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M E D I C A L

# CROSSFIRE®

DEBATES, PEER EXCHANGE, AND INSIGHTS IN MEDICINE®

**SPECIAL EDITION**

## Optimizing Treatment of Invasive Fungal Diseases

CME-Certified Monograph

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Jointly Sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ)—Center for Continuing and Outreach Education and **Medical Crossfire®**/Liberty Communications Network



**Release Date:** May 2007 • **Expiration Date:** May 31, 2008

This activity is supported by an educational grant from Schering-Plough Corporation.



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## Educational Overview

Immunosuppressed patients are at increased risk for invasive fungal infections (IFIs), which present significant treatment challenges. The incidence of IFIs in hospital settings is increasing and IFI profiles are changing. *Candida albicans* is still the most common fungal pathogen in the hospital setting, but non-*albicans Candida* species and rare moulds (e.g., *Fusarium*, *Scedosporium*, *Zygomycetes*) are becoming more common and many are resistant to current therapeutic options. Lipid formulations of amphotericin B, new azoles (e.g., voriconazole and posaconazole), as well as echinocandins offer clinicians options that can be effective in the prevention and treatment of life-threatening fungal infections.

Through debate and authoritative peer exchange, this *Medical Crossfire*® activity, conducted in conjunction with UMDNJ, will confront issues related to the treatment of life-threatening fungal infections.

## Target Audience

This educational activity is designed for physicians and other health care professionals interested in or involved with the management of invasive fungal infections.

## Learning Objectives

Upon the completion of this activity, participants should be able to:

- Evaluate recent clinical data regarding the efficacy and safety of newer triazoles and echinocandins.
- Identify emerging and potential resistance patterns among fungal pathogens.
- Utilize newer triazoles and echinocandins within the context of changing fungal infection patterns.
- Apply prophylaxis strategies that may improve patient outcomes.

## Method of Instruction

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the self-assessment test consisting of a series of multiple-choice questions.

The activity is complemented with references that contain the rationale for the correct answer to each self-assessment question as well as a description identifying the section of the activity that contains the correct answer, allowing participants to review the material as needed, thus finalizing their educational participation.

Upon completing this activity as designed, participants will receive a letter of credit awarding *AMA PRA Category 1 Credit*<sup>™</sup> three to four weeks after receipt of the registration and evaluation materials.

Estimated time to complete this activity as designed is 1 (one) hour.

## Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of UMDNJ–Center for Continuing and Outreach Education and *Medical Crossfire*®/Liberty Communications Network. UMDNJ–Center for Continuing and Outreach Education is accredited by the ACCME to provide continuing medical education for physicians.

UMDNJ–Center for Continuing and Outreach Education designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit*<sup>™</sup>. Physicians should claim credit commensurate with the extent of their participation.

The print monograph was peer-reviewed for relevance, accuracy of content and balance of presentation by David Alland, MD, and pilot-tested for time required for participation by David Cennimo, MD; Syed Hasan, MD; and Hema Sivadas-Dholakia, MD.

### **CME Academic Advisor**

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### **Disclosure Declarations**

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, individuals in a position to control the content of this education activity are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with proprietary entities producing health care goods or services, with the exemption of non-profit or government organizations and non-health care related companies, within the past 12 months; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

### **Faculty Disclosure Declarations**

**Dr. Drew** has received grant/research support from Cubist Pharmaceuticals, NeuTec Pharma, and Schering-Plough Corp.; has been a consultant for Merck & Co. and Theravance; and has served on the speakers' bureaus of Enzon Pharmaceuticals, Ortho-McNeil Pharmaceuticals, sanofi-aventis, Schering-Plough Corp., and Wyeth Pharmaceuticals.

**Dr. Marr** has received grant/research support from Astellas Pharma US; and has been a consultant for Astellas Pharma US, Basilea Pharmaceuticals, Enzon Pharmaceuticals, Merck & Co., Nectar Pharmaceuticals, Pfizer, and Schering-Plough Corp.

