



Opportunistic Fungi in the Immunocompromised Patient

The Mycology Initiative *Program One 2001*

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THE MYCOLOGY INITIATIVE IS AN ACCREDITED EDUCATIONAL program designed and implemented by members of the International Immunocompromised Host Society (ICHS).

The goal of this program is to provide leading-edge information in the area of medical mycology to physicians and other health-care providers.

The program has been designed to address important issues about fungal disease such as epidemiology, pathogenesis, diagnosis, prevention, and treatment of the immunocompromised patient. Thought leaders in medical mycology will develop content areas as monographs and slide/lecture sets that will be available to you at regular intervals.

This first monograph, *Opportunistic Fungi in the Immunocompromised Patient*, is an introduction to the general topic of fungal infections in high-risk patients. The initial section provides important demographic and incidence data to help you understand the causes of increased rates of opportunistic fungal infections in immunocompromised patients.

The monograph discusses risk factors most implicated in community-acquired and nosocomial fungal infections. The authors provide an overview of the pathogenesis of fungal infections, including mechanisms of mucosal acquisition, tissue invasion, and host immune responses to infection.

You will learn about environmental and host factors that should alert you that your patient is at risk. The monograph addresses new and important laboratory methods for diagnosing fungal infections in immunocompromised hosts, and reviews current antifungal therapies and their mechanisms of action. You will become familiar with the benefits and limitations of each of the antifungal agents used alone and in combination. Finally, the monograph reviews therapeutic approaches under investigation.

Target Audience

Hematologists, Oncologists, Infectious Diseases Specialists, Transplant Physicians, Bone-Marrow Transplant Physicians, Physicians in Training, and any physician who cares for patients at risk of developing invasive mycoses.

Course/Activity

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Pittsburgh School of Medicine and The International Immunocompromised Host Society. The University of Pittsburgh School of Medicine, as part of the Consortium for Academic Continuing Medical Education, is accredited by the ACCME to provide continuing medical education for physicians.

The Center for Continuing Education in the Health Sciences designates this continuing medical education activity a maximum of 4.0 hours of Category 1 credit toward the AMA Physician's Recognition Award. Physicians should claim only those hours of credit that they actually spend on this educational activity.

It is estimated that the average time required to read this text-based material and complete the test is 4 hours. Please complete the post test and program evaluation sections on the last pages of this monograph and return them to the CME office to receive CME credit.

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Conflict Disclosure

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The Changing Face of the Fungal Kingdom

In evolutionary terms, fungi are ancient. By 300 million years ago, all forms of fungi existed, and there is undisputed evidence of fungal fossils from 400 to 440 million years ago. Some estimates put the number of species at nearly 2.5 million, and well over 100,000 varieties have been categorized. In general, fungi are free-living in nature and are not dependent on humans or animals for their survival. They mostly have very limited pathogenicity, with few invasive properties. Prehistoric man must have coexisted with fungi for millions of years, and they probably never posed a serious threat to health. Until the latter decades of the 20th century, modern man would have been more familiar with the positive attributes of fungi: edible mushrooms and truffles; the yeast-producing bubbles in beer, champagne, and bread; and the discovery of one of the first antibiotics from the mould *Penicillium notatum*.

Fewer than 200 species have been associated with human disease and only a handful of these are capable of causing significant disease in otherwise healthy individuals. Pathology textbooks in the first half of the 20th century devoted little space to diseases due to fungi, restricting discussion to infections acquired from environmental sites in nature where the fungus grows as a saprophyte, or to superficial infections of skin, nails, and mucous membranes.

However, recent years have seen an increase in morbidity and mortality associated with the appearance of new or previously very rare mycoses. Systemic infection with organisms such as *Candida albicans*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* indicates an unprecedented change in the status quo of the relationship of the fungi to man.

True pathogens are few, and the majority of infected individuals are located in regions endemic for the fungus; infection results from inhalation of conidia (sometimes mistakenly called spores) released into the atmosphere. Examples in the United States include infections with *Histoplasma capsulatum* along the Mississippi River Valley, *Coccidioides immitis* in the Southwest, and *Blastomyces dermatitidis* in northern, central, and southeastern states.

The majority of people living in areas with endemic disease have been infected at some point. In most individuals, inhaling conidia causes a mild and transient chest infection with flu-like symptoms; other symptoms include rash and, rarely, arthritis. Dissemination to areas of the reticuloendothelial system occurs in most people infected with histoplasmosis, but this is generally asymptomatic. The infection normally resolves without treatment, although full recovery can take several months. Granulomas visible on chest X-ray and splenic calcification reflect healing of the infection. Until the 1980s, the incidence of disseminated disease remained low. However, in the last 20 years, the number of patients with significant morbidity and mortality related to these endemic organisms has increased. Population movements and climate may be important factors in localized outbreaks. For example, the number of reported cases of coccidioidomycosis in Arizona increased from 7.0 cases per 100,000 population in 1990 to 14.9 cases per 100,000 population in 1995 [1]. The disease disproportionately affected persons aged greater than 65 years. During this period, many older people moved to the state from areas where coccidioidomycosis was not endemic, and this factor together with underlying health conditions in this population may have contributed to the dramatic increase in infection rate. Severe drought followed by heavy rainfall was identified as a possible factor associated with an epidemic of coccidioidomycosis



in California [2]. Disseminated coccidioidomycosis and histoplasmosis are also increasing in persons with AIDS, not only in patients living in endemic areas but also in those living elsewhere, indicating that reappearance of prior infection can occur in this setting [3].

Factors Influencing the Emergence of Opportunistic Fungal Infections

The dramatic increase in the diversity and number of infections is due to a combination of improved recognition and laboratory diagnostic techniques and an increasing population of susceptible individuals. A number of factors are necessary for most invasive infections to occur:

- Exposure to the fungal organism
- Host acquisition of the potential pathogen
- Some species must compete with commensal microbial flora
- Breach of the barriers afforded by skin and mucous membranes
- Growth in sufficient numbers to overcome host immune defenses

The Susceptible Host

The most important factor in the emergence of opportunistic fungi and the changing epidemiology of fungal disease largely relates to advances in medical and surgical therapy. These successes that on the one hand have offered treatment to patients with previously severe or fatal diseases have on the other hand produced a hospitalized patient population of severely ill, immunocompromised individuals. This patient pool has been increased by the AIDS epidemic. The intricate systems of immune and nonimmune mechanisms that protect us from invading organisms are compromised; previously innocuous fungal species become virulent pathogens.

Table 1.
Underlying Causes of
Impaired Host Defense.

| Immunodeficiency | Organ damage/ dysfunction | Depletion of competing endogenous flora |
|---|---|--|
| <ul style="list-style-type: none"> • Inborn: CGD, SCID, MPD, hypogammaglobulinemia • Drug-induced: chemotherapy, radiotherapy, corticosteroids, other immunosuppressive agents • Acquired: AIDS, solid and hematologic malignancies, malnutrition, diabetes with ketoacidosis, cytomegalovirus infection • Age-related: neonates, elderly | <ul style="list-style-type: none"> • Skin: surgery, IV catheters and devices, eczema, burns • Mucosa: ulcers, depressed mucociliary action • Diabetes mellitus-associated • Renal failure • Liver failure • COPD/lung dysfunction | <ul style="list-style-type: none"> • Broad-spectrum antibiotics |

CGD, chronic granulomatous disease;
SCID, severe combined immunodeficiency;
MPD, myeloperoxidase deficiency;
COPD, chronic obstructive pulmonary disease.

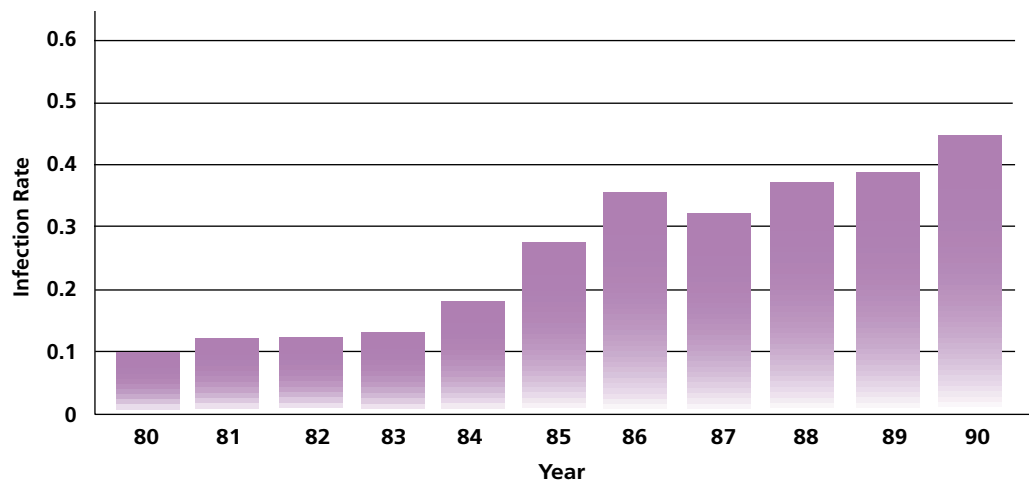


Primary immunodeficiencies are inherited and are of variable severity. For example, chronic granulomatous disease (CGD) and myeloperoxidase deficiency (MPD) are conditions in which neutrophil intracellular killing mechanisms are defective. Impaired T-lymphocyte function is associated with severe combined immunodeficiency syndrome in infants. AIDS and several hematologic malignancies are examples of acquired defects in T-cell function. However, many examples of impaired host defense are those acquired in hospital (Table 1).

The Rise in Nosocomial Infections

The Centers for Disease Control and Prevention (Atlanta) estimates that hospital-acquired infections affect approximately 2 million persons annually, and in 1992 cost more than \$4.5 billion [4]. About 250,000 cases of bloodstream infection (BSI) occur annually, engendering an attributable mortality of 35%, 24 days of additional hospital stay, and excess hospital costs of \$40,000 per survivor [5]. The National Nosocomial Infections Surveillance (NNIS) System conducts prospective surveillance of nosocomial infections. By the late 1980s, hospitalwide and ICU surveillance reported an increased prevalence [6] of pathogens not previously associated with the hospital setting. Of particular note was the emergence of *Candida* species as the sixth most common infection reported hospitalwide and the fourth most common pathogen among nosocomial BSIs [6]. Alarming secular trends were also noted, with a fivefold increase in incidence of bloodstream fungal infection over the decade (Fig 1).

Figure 1. Secular trends in rates of nosocomial bloodstream fungal infection (per 1,000 discharges. NNIS, January 1980 through December 1990). Modified from Jarvis [6].



