Antifungal Therapy: Lessons Learned over the Past 27 Years

William E. Dismukes
Department of Medicine, Division of Infectious Diseases, University of Alabama at Birmingham

As principal investigator of the National Institute of Allergy and Infectious Diseases–sponsored Mycoses Study Group for the past 27 years, I have been fortunate to play a role in the many advances in the field of clinical mycology and antifungal therapy. For the Finland lecture, I will briefly discuss the development of the Mycoses Study Group, provide an overview of the currently available antifungal agents, and describe advances and lessons related to the treatment and management of cryptococcal meningitis (the most common form of fungal meningitis), 3 important endemic mycoses (namely, blastomycosis, histoplasmosis, and coccidioidomycosis), candidemia and invasive candidiasis (the most common forms of nosocomial fungal disease), and invasive aspergillosis (the most common form of invasive mould disease). My concluding remarks will address the increasing hurdles and challenges, as well as the rewards, facing investigators who focus on clinical trials.

President Stamm, members and guests of the Society, I am deeply honored to be named the Maxwell Finland lecturer for 2005. As a resident in Internal Medicine at Peter Bent Brigham Hospital and a fellow in Infectious Diseases at the Massachusetts General Hospital in Boston in the 1960s, I had the privilege of meeting Dr. Finland and observing him during lectures and conferences. Dr. Finland was small in stature but a giant in terms of accomplishments and leadership. He was one of the fathers of our discipline of infectious diseases, a leading investigator in the area of clinical pharmacology of antimicrobial agents, an authority on the pneumococcus and its associated diseases, a revered teacher and mentor by his more than 100 fellows at Boston City Hospital and Thorndike Memorial Laboratory, a gifted clinician, and the first president of the Infectious Diseases Society of America [1]. Clearly, each of us with an interest in infectious diseases—whether academician, clinical practitioner, or trainee—owes much to Dr. Finland.

I am also proud to join the distinguished group of previous Finland awardees, including the first, Theodore Woodward, MD, in 1972, and the 2004 honoree, King Homes, MD. In addition, I am especially pleased to be the second Finland awardee whose research career has focused on mycology. The first was John Bennett, MD, my colleague and a longtime leader in our field, who was named the Finland lecturer in 1992.

In this lecture, I have chosen to highlight 10 lessons that provide an overview of my career in clinical investigation related to mycology over the past 27 years. Since the time allotted does not permit me to be all inclusive, I will focus on treatment and prevention issues pertinent to common systemic fungal diseases and will not discuss other strategies, such as prevention and empirical therapy for neutropenic patients with persistent fever.

LESSON 1: BE AT THE RIGHT PLACE
AT THE RIGHT TIME

In 1977, at the urging of several clinical mycologists, the National Institutes of Health (NIH) National Institute of Allergy and Infectious Disease (NIAID) issued a request for a proposal focusing on systemic fungal diseases, especially treatment-related clinical trials. Consequently, a group of us met in the Atlanta airport
to discuss the request for a proposal and to choose the leader of a fungal investigator group. Attendees included John Bennett, Gerry Medoff, Dick Duma, Merle Sande, Harry Gallis, and myself. I was chosen leader—a stroke of good fortune early in my career.

LESSON 2: SEIZE THE OPPORTUNITY

In 1978, the NIAID awarded the first contract to our group of investigators who we labeled the Mycoses Study Group (MSG). Since 1978 to the present, a period of 27 years, the MSG has had continuous NIH funding to provide resources for a Central Administrative Core Unit based at the University of Alabama School of Medicine at Birmingham, a Central Biostatistics Unit, distinctly focused disease or population at-risk study groups with designated principal investigators, an annual meeting, and partial funding for various types of clinical trials or epidemiologic studies. Throughout this entire period, I have been fortunate to be the principal investigator for the MSG. The organizational structure was consistent until 2001, when the latest contract expanded the scope of our work to include studies on nosocomial resistant bacterial pathogens and the name of our group was changed to the Bacteriology and Mycology Study Group. For purposes of this presentation with its emphasis on mycology, I will refer only to the MSG.