**Dr. Pappas** has received grant/research support from Astellas Pharma US, Enzon Pharmaceuticals, Merck & Co., Pfizer, and Schering-Plough Corp.; has been a consultant for Merck & Co., Pfizer, and Schering-Plough Corp.; and has served on the speakers' bureaus of Astellas Pharma US, Merck & Co., and Pfizer.

**Dr. Perfect** has received grant/research support from, has been a consultant for, and/or has served on the speakers' bureaus of Astellas Pharma US, Enzon Pharmaceuticals, Merck & Co., Pfizer, and Schering-Plough Corp.

**Dr. Pfaller** has received grant/research support from, has been a consultant for, has served on the speakers' bureaus of, and has served as a member of the Scientific Advisory Boards of Astellas Pharma US, Merck & Co., Pfizer, and Schering-Plough Corp.

**Dr. Alland, Dr. Cennimo, Dr. Hasan, and Dr. Sivadas-Dholakia** have no financial arrangements or affiliations to disclose.

### **Off-Label Usage Disclosure**

This activity contains discussion of off-label uses of approved products. Posaconazole has not been studied as initial therapy for invasive aspergillosis. The efficacy of micafungin against infections caused by fungi other than *Candida* has not been established.

### **Disclaimer**

The views expressed in this activity are those of the faculty. It should not be inferred or assumed that they are expressing the views of Schering-Plough Corporation, any other manufacturer of pharmaceuticals, UMDNJ, or *Medical Crossfire*/Liberty Communications Network.

It should be noted that the recommendations made herein with regard to the use of therapeutic agents, varying disease states, and assessments of risk, are based upon a combination of clinical trials, current guidelines, and the clinical practice experience of the participating panelist. The drug selection and dosage information presented in this activity are believed to be accurate. However, participants are urged to consult the full prescribing information on any agent(s) presented in this activity for recommended dosage, indications, contraindications, warnings, precautions, and adverse effects before prescribing any medication.

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# Optimizing Treatment of Invasive Fungal Diseases

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## PANELISTS

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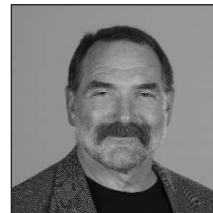
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## MODERATOR

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**John R. Perfect, MD**  
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Invasive fungal infections are associated with significant morbidity and mortality, especially in patients who suffer from neutropenia due to cancer therapy, long-term immunosuppressive therapy after organ transplantation, or complications arising from infection with HIV. Newer antifungal agents—including lipid formulations of amphotericin B, expanded-spectrum azoles such as voriconazole and posaconazole, and echinocandins—offer expanded treatment options to address prophylaxis, preemptive empiric treatment, and treatment of documented invasive fungal infections in susceptible patients. This **Medical Crossfire** provided a forum for a panel of experts in the treatment of invasive fungal diseases to discuss recent clinical trials, pathogen identification and resistance issues, and clinical management topics in these high-risk patients, providing an educational update for physicians who manage these challenging patients.

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## Clinical Trial Updates

### *Prophylaxis Trials*

John R. Perfect, MD, moderator of this *Medical Crossfire*, opened the discussion by inviting the panel to address recent clinical trials in antifungal agents, including recent prophylaxis trials with newer azoles and echinocandins. He invited Kieren A. Marr, MD, to offer her impression of these data.

“Before we talk about the most recent studies, we should address the historical studies that brought us to where we are now,” she began. She explained that initial placebo-controlled studies in patients who were immunocompromised due to hematopoietic stem cell transplant demonstrated that prophylaxis with the triazole fluconazole effectively prevented yeast infections, predominantly those due to *Candida albicans* and *C. tropicalis*.<sup>1,2</sup> She emphasized, however, that many complicated infections are now caused by moulds rather than yeasts, requiring new agents that are effective against these

organisms, especially *Aspergillus* species. Initial studies with itraconazole, followed by a trial employing the echinocandin micafungin, demonstrated the potential to prevent mould infections, although data did not definitively demonstrate improved patient outcomes.<sup>1,2</sup>