A recent report [7] from the Surveillance and Control of Pathogens of Epidemiologic Importance Project (SCOPE) confirmed that *Candida* species remain ranked fourth in order of nosocomial BSIs at 49 hospitals throughout the United States from 1995 to 1998 (Table 2). *Candida albicans* accounted for 46.8% of the isolates, with *C glabrata*, *C parapsilosis*, and *C tropicalis* accounting for 90% of the other isolates. Importantly, in this study *Candida* species infections were associated with the highest crude mortality (40%) compared to bacteria.

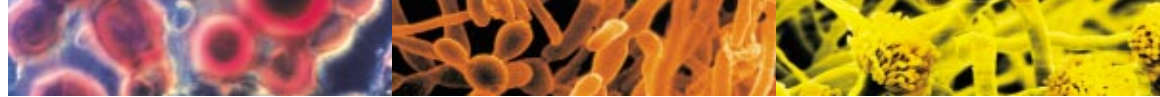


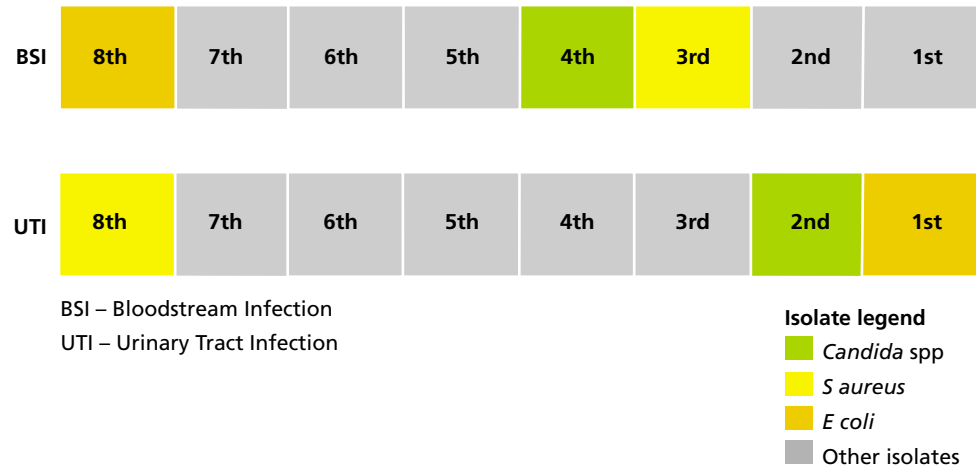
Table 2.
Rank Order of
Nosocomial Bloodstream
Pathogens and Associated
Crude Mortality Among
49 Hospitals Throughout
the United States
SCOPE: April 1995 -
April 1998.

| Rank | Pathogen | No. of Isolates | % | Crude Mortality (%) |
|------|----------------------------------|-----------------|------|---------------------|
| 1 | Coagulase-negative staphylococci | 3,908 | 31.9 | 21 |
| 2 | <i>Staphylococcus aureus</i> | 1,928 | 15.7 | 25 |
| 3 | Enterococci | 1,354 | 11.1 | 32 |
| 4 | <i>Candida</i> species | 934 | 7.6 | 40 |
| 5 | <i>Escherichia coli</i> | 700 | 5.7 | 24 |
| 6 | <i>Klebsiella</i> species | 662 | 5.4 | 27 |
| 7 | <i>Enterobacter</i> species | 557 | 4.5 | 28 |
| 8 | <i>Pseudomonas</i> species | 542 | 4.4 | 33 |
| 9 | <i>Serratia</i> species | 177 | 1.4 | 26 |
| 10 | Viridans streptococci | 173 | 1.4 | 23 |

Reprinted from Edmond et al [7]. SCOPE, Surveillance and Control of Pathogens of Epidemiologic Importance.

Increasingly, high-risk areas such as neonatal and surgical intensive care units account for as much as 25% to 50% of the reported cases of nosocomial infections. Data collected from 9 different types of ICU from January 1990 through May 1999 showed that *Candida albicans* remained the fourth most common isolate from BSIs. The report included data for isolates from urinary-tract infections where it was second [8]. Of interest was the ranking of *Candida* spp in comparison with bacterial infections such as *Escherichia coli* and *Staphylococcus aureus* (Fig 2).

Figure 2.
Ranking of common
infections by NNIS,
January 1990-May 1999 [8].

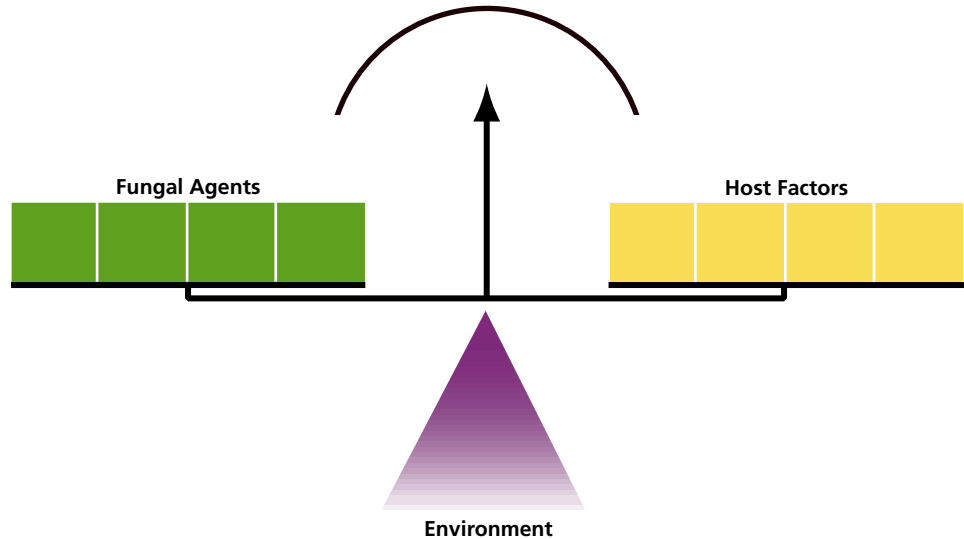




Epidemiology of Fungal Infection and Disease

Humans have evolved highly sophisticated mechanisms to resist invasion by material regarded as foreign or nonself such as bacteria or fungi. In the face of exposure to microbes, the balance between health and disease is determined by a number of interrelated factors. On one side of this balance are the factors associated with the infecting agent; on the other, the ability of the host to resist the attack. The “theater” of this combat is the environment.

Figure 3.
The balance determining
the probability of fungal
infection and disease.



Interactions between Agent, Host, and Environment

Factors associated with the agent, the host, and the environment will all interact to determine the final outcome. At one end of the spectrum, exposure followed by infection is all that is needed for disease to occur, for example, the rabies virus. At the other extreme, a large number of organisms can gain access to the host but will not cause disease in the majority of circumstances. Disease will develop only via interactions with other contributory factors related to the host and the environment.

The Agent

In the health-care setting, the key organisms causing nosocomial fungal disease are the opportunistic pathogens *Candida* species and *Aspergillus* species. However, the emergence of other fungal species not previously associated with pathology, e.g., *Fusarium*, *Trichosporon*, *Alternaria*, is a clear cause for concern (Table 3) [9].



Table 3.
Medically Significant Fungi
Causing Opportunistic
Infection.

| Classic Pathogens | Emerging Pathogens |
|--|---|
| <i>Candida</i> species <i>Aspergillus</i> species <i>Cryptococcus</i> Zygomycetes | <i>Fusarium</i> species <i>Trichosporon beigeli</i> Other agents of hyalohyphomycosis and phaeohyphomycosis |

Pneumocystis carinii is now established as a fungus and is a common cause of fatal pneumonia in AIDS patients. However, consideration of this opportunistic pathogen is beyond the scope of this publication.

Infection due to *Candida* species in critically ill patients usually arises from the patient's endogenous flora and highlights the importance of an intact host-defense system in resisting invasive fungal infection. Approximately 80% of normal healthy individuals carry one or more of the *Candida* species as part of the normal flora of the gastrointestinal or genitourinary tract. However, these commensal organisms can become pathogenic if competing bacterial flora are suppressed by antibiotics or if mucosal damage and neutropenia are present.

The incidence of aspergillosis has been increasing. In one US hospital, only 30 cases were reported in a 12-year period between 1951 and 1963, and this rose to 91 cases in a 5-year period between 1971 and 1976 [10]. *Aspergillus* species are ubiquitous in soil, water, and decaying vegetation. In the hospital environment, conidia can be isolated from the air, ventilation systems, and dust. Most infections are acquired via airborne transmission. Colonization of the respiratory tract is followed by invasive infection if host defenses are compromised. Data from the NNIS indicate that only 1.1% of hospitalwide fungal infections reported between 1980 and 1990 were caused by *Aspergillus* [6]; however, in specialized units the incidence is often much higher. The crude mortality is high, with estimates up to 95% in some patient populations.

The Environment

The environment is the background on which the host and agent interact and includes demographic, climatic, and societal factors that can influence the spread of infection. In the hospital setting, the surroundings are of major importance in the production of nosocomial infection. Reservoirs for *Aspergillus* spp and Zygomycetes in hospitals include unfiltered air, ventilation systems, contaminated dust during construction, carpeting, food, water, and even decorative potted plants [11]. In contrast, candidemia is mostly acquired endogenously through prior colonization of the mouth, vagina, skin, and gastrointestinal tract. However, exogenous acquisition of *Candida* spp has been reported, in particular person-to-person spread of *Candida* species via the hands of medical personnel [12].



Techniques and therapies used by health-care workers to support critically ill patients often disrupt the first lines of defense that protect humans from invading microorganisms.

These include:

- Barriers afforded by the skin and mucous membranes
- Low pH generated in gastric acid
- Normal commensal bacterial flora that compete for nutrients with invading fungal organisms

These defenses are independent of the immune system and although of paramount importance in preventing fungal infection, are often taken for granted (Table 4).

Table 4.
Underlying Nosocomial
Risk Factors for Fungal
Infection.

| Candidiasis | Aspergillosis |
|---|--|
| <i>Candida</i> colonization | Contaminated air |
| Central venous catheters | Contaminated water supplies |
| Broad-spectrum antibiotics | Broad-spectrum antibiotics |
| Chemotherapy/radiotherapy-induced mucositis | Surgery |
| Surgery on GI tract | Damage to skin |
| Hyperalimentation | Corticosteroids and other immunosuppressive agents |
| Hemodialysis | |
| Urinary catheters | |

Physical disruption of the barriers by burns, trauma, surgery, or by the placement of intravenous catheters or other invasive devices can provide an entry route for the organisms, such as *Candida* spp (Table 5) [13].

