Fungal Infections in the Immunocompromised Host

Bodo Wanke/+, Márcia dos Santos Lazéra, Marcio Nucci*

Serviço de Micologia, Centro de Pesquisa Hospital Evandro Chagas-Fiocruz, Av. Brasil 4365, 21045-900 Rio de Janeiro, RJ, Brasil *Laboratório de Micologia, Hospital Universitário Clementino Fraga Filho, UFRJ, Rio de Janeiro, RJ, Brasil

In recent years many remarkable changes occurred in our way of life, producing opportunities for microbes. All these changes are related to the recent emergence of previously unrecognized diseases, or the resurgence of diseases that, at least in developed countries, were thought to be under control. This concept is reviewed regarding fungal infections and their agents in the immunocompromised host. The changing pattern of these infections, the portals of entry of fungi into the human host, fungal pathogenicity and the main predisposing factors are analyzed. Opportunistic fungal infections in cancer, organ transplant and acquired immunodeficiency syndrome patients are reviewed, specially candidiasis and aspergillosis.

Key words: fungal infections - immunocompromised host - risk factors - candidiasis and aspergillosis

In this century and, more increasingly in the past two decades, many remarkable changes occurred in our way of life, producing opportunities for microbes. All these changes are related to the recent emergence of previously unrecognized diseases, or the resurgence of diseases that, at least in developed countries, were thought to be under control. This concept is also valid for the mycoses. As for all the infectious diseases, emergence of fungal infections result from (1) changes in human demographics and behavior; (2) changes in technology and industry; (3) changes in economic development and land use; (4) increasing and rapid international travel and commerce; (5) microbial adaptation to all the man produced changes. Consequently, this may lead to breakdown of public health measures (Cohen 1998).

Fungi have only emerged as significant pathogens during the past few decades when they became more and more frequently diagnosed as opportunistic infections in immunocompromised hosts. A review of the world's literature by Hurley in 1964 contained only 48 cases of disseminated candidiasis (Bodey & Anaissie 1989). In neutropenic cancer patients, the increase in the incidence of fungal infections was first described by Stefanini and Allegra (1957). Between 1943 e 1947, only 3% of patients with acute leukemia developed a fungal infection, compared to 22% between 1954 and 1956. Intensive cancer chemotherapy, organ transplantations, wide spectrum antibiotics and widespread use of parenteral alimentation are some of the major contributors to this current situation (Bodey & Anaissie 1989).

+Corresponding author. Fax: +55-21-590.9988
E-mail: wanke@fiocruz.br
Received 7 August 2000
Accepted 4 September 2000

FUNGAL PATHOGENICITY

With few exceptions pathogenicity among the fungi is not necessary for the maintenance or dissemination of the species. The ability of fungi to cause human disease appears to be an accidental phenomenon and the mycoses are primarily related to the immunological status of the host and environmental exposure, rather than to the infecting organism (Rippon 1988, Kwon-Chung & Bennett 1992, Ellis 1994).

Most fungi are unable to grow at 37°C. Thus, thermotolerance to survive at this temperature is essential to fungal growth within human body. Similarly, as most fungi are saprophytic, their enzymatic pathways function better at the redox potential of non-living substrates than at the lowered oxidation-reduction state of living tissue. However, many fungi prove to be able to surpass these two major physiologic barriers (Ellis 1994).

Host defenses are of non-specific and specific nature. The non-specific defenses include the antifungal activity of natural excretions, such as saliva and sweat; the protective effects of the endogenous normal microbiota of the skin and mucous membranes in competing for space and nutrients, thus limiting the growth of potential pathogens; and the mechanical barrier of the skin and mucous membranes preventing entry of fungi. Additionally, the body has the highly efficient non-specific inflammatory system to combat fungal proliferation involving the action of neutrophils, mono-

nuclear phagocytes and other granulocytes. The specific or acquired immunity defending from fungal growth in tissue consist basically of the cell-mediated immunity regulated by T-lymphocytes. The role of specific antibodies or humoral immunity regulated by B-lymphocytes is not so clear. In short, the mechanism of fungal pathogenicity is its ability to adapt to the tissue environment and to withstand the lytic activity of the host's defenses (Ellis 1994).

