Riches Usher Dilemmas: Antifungal Therapy in Invasive Aspergillosis

Pranatharthi Chandrasekar

Department of Internal Medicine, Wayne State University, Detroit, MI

Correspondence and reprint requests: Pranatharthi Chandrasekar, MD, Harper University Hospital, S Hudson Building, 3990 John R, Detroit, Michigan 48201 (e-mail: pchandrasekar@med.wayne.edu).

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INTRODUCTION

Despite the availability of potent new antifungal agents, systemic fungal infections are on the rise and are associated with significant mortality. Candida and Aspergillus species are the major fungal pathogens; although deaths from candidiasis have declined since the late 1980s, those due to invasive aspergillosis (IA) are increasing [1-3]. Fifty to ninety percent of patients with IA die despite therapy. Susceptible populations are hospitalized patients and immunocompromised hosts, such as cancer patients and transplant recipients.

The clinical outcome of patients with IA is largely dictated by the host immune status [4]. Two lines of host defense against aspergillus are resident macrophages and phagocytes [5,6]. Impaired monocyte/macrophage function and neutropenia lasting 3 weeks or longer adversely affect the prognosis, despite appropriate antifungal therapy. In recent years, in the setting of stem cell transplantation, IA has become infrequent during pre-engraftment because peripheral blood as the stem cell source and the use of growth factors have reduced the duration of neutropenia. IA is now seen most commonly during postengraftment in the setting of graft-versus-host disease (GVHD) in allogeneic recipients; both GVHD and its treatment (eg, steroids) contribute to a delay in immune reconstitution, and the prognosis in this cohort with IA is poor [7,8]. At present, regardless of the antifungal drug(s) used, a considerable number of transplant recipients with IA succumb to the infection in view of their persistently compromised immune status.

Successful management of IA consists of a decrease in immunosuppression, optimal antifungal therapy, and immune restoration (eg, correction of neutropenia with growth factors). The antifungal drugs available for therapy of IA are listed in Table 1.

Amphotericin B, the mainstay of treatment of IA for many decades, is associated with disappointing outcomes (approximately one third survive) and considerable toxicity [9,10]. There has been a recent surge in the development of new antifungal drugs, including new formulations of older drugs, new drugs in the older azole class, and entirely new classes of drugs with novel targets. In the polyene class, lipid forms of amphotericin B (LipAmB) are clearly less nephrotoxic than conventional amphotericin B deoxycholate (AmBD). Head-to-head comparative studies of AmBD and LipAmB are scarce. In the only comparative study of amphotericin B colloidal dispersion (ABCD) versus AmBD for treatment of IA, in a limited number of patients (n = 174), nephrotoxicity was less with ABCD (25% versus 49%), but efficacies were similar (52% and 51%) [11]. Reviewing several open-label studies, Ostrosky-Zeichner et al. [12] found better treatment response rates with LipAmB. The aggregate efficacy estimates for LipAmB and AmBD were 49% and 32%, respectively. They concluded that the superior safety profile of LipAmB and at least equivalent efficacy make these drugs preferable to AmBD for therapy of IA. Modestly sized open-label trials and databases from compassionate use with amphotericin B lipid complex or liposomal amphotericin B against IA in different populations suggest a 40% to 50% clinical response rate [13-16]. Among LipAmB, ABCD has fallen out of favor in view of its high rate of infusional toxicities [11]. An open-label study with ABCD for the prevention of fungal infection in neutropenic patients had to be stopped prematurely after severe infusion-related
side effects [17]. Data suggest that liposomal amphotericin B may have reduced nephrotoxicity and better tolerability during infusion, and dose escalations of the drug are feasible in serious infections [18,19]; however, it is difficult to choose between the 2 lipid forms in the absence of data from direct comparative trials for therapy of IA. Because newer agents are becoming available, it is unlikely that a prospective trial comparing the 2 drugs will ever be conducted.

Voriconazole has fared significantly better than AmBD in the treatment of IA. Herbrecht et al. [20] demonstrated the safety and superiority of voriconazole over AmBD as primary therapy of IA in a randomized, unblinded trial. At week 12, good clinical response was noted in 53% of voriconazole recipients and 32% of AmBD recipients. Also, improved survival (71% versus 58%) occurred in the voriconazole-treated group. With this prospectively collected large database, voriconazole is now considered the drug of choice for initial therapy of IA. It should be noted that voriconazole was compared with AmBD and not LipAmB. In the same study, clinical responses with voriconazole and AmBD among allogeneic stem cell recipients were 32% and 13%, respectively, thus underscoring the significance of host immune status for a good outcome.