Table 5.
Infection Related to
Intravascular Devices.

| |
|---|
| <ul style="list-style-type: none"> • Migration of skin organisms along catheter tract • Contamination of catheter hub from extrinsic (HCWs) or endogenous (skin flora) sources with passage through the catheter lumen • Contaminated infusate (parenteral fluids, medications, or blood products) from the manufacturer (intrinsic) or from poor aseptic technique during handling (extrinsic) • Hematogenous spread from a distant local infection (GI tract) |
|---|

Catheter-associated infection, including surgically implanted and percutaneous venous catheters, is frequently implicated as a risk factor for candidemia, in particular *C parapsilosis*. Total parenteral nutrition can predispose patients to disseminated candidiasis. There have been reports of disseminated infection due to *Malassezia furfur* in patients receiving intravenous lipid emulsions [14]. Infection with *Aspergillus* due to barrier disruption is uncommon, although case reports have described entry of the organism via the skin at the IV insertion site or at a site of prolonged skin contact with dressings or tapes.

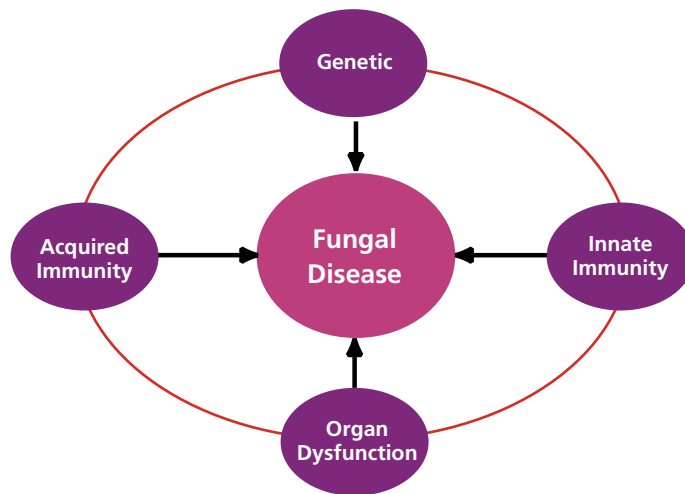
Broad-spectrum antibiotic agents can disrupt the normal bacterial flora and facilitate local overgrowth of normal fungal flora, e.g., *Candida* species [15] or growth of opportunists, e.g., *Aspergillus* [16]. This is of particular significance if increased gastrointestinal colonization occurs together with ulcerations after cytotoxic chemotherapy.



The Host

Vast arrays of host factors are important in the development and severity of nosocomial infection and disease. These risk factors are of differing degrees in different patient populations and will to varying degrees determine overall patient outcome.

Figure 4.
Major factors affecting
the host's ability to
resist fungal infection
and disease.



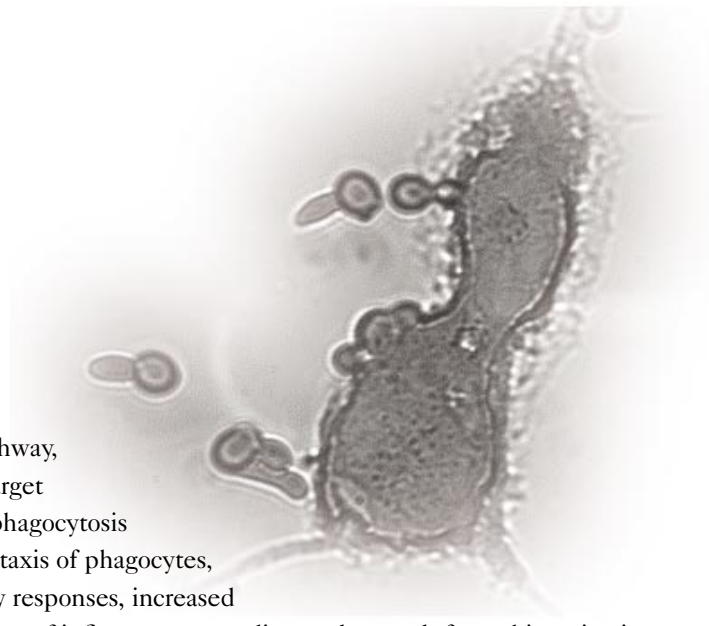
Immune Defense Systems

Healthy humans protect themselves against foreign invaders by intricate systems of immune and nonimmune mechanisms. Together with physical and chemical barriers, neutrophils, macrophages, and natural killer (NK) cells form the first line of defense against infection. Experimental evidence *in vitro* and *in vivo* confirms that phagocytic defenses are of paramount importance against mucosal infection. Lungs of experimental animals acutely exposed to *Cryptococcus neoformans* mount an acute neutrophil response followed by an influx of mononuclear cells [17]. Oxidants and granule products from stimulated neutrophils can kill *C. albicans* and *A. fumigatus*, and bronchoalveolar macrophages are particularly relevant in defense against fungal conidia [18].

Antibody-dependent cell-mediated cytotoxicity regulated by natural killer (NK) cells, cytotoxic T lymphocytes, helper T lymphocytes, and antibody-producing B lymphocytes are central to adaptive immune responses against fungal infections. The constant interaction of the different components of the immune system ensures successful protection of the host. After phagocytosis, monocytes may act to trigger the release of cytokines, in particular interferon- γ (INF- γ) and interleukin-2 (IL-2) that in turn activate effector cells to destroy the engulfed organism. Tumor necrosis factor- α (TNF- α) and granulocyte macrophage-colony-stimulating factor (GM-CSF) have also been reported to activate effector cells [18]. In addition, antibodies released by B lymphocytes can coat pathogens and change the capsular structure to allow more effective phagocytosis. Although this occurs in bacterial infection, the importance in fungal disease apart from *Cryptococcus* is not well established.



Figure 5.
Fungal organisms
under attack.



Complement activation, either via the classic or alternative pathway, facilitates the opsonization of target organisms, thereby enhancing phagocytosis and subsequent killing. Chemotaxis of phagocytes, induction of acute inflammatory responses, increased capillary permeability, and release of inflammatory mediators also result from this activation. Unlike bacteria, complement does not cause direct lysis of fungal cells. However, opsonization of invading fungi with complement fragments or antibody coating is important to facilitate phagocytosis and killing in some but not all species. Binding of certain fungi to macrophages can also be facilitated by cellular receptors for yeast mannose and beta-glucans [18].

At-Risk Populations

For the vast majority of populations in the developed world, exposure to fungal agents is of little consequence. Even otherwise healthy individuals who require hospitalization will not succumb to fungal disease even if risk factors such as integument breaches through surgery and intravenous therapy are present. The major reason for this is the presence of an intact immune system that can respond to and kill or inactivate the invading organism.

However, in patients with compromised immunity, due either to underlying medical conditions or to medical treatment, harmless fungi can transform into opportunistic pathogens. The major players in the immune system needed to defend against fungal infections are the neutrophil and T lymphocyte, in particular the CD4⁺ helper cell. Although specific medical conditions or treatments may primarily affect either the innate or cell-mediated immune systems, a great deal of overlap exists.

The Cancer Patient

Risk Factors In the cancer patient, the major factor in the pathogenesis of fungal infection is nosocomial impairment of the immune system, especially neutropenia due to chemotherapy or irradiation. The type, dose, and duration of the anticancer drugs administered can help identify patients at high risk of infection. Not all patients with cancer and not all anticancer drugs are associated with immunosuppression. While drugs such as cyclophosphamide, fluorouracil, and vinblastine cause bone-marrow suppression, bleomycin and tamoxifen have little or no effect on neutrophil count. Other drugs frequently given, including prednisone, inhibit the humoral and cell-mediated immune responses. Irradiation and malnutrition decrease T-lymphocyte function.



Other risks discussed previously as environmental factors, including antibiotics, indwelling catheters, surgery, chemotherapy-induced mucosal ulceration, and exposure to ICU environments are also important in the pathogenesis of infection, particularly in combination with neutropenia. Finally, there is growing evidence that potentially immunosuppressive viral infections (cytomegalovirus or CMV) are risks for both candidiasis [19] and aspergillosis [20].

Incidence and Mortality In one study, histologic evidence of fungal infection at autopsy was noted in 5% of patients with solid tumors, 12% of patients with lymphoma, and up to 25% of patients with leukemia [21]. In the absence of prophylaxis, *Candida* spp are the most common fungal pathogens in cancer patients. Between January 1, 1988, and December 31, 1992, 491 episodes of candidemia were identified at the M. D. Anderson Cancer Center [22]. By 3-month follow-up, 52% of the patients had died. Neutropenia, higher APACHE III score, and visceral dissemination were associated with poor prognosis. For many years *C. albicans* was the most common species causing infection. However, in a recent review of 1,479 cancer patients, *C. albicans* accounted for only 54% of infections [23]. Increases in infection caused by other *Candida* spp, namely *C. glabrata* and *C. krusei*, are being reported with increasing frequency. The Invasive Fungal Infection Group of the European Organisation for Research and Treatment of Cancer (EORTC) reported 249 episodes of candidemia (90 in patients with solid tumors, 159 in patients with hematologic malignancies) in centers throughout Europe over a 2-year period [24]. Overall 30-day mortality was 39%. This study confirmed the nosocomial nature of the candidemia: 50% of the patients had nonadvanced underlying disease, and only 10% of the episodes occurred outside the hospital.

Invasive aspergillosis is infrequent in patients with solid tumors, accounting for less than 1% of all infections [25]. Infection is mainly seen in patients with prolonged periods of neutropenia and most often reported in patients with acute leukemia. The mortality rate is very high. Emerging fungal pathogens such as *Fusarium* species and *Trichosporon beigelii* cause life-threatening infections, particularly in patients with hematologic malignancies.

Bone-Marrow Transplant Recipients

Risk Factors The degree and duration of neutropenia caused by myeloablative chemotherapy constitute the major risk factor for fungal infection in bone-marrow transplant (BMT) recipients. Cell-mediated immunity, in particular T-lymphocyte function, may be impaired by immunosuppressive agents. Allogeneic bone-marrow recipients are at higher risk than are autologous marrow recipients, due primarily to the high risk of graft versus host disease (GVHD) [26]. Mucositis, neutropenia, and antibiotic use are the major risk factors before engraftment. After engraftment, corticosteroids, acute GVHD, and CMV infection predispose the patient to a second, more significant risk period in which immune defenses are suppressed [19, 27].