Over the past 3 decades, the MSG has initiated 60 large, multiple-site clinical trials (treatment, prophylaxis, and empirical therapy), and completed 40 of these. In addition, numerous secondary substudies have been accomplished, resulting in a total of 150 manuscripts describing both primary and secondary studies. More importantly, the MSG has been the prototype of a unique and successful collaboration between academia, the NIH, and industry. Finally, the MSG structure has nurtured the development of numerous young mycology-focused investigators, including Scott Filler, Peter Pappas, Tom Patterson, Bill Powderly, John Rex, Mike Saag, and Tom Walsh.

LESSON 3: THE NEED FOR CRITERIA AND DEFINITIONS FOR USE IN MYCOLOGY-FOCUSED CLINICAL TRIALS

Prior to the launching of the MSG, no prospective randomized mycology-focused clinical trials had ever been conducted. As a result, in 1980, a group of us (clinical mycologists) developed the original criteria used for the evaluation of responses to antifungal drugs [2]. The next major advance was made a decade later, in 1992, when members of the MSG joined with the Invasive Fungal Infections Group of the European Organization for Research and Treatment of Cancer (EORTC) to develop an international consensus on the optimal diagnostic criteria for the most common invasive fungal infections seen in immunocompromised patients [3]. These criteria, which proposed 3 levels of disease—namely, “proven,” “probable,” and possible”—were intended for use primarily in the context of clinical and/or epidemiology research. The EORTC/MSG criteria, which have served well their purpose, are currently undergoing revision and expansion. More recently, over the past 5 years, 3 sequential forums have focused on specific and controversial issues relating to various aspects of study design, including outcomes, scoring systems, historical controls, etc. Participants have included leading United States and international mycology investigators, plus key representatives from industry and the US Federal Drug Administration; John Bennett has served as moderator of each of these forums [4–6]. These various activities noted above have been highly effective in standardizing criteria for diagnosis and definitions of outcomes for mycology-focused clinical trials and encouraging consistencies in study design from one study to another, thereby facilitating comparison of results between studies.

ANTIFUNGAL DRUGS

Before proceeding with additional lessons, it is important to briefly describe the current status of antifungal drugs and emphasize the progress made in this area, especially over the past 25 years. Figure 1 depicts the principal classes of antifungal agents on the basis of their targeted sites of action within the fungal organism. To date, the most successfully exploited targets are (1) the fungal cytoplasmic membrane and, more specifically, ergosterol, the principal sterol in this membrane; and (2) the rigid fungal cell wall, which is unique to fungi and does not exist within mammalian cells. The 3 major classes of drugs that target ergosterol are (1) polyenes (principally amphotericin B deoxycholate [AMBd; conventional amphotericin B] and the lipid formulations of amphotericin B, which bind to ergosterol), (2) allylamines (principally terbinafine), and (3) azoles. Both the allylamines and the azoles inhibit ergosterol synthesis. Among the first-generation azoles, itraconazole and fluconazole...
are the most utilized drugs and have represented a major advance in antifungal therapy. Voriconazole and posaconazole (not yet licensed in the United States) are second-generation azoles with an expanded spectrum of activity against the pathogenic molds, which are increasingly prevalent in immunocompromised hosts. Among the antifungal agents that target the fungal cell wall, the echinocandins have emerged as the most important class. Echinocandins inhibit the synthesis of glucan, a polysaccharide that, together with chitin, provides integrity and shape to the cell wall. Caspofungin and micafungin (currently licensed), along with anidulafungin (not yet licensed in the United States), are highly active against Candida and Aspergillus species (they have fungicidal activity against all Candida species, including those resistant to fluconazole, and fungistatic activity against Aspergillus species). The limitations of the echinocandin drugs are their availability only as intravenous formulations and their poor activity against other opportunistic pathogens (e.g., Cryptococcus, Fusarium, and Scedosporium species and Zygomycetes).

