Treatment of Systemic Mycoses in Patients with AIDS

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Abstract

Far and away the most common fungal infection associated with HIV infection is candidiasis. This tends to produce mucosal topical infections and local treatment may be enough to control them. Generally we prefer courses of 1-2 weeks rather than chronic suppression, for fear of eliciting overgrowth of resistant isolates. Fluconazole resistant Candida species may be an increasing problem over the next decade. For cryptococcoses the problem is both simpler and more complicated. Fluconazole is highly effective for chronic suppression, but not very effective for initial therapy. Here a short course of amphotericin B, just 2 weeks in length, is followed by chronic azole suppression. Fluconazole appears excellent, but itraconazole may also be effective. For histoplasmosis itraconazole appears to be the most advantageous drug, with excellent clinical response within 2 weeks. A role for fluconazole is unclear. Cocididiomycosis is uncommon, but difficult. I cannot offer any suggestions on "ideal" therapy here. Other diseases, such as aspergillosis, are extremely uncommon but still are AIDS associated mycoses. It is my personal fear that as we go along identifying the AIDS virus and its complications, aspergillosis and zygomycosis may establish themselves as the future "black hats" for which we will need to pull something out of the "box". What to pull is not very clear. (Arch Med Res 1993; 24:403)

KEY WORDS: Systemic mycoses; AIDS; Treatments.

Introduction

Until the 1970s, systemic mycoses were regarded as interesting, obscure illnesses worthy of relatively little attention to the medical community. There was uncertainty whether potential opportunists like Candida species were commensals or pathogenic, and for the "always" pathogenic fungi causing the endemic mycoses, infection was common but illness so rare as to be of relatively minor concern. Since the 1970s there have been three major events which have reshaped and dramatically enlarged the role of fungi in clinical medicine. All three events are still ongoing. They include: 1) the markedly increased spectrum of antibacterial drugs, 2) the sharply increasing use of immunosuppressive medications and cytotoxic drugs, and 3) the spread of the AIDS pandemic throughout the world. Cancer chemotherapy has predominantly targeted the hematopoietic cells of the neutrophil lineage, and a variety of antibacterial agents have acted effectively to suppress bacterial infections in these neutropenic patients. A variety of fungal pathogens have moved into this niche, and as a result we have seen sharp increases of fungemia caused by Candida species and Fusarium, and widespread infections caused by Aspergillus species, zygomycetes, and less commonly Trichosporon and dematiaceous fungi. The niche offered by AIDS is that of depressed cell mediated immunity. A number of mycoses have sharply increased to fill this need (1). The AIDS mycotic opportunists have generally had different identities, but more recently some of the exploiters of neutropenia have also come to infect patients with AIDS. We shall concentrate on these organisms for the remainder of this discussion.

The Setting

HIV infection appears as a depression of CD4 lymphocyte counts, initially unassociated with infection, but as CD4 counts slowly decline, at a rate of about 70 per year, in 6 to 10 years one eventually reaches a level below 500 cells, at which time the consequences of immunologic perturbation gradually become evident. Among these are feelings of malaise, lymphadenopathy, anorexia, and Thrush. Thrush is so common in HIV
infected patients that it has become a clear clinical marker for HIV infection (in the absence of other predisposing factors) and the extension of Candida infection into the esophagus is a clinical defining condition for AIDS (1-5). Although thrush may be confused with hairy leukoplakia, and although Candida esophagitis may clinically mimic esophagitis caused by cytomegalovirus, the implications of advancing immune depression are clear in all of these AIDS associated conditions. By the time a patient reaches the late phases of AIDS, his chances of experiencing Candida infection are over 90%. Over 90% of the Candida infections are caused by C. albicans, serotype B (4). Isolates are not unique or hypervirulent in patients with AIDS (6).

Along with thrush, there may be infections of other mucus membranes, and vaginal candidiasis has also been reported to be common by some, though less so by others (7). Vaginal infection occurs without a reduction in CD4 counts, and is followed in order by oropharyngeal candidiasis, and finally esophageal disease, the latter when the CD4 counts are very low (Table 1).

