Opportunistic Fungal Infections

Introduction

The opportunistic fungi usually cause infections in persons with impaired host defense, but do not cause disease in most of the immunocompetent hosts. Since these fungi become pathogens in individuals with impaired immunity by taking

advantage of the host's debilitated conditions, they are called opportunistic fungi.

In recent times, there is an increasing list of exotic and rare fungi, which have been associated to cause opportunistic infections. But most opportunistic infections are caused by *Candida albicans*, *Aspergillus spp*., *Penicillium marneffei*, and various Zygomycetes .

Candidiasis

Candida species are the most common fungal pathogens that affect humans. These species are true opportunistic pathogens that take advantage of the host's debilitated condition and gain access to the circulation and deep tissues. The genus *Candida* includes more than 100 species, of which only few cause disease in humans. *C. albicans* and occasionally other species cause candidiasis, a major infection in immunocompromiseds hosts.

Candida albicans

C. albicans is the most common *Candida* species, which causes opportunistic infections in immunocompromised hosts. It forms the part of the normal flora of the mucous membrane of the gastrointestinal, genitourinary, and respiratory tract.

Properties

■ *C. albicans* is ovoid or spherical yeast with a single bud.

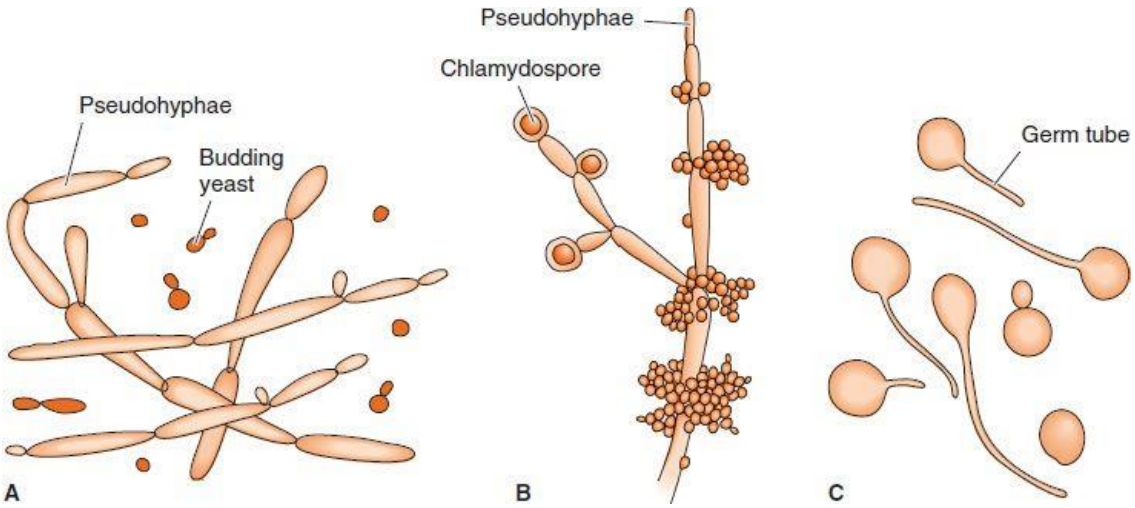
■ It forms the part of the normal flora of the mucous membrane of the gastrointestinal, genitourinary, and respiratory tract. It produces pseudohyphae in the cultures and in tissues. Pseudohyphae are elongated yeast that may resemble

hyphae morphologically, but are really not true hyphae. *Candida* grows readily on Sabouraud's dextrose agar and on bacteriological culture media. *C. albicans* produces creamy white, smooth colonies with a yeasty odor .

■ It can be differentiated from other *Candida* species by carbohydrate fermentation reaction and by characteristic growth properties.

■ Only *C. albicans* produces chlamydospores on cornmeal agar culture at 25°C.

