Opportunistic Mycoses in the Immunocompromised Host: Experience at a Cancer Center and Review
Author(s): Elias Anaissie
Reviewed work(s):
Source: Clinical Infectious Diseases, Vol. 14, Supplement 1. Focus on Fungal Infections: An Update on Diagnosis and Treatment (Mar., 1992), pp. S43-S53
Published by: Oxford University Press
Stable URL: http://www.jstor.org/stable/4456392
Accessed: 08/02/2013 05:45

Your use of the JSTOR archive indicates your acceptance of the Terms & Conditions of Use, available at http://www.jstor.org/page/info/about/policies/terms.jsp

JSTOR is a not-for-profit service that helps scholars, researchers, and students discover, use, and build upon a wide range of content in a trusted digital archive. We use information technology and tools to increase productivity and facilitate new forms of scholarship. For more information about JSTOR, please contact support@jstor.org.
Opportunistic Mycoses in the Immunocompromised Host: Experience at a Cancer Center and Review

Elias Anaissie

From the Section of Infectious Diseases, Department of Medical Specialties, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

The field of opportunistic mycoses in the patient with cancer is rapidly changing. Not only are fungal infections increasing in frequency in this patient population, but these infections are occurring earlier during the course of cytotoxic chemotherapy, and newer fungi are increasingly recognized as potentially lethal pathogens. Candidiasis remains the most commonly encountered infection. The spectrum of disease includes candidemia and acute and chronic disseminated candidiasis. Pulmonary aspergillosis and disseminated aspergillosis are common and remain relatively resistant to therapy. Disseminated fusariosis and trichosporonosis are almost always fatal in the setting of persistent profound neutropenia. Therapy for these mycoses relies on the use of amphotericin B and 5-fluorocytosine. Newer antifungal agents, such as fluconazole anditraconazole, appear to exhibit good activity against a variety of fungi. Newer approaches need to be tested for the treatment of the more-resistant mycoses and may include the use of maximally tolerated doses of antifungal agents, colony-stimulating factors, and combination therapy.

During the past decade, progress has been made in the treatment of patients with cancer, and the proportion of patients achieving complete remission and longer survival has increased [1]. A significant number of patients still fail to achieve complete remission, and infection remains a frequent cause of treatment failure, particularly in patients with hematologic malignancies [2]. Although the problem of high mortality rate associated with bacterial infections has been overcome with the administration of empiric antibiotics early in treatment, fungal infections have become one of the leading factors contributing to morbidity and mortality in this patient population [3–5]. Most opportunistic mycoses are caused by Candida species and Aspergillus species, although we have recently witnessed the emergence of several fungi—previously considered harmless colonizers—as the cause of life-threatening infections in humans [6, 7]. In this review, an attempt to define the magnitude of the problem of opportunistic mycoses in patients with cancer will be made and some approaches to management will be offered.

Incidence of Fungal Infections

The increasing incidence of fungal infection was first detected among patients with acute leukemia. Stefanini and Allegra [8] found that between 1943 and 1947 only 3% of their leukemic patients had had fungal infections, but that between 1954 and 1956 this figure had increased to 22%. In a study of autopsy findings of patients with acute leukemia [4], the 10% incidence of major fungal infections between 1954 and 1958 had increased to 30% between 1959 and 1964.

The increasing incidence of serious fungal infections has been documented at several other institutions [3, 5, 9–14]. Overall, fungi account for 4%–12% of nosocomial pathogens in this patient population. The increasing incidence of candidiasis has been reported from general hospitals. For example, Myerwitz et al. [14] found a 0.1% incidence of candidiasis from autopsy reports between 1963 and 1970 and a 1.2% incidence between 1971 and 1975. Recent results from a community teaching hospital showed an eightfold increase in incidence of candidemia (one case per 266 bed-years in 1982 and one case per 32 bed-years in 1985) [15]. The Centers for Disease Control (Atlanta) has been conducting a survey of nosocomial infections for over a decade that includes university, government, and community hospitals. The incidence of candidiasis has increased during this period and now accounts for 5.6% of all primary bloodstream infections [16].

Until recently, aspergillosis was a rare infection, even among immunocompromised patients. Only 30 cases of aspergillosis were found among patients on whom autopsies were performed between 1951 and 1963 at Memorial Sloan-Kettering Cancer Center (New York) [17]. Four cases of aspergillosis could be found in a review of 261 autopsy reports of patients with leukemia between 1930 and 1961 [18]. However, between 1964 and 1971, 93 cases of aspergillosis were detected at Memorial Sloan-Kettering Cancer Center [19], with the majority occurring among patients with hematologic malignancies. An additional 91 cases were reported from the same institution between 1971 and 1976 [20]. At the National Institutes of Health (Bethesda, Maryland) 22 cases of aspergillosis were indicated among 1,839 reports of
autopsy examinations; there was a 6% frequency among leukemic patients and a 0.5% frequency among patients with other cancers [21]. A total of 93 cases were found among 3,374 reports of autopsy examinations in a later series from the National Institutes of Health [22].