Associated with mucosal Candida infection there may be dermatophyte infection which is commonly extensive and varied in etiology (8-10). Seborrheic keratitis, argued by some to be of fungal etiology, is seen in a majority of patients by the time they reach severe stages of AIDS.

These infections are troublesome but not lethal. Unfortunately, as the immune deficit associated with HIV infection progresses, so does the risk of life-threatening fungal infection rise. Although the systemic mycoses may present as often as 50% of the time as the initial clinical AIDS defining infections, they commonly appear only when the CD4 count is less than 200, and usually are associated with counts below 100/mm³ (1). It is not widely appreciated, but the mycoses one encounters depend considerably upon the residence of the patient. Worldwide, Cryptococcus neoformans leads the list, with 6-9% in the United States, and 20-30% in Africa (1).

Europe and South America are also experiencing many patients with cryptococcoses, usually cryptococcal meningitis. However, in addition to cryptococcal disease there has been a dramatic increase in patients with histoplasmosis, almost uniformly the widely disseminated aggressive variety that may present to acutely as to be confused with bacterial sepsis, or more obscurely as adrenal insufficiency or colonic masses (11,12). The first cases were scattered, among immigrants from the endemic foci in the Caribbean Islands who later developed AIDS while living in New York or California, and then reactivated endogenous foci from infection long ago (13,14). However, as AIDS has moved into the midwestern USA primary histoplasmosis has been turning up in as many as 20-25% of patients with AIDS in Indianapolis, Kansas City and other midwestern cities (11).

This is a dramatic development which has made histoplasmosis truly a household word in these areas. Similar increases are now being experienced in other homelands of H. capsulatum, namely, Colombia, Brazil, Argentina and other Latin American countries. It is unclear why H. capsulatum is increasing not only in these areas but also in areas such as Africa, whereas H. capsulatum variety duboisii, so called African histoplasmosis, has not increased.

Along with histoplasmosis in the midwestern United States and South America there has been a rise in coccidioidomycosis (15). Coccidioidomycosis is still fairly uncommon in patients with AIDS, but like histoplasmosis tends to occur in patients with severe depressions of the CD4 counts. The disease is more variable than histoplasmosis, and may present as focal pulmonary lesions, meningitis, focal disseminated lesions, or widespread disease, the worst form, and associated with the lowest CD4 counts. Coccidioidomycosis is still much less common than histoplasmosis, and it is yet uncertain whether it will evolve into a major scourge like its midwestern relative H. capsulatum.

It is curious that while there is some increase in coccidioidomycosis in the desert areas of the southwest United States, there has been little increase in cryptococcoses in these areas. Perhaps this is because C. neoformans needs more rainfall or other factors unknown. It is also unclear why Blastomyces dermatitidis, endemic in the United States over much of the H. capsulatum endemic region, has only rarely affected patients with AIDS (16). It is also unclear why Paracoccidioides brasiliensis, resident in much of the H. capsulatum endemic area of South America, has also not been a problem of patients with AIDS (17).

Recently we have begun to appreciate yet another endemic mycoses, caused by Penicillium marneffei, which is yet confined largely to certain regions of Asia (18,19). Patients with this infection can develop pulmonary or disseminated disease, with isolation of P. marneffei in blood of 14, bone marrow of 15, and skin of 9 of a total 21 patients. There is a characteristic skin lesion which has the umbilicated shape of molluscum contagiosum. Elliptical shaped yeast cells loosely resembling H. capsulatum may be seen in the macrophages. The frequency appears to be increasing.

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**Table 1**

<table>
<thead>
<tr>
<th>Form of disease</th>
<th>N</th>
<th>Mean CD4 count per mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>31</td>
<td>741</td>
</tr>
<tr>
<td>Vaginal</td>
<td>10</td>
<td>516</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>16</td>
<td>230</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>9</td>
<td>30</td>
</tr>
</tbody>
</table>

*From Reference 7.
Finally, when the CD4 counts fall to very low levels, and initially thought to be associated only with concurrent severe leukopenia, one sees a reemergence of the “neutropenia” pathogens, Candida species and Aspergillus (20,21). Candidemia has been blamed on the intravenous (IV) catheters so common in late stage AIDS patients, whether used for nutrition or to treat cancers of cytomegalovirus.