Table I lists the three major components of the host defenses against fungi and the diseases or conditions associated with fungal infections. The spectrum of fungal infections is different according to the major deficit in host defenses. For example, candidiasis in patients with impairment in T-cell defenses presents as muco-cutaneous infection and rarely disseminate. On the other hand, neutropenic patients develop disseminated infection much more frequently. In the hospital setting, disruption in the cutaneous and mucosal barriers play a major role. Indeed, nosocomial candidiasis occurs more frequently in patients admitted in intensive care unit, where the presence of catheters and the use of antibiotics is very frequent.

PORTALS OF ENTRY

Fungal infections are usually classified according to the initial site of infection into (1) superficial mycoses, which are limited to the outermost layers of the skin, the nails and hair; (2) subcutaneous infections, involving the dermis, subcutaneous tissues and bone; (3) systemic mycoses, usually acquired through inhalation, causing initially lung lesions, but may spread to many other organs. Whereas this classification is commonly used for the mycoses observed in the normal host, opportunistic fungal infections which occur in individuals who are debilitated or immunosuppressed as a result of an underlying disease or its treatment, usually are not referred according to the initial site of infection.

Many of the opportunistic fungi are ubiquitous saprobes in the soil, on decomposing organic matter or in the air. Although new species of fungi are regularly identified as cause of disease in immunosupressed hosts, most of the reported opportunistic fungal infections still remain candidiasis, aspergillosis, cryptococcosis and mucormycosis (zygomycosis). Besides, many endemic systemic mycoses are increasingly frequent as opportunistic infection in immunosupressed patients, mainly histoplasmosis and coccidioidomycosis. In contrast to the ubiquitous distribution of the agents of aspergillosis, mucormycosis, candidiasis and cryptococcosis, the agents of systemic mycoses have a restricted geographical distribution, limited to regions where these organisms occur in nature. For instance, this is valid for *Histoplasma capsulatum* var. *capsulatum*, *Paracoccidioides brasiliensis*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Cryptococcus neoformans* var. *gattii*, which may cause opportunistic infection in immunosuppressed individuals. In addition, nosocomial

TABLE I

Predisposing factors associated to defects of the host defenses against fungi

Predisposing factors of the host:

1) Disturbance of the epithelial barrier caused by:
- Broad spectrum or multiple antibiotic therapy
- Indwelling catheters
- Peritoneal dialysis
- Burns, ulcers, trauma, surgeries
- Increased gastric pH, cytotoxins, radiotherapy

2) Defects or dysfunction of mononuclear phagocytes, neutrophils + other cells caused by:
- Chemotherapy, radiotherapy
- Aplastic anaemia
- Chronic granulomatous disease
- Diabetes mellitus

3) Defect or dysfunction of T-lymphocyte cell mediated immunity caused by:
- Aids
- Hodgkin's disease
- Transplantation
- Chemotherapy, radiotherapy
- Leukemia
- Corticosteroids

Source: Ellis 1994

outbreaks of aspergillosis, candidiasis and other yeast infections have become increasingly important (Rippon 1988, Kwon-Chung & Bennett 1992, Richardson & Warnock 1993, Hazen 1995, Wheat 1995, Patterson et al. 2000). The portal of entry, related to the source of the infective fungi are summarized in Table II.

MYCOSES IN CANCER AND ORGAN TRANSPLANT (INCLUDING NEUTROPENIC) PATIENTS

In the neutropenic patient virtually any fungus able to grow at 37°C that gains access to the bloodstream may cause disseminated infection. Neutropenia, chemotherapy induced damage of the mucosae and the use of broad spectrum antibacterial drugs that destroy the normal microbiota, are the major cause of systemic fungal infections in these patients, especially candidiasis (Ellis 1994). The importance of the opportunistic fungal infections in cancer and organ transplant patients, can be estimated on the basis of several reports (Table III).