More recently, however, there has been a disturbing change in the pattern of aspergillosis. While this infection was almost exclusively seen in leukemic patients in the past, the spectrum of underlying diseases associated with aspergillosis today is very broad [23]. Furthermore, the incidence of this infection among leukemic patients has increased significantly. Aspergillosis is also occurring earlier during initial remission induction therapy [2]. Analysis of the experience at the M. D. Anderson Cancer Center (Houston) over two decades provides an example of the changing pattern of aspergillosis [23]. During the 1981–1985 period, aspergillosis accounted for 35% of disseminated mycoses, as compared with only 12% during the 1966–1970 period. Among leukemic patients, 19% of major fungal infections were caused by Aspergillus species during 1978–1982; Aspergillus caused 7.5% of major fungal infections during 1966–1972. Experience from other institutions indicates a frequency of 20%–30% among leukemic patients [20, 24].

The presence of newly recognized fungal pathogens, such as Fusarium species, Curvularia species, Trichosporon species, and others, had been thought to represent contamination or harmless colonization when these species were isolated from humans. More recently, the role of these and other newly recognized fungi as serious pathogens in patients with cancer has been clearly established [6–7].

Factors Predisposing to Fungal Infections

Several factors predispose patients to invasive fungal infections. Defects of immune cells and ulcerations of the skin, oropharynx, and gastrointestinal tract are all known predisposing factors. Presence of any one of these defects may predispose a patient to infection, although it is not unusual for some patients to suffer from multiple defects simultaneously.

Neutropenia is probably one of the most important factors responsible for the increased frequency of fungal infections [4]. The duration of neutropenia depends primarily on the underlying disease and its treatment. Patients are at greatest risk for serious fungal infections when their neutrophil count falls below 100 cells/mL and when this profound neutropenia persists for >1 week. In addition, the trend exhibited by the neutrophil count is an important determinant of the course of the infection: a rising count during therapy is associated with a more favorable prognosis than a count that continues to decrease or one that remains low. In vitro, neutrophils ingest and kill Candida albicans and hence are recognized as the primary defense against infection caused by this organism [25–28]. The importance of neutrophils and macrophages in protecting against aspergillosis has also been documented. In vitro, macrophages prevent germination and kill spores, whereas neutrophils protect against hyphae [29]. Recent work in our laboratory indicates that similar defense mechanisms may be responsible for the control of infection by Fusarium species (unpublished observation from our laboratory). It is also likely that neutrophils may play an important role in protecting against trichosporosis, given the high incidence of neutropenia among patients with this infection, the poor response to antifungal chemotherapy if neutropenia persists [5], and the increased mortality and tissue fungal burden among neutropenic animals compared with controls (unpublished observation from our laboratory).

The ulcerations in the oropharynx and along the entire gastrointestinal tract caused by chemotherapeutic agents for treatment of cancer set the stage for colonization and invasion by Candida species. It is well established that the use of broad-spectrum antibacterial agents, particularly those that achieve a high concentration in the gastrointestinal tract and that exhibit good activity against gram-negative anaerobes, results in a substantial increase in the gastrointestinal concentrations of Candida species. This increased concentration, together with ulcerations following cytotoxic chemotherapy, may lead to disseminated candidiasis.

Other factors known to predispose patients with cancer to candida infections include adrenal corticosteroid therapy, abdominal surgery, and concomitant diabetes mellitus. Whether central venous catheterization and the administration of total parenteral nutrition predispose patients to disseminated candidiasis remains controversial, although several reviews implicate these factors in the pathogenesis of disseminated infection.

Adrenal corticosteroid therapy and neutropenia are the two most important predisposing factors for the development of aspergillosis and tend to act in concert, thus increasing the risk of infection [29–31].

Candidiasis

Candidiasis remains the most frequently encountered fungal infection in patients with cancer [2, 3, 5, 12–16]. For many years, C. albicans was responsible for the vast majority of these infections. In recent years, other species including Candida tropicalis, Candida parapsilosis, Candida guilliermondii, Candida krusei, and Candida lusitaniae have emerged as important pathogens in patients with cancer [12, 32–41]. With the introduction of antifungal prophylaxis with the newer triazoles, it is possible that this trend for infection with non-albicans species will be further accentuated and that C. krusei and Torulopsis glabrata will account for an increasing number of cases of disseminated candidiasis. Candida species can cause a variety of infections that can be either localized—such as oral thrush, esophagitis, peritonitis, and superficial urinary and cutaneous infections—or disseminated.
The spectrum of disseminated candidiasis in the neutropenic patient with cancer includes both an acute and a chronic presentation. Acute disseminated candidiasis (ADC) may be sudden in onset and usually evolves over days, with skin lesions, fungemia, and sometimes shock [42], while the chronic form of the infection—referred to as hepatosplenic candidiasis—extends over several months and is characterized by progressive debilitation [43]. Despite these differences, it is wise to consider these two aspects of disseminated candidiasis as occurring on a continuum. Although it is believed that the chronic infection usually follows an acute episode, the chronic syndrome may also convert to an acute infection when the patient’s immune status suffers further deterioration.