Incidence and Mortality In one series, fungal infections were found in 26% of 85 autopsies in BMT recipients [28]. The incidence of fungal infections increased dramatically with duration of neutropenia: 21% in BMT recipients whose neutropenia lasted less than 3 weeks, compared with 57% in patients who were neutropenic for 6 weeks or more [29]. Systemic candidal infections have been reported in approximately 12% of BMT recipients, with 25% mortality directly attributed to the infection [30]. A review in one transplant center noted a decrease in 1-year cumulative incidence of candidiasis before and after institution of fluconazole prophylaxis, decreasing from 11.4% to 4.6% [19]. Invasive aspergillosis has become a leading cause of death after allogeneic BMT, particularly in patients with GVHD [31]. A large retrospective study at the Fred Hutchinson Cancer Research Center between 1987 and 1993 revealed that the incidence of aspergillosis increased from 5.7% to 11.2% during the study [27]. The 1-year mortality in patients with invasive disease was 95%. More recent data from this center have documented a sustained increase in incidence subsequent to 1993, with 3-fold increased incidence in both allogeneic and transplant recipients [32].

Solid-Organ Transplant Recipients

Risk Factors Immunosuppressive therapy and corticosteroids, particularly when used to treat acute rejection, are once again the cause of the immune defect predisposing organ-transplant recipients to fungal infection. Cyclosporine and tacrolimus specifically affect T lymphocytes by decreasing CD4⁺ helper cells and IL-2 synthesis. Underlying disease and the presence of immunomodulating viral infections such as CMV are also important risk factors affecting neutrophil and macrophage function. The extensive surgery and invasive intensive-care procedures involved in treatment of this patient population mean that environmental factors such as impaired host barriers are of paramount importance in the risk of infection.

The transplanted organ is rarely a source of fungal infection, although this has been reported.

Incidence and Mortality Serious fungal infections can follow solid-organ transplantation and are associated with high mortality (27% to 77%) [33]. Incidence and timing of the infection vary according to the immunosuppressive treatment and type of organ transplanted [29, 34]. Retrospective analyses of organ-transplant outcomes reveal significant levels of fungal infection [34]. In one center for liver transplantation, the rates of disseminated candidiasis, aspergillosis, and combined infection were 6.5%, 7.2%, and 2.6%, respectively. Mortality rate was 80%, with only 1 of the 11 patients with aspergillosis surviving [35]. In 200 episodes of serious infection in 73 heart-lung recipients, reported [36] fungal infections were 14% (12 episodes of candidiasis and 14 episodes of aspergillosis). Cryptococcal infection after solid-organ transplant has been estimated to occur in up to 4% of renal-transplant recipients, with a direct mortality of 36% [37]. Zygomycetes have been reported to cause infection in 1% to 9% of transplant patients, and infection with endemic mycoses depends on the geographic exposure of transplanted patients either before or after the transplant [33].



HIV-Infected Individuals

Risk Factors CD4⁺ T cells are the main target of HIV infection both in vitro and in vivo. While the progression of HIV disease is driven by the viral burden, the precise mechanisms of CD4⁺ T-cell depletion are not altogether understood.

The effects of HIV that predispose the patient to fungal infections also include impairment of neutrophil and mononuclear cell function, cytokine production, and B-cell function in addition to T-cell depletion. Disruption of skin and mucous membrane barriers, indwelling intravascular catheters, and broad-spectrum antibiotics all increase the risk of infection.

Incidence and Mortality In HIV-infected patients, candidiasis is virtually always mucocutaneous, involving the oropharynx, the esophagus, and the vagina. It occurs in up to 90% of patients during the course of their disease [38]. Disseminated candidiasis is uncommon except in those with advanced AIDS. Mucocutaneous candidiasis is related to the development of clinical cellular immunodeficiency. In fact, oropharyngeal candidiasis is an independent predictor of immunodeficiency in patients with AIDS [39]. A CD4 lymphocyte count <200/ μ L is a major risk factor for the development of clinical thrush in HIV-infected persons [40]. The alarming increase in the number of oropharyngeal infections caused by azole-resistant *Candida* species seems to have been halted with the introduction of highly active antiretroviral therapy (HAART).

Cryptococcosis was identified early in the HIV epidemic as one of the most common life-threatening infections in AIDS patients [41], with the development of disease relating directly to the CD4 lymphocyte count [42]. It occurs in 5% to 10% of HIV-infected patients in most areas of the world, although the incidence is significantly higher in Africa and Thailand [34]. Invasive aspergillosis is becoming more prevalent in AIDS patients. Surveys of clinically diagnosed disease report an incidence of 0.9%–8.6% [43]. Endemic mycoses are problematic in this patient population, with primary infection of patients moving into an endemic area. Also, reactivation of infection can occur years after a person has left the endemic area. Histoplasmosis has been reported in 2% to 5% of patients with AIDS in areas of endemic infection in the US and up to 25% in selected cities [34].

Spotting the Patient at High Risk

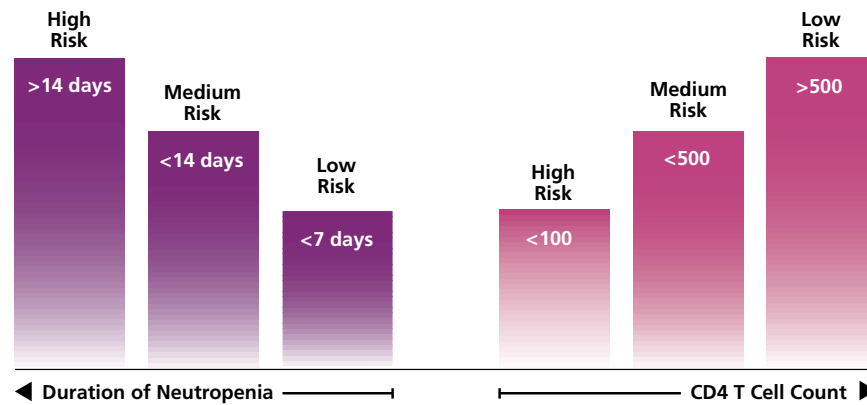
The possibility of fungal infection, as well as bacterial infections, in hospitalized patients must now be considered by clinicians. *Candida* now surpasses *Enterobacter*, *Pseudomonas*, and *E coli* and is the fourth leading cause [8] of BSI sepsis (Fig 2). The clinician's ability to identify high-risk factors for fungal infection will guide decisions regarding prophylaxis, diagnosis, and treatment.

It is important to realize that there is no such thing as a standard risk of fungal infection; patients must be assessed individually. The degree of risk and the factors most likely to predispose the patient to fungal infection differ between patient populations and are largely determined by interaction between exposure to the infecting organism and the net state of immunosuppression. The balance between the immune and nonimmune defenses is often of pivotal importance. Profoundly immunocompromised but infection-free individuals can rapidly develop devastating fungal disease if mucocutaneous barriers are disrupted.



Many events or factors can help identify patients at high risk of developing a fungal infection before, during, or after a period of hospitalization. *The type of immunocompromise* affecting, or likely to affect, the patient as a consequence of treatment can enable the clinician to predict which mycoses are likely to occur [18]. *Neutropenic patients* are at high risk of developing invasive mycoses. However, it is important to realize that neutropenia per se is not a good predictor of infection risk; the magnitude and duration of the neutropenia are the determining factors (Fig 6).

Figure 6. Duration of neutropenia and degree of T-cell depletion are important determinants of risk for invasive fungal infection.



Chemotherapy-induced neutropenia of short duration (<7 days) should not require antifungal prophylaxis during treatment cycles. However, patients in whom intensive chemotherapy leads to prolonged neutropenia have a high incidence of invasive fungal infection. Duration of neutropenia is shorter in autologous bone-marrow recipients than in allogeneic recipients, and this is reflected in a lower incidence of fungal infection in the autologous group [34]. *CD4 lymphocyte depletion* due either to AIDS or to immunosuppressive therapy increases the risk of infection, and the degree and time scale of this depletion provide valuable guidelines for antifungal therapy and prophylaxis (Fig 6).

Underlying medical conditions and diseases including hyperglycemia, uremia, and malnutrition are important considerations, since they can cause or amplify defects in host defenses.

Timetable of Infection

Treatment regimens for immunosuppression and chemotherapy have become standardized in recent years, thus facilitating the prediction of time to infection and type of infection. Exposure to fungal organisms can occur either in the community or in the hospital setting, and both recent and remote exposures are important in the development of invasive disease. Impaired host defenses can cause reactivation of dormant infection acquired some time previously, reinfection due to loss of immunity to a particular organism, or a primary infection. The timetable of infectious disease in organ-transplant recipients has been comprehensively documented (Fig 7) [44].

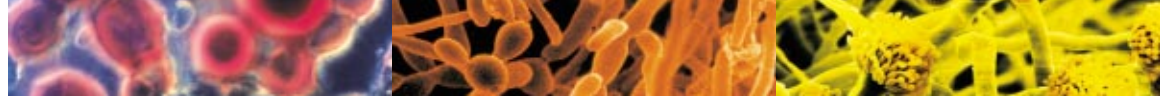
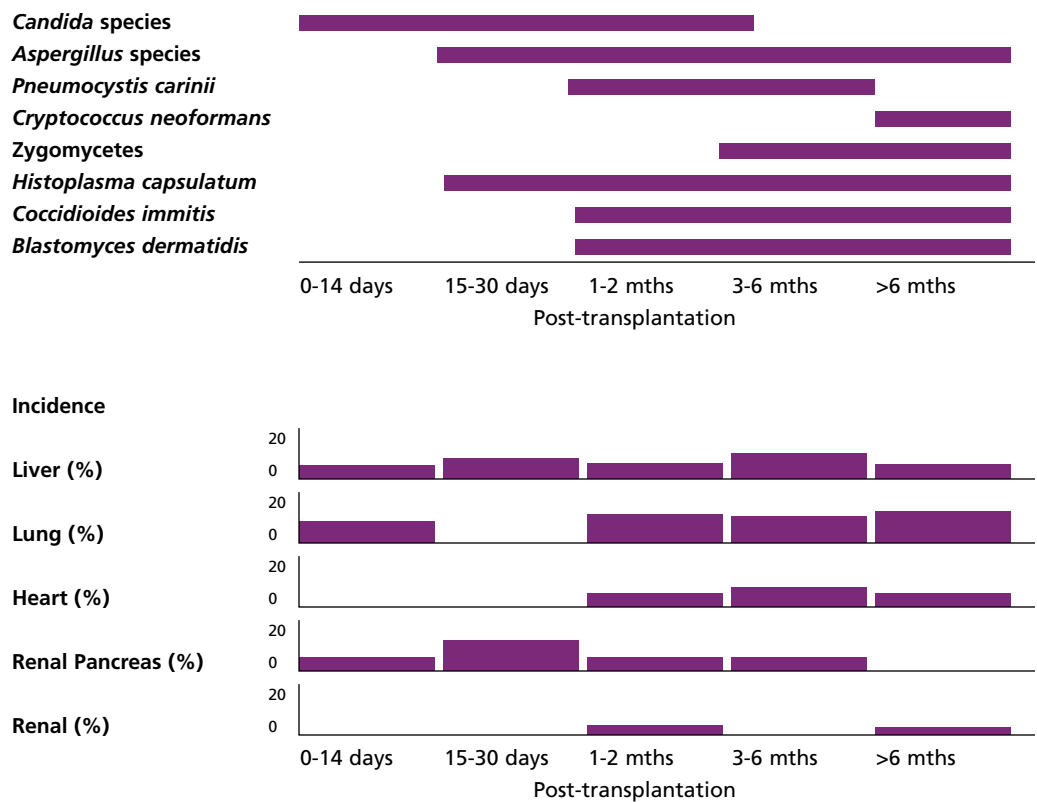


Figure 7. Fungal infections in organ-transplant recipients at Massachusetts General Hospital, 1988-1993. Fungal pathogens are listed in order of decreasing incidence. Reprinted with permission from Hibberd et al [44].