Dr. Marr also mentioned a recent study published by Cornely et al. in the *New England Journal of Medicine* which reported that in a population of patients who were immunocompromised due to chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes, the azole agent posaconazole was more effective in preventing invasive fungal infections than ‘standard azoles’ (either fluconazole or itraconazole), and also improved survival.<sup>3</sup> Furthermore, significantly fewer patients receiving posaconazole suffered from invasive aspergillosis compared to those receiving fluconazole or itraconazole.<sup>3</sup>

Dr. Marr continued by explaining that itraconazole has demonstrated the ability to prevent invasive mould infections, but its use

appears to be limited by tolerability issues.<sup>4,5</sup> “Meanwhile, other studies of micafungin to prevent invasive mould infections were limited because the efficacy end points included patients with unconfirmed infection<sup>6</sup>,” she added. “The recent posaconazole studies provide quite compelling results in showing that we can prevent all invasive fungal infections, including mould infections, with good clinical outcomes.”

“Historically, fluconazole was the first prophylactic regimen used, which prevented yeast infections and may have offered some survival benefit—a major step in protecting patients at risk,” reported Dr. Perfect. “Now we have the azoles and echinocandins that have shown some improvement in preventing mould infections and improving survival.” Addressing the panel, he asked, “We are talking about different patient types who may demonstrate different relative risks of mould infections. How have you addressed the relative risk of invasive mould infection in your institution?”

Dr. Marr answered by citing the larger issues of patient risk identification and diagnostic testing. “The next step is to define the patient population that is at a high enough risk to warrant prophylaxis with an agent that is effective against mould infections. Perhaps we can preempt the need to define these patients by standardizing a biomarker or diagnostic test that can detect the infection early. I think that these are the kinds of questions that need to be addressed in a randomized trial.” She explained that, until such trials are conducted, “as soon as a drug is available that is potentially active against invasive infections and has a known risk-benefit ratio, the next question that clinicians should ask themselves is, For whom would this drug be beneficial in my patient population? Are these patients at a high enough risk of infection to warrant exposing them to the potential adverse effects of the prophylactic agent?”

To elaborate, Dr. Marr noted that the recent posaconazole trial demonstrated that

aspergillosis can be prevented in an allogeneic stem-cell transplant population with graft versus host disease, but did not reveal which patients who are vulnerable to invasive fungal disease would be most appropriate for prophylactic therapy. “These drugs are complicated with regard to interactions with other agents, and their cost can also be an issue,” she said, adding, “right now, every institution is carefully analyzing the available data to determine which patients are most likely to benefit from prophylaxis with an agent that lowers the risk of invasive mould infection.” The results of an ongoing National Heart, Lung and Blood Institute (NHLBI)-coordinated trial comparing voriconazole with fluconazole in bone marrow transplant recipients may better characterize the risk-benefit ratio in these patients, and these data are projected to be available in late 2007.

“I would like to highlight a few things that Dr. Marr brought up, especially with regard to safety and cost,” interjected Richard H. Drew, PharmD, MS, BCPS, as he joined the discussion. He affirmed Dr. Marr’s assertion that not every patient benefits from prophylaxis, and that it is important to develop tools to identify those at the highest risk. “But the question is, How should we consider the data in terms of cost and safety when every patient does not benefit from prophylactic treatment?” He added that another important issue raised by Dr. Marr is the timing and duration of the prophylaxis. While clinical trials are able to measure outcomes observed during a specific length of therapy, he pointed out that Dr. Marr and others have demonstrated that the risk of invasive infection likely extends beyond the length of therapy investigated in clinical trials. “Questions still persist on the proper length of prophylaxis,” he claimed.

“The points raised by Dr. Marr and Dr. Drew bring up the question of what constitutes prophylaxis versus preemptive therapy,” remarked Peter G. Pappas, MD. He emphasized that targeted prophylaxis is

based on predictive models and risk factors that are not necessarily substantiated by laboratory cultures or other microbiologic analyses. He concurred with Dr. Marr, stating, “The next step in avoiding the complications of invasive fungal infections is to avoid the prophylaxis issue and aim for early preemptive therapy based on the use of biomarkers.”

