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# Introductory Chapter: Epidemiology of Invasive Fungal Infection - An Overview

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## 1. Introduction

Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality in hospitalized patients and the immunocompromised populations. Candidemia, invasive aspergillosis, mucormycosis, cryptococcosis, and *Pneumocystis* pneumonia (PCP) are IFIs associated with the highest incidence and mortality. The broader use of more aggressive treatment modalities, such as hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT), as well as chemotherapy for cancer patients and prolonged corticosteroid therapy, has increased the population of immunocompromised patients at risk for IFIs. Other groups at risk include individuals who have HIV/AIDS in which PCP is an AIDS-defining disease [1]. In this chapter, we aim to overview the epidemiology of the leading causes of IFIs in humans.

## 2. Aspergillosis

The genus *Aspergillus* contains more than 300 species described and is divided into 20 sections [2]. However, only a few are known to cause human disease. Human aspergillosis is primarily caused by *Aspergillus fumigatus* (the most common species described in aspergillosis cases), *A. flavus*, *A. niger*, *A. terreus*, and *A. nidulans*. *Aspergillus* species are ubiquitous, are found in soil and several organic debris, and produce conidia that are easily aerosolized. These conidia, when inhaled, can colonize the host's lungs, which can develop various clinical syndromes depending on their degree of immunocompetence. Ingestion of spores via the gastrointestinal tract or direct inoculation via skin injuries is an uncommon way of inoculation [3–5].

The major risk factors for infection include prolonged neutropenia, HSCT, SOT, corticosteroid therapy, chronic granulomatous disease, immunosuppressive treatment for malignancies, hematologic malignancy, myelodysplastic syndrome or aplastic anemia, advanced stage of human immunodeficiency virus (HIV) infection (facilitated by low CD4$^+$ cell counts), previous infections (such as cytomegalovirus infection), and patients with critical illness [4, 6]. The spectrum of disease is determined by the host's immune status and the virulence of *Aspergillus* species.

In immunocompetent hosts, aspergillosis causes mainly allergic symptoms without invasion and destruction of the host's tissues and chronic pulmonary aspergillosis. Allergic bronchopulmonary aspergillosis (ABPA) is a syndrome that arises from a hypersensitivity reaction to antigens from *Aspergillus* and may be developed in patients with asthma and cystic fibrosis [7]. In the chronic pulmonary aspergillosis, a preexisting pulmonary condition is generally observed. Chronic cavitary

pulmonary aspergillosis (aspergilloma or fungus ball) is the best-recognized form of pulmonary involvement due to *Aspergillus*, usually occurring in a preformed cavity in the lung (due to tuberculosis, sarcoidosis, or other necrotizing pulmonary processes) or in the paranasal sinuses [8, 9]. Subacute invasive aspergillosis (also called chronic necrotizing pulmonary aspergillosis) is a locally destructive invasion of lung parenchyma without invasion or dissemination to other organs [9, 10].

In immunocompromised patients, invasive aspergillosis (IA) can be a rapidly, progressive and frequently fatal disease. Invasive pulmonary aspergillosis (IPA) and rhinocerebral aspergillosis are the most common clinical forms of IA. Other clinical conditions included tracheobronchitis, invasive *Aspergillus* infection of the eye or heart, gastrointestinal invasive aspergillosis, cutaneous aspergillosis, and disseminated invasive aspergillosis [5]. Data from the Transplant-Associated Infection Surveillance Network (TRANSNET) [11] described that in HSCT recipients, invasive aspergillosis was the most common IFI (425 cases, 43%), followed by invasive candidiasis (276 cases, 28%) and zygomycosis (77 cases; 8%). One-year overall mortality rate reaches 75% [11]. In the Prospective Antifungal Therapy Alliance (PATH Alliance®) registry, from a cohort study of 960 cases of proven/probable IA, 48.3% of patients had hematologic malignancy, 29.2% received SOT, 27.9% were HSCT recipients, and 33.8% were neutropenic. The lung was the organ most frequently affected (76% of cases). The tracheobronchial tree, sinuses, skin, soft tissues, and the central nervous system were the most common extrapulmonary sites of infections. The most predominant species was *A. fumigatus* (72.6%), followed by *A. flavus* (9.9%), *A. niger* (8.7%), and *A. terreus* (4.3%). Overall Kaplan-Meier survival (12-week post-diagnosis) among all patients with IA was 64.4%.