Candidiasis is the most frequent nosocomial mycosis in cancer patients and *Candida* species constitute the leading cause of positive blood cultures for fungi. However, *Aspergillus* species, *Fusarium* species, *Trichosporon* species and dematiaceous fungi have also emerged as important nosocomial pathogens, most of them refractory to systemic antifungal therapy. These trends in hosts and pathogens have converged with the simultaneous development of new diagnostic, therapeutic and preventive procedures and strategies, which may improve the management of these infections (Walsh et al. 1994).

MYCOSES IN AIDS PATIENTS

The emergence of the HIV infection and the consequent epidemic of acquired immunodeficiency syndrome (Aids) have been responsible for a dramatic increase in human infections caused by *Candida* species and *Cryptococcus neoformans*. Mucosal candidiasis occurs in almost all Aids patients, with *C. albicans* responsible for more than 85% of infections. Haematogenous dissemination occurs rarely in candidiasis, probably because the polymorphonuclear function is good enough to prevent it. *C. neoformans* is the second most important fungus causing disease in patients with Aids. The prevalence of cryptococcosis varies from 3-6% in Europe, 6-10% in the USA and 10-30% in some tropical countries, especially in Central Africa. In Brazil, the prevalence is estimated to vary 5-10%. Cryptococcosis in Aids patients is considered incurable and needs lifelong therapy to suppress the infection. Almost all cases are caused by *C. neoformans* var. *neoformans* (Dupont et al. 1992, 1994, Ellis 1994, Kappe et al. 1998). Other fungal infections have been diagnosed in Aids patients, such as the group of systemic mycoses caused by the dimorphic fungi in the correspond-

TABLE II

Portal of entry of the main groups of opportunistic mycoses according to source of the infections

Sources →	Portal/s of entry →	Mycoses
Soil, decaying organic material	lungs	Aspergillosis Mucormycosis Cryptococcosis Hyalo + Phaeohyphomycosis Systemic mycoses[a]
Humans/animals	skin mucosae	Candidiasis other yeasts' infections

a: endemic areas

TABLE III

Importance of fungal infections in cancer and organ transplant patient

Fatal fungal infection	(up to)	Incidence of specific mycoses	(up to)
Leukemia	30%	Candidiasis	44-80%
Lymphoma	15%	Aspergillosis	20-30%
Solid tumor	5%	Zygomycosis	Rare
Bone marrow transplant		Cryptococcosis	Rare
neutropenia < 3 wks	21%	Dimorphic systemic mycoses	Rare[a]
neutropenia > 3 wks	57%	Hyalo + Phaeohyphomycoses	Rare
Renal transplant	5-15%		

Source: Ellis 1994; *a*: endemic areas

ing endemic areas, mainly histoplasmosis and coccidioidomycosis (Wheat 1995). Cryptococcosis caused by the yeast *C. neoformans* var. *gattii* should be included in the latter group as it behaves as a true pathogen like the dimorphic fungi (Rozenbaum et al. 1992). The importance of the opportunistic fungal infections in patients with Aids can be estimated on the basis of several reports (Table IV).

TABLE IV

Importance of fungal infections in patients with acquired immunodeficiency syndrome

Incidence of specific mycoses	(up to)
Oral candidiasis	44-90%
Oesophageal candidiasis	45-55%
Cryptococcosis	3-33%
Histoplasmosis	5-30%[a]
Cocci + Paracoccidioidomycosis	Rare[a]
Hyalo + Phaeohyphomycoses	Rare[a]

Source: Ellis 1994; *a*: endemic areas

CANDIDIASIS AND ASPERGILLOSIS

The two major groups of fungal infections in the immunocompromised host, candidiasis and aspergillosis, because of their obvious and increasing importance, are treated apart.

Candidiasis - The relevance of nosocomial candidiasis has been subject of several studies. According to Beck-Sagué et al. (1993) an analysis of data collected by the Centers for Diseases Control (CDC) in 115 hospitals in the United States between 1980 and 1990 demonstrated an almost 2-fold increase of the nosocomial fungal infections. Moreover, 78.3% of these infections were caused by *Candida* spp. Another study demonstrated an 487% increase in the incidence of fungaemia caused by *Candida* spp. acquired in university hospitals in the United States during the 80's (Banerjee et al. 1991).