LESSON 4: CRYPTOCOCCOSIS (ESPECIALLY CRYPTOCOCCAL MENINGITIS) HAS BEEN THE PROTOTYPE SYSTEMIC MYCOSES FOR INITIAL AND SUBSEQUENT CLINICAL TRIALS

Why? Cryptococcal meningitis was a relatively common systemic fungal disease in the pre-AIDS era and has been even more frequent after 1982. In addition, there are excellent markers of disease (India ink, cryptococcal antigen and culture of blood, CSF, and other body fluid/tissue specimens) for both diagnosis and assessment of response to therapy. As a result, the MSG has conducted 6 major clinical studies in patients with cryptococcal meningitis that I would like to discuss in some detail; together they tell a nice story about sequential trial designs and the progressive improvement in clinical outcomes.

In the late 1970s, the first clinical trial ever done by the MSG was also the first prospective, randomized, comparative treatment trial for any systemic fungal disease. Fifty-one patients without AIDS were assigned to receive either low-dose AMBd, 0.4 mg/kg/d, for 10 weeks or a combination regimen of AMBd, 0.3 mg/kg/day, plus high-dose flucytosine, 150 mg/kg/day, for 6 weeks [7]. The combination regimen cured/improved more patients (67% vs. 41%) and was associated with fewer failures/relapses, fewer cases of nephrotoxicity, and more rapid sterilization of CSF. Although this initial trial involved only a small number of patients, the promising results with combination therapy served as the springboard for subsequent trials. The second trial compared the same combination regimen (low-dose AMBd plus high-dose flucytosine) administered for 4 versus 6 weeks, in 191 patients without AIDS [8]. The 6-week regimen was more effective: 85% were cured or improved, versus 75% who were cured or improved for the 4-week regimen. However, significant toxicity was observed in both the 4- and 6-week treatment groups (44% and 43%, respectively); thus, shortening duration of therapy did not reduce toxicity. The third trial evaluated 194 patients with AIDS who had cryptococcal meningitis and compared 2 single-drug treatment regimens (AMBd vs. fluconazole for 10 weeks) [9]. Success was noted in only 40% AMBd recipients and 34% fluconazole recipients, and mortality was the same (18% vs. 14%, respectively). Flucytosine was not used as a comparator drug in this trial, because data from earlier small studies indicated poor tolerance of this drug by patients with AIDS. The poor outcomes in this trial were attributed in part to the severity of illness among patients with AIDS at this early stage of the AIDS epidemic, when HAART was not available, and the multiple comorbidities for many patients.

The disappointing results of these 2 larger trials mandated a different approach to treatment of this disease. Consequently, the MSG, in a joint study with the AIDS Clinical Trials Group, used a 2-step, more complex design and, more importantly, a higher dosage of AMBd (0.7 mg/kg/day) and a lower dosage of flucytosine (100 mg/kg/day) for 381 patients with AIDS with cryptococcal meningitis [10]. Step 1 (induction therapy) compared AMBd plus flucytosine versus AMBd alone for 2 weeks and was followed by step 2 (consolidation therapy), which evaluated fluconazole versus itraconazole for 8 weeks. Step 1 results at 2 weeks showed CSF culture negativity in 60% of AMBd-plus-flucytosine–treated patients and 51% of AMBd alone–treated patients (P = .06). The overall mortality was 5.5%, a reduced mortality rate, compared with regimens used in previous trials. Among step 1 patients, the study drug was stopped in only 2.9% because of toxicity. Step 2 results at 10 weeks showed clinical response in 68% fluconazole recipients and 70% itraconazole recipients. Negative CSF culture results were not significantly different (72% vs. 60%, respectively). Overall mortality for this step was 3.9%—again, there was no difference between the 2 treatment drugs. Multivariate analysis showed that the addition of flucytosine in step 1 plus treatment with fluconazole during step 2 was independently associated with CSF sterilization at 10 weeks.