Itraconazole, with good activity against aspergillus, is available as a capsule, an oral suspension, and an intravenous formulation. The capsule formulation has suboptimal bioavailability and is hence not recommended for serious fungal infections. Although available for treatment of aspergillosis since 1990, the drug has not undergone rigorous evaluation. A retrospective survey of clinical practice showed 58% complete or partial responses with itraconazole capsule as primary therapy of IA in 58 patients, most of whom were not severely immunocompromised [9]. Previous open-label studies have shown comparable response rates with itraconazole capsules and AmBD [21,22]. A regimen of intravenous itraconazole for 2 weeks followed by the oral formulation for 12 weeks was evaluated in 31 patients with pulmonary IA [23]. Forty-eight percent (15 of 31 patients) had a complete or partial response. Because large, randomized studies with itraconazole for therapy of IA are not available, this drug is not recommended as initial therapy.

Caspofungin does not have cidal activity against aspergillus and has not been evaluated for initial therapy of IA. It is approved for use in IA in patients intolerant of or who have infections refractory to other antiaspergillus drugs. When caspofungin was used as salvage therapy, 40 (45%) of 90 patients had a complete or partial response [24,25].

Hence, at present, voriconazole is the drug of choice for initial therapy of IA. LipAmB has not been evaluated as well as voriconazole, and on the basis of several open-label studies, LipAmB may be considered as a secondary option for initial therapy when voriconazole cannot be used. Caspofungin is not a drug for initial therapy of IA. Investigational drug classes include allylamines, nikkomycins, sordarins, and pradimicins.

Expansion in the antifungal armamentarium has ushered in several management issues for which evidence-based answers are lacking. Table 2 lists several relevant questions; some of the critical questions are discussed.

### VORICONAZOLE VERSUS LIPAMB FOR PROVEN OR SUSPECTED IA

If IA is proven or probable, therapy with voriconazole is preferred. In certain clinical situations, however, voriconazole may not be the optimal choice. Table 3 provides guidelines for choosing between voriconazole and LipAmB in different clinical scenarios. As antimold azole prophylaxis (itraconazole or

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**Table 1. Drugs for Invasive Aspergillosis**

<table>
<thead>
<tr>
<th>Polyenes</th>
<th>Amphotericin B deoxycholate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B lipid forms</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B lipid complex; Abelcet</td>
<td></td>
</tr>
<tr>
<td>Liposomal amphotericin B; Ambisome</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion; Amphocil</td>
<td></td>
</tr>
<tr>
<td>Azoles</td>
<td>Voriconazole; V-fend</td>
</tr>
<tr>
<td></td>
<td>Itraconazole; Sporanox</td>
</tr>
<tr>
<td></td>
<td>Posaconazole (not FDA licensed)</td>
</tr>
<tr>
<td></td>
<td>Ravuconazole (not FDA licensed)</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>Caspofungin; Cancidas</td>
</tr>
<tr>
<td></td>
<td>Micafungin (not FDA licensed)</td>
</tr>
<tr>
<td></td>
<td>Anidulafungin (not FDA licensed)</td>
</tr>
</tbody>
</table>

FDA indicates Food and Drug Administration.

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**Table 2. Clinical Questions Regarding Antifungal Therapy of IA**

1. What is the best drug for initial therapy for IA under different circumstances?
2. What is the role of combination of antifungal agents?
   - Which drugs to combine?
   - When to use a combination?
3. How to monitor therapy?
4. In patients showing improvement, what is the role of step-down therapy?
5. In patients not showing improvement, what is the role of changing therapy to a different regimen?
6. Adding other agents to an existing regimen?
7. Increasing the dose of existing drugs?
8. What is the role of adjunct therapy?
   - Immunomodulation–interleukins, colony-stimulating factors, interferons, granulocyte transfusions, or vaccines
   - Surgery
9. What should be the antifungal strategy for those with a history of IA who are about to become immunosuppressed (eg, awaiting transplantation or cancer chemotherapy)?
When histopathology of the biopsy specimen reveals hyphal forms suggestive of mold infection, aspergillosis and zygomycosis are the primary considerations; according to morphology, the pathogen needs to be identified before the empiric drug choice is made because zygomycetes are voriconazole resistant. Both aspergillosis and zygomycosis have similar clinical presentations, and, not infrequently, the histology cannot distinguish the 2 pathogens. Informing the pathologist about the possibility of zygomycosis is helpful because the growth in culture is improved if the tissue is not finely sliced during specimen processing. If zygomycetes and aspergillus are strong possibilities, then LipAmB is appropriate as empiric therapy or prophylaxis. Thus, in the setting of mold-active azole prophylaxis, treatment of IA or other mold infections with an azole is not optimal; in such patients, LipAmB would be appropriate.

