative agent

*Talaromyces marneffe* is a dimorphic mould. When it was classified as a *Penicillium* species it was regarded as the only species that can cause invasive disease, in contrast to other *Penicillium* species which are normally understood to be unimportant in human disease. In the saprophytic phase it produces a red pigment that diffuses in agar. In the parasitic phase, intrahistiocytic and intramacrophagic elements are found which divide by fission and not by bud formation.



Infection with *Talaromyces marneffe* in an AIDS patient. Remark the typical umbilicated papular skin lesions



Microscopy of thin bloodsmear of an AIDS patient from Southeast Asia. *Talaromyces marneffei*. Copyright ITM

## Clinical aspects

The portal of entry is the lung and the infection spreads rapidly or otherwise via the RES. In AIDS patients, fever, marked weight loss, hepatosplenomegaly and often also cutaneous lesions are seen.

DD with cryptococcosis, histoplasmosis. This infection is now increasingly recognized as a disease in solid organ transplant recipients who travel.

## Diagnosis

The diagnosis of this mycosis is based on direct examination of sputum, BAL, bone marrow and material from skin lesions or on histological examination where the intrahistiocytic elements can be observed. *T. marneffei* can be cultured but the manipulation should be

performed in a level 2 laboratory.

Reliable serological tests are being developed.

## Treatment

In severe disease treatment with amphotericin B IV or voriconazole IV should be started, followed by itraconazole or voriconazole po. Secondary prophylaxis with itra- or voriconazole is suggested when the CD4-count is below 100 cells/mm<sup>3</sup> in HIV-patients on HAART.

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# Coccidioidomycosis

The disease is endemic in the wilderness areas of the southwest of the United States. In addition, foci have been described in Central and South America. Despite the pathogenicity of all *Coccidioides immitis* strains, it is estimated that only 0.2% of cases showed symptoms of deep localisations and/or skin granulomas in the period before 1990. Since then the number of cases has steadily increased not only because of the AIDS epidemic, but also as a result of earthquakes and sandstorms (disturbance of soil structure).

## Causative agent

*Coccidioides immitis* is a dimorphic mould found in its filamentous phase in soil. The pathogenic spores are easily dispersed from dry ground or material. In vivo (parasitic phase) no yeasts are found, but instead spherules, large, spherical elements of 20-80 µm diameter. These spherules contain numerous endospores.

## Clinical aspects

60% of those infected exhibit no symptoms or only minor respiratory disorders. These people are coccidioidin-positive. Approximately 40% go on to develop lower respiratory tract infections after 1-3 weeks, sometimes with erythema nodosum or erythema multiforme. The fungus can be spontaneously eliminated but it is preferable to administer azoles. About 5% of



patients retain cavities and nodules in their lungs. Exceptionally in people with a normal immune system -but in 100% of AIDS patients- an extrapulmonary form is found with meningitis and bone involvement.

## Diagnosis

Spherules are found on direct or histological examination. The culture is relatively atypical and should only be performed in a level 3 laboratory. The coccidioidin skin test can be used for people who suffer a primary infection but anergy (absence of response) is possible in progressive disease. Spherulin is supposedly more sensitive. No cross-reactions have been described. There are other serological tests (latex agglutination, immunodiffusion, complement fixation, ELISA) for the detection of antibodies. PCR demonstrated high sensitivity.

## Treatment

Many infections in healthy patients do not require treatment. Only severe infections or infections in immunosuppressed people needs treatment with itra-, keto- or fluconazole for 3 to 6 months.

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# Paracoccidioidomycosis



South American blastomycosis or paracoccidioidomycosis, ulcers lips. *Paracoccidioides brasiliensis*. Photo Cochabamba



Paracoccidioidomycosis is caused by infection with *Paracoccidioides brasiliensis*. The yeasts have a typical steering wheel aspect caused by budding. Copyright ITM

Paracoccidioidomycosis or South American blastomycosis occurs in discrete foci in Latin America. It is thought that the fungus (*Paracoccidioides brasiliensis*) exists in the soil as a mold, with infections happening through the inhalation of conidia (spores). These spores convert into yeasts in the lungs and are then thought to spread to other sites haematogeneously and via the lymphatics. Most primary infections are self-limiting. The organism has the ability to remain dormant in the human host for long periods. It can cause clinical disease at a later time if host defense would become impaired (e.g. depression of cell mediated immune responses).