“One of the concerns that I have with prophylaxis in a heterogeneous patient population is that the agents we use, including the echinocandins and extended-spectrum azoles, protect against a wide range of organisms, and little effort is made to make an etiologic diagnosis when there is evidence of infection,” offered Michael A. Pfaller, MD, as he entered the discussion. “As patients are increasingly exposed to these broad-spectrum agents, antifungal resistance issues will surely arise in the future, and ultimately, no agent will be available to keep these vulnerable patients completely protected. Furthermore, some organisms of concern in the environment are not necessarily covered by even the best of these agents.” He concluded that while primary prophylaxis is important, it is equally critical to make an etiologic diagnosis of the causative organism whenever infection is suspected.

“We have made strides with the use of fluconazole as a prophylactic strategy to prevent yeast infections in patients at risk,” summarized Dr. Perfect. “More recent trials are demonstrating that we may be able to prevent mould infections in high-risk patients. Now is the opportune time to develop a consistent strategy for prophylactic therapy.”

### **Treatment Trials**

To introduce the next segment, Dr. Perfect asked the panel to offer their insight on newer agents, including echinocandins and azoles, based on recent clinical trials.

“Multiple completed studies now exist that address treatment for invasive *Candida* infections,” Dr. Pappas pointed out. “One of the most recent trials focused on voriconazole,

a new extended spectrum triazole, which in theory might have offered some advantage over fluconazole. But most of the attention, frankly, has been directed toward the echinocandins.” He cited recent treatment trials with echinocandins that demonstrated noninferiority, and in some cases superiority, to a wide range of comparators, including amphotericin B and fluconazole. Dr. Pappas summarized, “These studies suggest that the newer agents, including extended-spectrum voriconazole, are effective alternatives to traditional therapies in the prevention of invasive fungal infections. While the newer triazoles have not distinguished themselves from other regimens, including amphotericin B and fluconazole, the echinocandins have generally performed better than the comparator. Though statistically significant differences have not always been demonstrated, I think the conclusion that we can draw from recent studies is that the echinocandins offer an effective alternative to the older comparators.”

In one such trial comparing the echinocandin caspofungin with amphotericin B for the primary treatment of invasive candidiasis, caspofungin was at least as effective as amphotericin in the treatment of patients with invasive candidiasis, as well as a subgroup of patients with candidemia (a bloodstream infection with *Candida* yeast species). Caspofungin was associated with a significantly lower rate of adverse effects compared with amphotericin B.<sup>7</sup>

Meanwhile, a prophylaxis trial comparing voriconazole with amphotericin B in lung transplant patients found that the rate of mould infection due to *Aspergillus* species was significantly reduced in patients receiving voriconazole.<sup>8</sup> A trial comparing voriconazole with amphotericin B for the primary treatment of invasive aspergillosis also reported better response rates, improved survival, and a lower rate of serious adverse effects with voriconazole therapy.<sup>9</sup>

“One of my concerns with the use of voriconazole in the primary treatment of

candidemia, though, is the issue of cross-resistance between different azoles,” cautioned Dr. Pfaller. He explained that while cross-resistance is not really an issue for some *Candida* species, such as *C. krusei*, the pathogenic yeast *C. glabrata* demonstrates cross-resistance between azole drugs, so voriconazole therapy after patient exposure to fluconazole, for instance, is not recommended. Meanwhile, *C. glabrata* does not demonstrate this cross-resistance between echinocandins. “In my opinion, that places the echinocandins, given the ubiquity of the utilization of fluconazole in our medical centers these days, in a good position for primary therapy,” he concluded.

“What is your opinion of the significance of the recent trial that demonstrated noninferiority of voriconazole compared to amphotericin B followed by fluconazole,<sup>10</sup> as it pertains to patients who have previously received fluconazole?” Dr. Pappas asked Dr. Pfaller. “Is there a role for voriconazole in this setting?”

“I feel that there is a role for voriconazole, primarily because the drug is available in both oral and IV formulations.” He also explained that, in cases of *C. krusei* infection, a de-escalation approach to treatment may be an appropriate choice, especially if an agent such as an echinocandin is initiated, because the patient will need to be treated for an extended period of time. “This is a perfect situation in which to use voriconazole. The extended spectrum of activity with voriconazole may be useful in patients with causative yeast such as *C. guilliermondii* or *C. parapsilosis*. Finally, while there is concern in treating candidiasis with another azole after previous prophylaxis with fluconazole, this is not a concern in the case of aspergillosis.”