Table 3. Therapy of Suspected or Proven Aspergillosis: Choosing between Voriconazole and LipAmB

<table>
<thead>
<tr>
<th>Variable</th>
<th>Voriconazole</th>
<th>LipAmB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakthrough fungal infection (while receiving antifungal azole prophylaxis)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyphae on histopathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zygomycetes</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>Fusarium</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>Scedosporium</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Culture†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspergillus terreus</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Non-terreus Aspergillus sp.</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Invasive aspergillosis with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal renal status</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Yes†</td>
<td>No</td>
</tr>
<tr>
<td>Concomitant nephrotaxins</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*High-dose LipAmB. †Oral voriconazole.

Voriconazole) becomes commonplace, breakthrough aspergillosis with potential azole resistance or breakthrough zygomycosis may occur [26–29]. Several institutions have reported breakthrough zygomycosis and other fungal infections in stem cell recipients receiving voriconazole as empiric therapy or prophylaxis. Thus, in the setting of mold-active azole prophylaxis, treatment of IA or other mold infections with an azole is not optimal; in such patients, LipAmB would be appropriate.

The fact that only about 55% patients with IA have a complete or partial response with voriconazole underscores the clear need for treatment approaches other than monotherapy. What about simultaneous use of 2 or more agents? Distinction needs to be made between sequential therapy (one drug replacing another) and combination therapy (use of 2 or more drugs). With the latter strategy, 2 or more drugs may be started at the same time as the initial therapy or an additional drug or drugs may be added in a serial fashion to a failing monotherapy regimen. Previous in vitro/animal model studies with amphotericin B/fluconazole, amphotericin B/rifampin, and azole/rifampin combinations have produced conflicting data [35,36]. Results of in vitro studies or animal model data with the combination of amphotericin B plus azole have not been favorable [37–40], although this combination has frequently been used in desperate situations. The combination is no longer considered antagonistic, but no clear advantage over therapy with single agent has been shown. However, when an echinocandin is combined with an azole or amphotericin B, synergy is consistently noted both in vitro and in animal models [41–44]. Also, successfully treated cases with a combination of caspofungin and itraconazole or LipAmB have been reported [45–48]. Marr et al. [49] showed a significant reduction in mortality with caspofungin plus voriconazole as compared with voriconazole alone in a limited retrospective study of patients with aspergillosis who experienced failure of initial therapy with amphotericin B formulations. Overall, although the data for combination of amphotericin B plus azole are not encouraging, echinocandin-based combinations with an azole or polyene seem more promising.

With supportive clinical data lacking, combination therapy should not be the initial approach for all patients with IA. Because combination therapy is expensive, requires close monitoring (liver function tests [LFTs], calcineurin levels, and so on), and may turn out to be detrimental, this aggressive approach consisting of an echinocandin-based regimen may be reserved for situations with an anticipated poor outcome, such as a persistent, profound neutropenic state, severe GVHD/high-dose corticosteroid use, and disseminated or cerebral aspergillosis. Con-
trolled clinical trials evaluating the efficacy of combination therapy over monotherapy are urgently needed.