The most important human pathogenic *Candida* species are *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, *C. guilliermondii*, *C. lusitaniae* and *C. krusei*. In the meanwhile, the number of new species related to different clinical syndromes is increasing progressively as a consequence of new invasive diagnostic and therapeutic procedures, as well as the increasingly debilitated immunological status of the patients attended at tertiary hospitals facilitates the infection by microorganisms of low pathogenicity. The most important predisposing factors mentioned to be involved in these epidemiological changes are the pathologic and iatrogenic immunosupression and the increase in the use of broad-spectrum antibiotics. However, other factors may have contributed significantly, such as higher awareness and improved and more accessible diagnostic tools for diagnosing human mycoses (Hazen 1995).

The growing number of patients with candidiasis caused by non-*C. albicans* species was observed worldwide. However, the pattern of its geographic distribution is not uniform. In the USA and in some European countries a trend of increasing non-*C. albicans* infections, mainly the infections caused by *C. glabrata* and *C. krusei*, is observed. It has been suggested that the decreased susceptibility of these species to commonly used antifungal drugs, such as fluconazole, may be an important factor to their emergence as opportunistic pathogens (Johnson et al. 1995, Rex et al. 1995). In Brazil, *C. albicans* was the agent of 53 (37%) out of 145 episodes of candidemia in six different tertiary hospitals, while the most common non-*C. albicans* species were *C. parapsilosis* (25%), *C. tropicalis* (24%), *C. rugosa* (5%) and *C. glabrata* (4%). The relatively higher incidence of candidemia caused by *C. parapsilosis* in southeast Brazil may be due to mishandling of central venous catheters (Colombo et al. 1999, Colombo 2000).

Aspergillosis - *Aspergillus* species grow well on virtually any organic debris. They are saprobes commonly or occasionally found in soil, decaying vegetation, seeds and grains. Thermotolerant potentially pathogenic *Aspergillus* species were found even in human dwellings, ventilation and air conditioning systems, marijuana, old houses, hospitals and other constructions, water. Therefore, they are found almost everywhere. Beside candidiasis, aspergillosis is the second most frequent nosocomial fungal infection. Outbreaks of hospital-acquired aspergillosis were attributed to demolitions and re-buildings of old houses, hospitals and other constructions very close to the places where the risk patients were housed. Defective or incorrect handling of air conditioning systems also represent risk for nosocomial aspergillus outbreks (Rhodes et al. 1992, Summerbell et al. 1992, Summerbell et al. 1994, Pitt 1994, Richardson 1998).

A. fumigatus is by far the most important agent of aspergillosis, followed by *A. flavus*, *A. terreus*, *A. niger* and several others occasionally found. The predominance of *A. fumigatus* in contrast to other *Aspergillus* species may be due to its ability to (1) grow abundantly everywhere; (2) produce tiny conidia, that easily can penetrate deep into the alveolar region; and (3) grow at 37°C (Pitt 1994).

Aspergillosis represent a wide spectrum of syndromes and clinical manifestations, including allergic aspergillosis, colonization of cavities with

or without the formation of a fungus ball (mainly in the lungs, paranasal sinuses, bronchiectasis), acute to chronic necrotizing invasive forms, ocular infections (keratitis), otomycosis, endocarditis, osteomyelitis, skin infections.

Invasive aspergillosis remains a major cause of morbidity and mortality in immunosuppressed patients. It is the second most frequently diagnosed mycosis in patients treated with solid organ or bone marrow transplants. The initial and most common site of infection for invasive aspergillosis is the respiratory tract (paranasal sinuses, lungs), followed by severely traumatized skin. From these sites, dissemination to other organs by haematogenous spread occurs frequently.

Aspergillus species, as well as all the other hyphomycetes (agents of hyalohyphomycosis and phae-ohyphomycosis) and the Mucorales, have the tendency to invade the blood vessels causing haemorrhagic infarction and thrombosis in these severely immunosuppressed patients (Kwon-Chung & Bennett 1992, Richardson 1998, Patterson et al. 2000).