Pathogenesis and Immunity *Candida spp.* are usually present as part of normal on healthy mucosal surface of the oral cavity, gastrointestinal tract, and vagina. *Candida* shows colonization at these sites in more than 80% of healthy people. The organism, however, is rarely present on the surface of normal human skin, except occasionally from certain intertriginous area, such as the groin.



◗ Pathogenesis of Candida infection

Under certain conditions, *Candida* gains access to systemic circulation from the oropharynx of the gastrointestinal tract. Colonization of the mucocutaneous surface is the first stage in the pathogenesis of Candidal infection. The fungus causes invasion in human tissue through different routes. Disruption of the skin or mucosa allows the organism access to the blood stream. Massive colonization with large numbers of *Candida* also permits the organism to pass directly into the blood stream, causing the infection. In immunocompromised hosts, *Candida* may dis and also may involve skin in 10–30% of patients with disseminated infection. Deficiency in host defence mechanisms plays a significant role in development of *Candida* infection.

◗ Host immunity

Both cell-mediated and humoral antibodies confer protection against *Candida* in healthy adults. Cell-mediated immunity (CMI) is, however, most important. Alteration in CMI may cause extensive superficial candidiasis, despite having normal or elevated humoral antibodies. The humoral antibodies appear to play minimal role in protection against the disease. Humoral antibodies confer protection against Candida in healthy adults.

Clinical Syndromes

Candida causes a wide spectrum of clinical illnesses as follows:

Cutaneous candidiasis: Candida species in immunocompetent host can cause infection of any warm and moist part of the body exposed to environment. It causes infection of the nail, rectum, and other skin folds.

Mucocutaneous candidiasis: Mucocutaneous candidiasis (thrush, perianal disease, etc.) is the most common manifestation of candidiasis, but usually does not cause any mortality. In patients with advanced immunodeficiency due to HIV infection, Candida species can cause severe oropharyngeal and esophageal candidiasis that

result in poor intake of food, leading to malnutrition, wasting, and early death. These patients are also usually resistant to treatment with antifungal therapy.

Chronic mucocutaneous candidiasis: This is a heterogeneous group of clinical syndromes. This syndrome is characterized by chronic, treatment-resistant, superficial *Candida* infection of the skin, nails, and oropharynx. However, these

patients do not show any evidence of disseminated candidiasis.

Systemic candidiasis: These include endocarditis, gastrointestinal tract candidiasis, respiratory tract candidiasis, genitourinary candidiasis, and hepatosplenic candidiasis.

Disseminated candidiasis: This is increasingly becoming a problem in patients with serious hematologic malignancies that are treated with immunosuppressive drugs for over a long period of time. Severe neutropenia in these patients is the most important predisposing condition for life-threatening infection caused by *Candida*. In this condition, *Candida* usually spreads through the circulation and involves many organs, such as lungs, spleen, kidney, liver, heart, and brain.

Epidemiology

Candida species is distributed worldwide. In recent times, *Candida* species have replaced Cryptococcus species as the most common fungi affecting the CNS of immunocompromised patients worldwide. *C. albicans* and *Candida glabrata* are responsible for causing infection in 70–80% of patients with invasive candidiasis.

Candida tropicalis is an important cause of candidemia in patients with leukemia and in those who have undergone bone marrow transplantation . *Candida parapsilosis* is an important pathogen associated with the use of vascular catheters. Since *Candida* is present as a part of normal flora already in the skin and mucous membrane of the host, it causes infection in the infected host; it is therefore not transmitted.

Third year /Microbiology-Fungi/Semester Two
Lecture (4) Prof. Hiba Y. Khalaf
2024-2025

Laboratory Diagnosis

◗ Specimens

These include exudates or tissues for microscopy obtained from skin or nails examined by microscope for demonstration of pseudohyphae or budding yeast cells of *Candida.*

◗ Microscopy

Gram-stained smear of the exudates or tissue shows Grampositive, oval, budding yeast and pseudohyphae . Since Candida is found as a part of normal flora on normal skin or mucosa, only the presence of large numbers of Candida is of significance. Demonstration of pseudohyphae indicates infection, and tissue invasion is of more diagnostic value.