The early phase (within 1 month of transplantation) can be associated with infection in the patient before transplantation. Although actively infected patients rarely receive transplants, heavy colonization with agents such as *Candida* or *Aspergillus* may predispose patients to invasive infection when mucocutaneous barriers are disrupted. Further, fungal infection can be conveyed with the allograft, and rare cases of histoplasmosis and coccidioidomycosis have been reported. Infection can be nosocomially acquired during the perioperative period, primarily due to *Candida* species. More than 95% of infections in this early phase are the result of technical problems associated with the surgical procedure and postoperative management. *Aspergillus* species are notably absent.

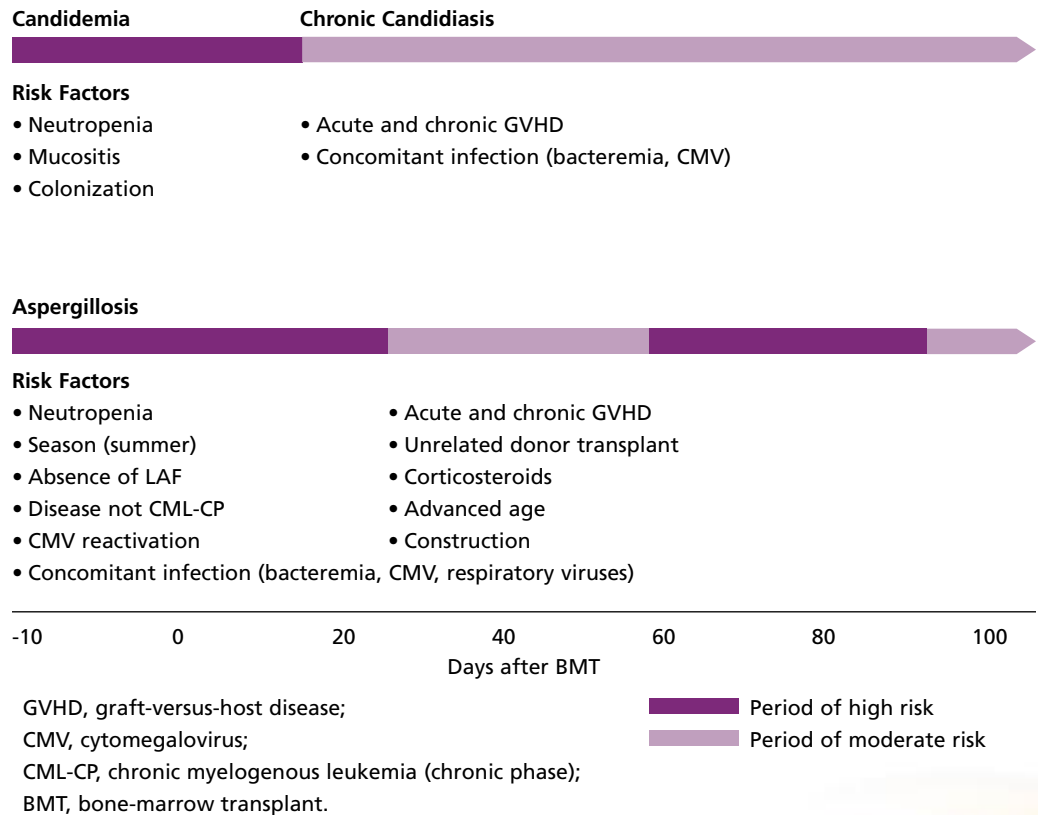
Up to 6 months after transplantation a high state of immunosuppression exists, and viral infections, particularly CMV, increase the chance of opportunistic infection. Protection of patients from environmental risks is of paramount importance.

Six months after transplantation patients with a successful allograft are at low risk of infection. However, patients with acute or chronic rejection who have required extensive immunosuppressive therapy and who are often infected with viruses are at increased risk of life-threatening infection.



Periods of risk have also been documented [19, 27, 45] for BMT recipients (Fig 8). During the *preengraftment period* (days 0 to 30), prolonged profound neutropenia exists, and barrier protection is lost as a side effect of the conditioning regimens. Risk of infection is high; at most treatment centers, the median onset is 2 weeks after transplantation, with *Candida* and *Aspergillus* species the most commonly reported organisms. The *postengraftment period* (days 30 to 100) normally sees resolution of neutropenia and mucosal repair. However, during this period, chronic disseminated candidiasis can occur as the increasing neutrophil count engenders an inflammatory response to *Candida* seeded in the liver during the neutropenic period. Also, the presence of GVHD and immunosuppressive agents for treatment are significant risk factors affecting the severity and type of infection. During the *late post-transplantation period* (100 days and later), systemic infections are generally uncommon in the absence of chronic GVHD and associated organ damage, and oropharyngeal candidiasis is the most frequent fungal infection.

Figure 8.
Risk of fungal infection post-bone-marrow transplantation.





Detection of Fungal Infections

The lack of reliable and rapid diagnostic procedures is a major obstacle in the successful management of fungal disease. Clinicians often have to rely on nonspecific signs and symptoms to guide antifungal therapy before laboratory findings become available. Standard microbiologic and histologic techniques remain important components of diagnosis, but both false-positive and false-negative results with standard tests remain a problem. Thus, new techniques have been developed to improve early detection (Table 6).

Table 6.
Diagnostic Methods of
Fungal Detection.

| Diagnostic Technique | Major Features | Useful | Not Useful |
|-----------------------------------|---|--|---|
| Microscopy/Histopathology | Rapid Relies on distinctive appearance of organism | Histopathologic identification of: <i>Cryptococcus</i> <i>Blastomyces</i> <i>Histoplasma</i> <i>Coccidioides</i> | Cannot give a specific species classification for: <i>Aspergillus</i> <i>Candida</i> |
| Culture-Based Methods | | | |
| • Traditional Culture | Inexpensive | <i>Cryptococcus</i> grows rapidly <i>Aspergillus</i> – tissue sample | Slow growth for most endemics Poor sensitivity for <i>Candida</i> and <i>Aspergillus</i> blood samples |
| • Automated Blood Culture Methods | Early detection of growth Capital expense | <i>Candida</i> and BSIs <i>Cryptococcus</i> and <i>Histoplasma</i> | No value for <i>Aspergillus</i> |
| Non-Culture Methods | | | |
| • Antigen | Sensitive and specific | <i>Cryptococcus</i> and <i>Histoplasma</i> <i>Aspergillus</i> – galactomannan may be useful | No reliable tests for other mycoses |
| • Antibody | Moderately sensitive and specific | Endemic mycoses | No reliable tests for opportunistic fungi |
| • PCR | Still experimental | Potential use for <i>Candida</i> and <i>Aspergillus</i> | |

Overview of Current Methodologies

Successful laboratory diagnosis of fungal infection depends in major part on collecting appropriate clinical specimens for investigation. These will differ depending on the suspected mycosis, site of infection, and clinical signs and symptoms.

Microscopic Examination of Clinical Specimens

Direct examination of clinical material is useful in diagnosing superficial and subcutaneous infections; histologic specimens can detect more deep-seated infections. Successful diagnosis depends on how distinctive the organism appears. It is a valuable procedure, as a tentative diagnosis can be made rapidly before growth occurs in culture. For example, in the diagnosis of cryptococcal meningitis, encapsulated budding yeast visualized with an India ink preparation can be detected in the CSF. Diagnosis of oropharyngeal candidiasis can be confirmed by Gram's stain or by 10% KOH preparation of oral scrapings that will show yeasts, hyphae, and pseudohyphae. *Histoplasma capsulatum* can sometimes be detected in blood or bone-marrow smears prepared by Giemsa stain.



Culture-Based Methods

Culture provides a definitive diagnosis of a fungal infection but has several limitations. Isolation and identification can take several weeks, and results may be too late to guide treatment. Traditional blood-culture methods are relatively insensitive. Technical modifications have aimed at improving sensitivity and/or reducing the time to positive blood culture. These include biphasic media [46], lysis centrifugation [47], marketed as the DuPont isolator[®] system (DuPont, Wilmington, DE), and automated monitoring using the BacT/Alert[®] system (Organon Teknika Corporation, Durham, NC) or the BACTEC[®] system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD) [48]. The sensitivity of these 2 automated systems is comparable to lysis centrifugation [49]. Lysis centrifugation is time-consuming, and many microbiology labs find its use difficult to justify on a financial basis.

Serologic Methods

The immunogenic properties of fungal organisms have been exploited in tests for the presence of both fungal antigen and antibody in biologic fluids. The diagnostic value of tests for antigen or antibody reactions is highly dependent on the organism. Numerous methodologies have been used or are being developed with varying degrees of sensitivity and specificity. These include counter-immunoelectrophoresis, radioimmunoassay, latex agglutination, immunoblot, and enzyme-linked immunoassay (ELISA). Reliable tests are available for accurately diagnosing endemic infections such as coccidioidomycosis and histoplasmosis; similar successes have not been achieved with invasive aspergillosis and candidiasis. Biochemical assays for circulating metabolic products such as mannose and D-arabinitol using gas-liquid chromatography have been described, although none are in regular use in the clinical laboratory. DNA fingerprinting and polymerase chain reaction (PCR) techniques are areas of expanding development [50].

Imaging Techniques

Radiographic imaging can be useful in certain circumstances, particularly in detecting early *Aspergillus* infection. Chest radiographs provide suggestive clues for respiratory mould infections, but high-resolution computerized tomography (CT) greatly enhances the diagnostic potential and can be useful to localize lesions for biopsy and to follow treatment.