Overt infection results in a progressive mycosis with lesions of the skin, mucous membranes (especially mouth, lips and nose) and internal organs. Long asymptomatic periods enable patients to travel far from endemic areas before developing clinical problems. Lesions in the

face, naso- and oropharynx resemble espundia (mucocutaneous leishmaniasis), lupus vulgaris (skin tuberculosis) and syphilis. Papules will ulcerate and enlarge both peripherally and deeper into the subcutaneous tissue. A hard hyperkeratotic border may surround a deep ulcerating crater on the skin. Extensive coalescent ulcerations may eventually result in the destruction of the uvula, epiglottis and vocal cords. Eating and drinking become difficult and painful. Lymphatic infections lead to painless enlargement of cervical, supraclavicular and/or axillary nodes.

Draining sinuses may form. Visceral lesions in liver, spleen and lymph nodes can lead to abdominal pain, hepatosplenomegaly and low-grade fever. Pulmonary involvement occasionally leads to mild symptoms, including cough and sputum production, although the radiograph of the chest can show dramatic involvement of the lungs. Infections tend to be very chronic, but not fatal. Diagnosis relies on demonstration of the yeasts in tissue/secretions. The yeasts are usually abundantly present in the bases and edges of slowly expanding ulcer. In tissue specimens, the yeasts are rather large (15 µm) with multiple buds, thereby resembling the steering wheel of a boat. Gomori staining of biopsies is useful.

Serology by immunodiffusion is positive in  $\pm$  98% of cases. Azoles such as itraconazole are usually very effective as treatment. Amphotericin B can be used if there is no success with oral itraconazole or in case of severe infection. Sulfonamides can be used, but have only moderate activity and should be administered for very long periods.

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## Blastomycosis

Blastomycosis -also known as North American blastomycosis or Gilchrist's disease- occurs in a geographically limited area of the south central and midwestern USA, upstate New York and southern Canada. A few cases have been described from Africa, the Middle East, India and Mexico. The fungus occurs in soil enriched with animal excreta and moist, acid, decaying organic material. Infection follows the inhalation of conidia (asexual spores) of *Blastomyces dermatitidis*. Both man and dogs can be infected. The spores will convert into yeasts, which will invade the lungs and occasionally spread haematogeneously to several organs, especially

skin, bone or urogenital system. Pulmonary infection can be asymptomatic. Genital involvement such as chronic epididymitis, mimicking tuberculosis. Cough, low to moderate fever, dyspnoea and chest pain, purulent/bloody sputum, pleural fluid, weight loss and prostration occur in symptomatic patients. Radiological studies usually reveal pulmonary infiltrates and enlarged hilar lymph nodes. Progressive pulmonary blastomycosis resembles tuberculosis or a neoplasm. Raised single or multiple verrucous cutaneous lesions that tend to have an abrupt downward sloping red-purplish border are usually present in disseminated blastomycosis. The border extends slowly, leaving a central atrophic scar. Those skin lesions can resemble skin cancer.

Bones such as ribs and vertebrae are frequently affected (25-75%). Lesions appear both destructive and proliferative on radiography. Central nervous system lesions are uncommon. Acute self-limiting blastomycosis is rarely diagnosed. The organism is found in clinical specimens as a thick, double-walled cell, 5-20  $\mu\text{m}$  in diameter, sometimes even reaching 30  $\mu\text{m}$ . Some yeast cells have a single bud. Definite identification is via culture but detection of the above mentioned yeast cells in pus, sputum or urine is very suggestive. Gomori's methenamine silver stain and PAS staining are useful for biopsies. Serology is not useful. Untreated disseminated blastomycosis is usually progressive and can be fatal. Itraconazole (200-400 mg/day) is used as a first-choice treatment. If no improvement occurs the dose of itraconazole can be increased to 800mg per day or switch over to IV amphotericin B. Follow-up in order to identify a relapse should continue for several years.