Aspergillosis was initially associated only with neutropenia, but is clearly occurring in many patients whose leukocyte counts are not severely depressed. It is my strong impression that aspergillosis is on the increase, and will become even more of a problem in the patients with AIDS.

Add to these infections scattered patients with zygomycetes, hyalohyphomycetes, and phaeohyphomycetes, and the menu for fungal opportunism becomes truly large.

Management of Mycoses in AIDS: General Considerations

At present, there are available a variety of topical medications for dermatophyte and for mucosal candidiasis. Of these, we have found topical clotrimazole to be particularly helpful in oropharyngeal candidiasis, and have often recommended this as an agent of first choice, as troches given 10 mg five times per day. However, this is less convenient for some to take than systemic agents, is less effective against esophageal disease, and is ineffective for other than topical infections.

The systemically administered antifungals include the polyenes amphotericin B and a variety of alternatives prepared in lipid vehicles, 5 fluorocytosine (5FC), and the azoles ketoconazole, fluconazole, and itraconazole. Saperconazole is a potent difluoronated derivative of itraconazole now entering clinical trials (22). Other potentazole and nonazole antifungals are under consideration or in preclinical development. A brief comparison of the major drugs appears in Table 2.

Polyenes

Of the polyenes, amphotericin B deoxycholate (AMB, Fungizone) has been the most broadly used derivative. AMB is associated with multiple toxicities, including fever, chills, nausea and vomiting and thrombophlebitis during administration. These can be minimized by premedication with meperidine, 25 mg per dose intravenously, acetaminophen (23). AMB also causes anemia from depression of erythropoietin and would presumably respond to recombinant erythropoietin. The most dangerous toxicity of amphotericin B is nephrotoxicity, which is manifested both by glomerulotubular blood flow imbalance, causing decreased glomerular flow and azotemia, and also distal renal tubular acidoses, manifested by hypokalemia and excess bicarbonate excretion. We have attempted to minimize the former by infusion of a liter of normal saline prior to each amphotericin B dose, and we have treated the latter with potassium and bicarbonate replacement. While renal toxicity is largely responsive to interruption of the amphotericin B dose (should be considered when creatinine raises above 2.5 to 3) eventually this may be irreversible. It is important to note that a patient receiving concurrent renally excreted drugs, such as 5FC, will have marked increases of serum concentration and resultant toxicity.

AMB is diluted in 5% glucose and administered intravenously over 1-4 h. Rapid administration is preferred by some patients because of shortening the time of fever and chills, but this is disputed by some (23). There is also a risk of rapid administration causing acute rises in serum potassium, especially in patients with renal failure.

A variety of lipid associated forms of AMB are under development. The purpose of most of these is to bypass the kidneys and reduce the nephrotoxicity. There is also the desire of raising concentrations in macrophage and sites of infection, and also avoiding systemic toxicities associated with administration of the drug. These have been less well realized than the clear reduction of nephrotoxicity. Anemia does seem to be minimized, but patients still have fevers and chills with all three forms of drug now used. The forms now include amphotericin B lipid complex (ABLC, Bristol Myers Squibb, Princeton, NJ, USA), in which the drug is as high as 30% in the lipids, and morphologically appears in a form consisting of ribbon or leaflike polymorphic bits. This preparation has seen the widest clinical use in controlled trials (24). AmBisome (Vestar, San Dimas, CA, USA) is a true liposomal form of drug and has been used in controlled fashion in Europe with 82% “cures” among 29 patients treated. However, some of these pulmonary infections were caused by Candida, which is a difficult diagnosis to confirm.