Because relapse rates in the late 1980s were high (50%–60%), after providing primary therapy to patients with AIDS and cryptococcal meningitis, the MSG next performed 2 trials to evaluate chronic suppressive (maintenance) therapy in patients who had successfully completed primary therapy. The first trial, a joint MSG and AIDS Clinical Trials Group study, compared intravenous AMBd given weekly with oral fluconazole given daily for 12 months [11]. Fluconazole was dramatically more effective (relapse rate, 2% vs. 19%). Moreover, serious drug-related toxicities were significantly more frequent in the AMBd group. These results prompted a second MSG trial to compare efficacy of 2 oral azoles (fluconazole vs. itraconazole) as long-
term suppressive therapy [12]. This study, which was terminated prematurely by the Data Safety and Monitoring Board, demonstrated a highly significant difference in relapse rates (fluconazole, 4%; itraconazole, 23%). In addition, the factor most associated with relapse was whether the patient received fluconosine during the initial 2 weeks of primary therapy.

Observations from other studies have also impacted management of patients with AIDS with this disease. First, mortality is highly associated with elevated intracranial pressure. In an MSG study, Graybill and coinvestigators [13] showed that the mortality rate is significantly higher among patients with CSF opening pressures of >250 mm versus <249 mm. Consequently, aggressive management of elevated intracranial pressure by various methods (e.g., serial lumbar punctures, ventriculostomy drainage, etc.) is an important adjunctive therapy. Second, recent non-MSG trials have shown that long-term suppressive therapy can be discontinued for patients with AIDS receiving HAART with CD4 cell counts >100 cells/μL and an undetectable HIV RNA level sustained for 3 months [14, 15].

I am most proud of the many contributions of the MSG sequential studies cited above which serve as the foundation for the current Infectious Diseases Society of America (IDSA) guidelines for management of all patients with cryptococcal meningitis [16]. I also wish to report that the ongoing activity of the MSG in this arena is an international trial of patients with AIDS comparing AMBd plus fluconazole versus AMBd alone as primary therapy for cryptococcal meningitis. The choice of fluconazole over fluocytosine for this study is based on the nonavailability of fluorocytosine in most of the underdeveloped countries of the world.

LESSON 5: ANTIFUNGAL AZOLES AS A CLASS HAVE REVOLUTIONIZED THE THERAPY FOR THE ENDEMIC MYCOSES (BLASTOMYCOSIS, HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, PARACOCCIDIOIDOMYCOSIS, AND SPOROTTRICHOSIS)

I will limit my remarks to only the first 3 of these diseases.

LESSON 6: ITRACONAZOLE IS THE DRUG OF CHOICE FOR MOST PATIENTS WITH BLASTOMYCOSIS

Prior to the 1980s, intravenous AMBd was the drug of choice for all patients with blastomycosis. Open-label, noncomparative studies indicated cure rates of up to 97% with an AMBd total dose of >2.0 g. However, prolonged intravenous therapy resulted in significant toxicity and much inconvenience for the patient. Beginning in the 1980s, a series of open-label, noncomparative trials by the MSG and other investigators established oral azole antifungal drugs as preferable therapy over AMBd. Trials to compare highly toxic intravenous AMBd versus a less toxic oral azole could not be justified. Ketoconazole, the first available azole, was shown to be an effective therapy for blastomycosis [17, 18]. However, significant toxicity and frequent relapses were observed, prompting 2 subsequent studies with itraconazole, a drug with a mechanism of action and pharmacokinetics similar to ketoconazole but a lower toxicity profile. Oral itraconazole therapy administered for 3–6 months was associated with cure rates of 90%–95%, less toxicity than ketoconazole, and significantly fewer relapses [19, 20]. Subsequent studies with oral fluconazole showed that higher doses of this azole were required to achieve similar efficacy to that of the other azoles [21]. On the basis of these noncomparative trials, itraconazole is regarded as the azole drug of choice for most patients with blastomycosis. In the occasional patient with severe, life-threatening disease, an amphotericin B formulation remains the preferred initial treatment; once the patient is stabilized while receiving amphotericin B, therapy can be switched to oral itraconazole.