**ASSESSMENT OF TREATMENT EFFICACY**

Clinical and radiologic changes have been the main tools to assess therapy. Gradual resolution of clinical symptoms and signs is anticipated with eradication of infection. Radiograph appearance may worsen initially before improvement; later, the abnormalities may remain unchanged once tissue scarring occurs. Recently, a noninvasive test, the serum aspergillus galactomannan (GM) assay, has become available for diagnosis [50,51]. The sensitivity and specificity of the test are 81% and 89%, respectively. Numerous factors influence the performance of this assay, including biological factors, site of infection, Aspergillus species, underlying condition/immunosuppression, prior exposure to antifungal drugs, and presence of GM antibodies [52]. Consequently, both false-positive and false-negative results are not uncommon. Notably, the antibiotic piperacillin/tazobactam (Zosyn; Lederle, Pearl River, NY) may contain GM antigen, and its concomitant use may produce a false-positive test [53]. Besides diagnosing IA, the GM assay has also been used to monitor disease progression [54]. Serial GM index measurements seem necessary in most studies, and an increase of the GM index >1.0 over baseline during the first week of therapy has predicted treatment failure. Increasing GM values suggest treatment failure, whereas decreasing GM corresponds with a complete or partial clinical response. At present, more clinical experience is needed with the aspergillus GM assay to reliably use the test for diagnostic or prognostic purposes. Also, the serum glucan assay was recently licensed for diagnosis, and the polymerase chain reaction assay is under intense scrutiny [55,56]. Reliable data are not available for use of these tests during therapy of IA.

**THERAPY IN PATIENTS SHOWING IMPROVEMENT**

For optimal outcome, appropriate antifungal drugs combined with an improvement in host immune status are essential. Defervescence and abatement of symptoms within 1 week of initial therapy suggest clinical improvement. Radiographic changes may seem worsened during the first several days of therapy before showing improvement. High-resolution computed tomography is helpful to observe the gradual diminution or disappearance of nodular or cavitary lesions. For patients showing clinical improvement, therapy may be changed from intravenous voriconazole to the more convenient oral formulation of the drug. The route of administration may be switched from intravenous to oral within a few days of treatment initiation. In the study by Herbrecht et al. [20], the switch from the intravenous to oral route occurred early, after a median of 10 days. Oral voriconazole has excellent bioavailability and, in comparison with the intravenous form, is considerably less expensive. Initiating therapy with the oral formulation of voriconazole may be appropriate in less critically ill patients with intact gastrointestinal absorption. If therapy was begun with LipAmB, then treatment may be switched to oral itraconazole or voriconazole upon clinical improvement. Completion of therapy with an azole after initial treatment with a polyene has become routine and seems safe. Although there is a theoretical concern of polyene/azole antagonism due to the common target site of ergosterol, sequential therapy with amphotericin B followed by itraconazole or voriconazole has been found to be effective [9,57]. Maintenance of adequate serum levels is a significant concern, particularly with oral itraconazole. For this reason, the capsule formulation of itraconazole is to be avoided in serious infections, and standard doses of intravenous itraconazole or oral suspensions are acceptable. The latter formulations in routine doses produce adequate serum levels [58]. Routine measurements of voriconazole levels with either oral or intravenous formulations are not necessary. Symptoms of nausea, vomiting, and diarrhea due to chemotherapy, radiation, or GVHD may preclude oral therapy. Laboratory tests for monitoring therapy include complete blood counts, renal status, and LFTs. LFT abnormalities may be due to the fungal infection, the antifungal drug or other drugs, other opportunistic viral infections, or GVHD. Identifying the exact etiology of abnormal LFTs may be difficult; thus, liver biopsy may occasionally be required.

The duration of therapy is determined by the clinical and radiologic response and the patient’s underlying immune status. In general, therapy is administered for at least 3 to 4 months.

**THERAPY IN PATIENTS SHOWING DETERIORATION**

Clinical deterioration, despite therapy, may be a result of impaired host factors, the pathogen, or the drug [59]. The importance of an intact immune status for a good outcome cannot be overemphasized. Aspergillus may be present in large numbers, overwhelming the antimicrobial agent, or may be drug resistant. Aspergillus terreus is inherently resistant to polyenes in vitro, and poor clinical response has been documented [31,33]. Resistance (primary or acquired) to polyenes among non-terreus Aspergillus species has been extremely rare, whereas in vitro/in vivo resistance to triazoles, though uncommon, has been reported [60-67]. The mechanism of resistance to vori-
conazole in a clinical isolate has been elucidated [66]. With increasing use of triazoles for prophylaxis or therapy, the emergence of azole-resistant aspergillus or breakthrough zygomycetes infections needs close observation [26-29]. Also, antifungal drugs may fail to cure the infection because of inappropriate dose, fungistatic activity, poor absorption/distribution and metabolism, or drug interactions. With more drugs available, clinicians may feel tempted to modify therapy sooner than before. All of this needs careful consideration before a therapeutic modification is made.