No patients were reported to have AIDS (25). The preparations are extremely expensive and difficult to prepare for administration, though more uniform than ABLC. Finally there is amphotericin B colloidal dispersion (ABLC) which is a very uniform preparation of amphotericin B intercalated with lipid in disclike structures only a few molecules thick (26). The preparation is stable, easily handled, and is now undergoing trials in aspergillosis. Which of these preparations will gain widespread use is at yet uncertain.

Flucytosine (5FC, Roche Laboratories)

5FC is a highly soluble agent which is effective in the limited spectrum of Candida and Cryptococcus infections, with anecdotal suggestions of efficacy in aspergillosis and chromoblastomycosis. Resistance
Table 2
Comparison of the Major Antifungals Drugs Used in Different Mycoses

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>Polyenes</th>
<th>5FC</th>
<th>Azoles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMB ABLC</td>
<td>SFC</td>
<td>KETO</td>
</tr>
<tr>
<td><strong>Candida</strong></td>
<td>+++</td>
<td>UNK</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Torulopsis</strong></td>
<td>++</td>
<td>UNK</td>
<td>++</td>
</tr>
<tr>
<td><strong>Aspergillus</strong></td>
<td>+++</td>
<td>UNK</td>
<td>±</td>
</tr>
<tr>
<td><strong>Cryptococcus</strong></td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Histoplasma</strong></td>
<td>+++</td>
<td>UNK</td>
<td>O</td>
</tr>
<tr>
<td><strong>Coccidioides</strong></td>
<td>+++</td>
<td>+++</td>
<td>O</td>
</tr>
<tr>
<td><strong>Phaeohypho mycoses</strong></td>
<td>+++</td>
<td>UNK</td>
<td>±</td>
</tr>
</tbody>
</table>

**P. marneffei**

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>IV</th>
<th>IV</th>
<th>ORA</th>
<th>ORAL</th>
<th>ORAL</th>
<th>ORAL, IV</th>
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</thead>
<tbody>
<tr>
<td>Acid needed</td>
<td>N/A</td>
<td>N/A</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Highest dose (in mg/kg)</td>
<td>1.5</td>
<td>5</td>
<td>150</td>
<td>30</td>
<td>9</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Excretion</td>
<td>R</td>
<td>H</td>
<td>R</td>
<td>H</td>
<td>H</td>
<td>R</td>
</tr>
</tbody>
</table>

**Toxicities**

<table>
<thead>
<tr>
<th></th>
<th>Fever</th>
<th>Nausea</th>
<th>Renal</th>
<th>Hepatic</th>
<th>Endocrin</th>
<th>Myelosup</th>
<th>Drug Interactions Which Reduce Level of Antifungal:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>++++</td>
<td>+++</td>
<td>++++</td>
<td>±</td>
<td>0</td>
<td>0</td>
<td>H2 Blocker:</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>+++</td>
<td>±</td>
<td>UNK</td>
<td>0</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>+</td>
<td>+++</td>
<td>O</td>
<td>Rifampin:</td>
</tr>
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<td></td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>±</td>
<td>0</td>
<td>O</td>
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<tr>
<td></td>
<td>O</td>
<td>O</td>
<td></td>
<td>±</td>
<td>0</td>
<td>O</td>
<td>Phenytoin:</td>
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<tr>
<td></td>
<td>O</td>
<td>O</td>
<td></td>
<td>±</td>
<td>0</td>
<td>O</td>
<td></td>
</tr>
</tbody>
</table>

**Drug Interactions Which Reduce Level of Antifungal:**

|        | Cyclosporine | 0 | 0 | 0 | +++ | ++++ | 0 | +++ | ++++ | ++ |

Unk = unknown; IV = intravenous; R = renal; H = hepatic.

emerges rapidly, and for this reason 5FC is used only in conjunction with other agents. Generally this has been amphotericin B. However, 5FC is excreted renally, and nephrotoxicity from concurrent AMB causes 5FC retention, and this in turn increases myelotoxicity, the major problem when using this drug. This is a problem when 5FC is used for a prolonged period of time in patients already neutropenic from AIDS and its complications. On the basis of some promising animal investigations, which show additive benefit of fluconazole and 5FC, some investigators are studying the clinical combination of fluconazole and 5FC in cryptococcal meningitis (27). Such a combination would have the potential of an entirely oral regimen that is not nephrotoxic.
Azoles