Chronic disseminated candidiasis is being recognized with increasing frequency [43–53]. Typically, the patient has a hematologic malignancy and acquires the infection after myelosuppressive chemotherapy. The diagnosis of the infection is usually made after the patient has recovered from myelosuppression but has persistent fever that is unresponsive to therapy with broad-spectrum antibacterial agents. Deep-seated abscesses of the liver, spleen, kidneys, and lungs can be best identified by computed tomography, and the infection can be confirmed by biopsy or isolation of the organism from an otherwise sterile site. This infection has been reported with increasing frequency, is responsible for significant delays in the therapy for the underlying malignancy, is highly likely to be fatal if therapy is not administered, is difficult to diagnose and treat, and therefore frequently requires long-term combination chemotherapy with amphotericin B plus 5-fluorocytosine. Only 50% of patients respond to therapy with amphotericin B with or without 5-fluorocytosine, and a significant number of patients die of infection despite antifungal therapy [43–53].

Although the previously used term “hepatosplenic candidiasis” suggests that the infection is limited to the liver and spleen, the clinicopathological features of this syndrome clearly indicate that the infection involves multiple organs. A more appropriate descriptive term is chronic disseminated candidiasis (CDC) [43]. This is not a purely semantic issue but has important diagnostic and therapeutic implications. Rather than causing a focus on hepatosplenic infection, a disseminated process would encourage the careful clinical and laboratory evaluation of the extent of involvement of various organs and the continuation of therapy until infection at all sites, including the extraabdominal sites, has responded. A disseminated process would also imply that agents that are distributed widely in body tissues should be given serious consideration in the treatment of this infection. Of note, however, is that CDC is almost exclusively limited to patients rendered neutropenic by cytotoxic chemotherapy and has been seen very rarely in non-neutropenic patients postoperatively. This syndrome should be clearly delineated from the candidemia and the ADC that occur in this latter patient population.

ADC has a more rapidly progressive clinical picture and usually refers to the presence of infection with *Candida* species at two or more noncontiguous sites. In the proper clinical setting, the presence of multiple deep-seated cutaneous lesions due to *Candida* species is also indicative of disseminated infection [54–58], even if cultures of blood specimens fail to yield the organism. Furthermore, the isolation of *Candida* species from the bloodstream of a patient with persistent profound neutropenia (<100 neutrophils/mL for >7 days) is usually, although not always, indicative of disseminated infection [3, 5, 51].

The distinction between ADC and candidemia may be difficult. At the M. D. Anderson Cancer Center, we consider candidemia to be present when there is clinical evidence of infection, at least one culture positive for *Candida* species from specimens obtained from the bloodstream (preferably through venipuncture), and no evidence of organ involvement after careful clinical and laboratory work-up.

The issue of catheter-related candidemia is somewhat confusing and usually refers to the presence of candidemia in a patient who has a central venous catheter. Whether the catheter and the hyperalimentation fluids are the primary source of the infection or whether the catheter is seeded from a remote source remains unknown. Evidence supporting or negating the role of the catheter in the pathogenesis or persistence of the infection is lacking. Hence, optimal management of bloodstream candidal infections in this setting remains to be defined.

Two studies from the pediatric literature suggest the need for catheter removal because of the higher rate of complication and death if the catheter is not removed. Both studies, however, included very few patients and were retrospective in nature. Furthermore, data on important predictors of outcome in ADC—the degree of immunosuppression, the performance status of the host, and the fungal burden—were not available [59–60]. On the other hand, it is important to recognize that the gastrointestinal tract is the most likely primary source of the infection in the neutropenic patient with cancer, that ADC can be reproduced in experimental animals after colonization of the gastrointestinal tract with *Candida* species, and that management of bloodstream candidal infections in this setting could be successful with the catheter left in place (D. Armstrong, personal communication, and author's personal experience).

Furthermore, in this setting of persistent profound neutropenia, repeated removals of central venous catheters fail to improve overall outcome because most patients with disseminated candidiasis in this setting will die of the infection unless recovery from myelosuppression occurs quickly (author's personal experience). It should be kept in mind that the routine removal of catheters may interfere with the medical management of these seriously ill patients with cancer by...
Aspergillus were dal D. Derating airborne cancer sive one [70]. This process is referred to as “persorption.” Its clinical relevance remains unclear, however. What appears to be a more accepted view is the dissemination of Candida species via subtle mucosal damage that occurs in a variety of medical and surgical illnesses. An abnormality in nodal killing of translocated organisms has been recognized in patients with serious burns [69].