◗ Culture

Culture on Sabouraud's dextrose agar (SDA) produces typical creamy white, smooth colonies. Different Candida species are identified by their growth characteristics, sugar fermentation, and assimilation tests. Germ tube is a rapid method for identification of *C. albicans* and *Candida dubliniensis*. This test depends on the ability of *C. albicans* to produce germ tube within 2 hours when incubated in human serum at 37°C. This phenomenon is called Reynold–Braude phenomenon Chlamydospores are typically produced by *C. albicans* on cornmeal agar at 25°C, but not by other *Candida* species. Moreover, CHROM agar allows for the presumptive identification of several Candida species by using color reaction in specialized media, thereby showing different colors of the colonies depending on the Candida species. Different *Candida* species can also be identified with more accuracy by biochemical assays, such as AP120C and AP131C. These assays evaluate the assimilation of various sugars for identification of different fungal species.

◗ Nonculture *Candida* detection tests

These include (a) *Candida* mannan assay, (b) *Candida* heat-labile-antigen assay, (c) D-arabinitol assay, (d) D-inositol assay, and (e) 1,3-beta-D-glucan assay. Beta-Dglucan assay is a broad-spectrum test that detects *Candida* as well as *Aspergillus, Fusarium, Acremonium,* and Saccharomyces species. This test depends on the principle that beta-D-glucan is a component of the cell wall of these fungi, which can be detected by its ability to activate factor G of the horseshoe crab coagulation cascade. This test is a highly specific and sensitive test.

◗ Immunological tests

Serological tests are not that useful in diagnosis of patients with candidiasis because antibodies against *Candida* appear in sera of patients as well as in that of normal persons. Skin test with *Candida* antigen is a delayed hypersensitivity skin test, which is used as an indicator of functions of the CMI. The skin test is uniformly positive in immunocompetent adults and indicates that the person has intact CMI. The skin test is negative in individuals who have deficient CMI. Such a person is anergic and is negative to other skin tests, such as purified protein derivative (PPD) skin test for tuberculosis.

Treatment

Antifungal therapy forms the mainstay of treatment of the infections caused by *Candida*. These agents include azoles (fluconazole, triazole, ketoconazole), nystatin, and amphotericin B. *C. glabrata* is becoming increasingly important worldwide and is intrinsically less susceptible to amphotericin B and other azoles (ketoconazole, fluconazole, etc). *Candida krusei* is increasingly recognized because of its resistance to many antifungal agents. It is intrinsically resistant to ketoconazole and fluconazole. It is also less susceptible to all other antifungal agents including itraconazole and amphotericin B. *C. lusitaniae* is also of clinical significance because it is resistant to amphotericin B, but it is susceptible to azoles and echinocandins.

Prevention and Control

Antifungal prophylaxis is indicated for patients with invasive candidiasis who are at high risk of developing invasive candidiasis. There is no vaccine available against candidiasis.

Aspergillosis

A broad spectrum of diseases in humans ranging from direct invasion to hypersensitive reactions are caused by *Aspergillus* species. Although more than 100 species have been described, the majority of human diseases are caused by *Aspergillus fumigatus* and *Aspergillus niger*, and less frequently by *Aspergillus flavus* and *Aspergillus clavatus.*

Aspergillus Specie

Properties

■ *Aspergillus* species are molds.

■ They have septate hyphae that form V-shaped dichotomous branches (Fig. 1). The *Aspergillus* species are identified by (a) their morphological features, (b) the pattern of conidiophore development, and (c) the color of the conidia.

■ The presence of septate hyphae that branch at 45° angles is the typical feature of *Aspergillus* species hyphae. The hyphae in tissues are best demonstrated with silver stains. The walls of the hyphae are more or less parallel, unlike those of *Mucor* and *Rhizopus*, which are more or less irregular.