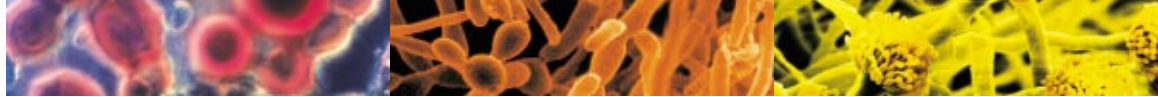
Specific Challenges to Laboratory Diagnosis

Invasive *Aspergillus*

Reliable techniques to confirm a diagnosis in patients with pulmonary or disseminated infection are currently not well established and impede successful management. Biopsy of skin lesions can reveal fungal hyphae, although the organism may not grow in culture media. Cultures of sputum or bronchoalveolar lavage (BAL) fluid are fairly specific (>80% in neutropenic patients); unfortunately, the sensitivity in proven cases is only 25% to 50% [51]. A negative culture from respiratory secretions has little meaning, as often the infection has to be well advanced before a positive culture is obtained. However, a positive culture in an immunocompromised patient suggests that the patient may already be infected or at high risk of becoming infected.

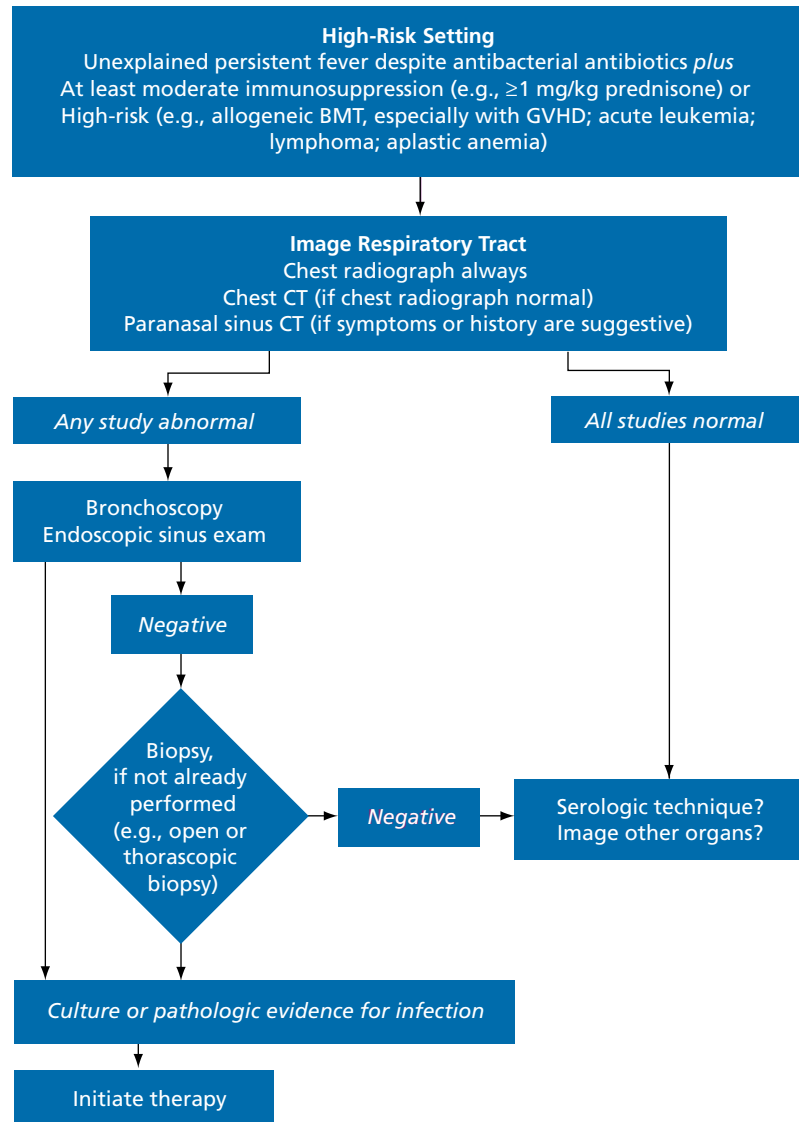
Antibody detection is not useful in most patients, as poor immune function and the speed of onset of the infection mean that antibody titers are low. Serologic methods to detect circulating free antigens or immune complexes have been or are under development using ELISA or radioimmunoassay [52]. Most techniques focus on detecting galactomannan, a component of the fungal cell wall. Galactomannan-based serologic diagnostics have now been intensively studied in vivo and in humans and appear very powerful [53, 54]. This marker can be used for both diagnosing and monitoring response. The current draft of the EORTC/MSG diagnostic criteria [55] includes a positive *Aspergillus* antigen as one component that can contribute to the diagnosis of probable aspergillosis. A recent study has shown greater than 90% specificity and sensitivity of a galactomannan assay in prolonged-neutropenic and/or steroid-treated patients with hematologic disorders [56]. A latex agglutination method to detect *Aspergillus* antigen is commercially available in Europe (Pastorex, Sanofi Diagnostics Pasteur, France), although its sensitivity and specificity are limited. More recently, a sandwich ELISA using monoclonal galactomannan antibody has been evaluated in high-risk patients, although it is not approved for clinical use in the US (Pastorex, Sanofi Diagnostics Pasteur, France). The newest development is the use of polymerase chain reaction (PCR)-based techniques to detect *Aspergillus* DNA in respiratory secretions and serum, but these techniques have not yet achieved the diagnostic consistency or broad acceptance seen with the galactomannan-based approaches [57]. The likelihood of false-positive results may preclude this tool as a stand-alone method to diagnose fungal infection.

Imaging the lungs of patients in whom *Aspergillus* infection is suspected can be very useful. Chest radiographs may show suggestive rounded parenchymal densities or pleural-based processes. Air crescents due to cavitation are strongly suggestive [58], but not diagnostic and not usually seen until recovery from neutropenia. High-resolution CT scans provide more information than chest radiography [43]. High-resolution CT shows that the parenchymal densities are angiocentric and also permits appreciation of the so-called halo sign (a zone of low attenuation surrounding these pulmonary nodules) that suggests vascular compromise of the region around the primary process [59]. While not absolutely diagnostic, the finding is certainly very suggestive [43]. More important, a negative high-resolution CT largely excludes the possibility of pulmonary aspergillosis [60].



Taken together, these ideas suggest a diagnostic approach based on clinical, microbiologic, and radiologic features (Fig 9) [61].

Figure 9.
Diagnosis of invasive
Aspergillus infection.
Reproduced from
Rex et al [61].





Invasive Candidiasis

There is a significant lag in developing detection methods for invasive candidiasis largely because there is no convincing gold-standard diagnostic strategy in any form. The spectrum of invasive candidiasis is quite broad, and no single approach has yet emerged.

Current strategies revolve around clinical approaches to detection of disease. The detection of *Candida* in the bloodstream is one of the simplest and most convincing bits of data, but this is seen in no more than about half of patients in whom invasive candidiasis is strongly suspected [62]. Positive cultures from other sites may represent colonization rather than invasive disease. As a consequence, significant effort has gone into nonculture-based diagnostic strategies. These have included detection of *Candida* enolase and antibodies to enolase, *Candida* mannoproteins, beta-glucan, other less defined antigens [63], the candidal metabolic product D-arabinitol [64], and candidal DNA by PCR [50]. All of these methods have shown promise, but none have achieved the degree of diagnostic accuracy that seems needed to justify widespread use. The principal problem is that the positive signal detected by each is strongly present only when the disease is fairly far advanced. Coupled with the rapid pace of invasive candidiasis and the time delay inherent in obtaining test results, these problems have thus far made these tests less than satisfactory outside of highly focused research settings.



Therapeutic Approaches to Fungal Disease

Fungi are eukaryotic organisms that differ from bacteria and other prokaryotic organisms in many ways. Like other human cells, fungal cells contain a nucleus, endoplasmic reticulum, mitochondria, and other organelles. Most fungal cells possess a rigid cell wall, the basic units of which are high-molecular-weight polysaccharides such as chitin and glucan, which differ from the sugar moieties of bacterial cell walls. The plasma membrane acts as a barrier between the intra- and extracellular components. It is involved in cell-wall synthesis and is responsible for the selective transport of molecules. The most significant difference between human and fungal cell membranes is in the sterols present. Ergosterol, instead of cholesterol, is the primary component of the cell membrane in fungi [65]. The primary function of ergosterols is to modulate membrane fluidity and provide a “sparkling” function used to initiate growth and increase the size of the yeast cell [65].

Development of successful antifungal agents has proved far more difficult than the development of antibacterial drugs. This is due in part to the eukaryotic fungal cell structure [66] coupled with the fact that since fungal infection tends to be subacute, duration of therapy has to be extended, thus exacerbating the challenge of nontoxic therapy. Billions of dollars have been invested in an enormous effort to develop new and improved antifungals. The primary agents currently licensed in the United States by the Food and Drug Administration (FDA) belong to 3 principal classes: the polyenes, the azoles, and the pyrimidines. In addition, a number of new agents are under investigation clinically, and still more are at the developmental stage. These agents act by interfering with either the cellular membrane, the smooth endoplasmic reticulum, or the cell nucleus. The latest experimental agents, the echinocandins and pneumocandins, target the fungal cell wall – a cell structure that human cells do not share (Fig 10).

Figure 10.
Fungal cell structure. Established and emerging antifungal agents are classified according to specific cellular target. Adapted with Permission. Georgopapadakou and Walsh [66].

Membrane Function

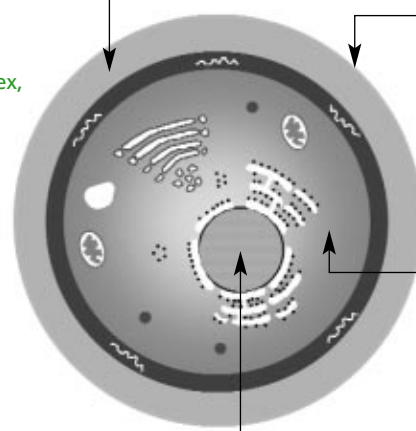
Polyenes:

- Amphotericin B
- Lipid Formulation AmB (amphotericin B lipid complex, amphotericin B colloidal dispersion, liposomal amphotericin B)
- Nystatin
- Liposomal Nystatin

Nucleic Acid Synthesis

- Pyrimidine analog:
- 5-Fluorocytosine

- Established Agents
- Newly Licensed Agent
- Undergoing Clinical Trial



Cell Wall Synthesis

- Echinocandins/
Pneumocandins:
- Caspofungin (MK 0991)
- Micafungin (FK 463)
- Anidulafungin (VER 002)

Ergosterol Synthesis

- Azoles:
- Fluconazole
- Ketoconazole
- Itraconazole
- Clotrimazole
- Voriconazole
- Ravuconazole
- Posaconazole



Amphotericin B

The polyene class of antifungals, specifically amphotericin B (AmB) remains the gold standard for the treatment of many invasive or life-threatening mycoses [67]. The drug binds to ergosterol in the fungal cell membrane, resulting in cell-wall disruption and killing. It has a broad spectrum of activity against both yeasts and moulds and is a valuable first-line agent against many species, including *Candida*, *Aspergillus*, *Zygomycetes*, *Fusarium*, *Histoplasma*, *Cryptococcus*, *Blastomyces*, and *Coccidioidomyces*, although it is not always effective for *Aspergillus* or *Fusarium* infections in severely immunocompromised patients. Treatment failure due to the development of amphotericin resistance is rare, although resistant strains of *Candida lusitanae* and *C. tropicalis* have been isolated during treatment.