Despite these findings, which indicate that the gastrointestinal tract appears to be the primary source of candidemia, one could still postulate that contamination of the central venous catheter during bloodstream infection may create a nidus of persistent infection. Data to substantiate this claim are not available, however. Hence, the management of candidemia in the non-neutropenic patient remains controversial. Removal of the central venous catheter in such a setting is an established practice that lacks scientific support. Only carefully planned, prospective studies may give a definitive answer to this controversial issue.

Aspergillosis

Aspergillus species are ubiquitous organisms, commonly found in soil, water, organic debris, and decaying vegetation [70]. In worldwide surveys of airborne fungi, Aspergillus spores accounted for 0.1%–22% of total spores collected, ranking Aspergillus species first to 15th in frequency among airborne molds. In the hospital setting, Aspergillus species can be isolated from the air, accumulated dust, and environmental surfaces. Most nosocomial aspergilloses are acquired via airborne transmission.

Colonization of the respiratory tract is followed by invasive disease if predisposing factors are present. Sources of airborne fungi in microepidemics have frequently been associated with construction within the hospital or at adjacent sites [71–74]. Disturbance of dust above false ceilings represents a significant risk to susceptible patients, and dust-generating activities, such as vacuuming, should be avoided in hospitals that care for patients at high risk for aspergillosis. In one study, fire-proofing material was contaminated with Aspergillus spores, and in two other studies, hospital air ducts were contaminated by bird droppings [75–77]. In most cases, the air supply of the patient’s room has been found to be contaminated [76, 78]. However, contamination of the operating room or the radiology department has been associated with microepidemics of aspergillosis.

Guidelines for hospital construction include the following: (1) sealing off areas of patient care from the construction activity with impermeable plastic barriers, and removing seriously immunocompromised patients from floors adjacent to construction activity (these patients should not be readmitted to renovated areas before these areas have been thoroughly cleaned) and (2) ensuring that the ventilation system near the construction area is working properly and is not circulating contaminated air from construction sites to other hospital areas [79].

Microepidemics of aspergillosis may be difficult to recognize. Only a few patients (those who are immunocompromised) may develop the infection. The common source may not always be detected, but if one is present, it is usually a defective or contaminated ventilation system [72, 74]. Because air sampling may be inadequate for detecting the source, the filtering system and intake ducts must be examined for contamination. Copper-8-quinolinolate can clean contaminated air systems [73]. High-efficiency particulate air (HEPA) filters remove almost all Aspergillus spores and reduce the risk of nosocomial aspergillosis [80]. Particular attention should be paid to preventing infiltration of unfiltered air (through drafts in elevator shafts and open doors and windows) in the hospital air supply system. Plant engineering and infection control personnel should routinely review the practices for preventive maintenance relating to the air handling system. Other modes of transmission of aspergillosis have been reported, including infections associated with foreign bodies, catheters, and bandages [81–83].

Acute invasive pulmonary aspergillosis is the most common form of Aspergillus infection in immunocompromised patients, particularly among leukemic patients who are undergoing remission induction chemotherapy [5, 23, 75, 84]. The organisms have a propensity for invading blood vessels, thus causing thrombosis and infarction of the surrounding tissues. The infection may manifest itself as acute vascular events, such as pulmonary embolus, myocardial infarction, cerebral hemorrhage, or Budd-Chiari syndrome [85]. Pulmonary infection includes necrotizing bronchopneumonia and hemorrhagic pulmonary infarction, each accounting for about one-third of these infections [19]. Pulmonary aspergillosis may extend to contiguous organs or lead to disseminated infection. The rhinocerebral form of aspergillosis occurs less often than does pulmonary infection. It originates in the sinuses and progresses through the soft tissues, cartilage, and bone, causing lesions in the palate and the nose. Occasionally, the infection progresses through the base of the skull and involves the brain.

Emerging Pathogens

Fungi such as Fusarium species, Curvularia species, Alternaria species, or Trichosporon beigelli had been thought to
represent contamination or harmless colonization when isolated from human tissue specimens. More recently, the role of these and other newly recognized fungi as serious pathogens has been clearly established [5–7].

_Fusarium species._ Patients with hematologic malignancies who are receiving cytotoxic chemotherapy are at an increased risk for disseminated fusarial infections [7, 86]. The clinical characteristics of patients with disseminated infection due to _Fusarium_ are similar in many respects to those with disseminated aspergillosis. They share in common the occurrence of nodular erythematous skin lesions with central necrosis. The portals of entry for both infections include the paranasal sinuses, lung, and skin. However, infection with _Fusarium_ species is associated with a significantly higher incidence of skin and subcutaneous lesions and a much higher yield of the organism in cultures of blood specimens than is infection with _Aspergillus_ species [7, 86]. Because the clinical features of fusarial infections are not distinctive and because of the histopathologic similarities between aspergilli and fusaria, fungal cultures are essential for establishing the diagnosis.

