Need for Alternative Trial Designs and Evaluation Strategies for Therapeutic Studies of Invasive Mycoses


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Studies of invasive fungal infections have been and remain difficult to implement. Randomized clinical trials of fungal infections are especially slow and expensive to perform because it is difficult to identify eligible patients in a timely fashion, to prove the presence of the fungal infection in an unequivocal fashion, and to evaluate outcome in a convincing fashion. Because of these challenges, licensing decisions for antifungal agents have to date depended heavily on historical control comparisons and secondary advantages of the new agent. Although the availability of newer and potentially more effective agents makes these approaches less desirable, the fundamental difficulties of trials of invasive fungal infections have not changed. Therefore, there is a need for alternative trial designs and evaluation strategies for therapeutic studies of invasive mycoses, and this article summarizes the possible strategies in this area.

The prospective, randomized, controlled trial is the “gold standard” for compar-
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<td>Aerosolized AmB-D versus placebo</td>
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<td>Initial treatment of fever</td>
<td>Fluconazole versus placebo</td>
<td>843</td>
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(continued)
line (salvage) therapy for invasive aspergillosis was based on data similar to those used for the approval of this indication for ABCD, ABLC, and itraconazole.

The registration approval of antifungal agents has usually relied on suboptimal amounts of clinical data. The 1959 package insert for AmB-D stated, “Clinical evidence indicates that Fungizone is effective against a wider variety of deep mycotic infections than any other antifungal agent now available for use in man. The antibiotic is ineffective against bacteria. Fungizone for Infusion is specifically intended for the treatment of disseminated mycotic infections including coccidioidomycosis, cryptococcosis, disseminated moniliasis, histoplasmosis, and North American blastomycosis” [46]. However, the first randomized clinical trial of AmB-D (a comparison with 2-hydroxystilbamidine for treatment of patients with blastomycosis) enrolled patients during the period of 1960–1969 and was not reported until 1972 [47]. The second randomized trial with this agent was reported in 1979, and it actually compared the use of amphotericin B alone to use of amphotericin B in combination with a second agent [9] for the treatment of patients with cryptococcal meningitis. The next randomized comparisons of amphotericin B with another antifungal agent did not occur until the early studies that compared amphotericin B with fluconazole for treatment of patients with cryptococcal meningitis and candidemia [5, 11].

The lack of comparative trial data is not caused by a lack of desire for such data. Comparative trials of antifungal agents have been difficult to implement for many reasons. First, invasive mycoses are relatively uncommon. Although the HIV epidemic changed this with regard to some forms of candidiasis and cryptococcosis, the widespread use of highly active antiretroviral therapy has since reversed the trend. Some mycoses occur only within limited geographic regions, and others are not seen with any meaningful frequency outside of specific patient populations. By any measure, invasive mycoses occur significantly less frequently than do serious bacterial infections. Second, invasive mycoses most often occur in patients whose health has already been compromised by other illnesses, and these illnesses can significantly confound the interpretation of clinical trial outcomes (e.g., the timing of recovery from neutropenia can be more important than choice of therapy). Third, establishing a firm diagnosis of an invasive mycosis is often difficult. Although the availability of antigen detection systems with high sensitivity and specificity makes the diagnosis of cryptococcal meningitis [48] and disseminated histoplasmosis [49] relatively easy, comparable tools for invasive candidiasis (the most common mycosis in patients without neutropenia in the critical care setting) and invasive aspergillosis (the most common mycosis of adults with cancer who have neutropenia) are still under development. Recent progress in the development of tests for invasive aspergillosis based on the detection of galactomannan release from the fungus are encouraging [50, 51] but these tests are not yet fully understood or widely licensed. Approaches based on other technologies are also possible, but they seem further from clinical fruition (see below).

Unfortunately, the lack of tools that provide a convincing early diagnosis often means that the patient who might have an invasive mycosis might start receiving empirical antifungal therapy before a firm diagnosis has been made. By the time a convincing diagnosis can be made, the amount of antifungal therapy required for the treatment of patients with disseminated mycoses or North American blastomycosis alone to use of amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; L-AmB, liposomal amphotericin B; wk, weeks.

### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Disease</th>
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<th>No. of subjects</th>
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<td>L-AmB (2 doses) versus AmB-D</td>
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<td>[36]</td>
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<td></td>
<td>ABCD versus AmB-D</td>
<td>213</td>
<td>[37]</td>
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<tr>
<td></td>
<td>L-AmB versus ABLC</td>
<td>244</td>
<td>[38]</td>
</tr>
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<td></td>
<td>Fluconazole versus AmB-D</td>
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<td>Systemic fungal infection</td>
<td>AmB-D versus itraconazole</td>
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<td>Fungal infections following liver transplantation</td>
<td>L-AmB versus placebo</td>
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<td>[41]</td>
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<td>Fluconazole versus nystatin</td>
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<td></td>
<td>Fluconazole versus placebo</td>
<td>212</td>
<td>[43]</td>
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**NOTE.** In general, only trials of systemically active agents that enrolled ≥200 patients are shown here; a few smaller trials that are of historical importance or that are among the only trials for a given disease area or drug are also included. ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex; L-AmB, liposomal amphotericin B; wk, weeks.

- a. The study enrolled 120 patients, but only 87 were evaluable.
- b. The study enrolled 174 patients, but only 103 were evaluable.
- c. Unpublished data.
- d. The study enrolled 194 patients, but only 91 were evaluable.
- e. There are many other trials in this area, and these have recently been reviewed [44, 45].
that the patient has received may exceed the limits allowed for entry into the trial. On a conceptual level, this difficulty is not unique to antifungal agents [52]. At present, the approved antifungal agents and our knowledge about how best to use them remain inadequate. There is significant interest in both development of new antifungal agents and exploration of new ways to use old agents. However, answering relevant questions regarding the use of new and old antifungal agents within the context of traditional trial designs may be so difficult, time-consuming, or expensive as to make such study impossible [53–55]. To attempt to summarize the relevant questions, contributing factors, and possible solutions to this problem, a consensus conference was held in July 1997, during the triennial meeting of the International Society for Human and Animal Mycology. The discussion was updated during a follow-up meeting held in May 2000, and this article summarizes the results of those discussions.

**ARE RANDOMIZED, CONCURRENTLY CONTROLLED TRIALS THE ONLY ACCEPTABLE TYPE OF TRIAL?**

Although clinical trials are undertaken for many reasons, most of the motivation for undertaking the time-consuming and expensive task of implementing a comparative trial design in the field of infectious disease research can be summarized as the following: (1) To compare the effectiveness and safety of one therapeutic strategy over another for specific infecting organisms and for specific clinical syndromes; a therapeutic strategy includes the choice of drug, dose of drug, timing of drug initiation, and duration of therapy. (2) To generate data that support registration of new pharmaceutical agents.

Because these 2 goals often overlap and because the pharmaceutical industry funds a significant portion of the studies of new antifungal agents, acceptable trials will usually address both of these goals. However, the information meant to satisfy these 2 goals might be quite different. In particular, the level of evidence needed to obtain registration approval evolves during the course of time. To see this evolution, consider the data that were used in the United States to support licensing of itraconazole and ABLC for use as salvage therapy for invasive aspergillosis. For itraconazole, the pivotal data were drawn from information that demonstrated a 50% response rate in 221 patients who were treated with open-label drugs [56]. Data that demonstrated a 0% response rate among 43 possible control patients who were treated with AmB-D were also presented, but these were patients for whom itraconazole had been requested but who did not receive the drug. Therefore, the patients who received treatment with AmB-D were contemporaneous with those who received itraconazole, but the former tended to be more ill, and the data on these patients were not found helpful. Rather, the licensing of itraconazole for treatment of patients with invasive aspergillosis without a control group was thought to be appropriate because this was the first oral agent available for the management of this disease, its toxicity was low, and 65% of the itraconazole-treated patients had culture-proven or histologically proven disease that was considered unlikely to remit spontaneously. An attempt to directly compare itraconazole with AmB-D in a study of primary therapy for invasive aspergillosis failed because of difficulties with patient accrual [53]—it was difficult to randomize patients to receive therapy with either oral itraconazole or 12 weeks of iv AmB-D for such diverse reasons as problems with maintaining intravenous access, issues of differential toxicity, issues regarding drug interaction, oral bioavailability, patient preference, and physician bias.