## 3. Candidiasis

*Candida* species are ubiquitous yeasts, being frequent colonizers of the skin and normal flora of mucocutaneous membranes of humans. Also, it was also recovered from soil, hospital environment, food, inanimate objects, and nonanimal environments [12]. *Candida albicans*, *Candida dubliniensis*, *Candida glabrata*, *Candida guilliermondii*, *Candida intermedia*, *Candida kefyr*, *Candida krusei*, *Candida lusitaniae*, *Candida parapsilosis*, *Candida pseudotropicalis*, *Candida stellatoidea*, and *Candida tropicalis* are the main species associated with candidiasis, although more than 200 species of *Candida* have been identified.

*Candida albicans* remains the predominant species in most studies [13]. However, a shift in the etiology can be observed in different regions of the world [14]. For example, in northwestern Europe and the United States, *Candida glabrata* is generally recovered as the most common species, whereas in Southern Europe, some Asian countries and Latin America, *Candida parapsilosis* and *Candida tropicalis* are more frequently recovered than *Candida glabrata*. Of notable concern is the emergence of *Candida auris*, a multiresistant species associated with outbreaks of candidemia in many countries that presents a serious global health threat [12, 14–16].

As opportunistic pathogens, *Candida* infections can occur due to factors related to the host, the microorganism, or both. The three major conditions that predispose the human infection are: (i) the use of broad-spectrum antibiotics (long-term and/or repeated use), (ii) mucosal barrier breakdown, such as those induced by cytotoxic chemotherapy and medical interventions, and (iii) iatrogenic immunosuppression, such as corticosteroid therapy or chemotherapy-induced neutropenia [15]. Long hospital or intensive care unit (ICU) stay is the most common health

care-associated risk [17]. Among the several virulence factors described for *Candida*, (i) the ability of most species to switch between yeast, pseudohypha, and hyphae morphotypes; (ii) the secretion of a variety of factors, such as secreted aspartyl proteases, phospholipases and candidalysin toxin; and (iii) the effective capacity of adherence (mediated by proteins such as agglutinin-like protein 3) and biofilm formation are the main microorganism-related factors that contribute to candidiasis [15].

The incidence of *Candida* infections varies according to several epidemiological and geographic characteristics. *Candida* species are among the top four main pathogens causing health care-associated bloodstream infections, particularly in ICU, affecting 250,000 people and causing more than 50,000 deaths worldwide every year, based on conservative estimates [18–20]. In an international study of prevalence and outcomes of infection in ICU, *Candida* was the third most common cause of infection (17%), after *Staphylococcus aureus* (20.5%) and *Pseudomonas* species (19.9%) [21].

*Candida* was the most common fungal pathogen that causes invasive infection in SOT population [22]. In bone marrow transplantation (BMT) under fluconazole prophylaxis, *Aspergillus* species replaced *Candida* as main cause of IFI [11]. Newborn infants [23], HIV-infected patient (without the use of antiretroviral therapy) [24], and patients who underwent abdominal surgery [25] are other populations at increased risk for *Candida* infections. Unadjusted mortality rates vary widely (from 29 to 76%) for candidemia. In the United States, the attributed mortality rate ranges from >30 to 40% and the median cost for inpatient care was $46,684 [15, 19, 26, 27].