■ Lactophenol cotton blue (LPCB) preparation of the colonies shows septate hyphae and branching conidiophores. Asexual conidia arranged in chains are present on elongated cells known as sterigmata. The latter is present on the vesicle of the conidiophores. The conidia of *Aspergillus* typically form radiating chains in contrast to *Rhizopus* and *Mucor*, which are found within sporangia.

■ The fungus grows rapidly on SDA and other culture media at 25°C. Aspergillus produces colonies within 1–2 days and shows a velvety surface.

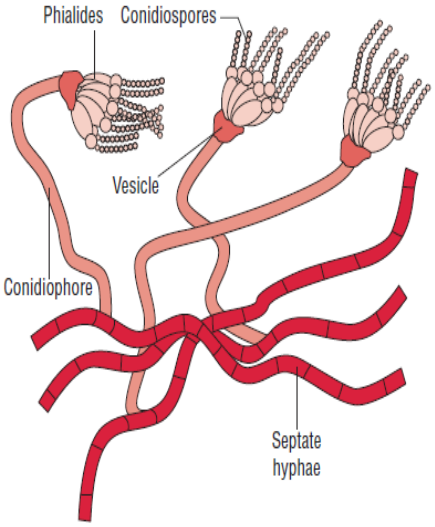


FIG. 74-3. *Aspergillus* species with septate hyphae that form V-shaped dichotomous branches.

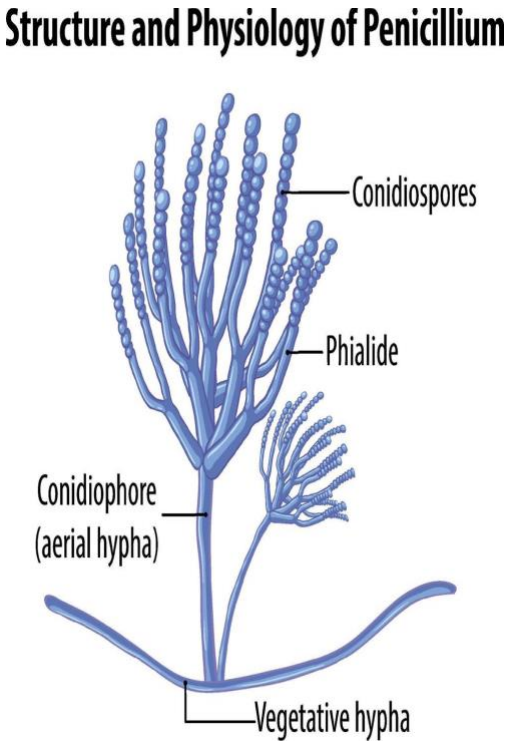


Fig.1 Fig.2

Pathogenesis and Immunity

Aspergillus species rarely cause infections in immunocompetent individuals. They cause invasive infections mostly in the patients who are immunocompromised either due to (a) use of immunosuppressive drugs, (b) underlying lung diseases, or (c) immunodeficiency diseases, such as HIV. In immunocompromised host, Aspergillus species cause invasion of the blood, thereby causing infarction, hemorrhage, and necrosis of lung tissues. *Aspergillus* spp. also produces toxic metabolites that inhibit macrophage and neutrophil phagocytosis, facilitating dissemination of the infection. *Aspergillus* species unlike *Candida* species do not form the part of normal flora of humans. They are ubiquitous in the environment; hence transmission of infection is mostly exogenous.

Clinical Syndromes

In immunocompetent hosts, Aspergillus species may primarily affect the lungs, causing four main syndromes including (a) allergic bronchopulmonary aspergillosis, (b) chronic necrotizing aspergillus pneumonia, (c) aspergilloma, and (d) invasive aspergillosis.

Allergic bronchopulmonary aspergillosis: It is a hypersensitivity reaction to *A. fumigatus* organisms, which have colonized in tracheobronchial tree. This condition occurs often in association with asthma and cystic fibrosis.