In the case of ABLC, licensing as salvage therapy for patients with invasive aspergillosis who had treatment failure with AmB-D was made on the basis of a nonrandomized comparison of ABLC-treated patients with AmB-D-treated patients [57, 58]. All therapy was open label, and the majority of the patients who were treated with ABLC had already received a course of AmB-D therapy. Although the large number of cases permitted an extensive case-matched analysis, differences between the groups remained [58]. In particular, patients who received treatment with ABLC had, by definition, survived long enough to be switched from AmB-D to ABLC, and they were also less seriously ill. However, as with the licensing of itraconazole, other factors were considered. ABLC’s lesser nephrotoxicity, determined on the basis of both the open-label data and on data from an as-yet-unpublished comparative study with amphotericin B for invasive candidiasis [7], combined with salvage data from other studies of mycoses [59] and the fact that ABLC was fundamentally a reformulation of a compound with known activity, played a part.

Therefore, these decisions regarding licensing these agents for use as salvage therapy for invasive aspergillosis were made without data from a prospective, randomized, controlled trial. Instead, a well-reasoned approval decision was based on suggestive but imperfect open-label data that were compared with historical control information and combined with secondary, drug-related factors. In addition, these agents were approved for use as salvage therapy—there has yet to be an agent other than amphotericin B licensed in the United States as primary therapy for invasive aspergillosis. Subsequent approval of ABCD and L-AmB in the United States was based on qualitatively similar data. It is interesting to note that the presence of these agents on the market may raise the standard required for obtaining registration for newer agents. For example, should future studies of salvage therapy require that patient have treatment failure with both a conventional and a lipid-associ-
ated amphotericin B preparation before studies of a new agent are allowed? Would a new, nontoxic, oral agent need to be extensively compared with itraconazole? Although these questions have no definitive answer, and although actual approaches will probably involve use of a generally accepted standard therapy as the comparator, the overall trend of requiring higher-quality data for newer agents is clear.

**Getting the dose right.** Although few randomized comparative studies of antifungal agents have ever been conducted, even fewer dose comparison studies have been performed. In the case of amphotericin B, the therapeutic window is narrow, and most clinicians have elected to give the maximum (or close to the maximum) dose to patients with a life-threatening disease [60–62]. With the advent of lipid-associated amphotericin, a wider therapeutic window was opened. Whereas escalation studies were performed during the early stages of drug development to determine the maximum tolerated dose [63–65], subsequent studies designed to find the best therapeutic dose have been rare. Although 2 studies to compare different doses of L-AmB for treatment of patients with febrile neutropenia have been completed [36, 66], these studies were powered for safety and not for efficacy. The only study to have compared 2 doses of a lipid amphotericin B formulation for treatment of patients with an established mycosis compared 1 mg/kg of L-AmB-D with 4 mg/kg of L-AmB-D for treatment of patients with invasive aspergillosis [2]; however, the study enrolled too few patients to permit strong conclusions about the possible superiority of 1 dose over another. Therefore, there remains uncertainty regarding the optimum dose of any form of amphotericin B for most indications.

In contrast to amphotericin B, the therapeutic window of the currently licensed azoles is wide. In studies of cases of coccidioidomycosis, histoplasmosis, and blastomycosis, ketoconazole at 800 mg per day was generally no more effective than at 400 mg per day, although the higher dosage was associated with more toxicity [17, 19, 67]. Some recent studies of itraconazole and fluconazole have also addressed issues of dose for the management of the endemic mycoses (table 1). These data are limited, and the studies were small [19, 20, 22, 23, 26]. However, they have defined the standard of care for treatment of patients with these mycoses [68, 69]. With regard to therapy for the nonendemic mycoses, Graninger [70] showed in 2 sequential cohorts of ~30 patients each with candidemia caused by *Candida albicans* who were in the intensive care unit that 10 mg/kg fluconazole might be ~25% superior to 5 mg/kg of fluconazole; a recently completed study of patients with candidemia has, as one of its objectives, confirmation of this finding. A dose-escalation study of fluconazole for treatment of serious mould infections in patients with cancer (for which fluconazole is relatively inactive) studied dosages of up to 2 g per day and demonstrated that these high dosages had no clinical benefit and little toxicity at up to 1200 mg per day [71]. Multiple studies of antifungal prophylaxis for neutropenia have been done with dosages that ranged from 50 mg per day to 400 mg per day, with no direct dose comparisons.