LESSON 7: ITRACONAZOLE IS THE DRUG OF CHOICE FOR MOST PATIENTS WITH HISTOPLASMOSIS

As with blastomycosis, prior to the 1980s, AMBd was the drug of choice for all patients with histoplasmosis. Cure rates ranged between 57% and 100%, depending on the type of disease (e.g., acute pulmonary interstitial disease, chronic fibrocavitary lung disease, and disseminated disease). However, high total dose of AMBd resulted in significant toxicity. As with blastomycosis, azole antifungal drugs have replaced AMBd as therapy of choice for most patients; the results of clinical trials with the azoles for histoplasmosis have closely paralleled the results with azoles for blastomycosis [18, 19, 22, 23]. Itraconazole is clearly the azole of choice; it is the most efficacious and is associated with fewer relapses, compared with ketoconazole and fluconazole. However, histoplasmosis differs from blastomycosis in one important aspect: *Histoplasma capsulatum* is an opportunistic pathogen in T cell–compromised hosts, especially patients with HIV/AIDS. As a consequence, management of these patients with disseminated histoplasmosis requires additional interventions. Patients with AIDS and acute life-threatening disseminated histoplasmosis should receive an amphotericin B formulation until stabilized and should then be switched to itraconazole for the duration of primary therapy [24]. In addition, patients with AIDS and disseminated histoplasmosis benefit from long-term suppressive therapy with itraconazole to prevent relapses [25]. Moreover, recent trials indicate that suppressive therapy for those patients receiving HAART can be discontinued if CD4 counts >150 cells/μL can be sustained [26].
LESSON 8: ITRACONAZOLE AND FLUCONAZOLE ARE BOTH EFFECTIVE THERAPIES FOR COCCIDIOIDOMICOSIS

AMBd was the drug of choice for therapy of coccidioidomycosis for ≈45 years (1955–1990) on the basis of retrospective non-comparative series that suggested clinical efficacy of AMBd approaching 70%. During this period, AMBd was often given for life via intravenous and intrathecal routes. Over the past 15 years, azole antifungal drugs have largely replaced AMBd as therapy of choice for coccidioidomycosis, especially for stable patients with chronic forms of disease. As with the other endemic mycoses, open-label clinical trials evaluating all 3 of the first-generation azoles (ketoconazole, itraconazole, and fluconazole) were performed by the MSG and other investigators [27–29]. To achieve reasonable efficacy, high doses of ketoconazole were needed, and as a result, significant toxicity was observed [27]. Subsequent studies of itraconazole and fluconazole showed higher cure rates and less toxicity than ketoconazole [28, 29]. To better define the treatment roles of these 2 azoles, Galgiani et al. [30] compared itraconazole with fluconazole as therapy for patients with pulmonary and other nonmeningeal forms of coccidioidomycosis (the first and only prospective, randomized trial comparing 2 differentazole drugs for treatment of an endemic mycosis). Results demonstrated that the 2 drugs were comparable in both overall efficacy (fluconazole, 50%; itraconazole, 63%; P = .08) and rate of relapse (fluconazole, 28%; itraconazole, 18%; P > .2). However, the response rate was higher in patients with bone disease treated with itraconazole (52% vs. 26%; P = .05). In addition, other studies have demonstrated the greater efficacy of fluconazole as therapy for coccidioidal meningitis [31]; in addition, for this group of patients, fluconazole must be continued for life [32]. Results of these several studies provide the evidence used in the development of IDSA guidelines for the treatment of the various forms of coccidioidomycosis [33].