At the onset of the AIDS pandemic, ketoconazole was the major systemic azole in use. Ketoconazole is absorbed optimally after oral administration to patients with an acid gastric milieu (28). Patients with AIDS are relatively achlorhydric, and ketoconazole absorption is markedly depleted in them. Further, drugs such as rifampin and other cytochrome p-450 enzyme inducers can accelerate degradation of the drug such that it is undetectable. These problems, and the lack of clinical experience in cryptococcal meningitis, coupled with the very high doses needed to treat coccidoidal meningitis, and the high failure rates seen in histoplasmosis (in the setting of AIDS) combined to make ketoconazole a poor choice for patients with AIDS (29). Further, ketoconazole has more gastrointestinal intolerance than the newer triazoles, and when well absorbed it can suppress adrenal function, which may be already depressed in patients with histoplasmosis, tuberculosis, or cytomegalovirus infection. We use ketoconazole minimally in patients with HIV infection.

Of the major antifungal triazoles, SCH39304 was perhaps the most potent in animal studies, and was highly effective in initial clinical studies (30). However, the discovery of animal carcinogenicity caused its termination from clinical studies. Saperconazole also looked very potent in animals, but ovarian tumors in rodent suggested that it too might be discontinued. However, these may be species specific, and clinical studies are resumed at this time. These developments leave two major triazoles in clinical use. Fluconazole has the advantages of water solubility (permitting IV administration) and excellent tissue penetration, and renal excretion, permitting evaluation for urinary tract infections (28). It also may be less susceptible to p-450 enzyme inducers than itraconazole. Itraconazole requires intragastric acid, and is hepatically degraded, which are potential disadvantages (31). However, a new cyclodextrinoral formation may avoid some of the absorption problems and provide higher blood levels, though intravenous dosing is not yet possible (32). The advantages of itraconazole lie in its excellent potency against all of the agents covered by fluconazole and also a much larger experience with agents covered by fluconazole and a much larger experience with Histoplasma capsulatu, against which it is extremely effective (Reference 33, Wheat LJ, unpublished observations for the AIDS Clinical Trials Group). However, Denning et al. (34) have found itraconazole relatively less potent in patients with aspergillosis in the setting of AIDS than in other patients (34). Itraconazole is also effective against Aspergillus and perhaps has greater potency against Sporotrich sscenckii (35). There is also some experience with the less common pathogens associated with HIV infection, including the phaeohypho-

Recommendations for Specific Mycoses

Candidiasis

As shown in Table 1, the severity of illness correlates closely with the immunologic status of the host. The most common forms are oropharyngeal and esophageal; vaginal disease appears less frequently associated with immune defect.

Disseminated candidiasis is rare, in one series seen in only 13 of 903 patients with AIDS (37). This was confirmed in a study of 446 cases, in which 28 fungemias were diagnosed, but only four blood cultures, all done in patients near death, yielded useful diagnostic information (38). Candidemia generally occurs as a complication of prolonged catheterization or in patients neutropenic in the last phases of disease (37).

For mild forms of oropharyngeal thrush clotrimazole at 10 mg five times per day is commonly used. For more extensive disease fluconazole at 50 to 100 mg per day is used (39-40). Some clinicians favor ketoconazole but problems with gastrointestinal tolerance and poor absorption have made this unattractive to me.