Studies that use a range of treatment options can create confusion about optimal therapy. For example, the first large clinical trial of amphotericin B versus fluconazole for the treatment of patients with AIDS who have cryptococcal meningitis had a target amphotericin B dosage of 0.3 mg/kg per day, but the patients actually received an average of 0.4–0.5 mg/kg per day, suggesting a broad range of actual delivered doses. In addition, optional use of flucytosine was permitted for patients who received amphotericin B, and the fluconazole regimen included a dose-escalation clause [11]. Low frequency of culture conversion in both treatment arms of this study, combined with a subgroup analysis that suggested that higher dosages might be more effective [72], prompted the use of higher dosages for both treatment arms of subsequent studies (e.g., amphotericin B 0.7 mg/kg given daily, and fluconazole, 400 mg given daily, in the 1997 study reported by Van der Horst et al. [12]). Because the original study did not address the efficacy of flucytosine, the later study also had to address this issue.

Therefore, for compounds with a wide therapeutic index, dose comparison studies, before or concurrent with large comparative studies, are desirable. Unfortunately, problems of patient accrual and heterogeneity make these trials as difficult to perform as those studies that are needed for initial licensure.

**What are the alternatives to a randomized, controlled trial?** The strengths of a randomized, controlled trial, especially if blinding is possible, are so important that a major effort to perform such a study should generally be undertaken [1, 73]. The principal exception to this rule would occur when a new agent offers an amazing improvement over existing therapies. If, for example, a new therapy seemed to produce 90% cure rates of an otherwise rapidly fatal illness, even open-label studies that verified such a claim in a carefully identified group of patients would likely be acceptable to both clinicians and licensing agencies. In a sense, this is the mechanism by which amphotericin B gained acceptance—other therapies simply had not worked. Because such advances are unfortunately uncommon, the advantage of new therapy is often limited to such factors as cost, ease of administration (both route and frequency), increased activity against less common organisms, and reduced toxicity. Although these latter factors can be significant (e.g., it would be desirable to replace an agent that requires iv administration 4 times per day with 1 that could be taken orally once per day), they are important only if the agent’s efficacy is really similar to that of preexisting agents.
The advantages of randomized, prospective trials are considerable, but it is interesting to note that such studies often have their own flaws. For example, substantial patient subpopulations may remain unstudied because of enrollment issues, secondary factors may be poorly controlled (e.g., catheter management in patients with candidemia), limited data may be generated in studies of less-common species (e.g., species of Candida other than C. albicans), or the use of ambiguous “consensus” response criteria that were not specifically designed for immunocompromised hosts with invasive fungal infections along with intention-to-treat analyses as primary analyses can lead to misinterpretation of study outcomes. In addition, all randomized, prospective trials share the difficulties of high cost, the requirement to use approved drugs as comparators, and the possibility that alternative therapies may develop during the study period should enrollment happen slowly (table 2). Despite these difficulties, prospective, randomized controlled trials remain our most convincing source of data, and we need to work to develop innovative approaches to these trials.