LESSON 9: SEVERAL REGIMENTS PROVIDE EFFECTIVE TREATMENT FOR CANDIDEMIA (AND OTHER FORMS OF invasive CANDIDIASIS).

Although treatment with AMBd or lipid formulations of amphotericin B has been associated with good outcomes for patients with candidemia and other less common forms of invasive candidiasis, this approach has also resulted in significant toxicity. As a result, a series of clinical trials was undertaken initially to evaluate azole drugs as treatment of candidemia in nonneutropenic patients and, more recently, to evaluate echinocandin agents. Results of the 6 major trials are provided in table 1. The first trial, which compared fluconazole with AMBd and was done by the MSG and led by Rex et al. [34], set the

**Table 1. Details of clinical trials of treatments for candidemia.**

<table>
<thead>
<tr>
<th>Agent class, study</th>
<th>Study design</th>
<th>Study population (percentage of subjects)</th>
<th>Treatment regimen (daily dose)</th>
<th>Efficacy rate*</th>
<th>Mortality rate, %</th>
<th>Persistent candidemia</th>
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<tbody>
<tr>
<td><strong>Azoles</strong></td>
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<tr>
<td>Rex et al. [34]</td>
<td>Randomized, NB</td>
<td>Nonneutropenic patients Flu (400 mg) 70 .22 33 15</td>
<td>AmB (0.5–0.6 mg/kg) 79</td>
<td>.22 33 15</td>
<td>.18</td>
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<tr>
<td>Phillips et al. [35]</td>
<td>Randomized, NB</td>
<td>Nonneutropenic patients Flu (400 mg) 57 .66 38 17</td>
<td>AmB (0.6 mg/kg) 62</td>
<td>.66 38 17</td>
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<tr>
<td>Rex et al. [36]</td>
<td>Randomized, DB</td>
<td>Nonneutropenic patients Flu (800 mg) 56 .04 39 17</td>
<td>AmB (0.7 mg/kg) 69</td>
<td>.04 39 17</td>
<td>.02</td>
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<tr>
<td>Kullberg et al. [37]</td>
<td>Randomized, NB</td>
<td>Nonneutropenic patients Vor (6 mg/kg) 65 .25 36 NA</td>
<td>AmB (0.7–1.0 mg/kg) followed by Flu (400 mg)</td>
<td>.25 36 NA</td>
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<td><strong>Echinocandins</strong></td>
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<tr>
<td>Mora-Duarte et al. [38]</td>
<td>Randomized, DB</td>
<td>Nonneutropenic patients (89) and patients with candidemia (81) Casp (50 mg) 73 .09 34 8</td>
<td>AmB (0.6–1.0 mg/kg) 62</td>
<td>.09 34 8</td>
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<tr>
<td>Reboli et al. (unpublished data)</td>
<td>Randomized, DB</td>
<td>Nonneutropenic patients (97) and patients with candidemia (89) Anid (100 mg) 76 .01 23 6</td>
<td>Flu (400 mg) 60</td>
<td>.01 23 6</td>
<td>.055</td>
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**NOTE.** AmB, amphotericin B; Anid, anidulafungin; Casp, caspofungin; Flu, fluconazole; NA, not available; NB, nonblinded; Vor, voriconazole.

* Data are from the evaluable population for azole trials and from the modified intent-to-treat population for the echinocandin trials.
standard for subsequent trials in terms of study design and end points. Rates of efficacy, mortality, and persistent candidemia were similar for the 2 regimens, whereas the toxicity rate was significantly higher in the AMBd-treated group. A second study, done by Phillips et al. [35], was very similar in design to Rex and colleagues’ trial and provided similar outcomes. These 2 randomized, nonblinded trials of nonneutropenic patients established that fluconazole, an azole, and AMBd, a polyene, were associated with similar rates of clinical response and survival in the treatment of candidemia.