Remission rates for fluconazole, at >80%, appear to be similar or superior to clotrimazole, but there is a more rapid recolonization (and relapse) in patients treated with clotrimazole. In a small series of 36 patients Koletar et al. (39) found fluconazole to be 100% efficacious in thrush, vs. only 65% for clotrimazole (39). Fluconazole is clearly more effective than ketoconazole in a large study with esophagitis (41). There were 129 endoscopically evaluated patients randomized to ketoconazole 200 mg per day or fluconazole 10 mg per day. Of fluconazole recipients 91% were cured, vs. 52% of ketoconazole recipients (p <0.001). One criticism of that study is that the ketoconazole dose, only 200 mg per day, was too low to be efficacious, but higher doses of ketoconazole approach the cost of fluconazole, losing one advantage, and are less well tolerated. Fluconazole treatment should be probably 100 mg/day minimally, and 200 mg per day may be more effective. How long to treat is unclear. Some treat only until the disease is suppressed, which may be 4 or 5 days to a few weeks. One small report of 23 patients documented favorable responses to a single 150 mg dose of fluconazole with five relapses at 3 weeks post treatment, and another four relapses at 42 days (42).

The experience with itraconazole is quite small. The dose is 50 to 400 mg per day, depending on severity of illness. Failures and relapses will undoubtedly become larger problems. There is some evidence that relapses are caused by new isolates (43). Whether it is these new
isolates or persistent “educated” isolates, in the past few years there has been increasing informal experience with patients failing both clotrimazole and fluconazole. The former may relate to factors of drug penetration into involved tissues, but the latter appears to be increasing drug resistance. Fluconazole resistance has emerged in increasing numbers of laboratory isolates (Rinaldi M, personal communication). Because pretreatment isolates are generally not available for testing, it is yet unclear whether the failures are mutations to resistance of the original strains, or whether they are new isolates. When resistant isolates extend to esophagitis, severe dysphagia and malnutrition can follow, so the consequences are significant. The in vitro studies and smaller clinical experience with itraconazole do not have resistance emerging yet, but this may be only a matter of lesser use of itraconazole and delays in reporting. Accordingly there persist questions as to whether azole resistance will be limited to fluconazole, how great a problem it will be, and whether moderate degrees of resistance will cross to other azoles in the future. The nonstandardized in vitro study methods further compound guidance in selection of drugs.

Cryptococcosis

Patients with cryptococcal meningitis outside of the setting of AIDS respond well to amphotericin B and 5FC given for either 4 weeks (uncomplicated patients) or 6 weeks (more complicated patients) and fewer than 30% relapse in the year following treatment (44). Cryptococcus tends to be more widely disseminated in patients with AIDS than in non-HIV infected patients (33,45). In one series of 68 patients 68% of those cultures had positive cultures of blood, 54% for sputum, 30% of bone marrow, and 57% from urine (46). The prostate appears to be not only a major site for extrameningeal disease, but also a primary site for relapse after treatment with amphotericin B (47); and relapse is a major problem after amphotericin B initial therapy. Initial reports by Kovacs et al. (48) had a failure rate above 60%, with a relapse rate also as high as 60% in those who initially responded to a fixed course of amphotericin B and 5FC (48). Kovacs et al. (48) also noted great problems with myelotoxicity due to 5FC. Chuck and Sande (49), in reviewing their experience with 106 patients, found that 5FC had to be stopped because of toxicity in half of the 49 recipients. Also, 5FC added no apparent survival benefit (49).

Chronic suppression with amphotericin B was then examined in open studies. Zuger et al. (50) confirmed the value of maintenance suppression with amphotericin B (50). Those relapses which occurred appeared to originate from the prostate (51). Relapses were systematically examined in a study by Bozzette et al. (52). Relapse rates were above 30% in patients randomized to placebo after completing a course of AMB+5FC, and were 4% in patients continued on fluconazole prophylaxis. This low relapse rate was confirmed in a large Mycoses Study Group trials of suppression therapy, in which fluconazole recipients (200 mg per day) had 8% relapses or protocol noncompliance, vs. 37% of those randomized to weekly AMB at 1 mg/kg/dose (53). There were also more bacteremias in patients with intravenous catheters placed for long term administration of amphotericin B. Thus chronic suppression with fluconazole at 200 mg per day is the regimen of choice for both efficacy and tolerance. There is now ongoing a trial comparing itraconazole (200 mg per day) with fluconazole for chronic suppression.