The principal alternative to a randomized controlled trial is an observational (or open-label) trial with a historical control group. Data collection for both groups may either be retrospective or prospective. Although the higher quality of prospectively collected observational data can alleviate the problem of missing data that so often limits analyses of retrospective data, comparisons of therapies are difficult no matter how the data are collected. Failures of the new therapy should be scrutinized carefully, particularly in cases of failure to control the infection (rather than failure for toxicity). In such cases, additional insight may be provided by suitably collected and analyzed pharmacokinetic samples. Use of a concurrent control group helps researchers avoid effects caused by advances in the overall level of medical technology, but biases in selection and differences in underlying disease between patients in the treatment group and those in control groups almost certainly introduce an unavoidable (and often immeasurable) confounding bias that may overwhelm any effect caused by the drug. A critical factor is that patients who are selected for the historical control group may simply be persons who did not live long enough to qualify for the study of the new agent. This fundamental difference is hard to eliminate.

There are few strategies for circumventing the need for a randomized clinical trial. Large surveillance databases can provide some types of information [52], but they are fundamentally just observational data sets and are not currently available for invasive fungal infections. Matched-pair analyses (case-control analyses) have been used in mycology [74–76]. However, matching can control only for known confounding variables. Unknown (or unmeasured) confounding variables may remain. Instrumental variables (variables that influence the choice of treatment but not outcome) are a clever way to adjust for unmeasured confounding variables. As an example of this technique, McClellan et al. [77] explored a large observational Medicare database by using distance from the patient’s home to the nearest hospital as an instrumental variable in an investigation of the impact of cardiac catheterization on outcome of patients with myocardial infarction. Patients who lived near a hospital that used protocols that favored catheterization were found to have demographic characteristics that were essentially identical to those of patients who lived near a hospital that did not perform catheterization. However, the groups had different rates of catheterization, and the authors were thus able to investigate the effect of catheterization on outcome. Although analyses based on instrumental variables have the added advantage of allowing one to look at outcomes for all patients, it is not currently clear how they could be applied to patients with invasive mycoses. However, this idea is intriguing, and applications for instrumental variables should be sought. Meta-analyses can be performed only after randomized trials have been performed. Although one might choose to pool several small randomized trials in an effort to create 1 adequate data set, this merely exposes one to the problems of meta-analysis itself [78]: meta-analyses do not improve the quality of the underlying studies, they depend on the ability to pool the underlying studies (similar baseline characteristics, and so on), they cannot compensate for publication bias (negative studies are less likely to be published), they introduce new types of heterogeneity, and neither primary nor secondary end points (e.g., partial responses) are likely to be defined uniformly across the studies.

**CAN NONTRADITIONAL MARKERS OF DISEASE AND DISEASE-RESPONSE BE USED TO SIMPLIFY ENROLLMENT AND EVALUATION IN TRIALS OF ANTIFUNGAL AGENTS?**

One of the principal challenges for trials of antifungal agents is the difficulty in making a clear diagnosis before any significant amount of empirical therapy has been administered. Clinical findings from fungal infections are often nonspecific, and detailed supporting information is required for a convincing diagnosis. The magnitude of this challenge varies according to fungus. In the case of cryptococcosis, the availability of a good antigen-based diagnostic strategy, combined with the relative ease of recovering the organisms from clinical specimens, has made a large number of trials possible (table 1). Likewise, rapid enrollment into studies of empirical therapy in the persistently febrile patient with neutropenia is possible because the syn-
Table 2. Problems with prospective, randomized, clinical trials of therapies for invasive fungal infections.

<table>
<thead>
<tr>
<th>Problem</th>
<th>Possible solutions</th>
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<tr>
<td>Relative infrequency of disease under study (including problems with rare, specific fungi)</td>
<td>Expanded number of study sites&lt;br&gt;National surveillance networks&lt;br&gt;International cooperation on study regulations&lt;br&gt;Long-term support for studies of these orphan diseases&lt;br&gt;Use of supportive non-culture-based surrogate markers&lt;br&gt;Improve targeting of infected tissue during biopsy by use of high-resolution imaging or metabolic scanning</td>
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<tr>
<td>Difficulties with timely diagnosis</td>
<td>Innovative approaches to extended patent life, marketing exclusivity, or orphan drug regulations</td>
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<tr>
<td>High cost because of slow enrollment and need for many study sites</td>
<td>Innovative approaches by regulatory authorities and the academic community</td>
</tr>
<tr>
<td>Design flaws (e.g., inadequate disease definitions and end points)</td>
<td>Standardized definitions of diseases&lt;br&gt;Better diagnostic tools&lt;br&gt;Prospective standardized response definitions&lt;br&gt;Standardized timing of therapeutic intervention (e.g., in relation to recrudescence fever, radiographic changes, or clinical findings)</td>
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<tr>
<td>Variable spectrum of severity of illness and underlying disease</td>
<td>Stratified randomization&lt;br&gt;Stratified analyses of large cooperative trials</td>
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<tr>
<td>Need to use approved drugs as comparators</td>
<td>Innovative approaches by regulatory authorities and the academic community</td>
</tr>
<tr>
<td>Inadequately trained clinical site personnel</td>
<td>Formal training in design and implementation of clinical trials&lt;br&gt;Ongoing (real-time) data acquisition with active and consistent management of patients by a study oversight team&lt;br&gt;Support for ongoing international cooperative study groups</td>
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</table>