With the goal to determine the efficacy of an azole-polyene combination regimen, the MSG, again led by Rex and colleagues [36], next compared high-dose fluconazole plus AMBd with high-dose fluconazole plus placebo. In this double-blind trial, again involving nonneutropenic patients with candidemia, overall success rates were 56% in the fluconazole alone arm and 69% in the combination therapy arm ($P = .043$); in addition, failure to clear Candida from the blood was less likely in the combination therapy patients (6% vs. 17%; $P = .02$). This trial is the only one of the trials shown in table 1 to show a significant difference between the 2 treatment regimens in the rates of persistent candidemia. Perhaps most importantly, this trial also showed that the combination of fluconazole plus AMBd was not antagonistic. As expected, renal dysfunction was associated with similar rates of clinical response and survival in the treatment of candidemia.

The other 2 clinical trials shown in table 1 evaluated echinocandin agents as treatment for candidemia and other forms of invasive candidiasis. Mora-Duarte et al. [38] compared caspofungin with AMBd in primarily nonneutropenic patients (89%), most of whom had candidemia (81%). In the modified intent-to-treat analysis, the efficacy of the 2 drugs was similar, but in the analysis of evaluable patients, caspofungin was superior to AMBd (87% vs. 75%; $P < .05$). The overall mortality for recipients of the 2 regimens was similar, but there were fewer drug-related adverse events in the caspofungin group. The second echinocandin trial, done by Reboli and colleagues (unpublished data), again involving primarily nonneutropenic patients (97%) with candidemia (93%), compared anidulafungin with fluconazole (the first randomized study to compare an echinocandin drug with an azole drug among patients with invasive candidiasis). Anidulafungin was superior in efficacy in both the modified intent-to-treat and evaluable patient analyses. In addition, the overall mortality rate of anidulafungin-treated patients was only 23%, the lowest mortality rate associated with any of the treatment regimens shown in table 1. Anidulafungin was also associated with a lower rate of persistent candidemia than was fluconazole (6% vs. 14%; $P = .055$).

The results of the 6 comparative trials, which are detailed in table 1, demonstrate that there are several effective options for the treatment of candidemia (and by extrapolation, treatment of other invasive forms of candidiasis). These regimens include an amphotericin B formulation, fluconazole alone (400–800 mg), caspofungin or anidulafungin, and the combination of fluconazole plus amphotericin B [39]. The choice of initial therapy in the individual patient should be based on several factors, including prior significant exposure to fluconazole, condition of the patient (stable or life-threatening), microbiologic data about the infecting Candida species in the blood or (less helpful) recovered from colonized sites (e.g., urine, wound, and tracheal aspirate), and the presence of organ dysfunction that would affect drug clearance.

**LESSON 10: THE NEED FOR MORE EFFECTIVE THERAPY AGAINST INVASIVE ASPERGILLOSIS**

Invasive aspergillosis has emerged over the past 2 decades as one of the most dreaded infections complications in immunocompromised hosts, especially for patients who have sustained neutropenia, who are receiving prolonged courses of high doses of corticosteroids, or who are undergoing bone marrow or solid organ transplantation. Amphotericin B formulations have long been the mainstay of treatment for invasive aspergillosis, but multiple studies, including retrospective case series and prospective randomized trials, have consistently shown disappointing outcomes, regardless of the specific amphotericin B agent (AMBd or a lipid formulation) [40]. In the late 1990s, a landmark randomized, nonblinded trial was performed by Herbrecht and fellow investigators [41] in worldwide sites to compare voriconazole, a second-generation azole, with AMBd for treatment for invasive aspergillosis. Other licensed antifungal treatment (OLAT) was allowed if initial therapy failed or if the patient could not tolerate the initial randomized drug. By all outcome parameters, voriconazole plus OLAT significantly outperformed AMBd plus OLAT: it had greater success at 12 weeks of treatment (53% vs. 32%), success at end of initial randomized therapy (54% vs. 22%), survival at 12 weeks (71% vs. 58%), and median duration of initial randomized therapy (77 days vs. 11 days) and fewer severe side effects.