Probably the most important factor predicting the outcome of infection due to _Fusarium_ is the immune status of the host. All patients with an underlying malignancy and disseminated fusarial infection had severe neutropenia at the onset of their infection [7]. Except for three patients reported by Merz et al. [86], no patient with disseminated multiple-organ infection survived even when adequate doses of amphotericin B were given.

In the above-mentioned report, three of four patients with disseminated fusarial infection responded. Of note, in two of these three patients myelosuppression rapidly resolved and there did not appear to be extensive multiple-organ infection. Because of the paucity of data on the management of invasive fusarial infections, we developed a murine model of systemic fusariosis in CF1 male mice made by injection of 1 × 10⁶ conidia of _Fusarium solani_. The activity of the triazoles—fluconazole, itraconazole, saproconazole, and SCH 39304—at doses of 50 mg/kg twice daily was compared with the activity of amphotericin B at doses of 1 and 2 mg/kg injected ip daily. As expected from the poor activity of amphotericin B against disseminated human fusarial infections, amphotericin B therapy was not associated with prolongation of survival or significant reduction in fungal clearance from the organs in treated compared with control animals, despite administration of escalating doses of the drug. Treatment with the triazoles, particularly SCH 39304 and fluconazole, led to significantly longer survival [87]. However, the triazole doses given were significantly higher than standard doses. The use of combination chemotherapy is currently being investigated in this animal model.

_Trichosporon beigelii._ Not much is known about the pathogenesis and treatment of infection caused by _Trichosporon beigelii_. The most likely primary source of the infection is the patient’s own gastrointestinal and respiratory flora, which have been shown to be sites of fungal colonization in hospitalized patients.

The most important systemic host factors for this infection are similar in many respects to those for disseminated candidiasis. They include granulocytopenia and the administration of adrenal corticosteroids [5]. Hemochromatosis and the presence of a prosthetic cardiac valve are also known predisposing factors for disseminated trichosporosis [5, 88]. It is not surprising that _Trichosporon_ species may have (as do other microbial agents) a siderophore receptor, and iron stores in the host may very well be important in the pathogenesis of trichosporosis. It is interesting to note that most reported cases of _T. beigelii_ infection were in the United States, whereas infections caused by _Trichosporon capitatum_ were more commonly encountered on the European continent.

The clinical presentation of disseminated trichosporosis mimics that of disseminated candidiasis and may be acute or chronic. Acute disseminated trichosporosis may have a sudden onset; be associated with skin lesions, fungemia, pulmonary infiltrates, renal and ocular involvement, and hypotension; and usually evolves over days [5]; whereas chronic disseminated trichosporosis extends over several months and is characterized by progressive debilitation. Chronic disseminated trichosporosis presents clinically in the same way as does CDC (also known in the literature as hepatosplenic candidiasis).

The diagnosis of disseminated trichosporosis rests on a combination of clinical and laboratory findings. Histopathologically, the infection is characterized by the presence of arthroconidia, blastoconidia, hyphae, and pseudohyphae. The result of the latex agglutination test for _Cryptococcus neoformans_ may be positive.

The outcome of disseminated trichosporosis in neutropenic patients with cancer has been poor. _Trichosporon_ species seem relatively resistant to amphotericin B [89, 90]. Of 25 patients who had disseminated trichosporosis and persistent profound neutropenia who were treated with amphotericin B at our cancer center, 21 died with infection. Data on the susceptibility of _Trichosporon_ species to various antifungal agents are scarce. Results from our laboratory and others indicate that _T. beigelii_ may be resistant to amphotericin B in vitro [89, 90]. Recent findings in our murine model of disseminated trichosporosis indicate that triazoles, including fluconazole and SCH 39304, appear to exhibit good activity (superior to that of amphotericin B) against 10 pathogenic strains of _T. beigelii_ (unpublished observation from our laboratory). Similar findings were shown in a rabbit model of infection with _T. beigelii_ [91]. The successful treatment of disseminated trichosporosis with fluconazole in five of our patients with cancer, including one with chronic disseminated trichosporosis, is encouraging (unpublished observation from our institution). Additional work is clearly needed, however, for determination of the efficacy of the triazoles in the management of disseminated trichosporosis.
Several other newer fungi have been reported as causing life-threatening infection [6, 92].

**Therapy for Invasive Mycoses**

A major obstacle to the successful management of serious fungal infections is the inability to establish the diagnosis. Thus, empiric therapy with amphotericin B has become standard practice for the management of neutropenic patients with persistent fever that is unresponsive to therapy with antibacterial agents. One study evaluated neutropenic patients who had fever of unknown origin for 1 week after receiving an antibacterial regimen [93]. Patients were randomly assigned to three groups: (1) to continue the same antibacterial regimen, (2) to discontinue all antibacterial therapy, or (3) to receive amphotericin B in addition to the antibacterial regimen. Significantly fewer fungal infections were documented in the group of patients receiving amphotericin B.

Another prospective study randomly assigned patients who remained febrile after 4 days of antibacterial therapy to two groups: (1) to continue the same antibacterial regimen or (2) to receive amphotericin B in addition. The subsequent response rates were 53% and 69%, respectively ($P = .09$) [94].