An antifungal trial design is common. In addition, diagnosis of a fungal infection is not required before a patient enrolls in a study, which dramatically simplifies enrollment.

However, the most important proven mycoses in the patient without neutropenia (i.e., invasive candidiasis) and in the patient with neutropenia or the bone marrow transplant recipient (i.e., aspergillosis) remain difficult to study. At present time, the only common and easily diagnosed form of invasive candidiasis is candidemia. Three large randomized trials of therapy for candidemia have now been completed, of which 2 have been published [5, 6] and the third recently closed (Mycoses Study Group Study no. 33). The first study required 40 months to enroll 237 patients from 24 centers [5]. The second enrolled 106 patients from 13 centers during a period of 39 months [6]. The third enrolled 236 patients from 26 centers during a period of 45 months (J. H. R., unpublished data). Collectively, these studies enrolled 2.6 patients per site per year during study periods that totaled >10 years. By comparison, a randomly chosen study that compared the use of 2 antibacterial agents as therapy for serious bacterial infections enrolled 325 patients from 10 centers in 23 months, for a rate of 17 patients per center per year [79].

In studies of both invasive aspergillosis and invasive candidiasis, the difficulty lies in proving quickly enough that a patient has the target disease [81–84]. In the case of invasive aspergillosis, the ability to generate a culture-based diagnosis is severely limited by the need to obtain tissue specimens for meaningful results. Because...
many of the patients at risk have thrombocytopenia, and because the process of obtaining the required tissue is not simple (e.g., biopsy of a lung or brain specimen), diagnoses are quite frequently delayed or incomplete.

This limitation in our ability to document invasive fungal infections has led to nomenclature that assigns a probability to the certainty of diagnosis (e.g., "proven," "probable," and "possible" aspergillosis) on the basis of the validity of diagnostic evidence for infection [88]. These levels of uncertainty of mycoses influence outcome responses in clinical trials. For example, depending on the classification being used, patients with possible aspergillosis often have a more favorable response, possibly because invasive aspergillosis was never present. Therefore, additional tools are needed to further complement our existing diagnostic modalities for candidiasis, aspergillosis, and other deeply invasive mycoses.

The issues involved with making a diagnosis are paralleled by problems with regard to scoring response. It may be difficult to obtain tissue specimens at follow-up for biopsy, or the biopsy may have only limited sensitivity, which would make subsequent evaluation of the patient dependent entirely on indirect clinical measures of disease burden. Unfortunately, resolution of fever and overall clinical improvement are valuable but nonspecific. In particular, fever may persist or recur because of overlapping but unrelated clinical events.

Recent work with non–culture-based methods for the diagnosis and monitoring of these infections is encouraging. In the case of aspergillosis, the combination of high-resolution thoracic CT scan and assay kits that detect the presence of circulating galactomannan seem to have the potential to provide both an early, reasonably specific diagnosis of invasive aspergillosis [50, 89–91] and a measure of response to therapy [92, 93]. Work with other approaches for diagnosis of aspergillosis (e.g., diagnosis based on PCR [94, 95]) requires additional validation. Work with serodiagnostic approaches for detection of candidiasis is not as advanced, but encouraging results of several different assay systems have been reported [96–103]. However, none of the approaches to detection of candidiasis has yet produced the consistent quality of data from multiple centers that has now been reported with the Aspergillus species galactomannan assay systems.