## 4. Cryptococcosis

*Cryptococcus neoformans* and *Cryptococcus gattii* are the two species that commonly cause cryptococcosis in humans. Historically, these species were classified into three varieties, five serotypes, and eight molecular subtypes. However, based on phylogenetic and genotyping studies, it was proposed to split *Cryptococcus neoformans* into two species (*Cryptococcus deneoformans* and *Cryptococcus neoformans*) and *Cryptococcus gattii* into five species (*Cryptococcus bacillisporus*, *Cryptococcus decagatti*, *Cryptococcus deuterogattii*, *Cryptococcus gattii*, and *Cryptococcus tetragattii*) [28]. Nonetheless, considering that more data about the genetic diversity of *Cryptococcus* were recently described and the absence of defined biological and clinical differences between the seven new species, some authors recommend the use of "*Cryptococcus neoformans* species complex" and "*Cryptococcus gattii* species complex" as a practical intermediate step until this species differentiation is clinically relevant [29].

*Cryptococcus neoformans* has been isolated in decaying material within hollows of several tree species, fruit, and soil enriched by avian excreta (such as feral pigeons) and is globally distributed. *Cryptococcus gattii* is classically associated with eucalyptus tree and limited to tropical and subtropical regions. However, recent outbreaks in Canada, Northern Europe, and Northern USA suggest that the ecological range of this species may not be fully recognized. Both species can survive and replicate in environmental scavengers such as free-living amoebae and nematodes [30, 31]. The respiratory tract is the main portal of entry for the aerosolized infectious particles from the disrupted and contaminated environment (soil, tree, or bird droppings-enriched areas). Lung and the central nervous system (CNS) are the primary sites of infection, but eyes, prostate, and skin can be frequently involved. Traumatic inoculation may occur but is infrequent [31–33].

HIV infection, idiopathic CD4$^+$ lymphopenia, corticosteroid treatment, SOT, malignant and lymphoproliferative disorders, sarcoidosis, treatment with some monoclonal antibodies (such as alemtuzumab, infliximab, etanercept, adalimumab, or anti-GM CSF), rheumatologic diseases (such as systemic lupus erythematosus and rheumatoid arthritis), chronic liver disease, renal failure and/or peritoneal dialysis, hyper-IgM syndrome or hyper-IgE syndrome are the main risk factors for cryptococcosis [31, 33, 34].

*Cryptococcus* infections in humans were considered uncommon before the 1970s. Cryptococcosis incidence increased significantly in the HIV epidemics in the 1980s. The overall incidence of 0.8 cases per million persons per year in the pre-AIDS era reached almost five cases per 100,000 persons per year in the peak of the AIDS epidemic. The incidence of cryptococcosis declined and stabilized from the mid-1990s with the use of fluconazole for the treatment of oral candidiasis and with the widespread use of active antiretroviral therapy (ART) [34–36]. However, HIV-associated cryptococcosis mortality remains unacceptably high, and globally, cryptococcal meningitis accounts for 15% of AIDS-related deaths. Cryptococcal infection-related deaths were estimated at 181,100 globally, with 75% (135,900) occurring in sub-Saharan Africa [37–39].

In HIV-negative individuals, cryptococcosis occurs in transplant recipients and other patients with primary or acquired defects in cell-mediated immunity [32]. In a recently multicenter, longitudinal cohort study in the United States [40], the demographics of 145 HIV-negative patients with cryptococcosis demonstrated that SOT (49 cases, 33.8%) was the main underlying disease, followed by autoimmune syndromes (15.9%), hematologic malignancy (11.7%), decompensated liver disease (9.7%), solid tumor (5.6%), primary immunodeficiency (2.1%), and HSCT (2.8%). Glucocorticoid therapy and cytotoxic chemotherapy were the immunosuppressive medications described for more than 40% of patients. CNS involvement was observed in 71 patients (49%).

## 5. Mucormycosis

*Rhizopus* is the most common genera causative of human disease, followed by *Mucor*, *Lichtheimia*, *Apophysomyces*, *Rhizomucor*, and *Cunninghamella* species. Less frequently, members include *Actinomucor*, *Cokeromyces*, *Saksenaea*, and *Syncephalastrum* [41–43]. These members from Mucorales family are ubiquitous in the environment, are taken by the host via inhalation of spores or ingestion of contaminated food, but rarely cause infection without obvious predisposing host factors [44].