Empirical therapy with amphotericin B is clearly indicated for some patients, but unfortunately, many patients who do not have fungal infection suffer the toxicities of amphotericin B unnecessarily. In addition, amphotericin B–deoxycholate may not be well available to fungi. Despite the presence of high drug concentrations in various tissues of patients with cancer on whom an autopsy was performed and despite the good susceptibility of these fungi in vitro to the drug, in one study patients still died of disseminated fungal infections and were determined to have had extensive mycoses at the time autopsy was performed [95].

In another study of patients with cancer succumbing to fungal infections, amphotericin B was detected in very small concentrations in kidneys and lungs, which are usual sites of serious mycoses; fungicidal concentrations of the drug were seldom achieved in tissues; and biodiffusion and bioavailability of the drug were poor [96]. In addition, substances in serum and tissue seem to inhibit the fungicidal activity of amphotericin B [97]. In vitro, *Candida* species can convert to slow anaerobic growth in the presence of amphotericin B and thus not be susceptible to the fungicidal effect of the drug [98]. Since no prospective studies have addressed the role of amphotericin B in the therapy for ADC, one must rely on retrospective analysis of patients treated with this drug. Overall, a 45% response rate has been reported in a cumulative review [99]. However, a recent study indicated that no significant differences in rates of survival could be observed between patients with disseminated candidiasis who received amphotericin B and those who did not [100]. Although the latter was a retrospective study, the serious limitations of the use of amphotericin B, particularly in severely immunocompromised patients, were nonetheless indicated. On the other hand, another retrospective study indicated that use of amphotericin B early in the course of infection decreased the mortality associated with fungal infection and reduced the incidence of disseminated mycoses and the frequency of persistent fungemia [101].

The apparent lack of activity of amphotericin B in severely ill patients has been further compounded by the emergence of resistance to this agent in this patient population [39, 102]. Amphotericin B remains, however, the drug of choice for the treatment of invasive aspergillosis [5, 23, 84].

Other agents that could be useful in the treatment of systemic mycoses include 5-fluorocytosine. However, high rates of failure and secondary emergence of resistance have been reported when 5-fluorocytosine was used alone in the therapy for cryptococcosis, and serious concerns exist regarding the myelosuppressive potential of this drug [103, 104]. A review of the results from five studies from the literature on the activity of 5-fluorocytosine in the treatment of ADC and candidemia indicates a good response rate [105–109]. Responses were seen in 31 of 40 patients (78%), including three patients with *T. glabrata* infection. On the basis of the pharmacokinetics of 5-fluorocytosine and of the in vitro susceptibility of *Candida* species to the drug, much lower doses of 5-fluorocytosine will likely maintain serum and tissue levels significantly higher than the MIC needed for most susceptible strains throughout the course of therapy. For example, a dose of 50 mg/(kg·d) given at 6-hour intervals would result in peak and trough serum levels of ~50 and 10 µg/mL, respectively, assuming a steady state and a normal kidney function in a 70-kg male patient. Since the MIC of 5-fluorocytosine for most susceptible *Candida* species is usually <1 µg/mL, such a dosage schedule will probably constitute appropriate therapy, particularly if the drug is used in combination with other antifungal agents. This approach may decrease the myelosuppressive potential of this drug, usually associated with levels of 100 µg/mL, and may lead to its wider use.

Yet another family of promising antifungal agents is the triazoles, such as itraconazole, fluconazole, SCH 39304, and saperconazole. These agents have clearly demonstrated significant in vivo activity against various mycoses [110–113]. In our experience at the M. D. Anderson Cancer Center, fluconazole achieved an 88% response rate in a series of 16 patients who had cancer and CDC and who had failed to respond to adequate doses of amphotericin B ($\geq$ 2 g) or had significant dose-limiting toxicities [43]. This good response rate was seen even among those patients who had failed to respond to large doses of amphotericin B and among patients who continued to receive cytotoxic chemotherapy for underlying leukemia. Although it could be argued that despite clinical and laboratory evidence of ongoing infection in all our patients at the time of initiation of fluconazole therapy, amphotericin B could have already induced a major response.
in the refractory patients, previous experience suggests otherwise. In fact, patients treated with similar doses of amphotericin B, as used in this study, had such a high rate of failure that recommendations for using much higher doses in combination with 5-fluorocytosine were made [46].