Many studies have shown that invasive aspergillosis is now more widely recognized, reflecting its main association with severe immunosuppression as a result of both neutropenia and compromised cell-mediated immunity. Computerized tomography scanning of the lungs has proven to be an excellent diagnostic method for early recognition of an "halo" sign with a ground-glass appearance surrounding a nodule, or the "air-crescent" sign with cavitation in later stage disease (Bartlett 2000, Denning 2000).

CLOSING REMARKS

Many other opportunistic fungal infections not mentioned herein may become an emerging health problem in some particular risk groups. *Malassezia* and *Trichosporon* are considered two emerging pathogenic yeast-like basidiomycetous fungi (Guého et al. 1994, 1998) and the importance of *Candida* species other than *C. albicans* as opportunistic pathogens is frequently reported (Coleman et al. 1998) as well as the increasing importance of some hyphomycetes, such as *Fusarium* species, *Pseudallescheria boydii* (*Scedosporium apiospermum*) and the Mucorales (Rippon 1988, Kwon-Chung & Bennett 1992, Richardson & Warnock 1993).

Keeping in mind that fungi are significant and increasingly cause of morbidity and mortality in immunocompromised patients and that the opportunistic infections they cause are severe and life threatening, a rapid diagnosis and efficient therapeutic measures are essential. Of course, collaboration between the clinicians and the laboratory is absolutely necessary. Additionally, the precise diagnosis is based on the morphologic identification of the tissue forms in biopsy material or pus by microscopy and culture. The final diagnosis of the agent is achieved only after culture of material obtained from the lesions. Detection of specific antibodies and specific antigens and/or metabolites in body fluids or tissues may be of great value in the future, specially molecular diagnostic techniques.

REFERENCES

Banerjee SN, Emori TG, Culver DH, Gaynes RP, Jarvis WR, Horan T, Edwards JR, Tolson J, Henderson T, Marton JW, and the National Nosocomial Infections Surveillance System 1991. Secular trends in nosocomial primary bloodstream infections in the United States, 1980-1989. *Am J Med* (Suppl. 3B)*:* 86S-89S.

Bartlett JG 2000. Aspergillosis update. *Medicine 79:* 281-282.

Beck-Sagué CM, Jarvis WR, and the National Nosocomial Infections Surveillance System 1993. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. *J Infect Dis 167*: 1247-1251.

Bodey GP, Anaissie EJ 1989. Opportunistic fungal infections: a major problem in immunocompromised patients. In RG Richardson, *Opportunistic Fungal Infections: Focus on Fluconazole*, International Congress and Symposium Series, Royal Society of Medicine Services Limited, London, p. 1-16.

Cohen ML 1998. Resurgent and emergent disease in a changing world. *Br Med Bull 54*: 523-532.

Coleman DC, Rinaldi MG, Haynes KA, Rex JH, Summerbell RC, Anaissie AL, Sullivan DJ 1998. Importance of *Candida* species other than *Candida albicans* as opportunistic pathogens. *Med Mycol 36* (Suppl. 1): 156-165.

Colombo AL 2000. Epidemiology and treatment of hematogenous candidiasis: a Brazilian perspective. *Braz J Infect Dis (BJID) 4*: 113-118.

Colombo AL, Nucci M, Salomão R, Branchini MLM, Richtmann R, Derossi A, Wey SB 1999. High rate of non-*albicans* candidemia in Brazilian tertiary care hospitals. *Diagn Microbiol Infect Dis 34:* 281-286.

Denning DW 2000. Early diagnosis of invasive aspergillosis. *Lancet 355:* 423-424.

Dupont B, Denning DW, Marriott D, Sugar A, Viviani MA, Sirisanthana T 1994. Mycoses in AIDS patients. *J Med Vet Mycol 32* (Suppl. 1): 65-77.

Dupont B, Graybill JR, Armstrong D, Laroche R, Touzé JE, Wheat LJ 1992. Fungal infections in AIDS patients. *J Med Vet Mycol 30* (Suppl. 1): 19-28.

Ellis D 1994. *Clinical Mycology. The Human Opportunistic Mycoses,* Pfizer Inc. (Pub.), New York, 166 pp.

Guého E, Boekhout T, Ashbee HR, Guillot J, Van Belkum A, Faergemennn J 1998. The role of *Malassezia* species in the ecology of human skin and as pathogens. *Med Mycol 36* (Suppl. 1): 220-229.