For primary cryptococcal meningitis the choices are less clear. As recently as 1988, Dismukes (54) recommended amphotericin B as primary therapy for cryptococcal meningitis (54). At about the same time as this recommendation, others were reporting responses in over half of the patients given fluconazole at 200-400 mg per day (55-57). The first comparison of amphotericin B and fluconazole was done in a small study by Larsen et al. (58), in which 6 patients were randomized to high dose AMB (0.7 mg/kg/day for 1 week then continued at three times per week) and 5FC (150 mg/kg/day) vs. fluconazole (400 mg per day) found 0/6 AMB/5FC failures vs. 8/14 failures (persistent positive cultures or clinical failures) on fluconazole (58).

The difference was significant but the study was so small as to have little power. A much larger study in which fluconazole (200 to 400 mg per day) was compared with a lower dose of AMB (minimum 0.3 mg/kg/day, usually without accompanying 5FC) had only 34% of fluconazole recipients and 40% of AMB recipients culture negative in the cerebrospinal fluid at 10 weeks (59). Of the culture positive patients at 10 weeks, 27% of the amphotericin B recipients and 34% of the fluconazole recipients had positive cerebrospinal fluid cultures but were clinically improved. These were called “quiescent” patients and were grouped as failures, but as followup was terminated at that point, it is not known whether they would have eventually worsened clinically or converted to negative cultures. Additionally, deaths in the first 2 weeks among fluconazole recipients (15%) were more commonly seen than in AMB recipients (59) and the cerebrospinal fluid cultured turned negative more rapidly in AMB recipients than fluconazole recipients. However, the differences were not statistically significant. In this study, pretreatment factors predicting early death included cerebrospinal fluid antigen titer >1:1024 (p=0.01) and fewer than 20 leukocytes per mm³ of cerebrospinal fluid.

Other regimens for treatment of cryptococcal meningitis are under consideration. Combined fluconazole/flucytosine is a regimen which offers an all oral therapy without nephrotoxicity, and in a small pilot study appears promising (27). In addition to fluconazole there has been some interest in itraconazole. The drug does not appear in cerebrospinal fluid, but it is efficacious in rabbits with
Histoplasmosis in non-AIDS patients responds well to amphotericin B, ketoconazole, or itraconazole (62-65). Patients with disseminated histoplasmosis in the setting of AIDS also respond well to histoplasmosis, with over 80% remissions (11). Patients respond frequently within 2 weeks of initiation of amphotericin B, with rapid resolution of fever, weight gain, and return of sense of well being. In addition to clinical response, histoplasma capsular polysaccharide antigen titers can be used for both diagnosis and assessing response to treatment and in predicting later relapse (66). However, if amphotericin B is discontinued many patients relapse within the ensuing months, and as with Cryptococcus, chronic suppression is necessary (50,52-53,66-68). As recently reported in a large experience, suppression with amphotericin B can be accomplished readily, but the morbidity of weekly amphotericin E is considerable, in addition to the complications associated with long term intravenous catheter placement. Amphotericin B is not my drug of choice for histoplasmosis in the setting of AIDS.

Itraconazole has been used for both initial treatment and as suppression therapy, and in neither case is the drug very satisfactory. With failures and relapses exceeding 50% each, a small experience with ketoconazole has not been further developed (29).

A small but positive experience with eight of nine patients responding to itraconazole was published by Graybill (67). This led to a much larger study by the ACTG, in which itraconazole was given to patients with both primary infection, and for suppression after an induction course of amphotericin B. The drug was given initially at 600 mg per day, and then continued for suppression at 400 mg per day (Wheat JL, unpublished observations). Itraconazole has been extremely effective in treatment of histoplasmosis, with above 80% responses, even in patients who were quite ill when they started the drug. Given its excellent tolerance and high efficacy, itraconazole is recommended as the drug of choice for histoplasmosis in the setting of AIDS. Drug should be continued indefinitely.