It is not unlikely, however, that amphotericin B could have caused some inhibition of growth, thus allowing fluconazole to exert its activity on an already reduced fungal inoculum. On the basis of the long half-life (t1/2) of amphotericin B in humans and the known additive or synergistic effect between amphotericin B and the triazoles, an additive effect of amphotericin B and fluconazole may possibly have occurred in patients who had received ≥2 g of amphotericin B. Similar results with fluconazole in the therapy for CDC have also been reported by others [53]. In an open prospective study conducted at our institution, fluconazole (400 mg) was given once daily iv to 21 patients who had cancer and either candidemia (13 patients) or ADC. Eight patients had hematologic malignancies and 13 had solid tumors. Six patients had profound neutropenia (<500 neutrophils/mL). The distribution of Candida species was as follows: C. albicans, eight patients; C. parapsilosis, five; C. tropicalis, three; T. glabrata, two; C. guilliermondii, one; and mixed infections, two. Ten of 13 patients with candidemia (77%) responded, compared with four of eight patients (50%) with ADC. Responses were observed in four of six neutropenic patients and corresponded with neutrophil recovery in all four patients. Outcome was unrelated to fungal species.

In two clinical trials, ketoconazole was compared to amphotericin B in the empiric therapy for neutropenic patients with fever. The results of the first study indicate that both agents had similar activity, although amphotericin B appeared to have superior activity in cases of established C. tropicalis infection [114]. Results of the other randomized trial indicated that significant differences between amphotericin B and ketoconazole could not be detected with regard to the overall survival rate, the number of deaths due to fungal infection, the number of documented mycoses, and the number of days before defervescence occurred [115].

In addition, empirical therapy with miconazole has been found to significantly decrease the incidence of life-threatening mycoses in patients with fever and neutropenia [116]. It is clear, however, that despite early institution of antifungal chemotherapy, a significant number of patients with cancer will have progressive fungal infection and die. Several approaches could be considered for the management of these resistant mycoses:

1. **More effective prophylaxis.** In a prospective, randomized, double-blind, placebo-controlled, multicenter study of patients undergoing bone marrow transplantation, prophylaxis with fluconazole (400 mg/d) effectively prevented fungal infections, including superficial and disseminated candidiasis [117]. In addition, we have compared in a prospective, randomized trial the role of oral fluconazole (400 mg/d) or iv amphotericin B (0.5 mg/kg thrice weekly) in the prophylaxis for neutropenic patients with acute leukemia [118]. Seventy adults with leukemia undergoing remission induction chemotherapy were studied. Both drugs were 100% effective in preventing thrush. Five cases of disseminated infections occurred: C. albicans (one) and Aspergillus species (two) in the amphotericin B group, and T. glabrata (one) and Aspergillus terreus (one) in the fluconazole group. Fluconazole was well tolerated, and the adverse effects of nausea (two patients) and diarrhea (three patients) did not necessitate discontinuation of prophylaxis. Significant nephrotoxicity was observed in six patients in the amphotericin B group, and discontinuation of drug therapy was required in all six cases.

2. **Chemotherapy with higher, maximally tolerated doses.** Higher doses of amphotericin B in combination with 5-fluorocytosine have been associated with an improved response rate in cases of aspergillosis [119]. Liposomal formulations of amphotericin B allow the administration of much higher doses of amphotericin B [120, 121]. These formulations have been shown to have significant antifungal activity in patients failing to respond to standard therapy with amphotericin B. However, factors other than the higher doses may be responsible for the observed therapeutic effects with these liposomal formulations. We are currently also looking at the activity of maximally tolerated doses of fluconazole (up to 2,000 mg/d) in various mycoses. Preliminary evidence indicates that the drug is well tolerated even at these very high doses.

3. **Combination chemotherapy.** The role of combination antifungal chemotherapy has been established in a study comparing amphotericin B plus 5-fluorocytosine to amphotericin B alone for the treatment of cryptococcal meningitis [122]. We and others have been reluctant, however, to use a combination of amphotericin B and an azole because of a previous report of the potential antagonism between amphotericin B and ketoconazole in murine aspergillosis [123]. Subsequent reports from several investigators indicate that such combinations involving a triazole and amphotericin B may, at times, be associated with an improved response rate in certain animal models of infections, including disseminated candidiasis, cryptococcosis, and trichosporosis [124–127]. Furthermore, enhanced antifungal activity can be achieved when azoles, such as ketoconazole or fluconazole, are combined with 5-fluorocytosine. We are currently considering a prospective study of the role of triplecombination chemotherapy with amphotericin B, fluconazole, and 5-fluorocytosine for resistant mycoses. The future availability of β-1,3-glycan synthetase in-

---

This content downloaded on Fri, 8 Feb 2013 05:45:50 AM
All use subject to JSTOR Terms and Conditions
hibitors may render combination chemotherapy even more attractive [128, 129].

4. Immune modulation. Since one of the most important predictors of outcome in invasive mycoses remains the status of the patient’s immune system, it would seem logical to use antifungal chemotherapy in combination with biological response modifiers. We have examined the activity of amphotericin B in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment of serious fungal infections [130]. GM-CSF was given in a dose of 400 µg/(m²·d) and amphotericin B in a dose of 1 mg/(kg·d). Therapy with GM-CSF was continued until resolution of neutropenia or serious toxicities occurred. Eight patients (seven patients with leukemia and one recipient of a bone marrow transplant) were enrolled. The results of this pilot study were encouraging: five of eight patients achieved a complete clinical and laboratory response. However, serious toxicities were encountered, in particular capillary leak syndrome, known to be associated with administration of the higher doses of GM-CSF used in our study. Other immuno-stimulatory agents may also prove to be useful for the management of systemic mycoses.