Chronic necrotizing pulmonary aspergillosis: It is a subacute infection seen in patients with some degree of immunosuppression. The condition occurs in conjunction with alcoholism, underlying lung disease, or chronic corticosteroid therapy.

Aspergilloma: It is a condition that occurs in a preexisting cavity in the lung parenchyma. This cavity may have been caused earlier by tuberculosis, sarcoidosis, cystic fibrosis, and emphysematous bullae. The condition is characterized by the presence of a ball of fungus within the cavity. The fungus,

however, does not invade the cavity. It may cause hemoptysis.

Invasive aspergillosis: It is a rapidly progressive infection in patients who are severely immunocompromised. The condition is mostly fatal. In immunocompromised host, *Aspergillus* organisms cause a disseminated disease, leading to endophthalmitis, endocarditis, and abscesses in the viscera, such as liver, spleen, kidney, soft tissues, and bone.

Epidemiology

Various clinical manifestations of *Aspergillus* infection have been documented worldwide. The incidence of allergic bronchopulmonary aspergillosis has been increasingly documented in people with asthma in United Kingdom. *Aspergillus* species unlike *Candida* species do not form the part of normal flora of humans.

They are ubiquitous in the environment; hence transmission of infection is mostly exogenous.

Laboratory Diagnosis

Laboratory diagnosis of invasive aspergillosis or chronic necrotizing aspergillus pneumonia depends on demonstration of *Aspergillus* in tissue by direct microscopy and culture.

Treatment

Amphotericin B is most frequently used for treatment of invasive aspergillosis. However, the outcome of treatment is not satis factory. Caspofungin is analternative drug given to patients who do not respond to amphotericin B. Aspergilloma is treated best by removal of the fungus ball from the cavity by surgery.

Prevention and Control

There are no specific preventive measures available against aspergillosis.

Penicilliosis

Penicillium species rarely cause opportunistic infections in humans. The *Penicillium* species are identified by their typical morphology (Fig. 2), culture characteristics on the SDA medium , and microscopy . *P. marneffei* is the only dimorphic fungus in the genus *Penicillium* known to cause opportunistic infection.

Penicillium marneffei

P. marneffei is the only dimorphic fungus in the genus *Penicillium*. It has been reported as an important opportunistic pathogen in AIDS patients. The fungus causes tuberculosis-like disease in patients with AIDS in Southeast Asian countries like Thailand. Few case reports have also been documented from India.

Incubation period is variable from few weeks to years. *P. marneffei* causes asymptomatic infections in immunocompetent hosts. It causes granulomatous or

suppurative reaction, bronchopneumonia with or without adenopathy, and cavitary lung lesion. It produces chronic cervical lymphadenitis resembling tuberculosis. Disseminated infections occur rarely in immunocompetent hosts.

P. marneffei causes disseminated infection in immunocompromised hosts, such as patients with HIV. It develops a necrotizing reaction and involves the skin, lung, and intestine. It causes disseminated infections of reticuloendothelial system, and also allergic diseases and mycotoxicoses. The disseminated infection is more common in adults than in children. *P. marneffei* is widely distributed in the nature. Its natural habitat is soil. The fungus infects no mammals other than humans and bamboo rat. Fungus is found in feces of rats and also in burrows made by the rats in the soil. The infection is transmitted by inhalation of conidia, direct inoculation of the skin, and rarely, by ingestion of infected rats. The condition is more common in rainy season, in rural areas. Cell-mediated immunodeficiency, steroid treatment, and HIV infection are predisposing factors. The fungus is endemic in Southeast Asian countries of Thailand, Vietnam, Laos, Myanmar, Singapore, and Indonesia. There has been recent increase in cases due to onset of AIDS pandemic. In India, 4 cases were reported by Singh and colleagues (1999) from eastern state of Manipur.

Laboratory diagnosis of the infection is made by microscopy, culture and serology.