When do these tools become sufficiently accurate and reliable to be used as surrogate markers? For example, are we ready for a trial in which invasive aspergillosis is diagnosed on the basis of a CT scan plus a serodiagnostic result and in which the response to therapy depends upon the normalization of these parameters? As has been required of surrogate markers used in the study of HIV infection [104], have the studies to date of these mycological surrogate markers adequately validated a direct correlation between the marker and a relevant clinical end point? If so, could such surrogate markers be used both as diagnostic tools for enrollment and as measures of outcome? If the majority of the patients in a clinical trial received diagnoses or were evaluated in this manner rather than by use of a culture- or pathology-based approach, would such a trial be acceptable to physicians or regulatory authorities?

Although the answers to these questions are not fully known, it is clear that a consensus is being built that favors the use of the galactomannan-based test for diagnosis of invasive aspergillosis. One example of this is the standardized definitions for invasive fungal infections recently jointly proposed by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group, which have included Aspergillus antigen detection as part of the definition for “probable invasive aspergillosis” [88].

**THE FUTURE OF TRIALS OF ANTIFUNGAL AGENTS**

The problems outlined above are substantial and not entirely resolvable. Randomized clinical trials, for all their faults [73, 105], remain the single best tool known for minimizing bias and generating high-quality data. Because of competition for the small number of available patients, clinical trials with new antifungal agents are only going to become more difficult as new agents are introduced. The increasing availability of good oral agents will further hamper the enrollment of patients into studies of potentially more potent but less convenient iv agents. Performing studies with agents that do not possess both iv and p.o. formulations can also be difficult—this was part of the reason for the premature discontinuation of a study that attempted to compare itraconazole with amphotericin B for treatment of patients with invasive aspergillosis [53].

The conditions in greatest need of management are clearly invasive candidiasis and aspergillosis. Several new
drugs, including entirely new classes of agents, are now entering development. Table 2 lists potential solutions to the issues discussed above. Increasing enrollment is critical. International cooperation on uniform study regulations, the use of uniform disease definitions (such as those recently proposed by a European Organization for Research and Treatment of Cancer-Mycoses Study Group collaboration [88]), and development of surveillance networks would be important steps toward resolution of enrollment-related issues. Appropriate use of improved diagnostic imaging and surrogate markers of infection (e.g., antigens, metabolites, and nucleic acids) could also expand enrollment. Provisions for the use of lipid preparations of amphotericin B (rather than the traditional “gold standard” of deoxycholate amphotericin B) as the comparator in first-line therapy studies would be very valuable. The formidable pharmaceutical resources required for these studies could be recognized through innovative approaches to patent life or marketing exclusivity.

Although randomized trials should be conducted wherever possible, new approaches to study design are also needed. Prospectively designed, historically controlled observational trials are feasible, and criteria for acceptance of such trials can be devised (table 3). For example, a historical comparison group extracted from a recent study [5] was recently used for analysis of an open-label treatment group [106]. The comparison between the groups was excellent (virtually identical enrollment criteria, similar patient age, and similar distribution of underlying disease), in part because the open-label cases were enrolled under a protocol that had sought to mimic the previously published study. However, the lack of detail in the published comparison group limited the quality of the comparison. Highly detailed, publicly available control data sets could be constructed from data from completed trials without compromising the data analysis and control requirements of the trial sponsors. The interdisciplinary collaboration that characterizes work on antiretroviral agents suggests that this is feasible. Acceptance of such data by physicians and regulatory authorities may also be modeled on the approaches used in studies of antiretroviral agents. Recent suggestions that observational trials may generate data comparable in overall accuracy to that from randomized trials [107–109] lend further credence to this strategy.

We believe that future antifungal therapeutic trials would be improved by these measures. Now is the time to initiate a discussion of these ideas. Otherwise, 10 years hence, we may still be wondering whether even our newest drugs really work.

References


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