Amphotericin is not absorbed when given orally, and intravenous formulation must be used to treat systemic disease. The formulation is inconvenient to use and necessitates prolonged intravenous access. The drug has a very narrow therapeutic index. Administration is unfortunately accompanied by a number of harmful side effects and unpleasant reactions that often limit the amount that can be given. Immediate side effects may include headache, fever, chills, and rigors. Nausea and vomiting are less common and, as with fever, often diminish as treatment proceeds. Local phlebitis at the injection site can occur but can be avoided by giving the drug through a central venous catheter. Heparin addition to the infusate has been suggested to improve the tolerability of peripheral injection.

The most serious toxic effect of amphotericin is renal damage likely caused by increased renal vascular resistance leading to decreased glomerular filtration and damage to renal tubular cells [68-70]. Renal loss of potassium and, less commonly, magnesium will in time cause substantial depletion in total body stores. Most patients with invasive fungal infection receive AmB at a daily dose of greater or equal to 0.5 mg/kg/day. This dose is associated with reversal impairment of renal function that occurs early during treatment (within 2 weeks) in up to 80% of patients. Renal tubular acidosis can occur in patients receiving doses of 500 mg to 1 gram or more. It is generally reversible, with renal function returning to pretreatment levels after discontinuation of therapy or (rarely) even with continued use. Irreversible renal damage, with necrosis and calcification of renal tubules, is uncommon unless the cumulative AmB dose exceeds 4 to 5 grams. Patients with preexisting renal impairment and those receiving other nephrotoxic drugs are at increased risk of renal damage. Careful monitoring of renal function during treatment can reduce or prevent renal damage.

Lipid Formulations of Amphotericin B

The dose-dependent toxicity of conventional AmB is the rationale for the development of lipid-based formulations [71]. By encapsulating AmB into liposomal vesicles or binding it to other lipid carriers, it is hoped that a significant reduction of toxicity and possibly an increased therapeutic index of the drug will be achieved. These new agents aim to improve the therapeutic ratio with a higher concentration of drug reaching target tissue, such as lung, liver, and spleen, and with lower concentrations of the drug in the kidney.



Three lipid formulations of amphotericin B (LFAB) are now licensed and marketed in the US:

- Amphotericin B lipid complex – ABLC
- Amphotericin B colloidal dispersion – ABCD
- Liposomal amphotericin B

These 3 formulations differ significantly in composition and pharmacokinetics.

Amphotericin B serum levels, after administration of ABLC and ABCD, are relatively low when compared with liposomal amphotericin B. A much higher dose (3 to 6 mg/kg/day) of all the lipid formulations must be administered for therapeutic efficacy, although there are limited data on optimal therapeutic dosages. The therapeutic index is much wider than that of AmB and toxicity is less likely even at these higher doses administered for prolonged periods. All of the preparations appear to be preferentially accumulated in organs of the reticuloendothelial system, as opposed to the kidney, and have considerably reduced nephrotoxicity.

Approved indications are for patients who have systemic mycoses, primarily invasive aspergillosis, and who are intolerant of, or their disease is refractory to, conventional AmB. In addition, liposomal amphotericin B is approved as empiric therapy for the neutropenic patient who has persistent fever despite broad-spectrum antibiotic therapy.

Clinical Experience

All 3 agents have been used to treat adult and pediatric patients with confirmed or presumed fungal infections intolerant of or refractory to conventional amphotericin B deoxycholate [72-79]. Liposomal amphotericin B has also been used as empirical antifungal therapy in febrile neutropenic patients [80-84].

The lipid-based products have demonstrated equivalent efficacy when prospectively compared with conventional AmB in the treatment of presumed or documented infections [76, 77, 79] and empirical treatment of febrile neutropenia [73, 80-82, 85]. In preventing proven emergent fungal infections, liposomal amphotericin B was superior to AmB; however, the short-term survival rate was not improved [83]. The impact of prior fluconazole prophylaxis on the results of empirical antifungal therapy was not assessed in this and similar published studies and remains an important need.

Published reports to date support the contention that lipid formulations are better tolerated than conventional amphotericin B. Nephrotoxicity is less common with all 3 lipid formulations of amphotericin B than with conventional AmB. However, the degree of tolerance varies among the 3 formulations [80, 82-84]. All 3 have been evaluated in clinical trials, usually at doses 1-5 mg/kg of body weight per day. A recent randomized controlled trial compared efficacy and toxicity between liposomal amphotericin B and amphotericin B lipid complex [84]. Febrile neutropenic patients were randomized to receive either liposomal amphotericin B 3 mg/kg/day or 5 mg/kg/day, or ABLC 5 mg/kg/day for the empiric treatment of suspected fungal infection. The incidence of nephrotoxicity defined as a doubling of serum creatinine level over baseline was significantly lower in both liposomal amphotericin B groups than in the amphotericin B lipid complex group (liposomal AmB 3 mg/kg/day 14%; 5 mg/kg/day 15%; ABLC 42%) [84].



The incidence of infusion-related adverse events (IRAEs) varies among the 3 lipid formulations [74]. Estimates are imprecise due to lack of comparability of dosing, variability in administration of premedications prior to dosing, and little standardization of definitions of adverse events. However, infusion-related reactions with amphotericin B colloidal dispersion and amphotericin B lipid complex appear to be considerably more common than those associated with liposomal amphotericin B, and similar in frequency to infusion-related events associated with conventional AmB [72, 76, 77, 80, 83, 84, 86]. One prospective randomized trial reported a higher incidence of IRAEs with ABCD compared to conventional AmB [80]. In 2 randomized controlled trials in febrile neutropenic patients, liposomal amphotericin B-treated patients experienced significantly fewer infusion-related reactions compared to those treated with conventional amphotericin B (chills, 18% versus 54% of patients; fever 17% versus 44%) [83] or those treated with ABLC (chills, 21% versus 79% of patients; and fever, 22% versus 58%) [84].

The lipid formulations are considerably more expensive than conventional AmB, ranging from 10- to 20-fold higher costs per dose; the pharmacoconomics of liposomal versus conventional therapy in febrile neutropenic cancer patients was recently reported [87].

Azole Antifungal Agents

In recent years, ketoconazole, itraconazole, and fluconazole have become frequent therapeutic alternatives to AmB. These azole compounds inhibit 14- α -demethylation of lanosterol by binding to fungal cytochrome P450 enzymes. Ergosterol in the cytoplasmic membrane is reduced, leading to inhibition of cell growth. These drugs are considered fungistatic, as opposed to the fungicidal actions of the polyenes, although newer azoles demonstrate in vitro fungicidal activity for *Aspergillus* spp and other moulds. Their greatest benefit over AmB is their oral formulation and limited toxicity. Fluconazole and itraconazole are better tolerated than ketoconazole. One limitation of this group of antifungal compounds is the frequency of their interactions with coadministered drugs. Decreased absorption is particularly a problem with itraconazole [88], but not with fluconazole. Absorption of itraconazole has been improved with an oral suspension, and the newly available IV formulation. Increasing emergence of fungal organisms resistant to fluconazole, especially the *Candida* species, is becoming problematic, a turn of events traceable in part to the prophylactic and empiric use of fluconazole and the other azoles.

New Azoles Undergoing Clinical Trials

Two new azoles with structures derived from fluconazole are in clinical trials. They have broad-spectrum activity and are generally well tolerated. Voriconazole (UK-109496) is active against *C. krusei*, *C. glabrata*, and *Aspergillus* species and also a variety of emerging pathogens [89]. It is available as an oral and intravenous formulation and the drug has high oral bioavailability. Safety is satisfactory and excellent patient tolerance has been reported, although reversible, transient visual side effects have been noted in up to 30% of patients. Phase II clinical trials are in progress for treatment of aspergillosis, moulds, and resistant yeasts; phase III trials are investigating empirical therapy, candidemia, and primary therapy for aspergillosis. Ravuconazole (BMS-207.147) [89] also has activity against fluconazole-resistant *Candida* strains and moulds. Intravenous formulations are under development and phase II studies are in progress. An itraconazole derivative, Posaconazole



(SCH-56592), has similar broad-spectrum activity, is available only as an oral suspension, and is in phase III clinical trials for treatment of invasive candidal infection, high-risk prophylaxis, and fluconazole-resistant oropharyngeal candidiasis [89].

Flucytosine

5-Fluorocytosine (flucytosine or 5-FC) is a pyrimidine analog closely related to the cancer chemotherapeutic agent 5-fluorouracil (5-FU). Flucytosine is unique, since its mode of action is intracellular, instead of affecting the cell membrane. It is deaminated within the fungal cell to 5-FU and metabolized to 5-fluorouridine triphosphate (5-FUTP) and 5-fluorodeoxyuridine monophosphate (5-FdUMP). 5-FUTP is incorporated into fungal RNA in place of uridylic acid and disturbs protein synthesis. Additionally, 5-FdUMP is a potent inhibitor of thymidylate synthase, a key element in DNA synthesis. One limitation of 5-FC is the development of drug resistance by loss or mutation of the enzymes that activate the drug. This can occur readily if flucytosine is used alone; consequently, it is used primarily in combination with AmB. This combination is widely accepted as the standard induction treatment for cryptococcal meningitis, and refractory, life-threatening *Candida* infections, especially with nonalbicans *Candida* species. Apart from these indications, the spectrum of activity is fairly limited, and the drug has significant potential for toxic side effects, including hepatotoxicity and bone-marrow suppression.

Echinocandin/Pneumocandin Agents

An important new class of antifungal agents called echinocandins is on the horizon [90]. These drugs have been described mechanistically as the “penicillins” of antifungal therapy—cell-wall synthesis inhibitors. Echinocandins act by inhibiting glucan synthesis via inhibition of 1,3-beta-D-glucan synthase. This interferes with the synthesis of chitin, an important cell-wall component, and results in fungal cell lysis. These drugs have fungicidal activity against *Candida* species, including fluconazole-resistant *C. albicans* and pathogenic nonalbicans yeasts. In addition, in vitro and in vivo activity against *Aspergillus* species have been shown [91]. A notable limitation is the lack of activity against *C. neoformans* and Zygomycetes as well as other pathogenic moulds. However, the unique mechanism of action will offer the potential use of the echinocandins in combination with other antifungal regimens.