Uncontrolled diabetes, hematological malignancy, malnutrition, solid organ transplantation, hematopoietic stem cell transplant, and liver disease are the primary underlying conditions associated with mucormycosis. Predisposing factors include corticosteroid use, neutropenia, trauma, anticancer therapy, use of calcineurin inhibitors, biological and renal replacement therapies, prior antifungal prophylaxis (e.g., voriconazole), iron overload and deferoxamine therapy [41, 42, 44].

Rhinocerebral, pulmonary, cutaneous, gastrointestinal, and disseminated mucormycosis are the common types of disease described. The mortality and morbidity rates are dependent on affected organ, Mucorales species, and medical status of the patient. Mucormycosis can be an extremely aggressive disease, and mortality rates can reach 46% in sinus infection, 73% in mucormycosis after exposure to voriconazole, 76% in pulmonary disease, and 96% in disseminated infections [42, 45].

Based on autopsy reports [46], mucormycosis is the third most common cause of invasive fungal infection, after candidiasis and aspergillosis. In developed countries, hematologic malignancies and hematopoietic stem cell transplantation

are the leading underlying conditions in mucormycosis cases while in developing countries, particularly in India, the major causes of the disease are associated with uncontrolled diabetes or trauma [43, 47]. Data from Transplant-Associated Infection Surveillance Network show that mucormycosis (formerly zygomycosis) was the third most common IFI (8%) in HSCT [11] and sixth most common IFI (2%) among organ transplant recipients [22].

## 6. Pneumocystis

*Pneumocystis jirovecii* (previously *Pneumocystis carinii* f. sp. hominis) is an opportunistic pathogen causing pneumonia in patients with immunodeficiencies and can colonize the lung of healthy individuals. Initially classified as a protozoan species, it is now recognized as a fungus based on phylogenetic data and the genus comprising a group of highly diversified species with a high degree of hosts-species specificity [48]. The environmental reservoir was not identified so that the mammalian hosts can be considered as reservoirs. Indeed, it was demonstrated that close person-to-person contact could facilitate the transmission, and nosocomial transmission has been reported [48, 49].

Despite the genus *Pneumocystis* being known for years, its life cycle remains poorly understood, principally by the lack of a reliable continuous culture system. The hypothesized life cycle comprises different morphologic forms: trophozoites, cysts, and intracystic bodies (sporozoites) and all these forms reside in the alveoli of the lung with the cyst being considered the infectant and transmissible form [48, 50]. Evidence suggests that the gateway to infection is through inhalation since controlled studies in different animal models have demonstrated airborne transmission [48, 51]. As the organism is host specific, transmission from animals to humans is unlikely [51].

The occurrence of *Pneumocystis* pneumonia (PCP) is related to severely immunocompromised people, principally in HIV/AIDS patients, and with other immunosuppressed conditions, that is, cancers, autoimmune disorders, transplantation, chronic lung disease, especially obstructive pulmonary disease (COPD) [48]. Colonization rates have been reported on the order of 20–69% for HIV patients, from 0 to 20% for healthy adults, and in 6% of organ transplant recipients if no prophylaxis is given [51]. Primary exposure appears to occur at early childhood as demonstrated by the seroconversion seen in 85% of children up to 20 months of age [52]. Colonization of both children and adults may be a source of transmission of *Pneumocystis jirovecii*, serving as potential reservoirs. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents include: treating patients with PCP together with prophylaxis of susceptible individuals (HIV patients with CD4 counts of <200 cells/μl or CD4 percentages of <14%); it is also recommended that a patient with PCP should not be placed in the same room with an immunodeficient patient. The prophylaxis among transplant recipients has been proved to be the most effective approach for ending outbreaks of PCP [48, 53].

## 7. Conclusions

The changes in the spectrum of the fungal infections associated with new risk factors and the emergence of resistant fungi highlight the necessity of a continuous update on knowledge of the epidemiology of fungal infections. Besides, the reduction of mortality among patients with IFIs must be accompanied by research that allows the development of new antifungal treatment strategies and earlier diagnosis by traditional and non-culture-based molecular tests.

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