Treatment modifications in patients with progressive IA on monotherapy include switching from one drug to another (sequential therapy), adding 1 or more drugs to an existing drug, or increasing the dose of drug. As with combination therapy, there are no convincing clinical data to support the use of sequential therapy. Voriconazole has been used with reasonably good results (approximately 50% response) as salvage therapy in most patients initially treated with amphotericin B [57]. At present, however, because voriconazole is commonly used as initial therapy, progressive IA may occur despite the azole. In such cases, the patients could theoretically be at a higher risk for treatment failure with a polyene because the prior azole exposure may have depleted the common target (ie, ergosterol) [68]. No clinical study, thus far, has implicated prior azole exposure (as prophylaxis or therapy) as a cause for subsequent failure with a polyene, but such patients may need close observation. Echinocandins have been used in a sequential fashion with encouraging results. The response rate with caspofungin as salvage therapy in refractory IA was 40%. A 22% to 28% response rate was observed when micafungin was added to a failing regimen of LipAmB [69]. In a retrospective study of salvage therapy with voriconazole or voriconazole plus caspofungin, the survival rate was 35% and 65%, respectively [49].

Another strategy during progressive IA is to increase the dose of drug. The dose of LipAmB may safely be increased from 5 mg/kg to higher doses [19,70], and, likewise, the dose of caspofungin may safely be increased; whether higher doses are more effective is not clear.

ADJUNCT THERAPY

In the compromised host with IA, immune enhancement with interleukins, colony-stimulating factors, and γ-interferon are adjunct strategies [34]. Although supportive data from in vitro and murine model studies are available, clinical evidence for the use of such expensive agents is lacking. A European Organization for Research and Treatment of Cancer multicenter prospective survey involving 20 hospitals in 8 countries concluded that the use of growth factors did not influence outcome in patients with IA and underlying hemologic malignancies [71]. Thus, routine use of these agents is not recommended. Likewise, an absence of clinical evidence negates the routine use of white blood cell transfusion in patients with IA.

Surgical resection may play an important adjunct role in patients with hemoptysis or in those with lesions close to large blood vessels, threatening hemorrhage. Surgery is likely to be successful with solitary and easily accessible lesions in patients who are surgical candidates. Caillot et al. [72] documented an 84% cure rate with a combination of medical and surgical therapy in neutropenic patients with IA. However, surgical resection may not be feasible in many patients. At present, the role of surgery needs to be individualized. Surgery alone, however, is not adequate and must always be combined with medical therapy.

SECONDARY PROPHYLAXIS

Deep-seated foci of IA often remain after treatment, and reactivation of IA during a new neutropenic episode and during stem cell transplantation is estimated to be 30% to 50% [73]. In the past, prior IA was considered a major contraindication for stem cell transplantation; at present, this opinion is changing [74]. In a retrospective study of 48 stem cell recipients with prior IA, the risk of aspergillus relapse was 33%, and the death rate among those with relapsed IA was 88% [75]. The study showed that patients receiving secondary prophylaxis with absorbable or intravenous antifungal drugs had fewer relapses of IA than those who did not receive prophylaxis. There are no prospective studies of secondary prophylaxis in cancer patients or transplant recipients with prior IA. In a small study of 11 leukemic patients with previous aspergillosis (n = 10) or candidiasis (n = 2), voriconazole was administered as prophylaxis for 44 to 245 days during transplantation or consolidation chemotherapy; none had relapse of fungal infection [73]. Given the poor outcome in patients with IA, it is widely accepted to administer antifungal chemoprophylaxis to patients with prior IA who are about to become neutropenic for a prolonged period or who are about to undergo stem cell transplantation.

CONCLUSION

In summary, with the arrival of new drugs belonging to old and new classes, there is renewed optimism in the management of IA. Concomitantly, several questions have arisen. These issues are not just academic but are of increasing clinical importance, because more than half of patients with IA succumb to
this infection. Appropriate clinical data in the management of aspergillosis are urgently needed to practice evidence-based medicine. However, relevant data are difficult to generate with rapidly changing practices in the management of both transplantation and infection. In the absence of such evidence, management practices will continue to vary widely among institutions, frequently at great economic cost and increased patient morbidity.

REFERENCES