5. Fungus, host, and site-specific therapy. The response of specific fungal infections to antifungal chemotherapy depends on several factors, including the susceptibility of the pathogen to the antimicrobial agent used, the severity and extent of disease, the status of the host’s immune system, and the concentrations of drugs achieved at various infection sites. For example, although both amphotericin B and fluconazole appear, in our experience, to exhibit good activity against candidemia in the “normal host,” neither agent alone would be appropriate for the treatment of this infection in patients with persistent profound neutropenia. And while candidemia may require a few weeks of therapy, a much longer period of time is required for treatment of CDC. Overall, it is likely that achieving successful therapy would require the maintenance of serum and tissue levels several times higher than the MIC of the offending pathogen in the “normal host” and higher than the minimal fungicidal concentration in the “severely immunosuppressed host.” These requirements are particularly relevant with azole therapy, for which a dose-response curve has been established, and with use of liposomal formulations of amphotericin B, which may allow delivery of significantly higher doses of the drug.

Conclusions

We have learned several lessons from our experience and those of others with fungal infections and antifungal chemotherapy. Clearly, amphotericin B is not an “all-around” anti-
fungal agent, given the very high rate of failure among immunosuppressed patients with cancer (nor is it likely that any such “all-around” agent will be available soon). We have also learned that the status of the immune system is the most important predictor of outcome in cases of invasive mycoses and that fungi that were considered simple colonizers or contaminants only a few years ago have now emerged as significant pathogens in this patient population. Only through collaboration between clinicians, pathologists, microbiologists, and pharmacologists can these fungal infections be recognized and treated effectively. It is hoped that the advent of newer antifungal agents and biological response modifiers will result in significant improvement in the prevention and treatment of these life-threatening opportunistic infections.

References

18. Baker RD. Leukopenia and therapy in leukemia as factors predispos-


64. Odds FC, Evans EG. Distribution of pathogenic yeast and humoral
87. Anaissie E, Hackern R, Bodey GP. Comparative activities of fluconazole, itraconazole, sapoperazol, SCH 39304, and amphotericin B against disseminated F. solani infection in mice (abstract no 288).

100. Komshan SV, Uwaydah AK, Sobel JD, Crane LR. Fungemia caused by Candida species and Torulopsis glabrata in the hospitalized patient: frequency, characteristics, and evaluation of factors influencing outcome. Rev Infect Dis 1989;11:379–90.

106. Harder EJ, Hermans PE. Treatment of fungal infections with fluco-

107. Tassel D, Madoff MA. Treatment of Candida sepsis and Cryptococcus menigi-


112. Walsh TJ, Aoki S, Mechinaud F, et al. Effects of preventive, early, and late antifungal chemotherapy with fluconazole in different granulo-


114. Fainstein V, Bodey GP, Elting L, Maksymyk A, Keating M, McCredie KB. Amphotericin B or ketoconazole therapy of fungal infec-

115. Walsh TJ, Rubin M, Hathorn J, et al. Amphotericin B versus high-

ized double-blind placebo-controlled trial of intravenous micona-

117. Goodman J, Buell D, Gilbert G. Fluconazole prevents fungal infec-
tions in bone marrow transplantation: results of a placebo-con-
trolled, double-blind, randomized, multicenter trial (abstract no PS3.114). In: Program and abstracts of XI Congress of the Interna-
tional Society for Human and Animal Mycology (Montreal, Que-
bec, Canada). San Antonio, Texas: International Society for Hu-

118. Anaissie E, Reuben A, Cunningham K, Bodey GP. Randomized trial of fluconazole vs intravenous amphotericin B for antifungal pro-
phylaxis in neutropenic patients with leukemia (abstract no 572). In: Program and abstracts of 30th Interscience Conference on Anti-

119. Karp JE, Burch PA, Merz WG. An approach to intensive antileuke-


121. Anaissie E, Paetznick V, Proffitt R, Adler-Moore J, Bodey GP. Com-
parison of the in vitro antifungal activity of free and liposome-en-

122. Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of ampho-


124. Albert MM, Graybill JR, Rinaldi MG. Treatment of murine crypto-
coccal meniginis with an SCH 39304-amphotericin B combina-


128. Sugar A, Goldani L, Picard M. Treatment of murine invasive candi-

129. Hanson LH, Perlman AM, Clemens KV, Stevens DA. Synergy be-
tween cilofungin and amphotericin B in a murine model of candi-

ericin B for disseminated mycoses in neutropenic cancer patients (abstract no 73). In: Program and abstracts of the 29th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washing-


This content downloaded on Fri, 8 Feb 2013 05:45:50 AM
All use subject to JSTOR Terms and Conditions