Of these agents, caspofungin received FDA approval in early 2001 and clinical trials of anidulafungin (previously known as VER 002 or LY 303366), and micafungin (FK 463) are in progress. All these agents require parenteral administration and are minimally cleared by the kidney. They have demonstrated excellent safety profiles in phase I and II clinical trials reported to date.

Preliminary results of phase II trials comparing caspofungin 50 or 70 mg/d IV for 2 weeks (n = 74) with amphotericin B 0.5 mg/kg/d IV for the same period (n = 54) in patients with candidal esophagitis have shown promise for this group of compounds. Efficacy was equivalent in the echinocandin group, and adverse effects, including renal dysfunction, were uncommon in patients receiving caspofungin [92]. Recent studies have also demonstrated the utility of caspofungin in a salvage study of invasive aspergillosis in which response rates of 41% were demonstrated in 54 patients who were intolerant of or were failing standard antifungal regimens [93].



Strategies to Control Infection

Strategies to prevent or reduce fungal infection:

- Reduce exposure to and acquisition of pathogen
- Suppress colonization
- Avoid/limit invasive procedures
- Enhance host defense

Infection-control methods in the hospital setting are of paramount importance to prevent the spread of nosocomial infections. Environmental issues such as exposure to dust, especially from building construction, and use of air filters are crucial to prevent acquisition of exogenous organisms such as *Aspergillus*. Hand washing minimizes the spread of endogenous organisms such as *Candida*. Suppression of colonization using antifungal agents such as nystatin, clotrimazole, fluconazole, and ketoconazole has had only limited success. These agents have limited activity against *Aspergillus* and nonalbicans *Candida* species and may select for the latter. Prophylaxis with low-dose AmB can be given with little nephrotoxicity, but consistent benefit to prevent infection has not been demonstrated.

Strategies to Enhance Host Defenses

The pathogenesis of fungal infection highlights the relative importance of the different components of host defense, particularly in the immunocompromised patient. Deficiency in number and function of white cells is especially correlated with the degree and progression of disease in many patient populations. Newly developed research is directed at using cytokines as immunomodulators in both neutropenic and nonneutropenic patients [94]. Four cytokines (granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor, and interferon gamma) have been used as adjuvant therapy for proven fungal infections in this setting, although clinical experience is still too limited to be evaluated. There have been reports of use of these agents as adjuncts to AmB therapy, but the data are insufficient to derive any conclusions [95]. As an additional approach, the concept of white blood cell transfusions has been revived by the use of granulocyte colony-stimulating factor to increase the yield from donors and may prove helpful in the setting of short-term neutropenia.

Repair of chemotherapy-induced mucositis is a desirable goal, and keratinocyte growth factor (KGF) is undergoing clinical trials. Interleukin-11 is now approved by the FDA as a thrombopoietic agent, but it also has reparative effects on the mucosa in vitro and in animal models.

Conclusions

Fungal organisms considered as simply colonizers or contaminants a decade ago are now significant pathogens in the immunocompromised patient. It is now recognized that the net state of immunosuppression is of paramount importance, influencing incidence and severity of infection and patient outcome. Progress in dealing with invasive fungal infection has been made, but emphasis must be placed on increasing awareness of the importance of these infections and the development of better methods of diagnosis, treatment, and prevention.



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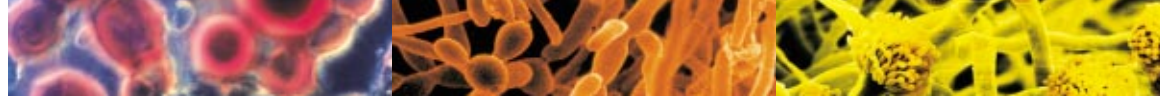
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Program One, 2001 Opportunistic Fungi in the Immunocompromised Patient

Course No.
V035B.043001

Post Test

- Which of the following best explains the increase in opportunistic fungal infections?
 - The success of chemotherapy in treating cancers
 - The AIDS epidemic
 - Use of invasive devices in the ICU
 - Use of corticosteroids
 - All of the above
- Which patient is most at risk for a serious fungal infection?
 - AIDS patient with a CD4 count of 300/ μ L
 - Cancer patient with a neutrophil count <500/ μ L for 2 days
 - Patient with an acquired immunoglobulin deficiency
 - Bone-marrow transplant patient with neutrophils <500 for 2 weeks
 - All of the above
- Most infections due to *Candida* species arise from the host's endogenous flora.
 - True
 - False
- A very specific and sensitive antigen test is available for:
 - Candida albicans*
 - Aspergillus fumigatus*
 - Blastomyces dermatitidis*
 - Cryptococcus neoformans*
 - Coccidioides immitis*
- Which best describes the structure of fungi?
 - Primitive prokaryotic cells
 - Eukaryotic cells similar to human cells
 - Prokaryotic cells with cell wall
 - Cell membranes containing cholesterol
 - Eukaryotic cells with cell walls
- Which of the following environmental and host risk factors is *not* important in the development of nosocomial *Aspergillus* infection?
 - Gastrointestinal colonization
 - Contaminated water
 - Prolonged neutropenia
 - Contaminated air
 - Corticosteroid use
- The highest risk of fungal infection in recipients of liver transplants is immediately after transplantation and again in the second year post-transplant.
 - True
 - False
- Candida* species are the fourth most common cause of nosocomial bloodstream infections in the United States.
 - True
 - False
- Which of the following contribute to the risk of *Candida* infection in an ICU patient?
 - Central venous catheter
 - Broad-spectrum antibiotics
 - GI tract surgery
 - Hemodialysis
 - All of the above
- PCR for *Aspergillus* is both sensitive and specific and has become the preferred diagnostic test for invasive aspergillosis.
 - True
 - False
- Which of the following is *not* true regarding fungal infections in bone-marrow transplant recipients?
 - Prolonged neutropenia increases the risk of fungal infections
 - Candida* and *Aspergillus* are the most common fungal infections
 - The occurrence of graft versus host disease decreases the risk of fungal infections
 - The incidence of fungal infections is greatest in the pre-engraftment period
 - Conditioning regimens increase the risk of infection due to loss of mucosal barriers
- Which of the following are underlying causes of impaired host defense?
 - Age extremes
 - Acquired immunodeficiency
 - Mucosal damage/dysfunction
 - Organ dysfunction
 - All of the above



13. A neonate receiving TPN in the ICU develops fever and appears quite ill. The fungus most likely to cause infection in this setting is:
- A. *Aspergillus flavus*
 - B. *Candida albicans*
 - C. *Cryptococcus neoformans*
 - D. *Coccidioides immitis*
 - E. *Fusarium* species
14. Which is true of both histoplasmosis and coccidioidomycosis?
- A. Are restricted to certain geographic areas
 - B. Cause disseminated infection in AIDS patients
 - C. Treatment of primary infection is not required in most patients
 - D. Rarely cause symptoms in healthy patients with infection
 - E. All of the above
15. A bone-marrow transplant recipient who is neutropenic develops fever, pleuritic chest pain, and shortness of breath. Chest x-ray shows a wedge-shaped infiltrate and CT scan reveals 3 additional nodules that appear next to blood vessels. The most likely diagnosis is:
- A. Histoplasmosis
 - B. Cryptococcosis
 - C. Aspergillosis
 - D. Candidiasis
16. Which best describes amphotericin B?
- A. Increasing resistance has limited its usefulness
 - B. Static against most fungi
 - C. Remains the first-line antifungal agent for invasive aspergillosis in immune-compromised hosts
 - D. Infusion-related side effects, such as nausea and fever, increase with the duration of therapy
 - E. Ineffective against the endemic mycoses
17. Flucytosine is almost always used as a single agent for the treatment of cryptococcosis:
- A. True
 - B. False
18. All currently available azole antifungal agents:
- A. Interact with many other drugs
 - B. Are nephrotoxic
 - C. Are fungicidal
 - D. Are available only as parenteral formulations
 - E. Have limited clinical use
19. Which is true of the echinocandins?
- A. Only available as oral formulations
 - B. Active against *Cryptococcus neoformans*
 - C. First-line agents for candidiasis
 - D. Inhibit beta-glucan synthesis in the cell wall
20. Which statement best describes the 3 lipid formulations of amphotericin B?
- A. Cause severe hepatotoxicity in cancer patients
 - B. Can be given orally
 - C. Have been proven to be less nephrotoxic than amphotericin B
 - D. Have similar pharmacokinetic characteristics
 - E. Show superior efficacy to standard amphotericin B
- This CME activity expires on July 1, 2003; no test sheets will be accepted after this date.



Program One, 2001 Opportunistic Fungi in the Immunocompromised Patient

**Course No.
V035B.043001**

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Post Test Answer Sheet:

Circle correct answer:

- | | | | | | | | | | | | |
|-----|------|-------|---|---|---|-----|------|-------|---|---|---|
| 1. | A | B | C | D | E | 11. | A | B | C | D | E |
| 2. | A | B | C | D | E | 12. | A | B | C | D | E |
| 3. | True | False | | | | 13. | A | B | C | D | E |
| 4. | A | B | C | D | E | 14. | A | B | C | D | E |
| 5. | A | B | C | D | E | 15. | A | B | C | D | |
| 6. | A | B | C | D | E | 16. | A | B | C | D | E |
| 7. | True | False | | | | 17. | True | False | | | |
| 8. | True | False | | | | 18. | A | B | C | D | E |
| 9. | A | B | C | D | E | 19. | A | B | C | D | |
| 10. | True | False | | | | 20. | A | B | C | D | E |

This CME activity expires on July 1, 2003.



Program One, 2001 Opportunistic Fungi in the Immunocompromised Patient

CME Evaluation Form

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Title of Presentation:
Opportunistic Fungi in the Immunocompromised Patient

Course No.
V035B.043001

Part 1.

| | Strongly Agree | | Strongly Disagree | | |
|--|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| <i>Educational Value:</i> | 5 | 4 | 3 | 2 | 1 |
| I learned something new that was important. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| I verified some important information. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| I plan to discuss this information with colleagues. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| I plan to seek more information on this topic. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| My attitude about this topic changed in some way. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| This information is likely to have an impact on my practice. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Program Rating:

5 = Excellent 4 = Above Average 3 = Good 2 = Below Average 1 = Poor

| | 5 | 4 | 3 | 2 | 1 |
|---|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Overall quality of this activity | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Other similar CME activities | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| How well were the course objectives met | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Was this activity free of commercial bias | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Was the use of this text-based modality appropriate for this activity | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

Additional comments: _____

_____ **See over**



Part 2.

Commitment to change: What change(s) (if any) do you plan to make in your practice as a result of viewing this presentation?

Please mail this completed evaluation page, your post test answer sheet, and your \$25 payment to:

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