There has also been a largely anecdotal and unpublished series of patients treatment with fluconazole. One's impression is that fluconazole given in low doses is not very effective, but at 400 mg per day fluconazole is also quite effective in histoplasmosis. Much of the "evidence" has not been submitted to peer-reviewed publications, and the role of fluconazole vs. itraconazole is not clearly elucidated.

Coccidioidomycosis

Coccidioidomycosis tends to present rather late in the course of HIV infection, with CD4 cell count similar to or below 200 (15,69-70). The disease may take a focal form, such as meningitis or bone/joint disease, or a more widely disseminated one associated with diffuse pulmonary infiltrates. The lower the CD4 count, the more diffuse and widespread the disease.

Treatment for coccidioidomycosis has been varied, with a number of patients receiving amphotericin B, others ketoconazole, and far fewer either itraconazole or fluconazole (15,69). In one study of 14 patients with meningitis, 55% of 9 patients treated with amphotericin B or ketoconazole died, vs. none of 5 treated with fluconazole (71). Coccidioidal meningitis appears to respond well, either with or without concurrent HIV infection, to fluconazole at 400 mg per day (68,70-72). However, the mortality for all forms of coccidioidomycosis in one large study of 77 patients was 43%, and it was not clear that any drug was consistently superior (69). In particular, diffuse pulmonary disease had a mortality of 60%. Our impression is that coccidioidomycosis associated with AIDS may respond initially to fluconazole, amphotericin B, or ketoconazole, but that it relapses, and may do so explosively. For 18 patients with reticulonodular disease given amphotericin B, 70% died, with a median survival of 1 month (15). Thus there is no clear drug of choice.

Penicilliosis

Penicillium marneffei infects residents (or emigrants from) predominantly of southeast Asia (19). Given the dramatic increase of HIV infection, especially in women, and the tendency for certain groups of businessmen to "holiday" in endemic areas, one must consider this a real
risk for the traveler to Thailand and its environs. The disease is slowly progressive, and responds to amphotericin B and azoles, to which it is broadly susceptible (17-19).

Aspergillosis

Aspergillus may colonize the respiratory tract in up to 10% of patients with AIDS, but of these only about 10% develop invasive disease (20). The majority of such patients develop pulmonary disease (21,31). The lungs were the sole site of disease in 18 of 37 patients in one series (21). The brain was also invaded in five of these patients. Most patients ultimately failed therapy. Aspergillosis was thought initially to be a disease of the late AIDS patient with leukopenia, and to depend more on neutropenia than the depression of cell mediated immunity (20). Denning et al. (34) reported a discouraging experience with 13 AIDS patients who had pulmonary aspergillosis (34). Even though patients were treated aggressively, most went on to die of progressive disease. Denning et al. report "responses" in 9 of 13 patients, but these are generally transient. Ten of their patients died, with a median survival of only 3 months after the diagnosis. We have treated also two patients with disseminated disease; one patient with sinusitis of the maxilla progressed despite decompression, high dose amphotericin B, SCH39304, and itraconazole therapy. Another with sinusitis also succumbed to aspergillosis despite aggressive antifungal therapy. Therefore, while amphotericin B or itraconazole may be utilized, the overall response for invasive aspergillosis is poor in patients with AIDS, and novel approaches are needed.

Other Fungal Pathogens

Trichosporon beigelli is a common commensal of the anal mucosa, and a rare pathogen of AIDS patients. It has caused at least one case of catheter sepsis (73). Even mushroom fungi can cause invasive sinusitis, and fortunately one patient reported responded well to amphotericin B (74).

Zygomycetes and phaeohyphomycetes occasionally infect patients with AIDS (17). There are insufficient numbers of patients to make any recommendations other than "usual" therapy. In the case of zygomycetes, this is high dose (1 to 1.5 mg/kg) amphotericin B and debridement if at all possible. In the case of phaeohyphomycetes this may be amphotericin B or itraconazole (36). I would be inclined to use itraconazole, which has about a two thirds response rate, even in patients who have failed amphotericin B.

References


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