Guého E, Faergemann J, Lyman C, Anaissie EJ 1994.

Malassezia and *Trichosporon*: two emerging pathogenic basidiomycetous yeast-like fungi. *J Med Vet Mycol 32* (Suppl. 1): 367-378.

Hazen KC 1995. New and emerging yeast pathogens. *Clin Microbiol Rev 8:* 462-478.

Hurley R 1964. Acute disseminated (septicaemic) moniliasis in adults and children. *Postgrad Med J 40:* 644-653.

Johnson EM, Warnock DW, Luker J, Porter SR, Scully C 1995. Emergence of azole drug resistance in *Candida* species from HIV-infected patients receiving prolonged fluconazole therapy for oral candidosis. *J Antimicrob Chemother 35*: 103-114.

Kappe R, Levitz S, Harrison TS, Ruhnke M, Ampel NM, Just-Nübling G 1998. Recent advances in cryptococcosis, candidiasis and coccidioidomycosis complicating HIV infection. *Med Mycol 36* (Suppl. 1): 207-215.

Kwon-Chung KJ, Bennett JE 1992. *Medical Mycology,* Lea & Febiger, Philadelphia, 866 pp.

Patterson TF, Kirkpatrick WR, White M, Hiemenz JW, Wingard JR, Dupont B, Rinaldi MG, Stevens DA, Graybill JR 2000. Invasive aspergillosis. Disease spectrum, treatment practices, and outcomes. *Medicine 79*: 250-260.

Pitt JI 1994. The current role of *Aspergillus* and *Penicillium* in human and animal health. *J Med Vet Mycol 32* (Suppl. 1): 17-32.

Rex JH, Rinaldi MG, Pfaller MA 1995. Resistance of *Candida* species to fluconazole. *Antimicrob Agents Chemother 39*: 1-8.

Rhodes JC, Jensen HE, Nilius AM, Chitambar CR, Farmer SG, Washburn RG, Steele PE, Amlung TW 1992. *Aspergillus* and aspergillosis. *J Med Vet Mycol 30* (Suppl. 1): 51-57.

Richardson MD 1998. *Aspergillus* and *Penicillium* species. In L Ajello & R Hay, *Topley & Wilson's Microbiology and Microbial Infections, Medical Mycology,* Vol. 4, Arnold, London, p. 281-312.

Richardson MD, Warnock DW 1993. *Fungal Infection. Diagnosis and Management,* Blackwell Scientific Publications, London, 207 pp.

Rippon JW 1988. *Medical Mycology. The Pathogenic Fungi and the Pathogenic Actinomycetes,* 3rd ed., WB Saunders, Philadelphia, 797 pp.

Rozenbaum R, Gonçalves AJR, Wanke B, Caiuby MJ, Clemente H, Lazera MS, Monteiro PCF, Londero AT 1992. *Cryptococcus neoformans* varieties as agents of cryptococcosis in Brazil. *Mycopathologia 119*: 133-136.

Stefanini M, Allegra S 1957. Pulmonary mucormycosis in acute histiocytic leukemia. *N Engl J Med 256*: 1026-1030.

Summerbell RC, Staib F, Dales R, Nolard N, Kane J, Zwanenburg H, Burnett R, Krajden S, Fung D, Leong D 1992. Ecology of fungi in human dwellings. *J Med Vet Mycol 30* (Suppl. 1): 279-285.

Summerbell RC, Staib F, Ahearn DG, Ando M, Ajello L, Crow SA, Fung D, Gregor T, Noble J, Price DL, Simmons RB, Tarlo SM, Woychick W 1994. Household hyphomycetes and other indoor fungi. *J Med Vet Mycol 32* (Suppl. 1): 277-286.

Walsh TJ, De Pauw B, Anaissie E, Martino P 1994. Recent advances in the epidemiology, prevention and treatment of invasive fungal infections in neutropenic patients. *J Med Vet Mycol 32* (Suppl. 1): 33-51.

Wheat J 1995. Endemic mycoses in AIDS: a clinical review. *Clin Microbiol Rev 8*: 146-159.