As a result of this trial, voriconazole has become the drug of choice of most clinicians for primary therapy of most patients with invasive aspergillosis. However, controversy has arisen about whether single-drug therapy or combination therapy (e.g., voriconazole plus an echinocandin, such as caspofungin) is optimum therapy. Recent studies provide some insights into the potential role of combination therapy. First, caspofungin has been approved for salvage treatment of invasive...
Table 2. Hurdles, challenges, and rewards associated with clinical trials.

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<tr>
<th>Hurdles</th>
<th>Challenges</th>
<th>Rewards</th>
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<tr>
<td>Institutional review boards and HIPAA regulations</td>
<td>Multiple study sites are necessary to insure adequate power of study</td>
<td>Improved patient outcomes and satisfaction</td>
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<td>Increasing other levels of oversight, protocol review, and approval</td>
<td>Joint academia, industry, and/or NIH or other partnerships require</td>
<td>Development of most effective, least toxic, and cost-effective treatment and prevention strategies</td>
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<td>(e.g., NIH and FDA)</td>
<td>much negotiation and mutually agreed-upon goals</td>
<td>Gratification for investigators and protocol team</td>
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<td>High costs</td>
<td>The most relevant clinical questions should be identified and then</td>
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<td>Necessity for independent data review and biostatistical analyses</td>
<td>assigned high priority</td>
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<td>Must shorten time period from development of concept to initiation of</td>
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<td>trial (&quot;ticking clock&quot;)</td>
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NOTE. FDA, US Food and Drug Administration; HIPAA, Health Insurance Portability and Accountability Act; NIH, National Institutes of Health.

Aspergillosis on the basis of data from 83 patients with invasive aspergillosis who were refractory to or intolerant of standard antifungal therapy and who received caspofungin [42]. Thirty-seven patients (45%) had a favorable response. Second, data from an animal model (guinea pig and rabbit) in vivo studies of invasive aspergillosis indicate an additive activity between an echinocandin and a second-generation azole [43, 44]. Third, Marr et al. [45] performed a recent analysis of outcomes in patients with invasive aspergillosis for whom initial therapy with amphotericin B formulations failed and who received either voriconazole (31 patients) or a combination of voriconazole and caspofungin (16 patients) as salvage therapy. In this small retrospective study, therapy with the combination regimen was associated with a reduced mortality rate, compared with voriconazole alone. Although these studies provide encouraging results about the potential for improved efficacy of combination therapy for invasive aspergillosis, a prospective, randomized trial with human patients with proven or probable invasive aspergillosis is necessary to establish definitively the efficacy, safety, and cost-effectiveness of combination therapy versus single-drug therapy [46]. In our roles as infectious diseases, transplantation, and cancer physicians, as clinical investigators, and as industry leaders, we owe it to our patients with invasive aspergillosis to determine the best treatment paradigm for this highly lethal disease. Thus, it is my fervent hope that groups such as the MSG and EORTC will join together with the NIH and industry sponsors to accomplish this important trial.

In closing, as clinical investigators (especially clinical trialists), we must acknowledge the increasing number of hurdles and challenges associated with the development and performance of meaningful, quality clinical trials (table 2). Large clinical trials are not easy and at times can be quite frustrating for the investigators, protocol team, and even our patients. Nevertheless, clinical trials are absolutely essential for the translation of many fundamental observations from the bench to the bedside. Moreover, development of the most effective and least toxic treatment and preventive strategies provides significant rewards for not only our patients but also for us, the clinical investigators. Having served as an investigator and leader of the MSG for almost 3 decades has given me great personal enjoyment and professional satisfaction. Finally, I owe much to the support of my collaborators (site investigators, industry sponsors, and NIH leadership); my fellows, study nurses and coordinators; my central unit administrators and biostatisticians; and, most of all, my wife and family. Many thanks to the IDSA for naming me the 2005 Finland awardee.

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