# Fungal Pathogens

## Primary Pathogens

Primary dimorphic fungal pathogens are those found in specific geographic areas of the world, their endemic areas, and have the capacity to cause infection in any individual (i.e., immune-normal or compromised).

There are ***Coccidioides*** species, ***Blastomyces dermatitidis***, ***Histoplasma capsulatum***, and ***Paracoccidioides brasiliensis***. Infection is initiated after the infectious **propagules** (conidia) are inhaled when they are aerosolized by a disturbance of the environment. Subcutaneous mycoses are also caused by primary pathogens. In the case breaching the normally intact anatomic barrier of the skin by a puncture wound may be sufficient to initiate the pathogenic process.

### Susceptibility to Primary Pathogens

**Who is susceptible to primary pathogens?** Immune normal persons are at risk to become exposed to primary pathogens and to develop disease along a spectrum from subclinical to moderate self-limited, to disseminated disease, the latter requiring timely therapeutic intervention. Whether exposure is benign, self-limited, or moderate to severe, and whether or not it will **disseminate** depends on a number of factors, among which are age, sex, race, physical health, immunologic status, and the number of infectious propagules inhaled. Diseases caused by these fungi are, with rare exceptions, not communicable. When an immunocompromised individual is exposed to a primary pathogen the clinical course may be severe.

Up to now, there are no vaccines available for these diseases, although a vaccine for **coccidioidmycosis** is under investigation. Primary systemic fungi differ in whether recovery from an infection results in durable immunity.

## Endemic Versus Worldwide Presence

Primary systemic fungal pathogens are found in geographically restricted (endemic) areas, whereas fungi producing opportunistic fungal disease are generally found worldwide. An exception is the fungal opportunist *Penicillium marneffei*, a dimorphic endemic restricted to Southeast Asia.

## Opportunistic Fungal Pathogens

**What are opportunistic pathogens? Where are they found?**

Opportunistic fungal pathogens may be common environmental molds (and some yeasts) whose cells and conidia circulate in the **aerospora** (e.g., *Aspergillus* species, *Cryptococcus* species). Otherwise, they may be endogenous commensal fungi such as *Candida albicans* , a yeast that has adapted to an ecologic niche on the oral, intestinal, and vaginal mucosae of warm-blooded animals and especially humans where it lives an inconspicuous existence, all the while probing the mucosal epithelium for signs of the decreased immune surveillance or lack of anatomic integrity. Given the opportunity, any fungus with the ability to grow at 37°C may become an opportunistic pathogen. Physicians and laboratory personnel alike must be aware of this when diagnosis is difficult or unusual.

## Susceptibility to Opportunistic Fungal Pathogens: Host Factors

### 1- Immunocompromised Status

**Who is susceptible to opportunistic fungi?** Persons may become susceptible to opportunistic fungal pathogens because of immunodeficiency disease (either inborn or acquired, e.g., HIV infection); deliberate immunosuppressive therapy to treat cancer, **collagen vascular disease**, or for maintenance of stem cell or solid organ transplants.

## 2- Immune-Normal Host

Some of the host factors that allow immune-normal persons to become susceptible to systemic mycoses due to opportunistic pathogens are:

- Age (low birthweight-premature infants; the elderly)
- Burns
- Chronic respiratory disease
- Debilitating illness
- Dialysis, whether hemodialysis or peritoneal
- Endocrine disorders (e.g., diabetes mellitus)
- Intensive care requiring parenteral nutrition, high **APACHE II** score
- Surgery (e.g., cardiothoracic or abdominal)
- Traumatic injury

## Determinants of Pathogenicity

**Why are fungi pathogenic for humans?** As eukaryotes, fungi use various stratagems to evade host defenses. The list below is a summary of microbial factors that have been shown to influence pathogenicity.

**1- Thermotolerance.** Fungi that can grow at 37°C are potential pathogens in a suitably susceptible host.

**2- Adaptation to a parasitic lifestyle, sometimes in an intracellular environment.** The traditional assumption is that most primary and opportunistic fungal pathogens are free-living saprobes in nature.

- Evidence is accumulating that the ecologic niche of *Cryptococcus neoformans* may include intracellular survival within soil amebae. In the case *C. neoformans* "learned how to become a pathogen." This theory may also apply to other environmental fungi and may help explain how some fungi have become adapted to intracellular survival within phagocytes.

- Environmental fungi can infect other mammalian hosts, including small rodents, and have adapted to a parasitic lifestyle.

**3- Adhesins.** Pathogenesis of microbial disease proceeds via adherence to host tissues, a process of receptor-ligand intraction: for example, **BAD-1 adhesin of *Blastomyces dermatitids***, the **A1s family of surface adhesins of *Candida albicans***.

**4- Attack on host tissues using invasion promoting enzymes**:

- Secreted enzymes that damage host tissues: for example, **aspartyl proteinases** and **phospholipases** of *C. albicans*.
- Production of **catalase** that decomposes hydrogen peroxide, thus interrupting the oxidative microbicidal pathway of polymorphonuclear neutrophilic granulocytes: for example, **Catalase of *Aspergillus fumigatus* and *Histoplasma capsulatum***.

**5- Dimorphism.** Morphogenesis to distinct tissue forms confers an advantage to the pathogen. For example, ***H. capsulatum*** yeast forms are translocated intracellularly within monocytes from the lung to the spleen and liver; **spherules and endospores of *Coccidioides* species** spread the infection; yeast forms of *B. dermatitidis* are too large for endophagocytosis.

**6- Evasion of host immune defenses.** For example, ***Histoplasma capsulatum*** survival in the phagosome is linked to preventing phago-lysosome fusion and by being a resourceful scavenger of iron from the host through secretion of siderophores, ferric reductase, and directly from host transferrin.

**7- Cell wall molecules are barriers that resist lysis by phagocytes and antifungal agents:** for example, cell wall polymers, including **α-(1→3)-D-glucan**, **melanin**, and the **glucuronoxylomannan polysaccharide capsule** of *Cryptococcus neoformans.* To this list we add β-(1→3)-D-glucan of *Candida* species, in shielding the yeast from antifungal agents by functioning as a major component of extracellular matrix material of biofilms embedded on intravascular catheters.