“Voriconazole does have a very limited role based on the concerns expressed by Dr. Pfaller,” opined Dr. Marr. She explained, “For a patient with a *C. krusei* infection who is eligible for oral therapy, there is a role for voriconazole. Otherwise, not only is there

"These studies suggest that the newer agents, including extended-spectrum voriconazole, are effective alternatives to traditional therapies in the prevention of invasive fungal infections."

—Dr. Pappas

the issue of cross-resistance with this agent, but also the difficulty in administration compared to fluconazole. Fluconazole is still a good staple therapy for candidiasis.” She also referred to recent data presented during a poster session during the 2005 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), which demonstrated improved survival with the echinocandin anidulafungin compared to fluconazole.<sup>11</sup> She asked Dr. Pappas, “Do you think that these data demonstrate that the echinocandins are better at killing the causative organisms, or that they are simply safer treatment options?”

“I believe that it is a combination of better efficacy and safety,” responded Dr. Pappas. “The echinocandins have uniformly performed better than their comparators, both with significant and nonsignificant improvements in outcomes. I believe that clinicians are comfortable using echinocandins because they are safe and easy to administer. This is reflected by the fact that these agents have been widely adopted. Results from clinical trials awaiting publication involving echinocandins consistently suggest a treatment success rate of 75%,<sup>12</sup> and these are some of the best results we have seen in the treatment of invasive *Candida* infections.”

Dr. Pfaller then posed a hypothetical patient to Dr. Pappas: “If you have a patient who started with an echinocandin and it was subsequently determined that the candidemia was due to *C. albicans*, would you give a full course of the echinocandin or switch to fluconazole?”

“This is where the studies fall short,” replied Dr. Pappas. “Because of the nature of clinical trial design, most of these trials have only examined echinocandin therapy administered for 10 days to 14 days, but in practice, most clinicians do not administer the drugs on these schedules. The relative risks and benefits of long-term management with echinocandins, versus transition from an echinocandin to oral therapy, should be addressed in clinical studies.” Dr. Pappas

concluded that if a clinically stable patient was receiving an echinocandin and it was subsequently determined that the causative organism was *C. albicans* or *C. parapsilosis*, it would be appropriate to transition the patient to fluconazole.

“I agree with all of the panelists that fluconazole is still a very effective drug, and that the extended spectrum azoles do not really improve upon the older azoles,” noted Dr. Perfect in concluding this segment of the discussion. “Echinocandins, however, have become attractive alternatives for use in candidiasis. Finally, the use of an echinocandin at the start of therapy followed by a switch to maintenance therapy with an older azole such as fluconazole is now commonplace in clinical practice.”

## Diagnostic and Resistance Issues

### *Beta-Glucan and Galactomannan Immunoassays*

“I would like to ask the panel to discuss the issues surrounding diagnostics and resistance,” said Dr. Perfect. “Could you give us your views on the role of the microbiology laboratory in the clinical management of fungal infections, and perhaps the role of biomarkers such as galactomannan?”

“There should be a rational approach to the use of *in vitro* diagnostics,” posited Dr. Pfaller. “It is important to emphasize that we cannot depend on an agent to cover all eventualities, and an etiologic diagnosis should be made whenever possible, so we cannot ignore cultures and histopathology studies when considering the right therapy for the patient. However, we also need to consider the testing that needs to be done beyond culture and histopathology, including peptide nucleic acid *in situ* fluorescent hybridization (PNA-FISH) stains that are available to identify *C. albicans* directly from blood cultures.” He noted that, while this test is not commonly used, one study reported this strategy to be very cost effective in a setting where up

to half of candidemia cases are due to *C. albicans* and echinocandins are used broadly.<sup>13</sup>

Dr. Pfaller said that confirming the causative organism as *C. albicans* by performing PNA-FISH staining during the initial culture evaluation can give clinicians confidence to prescribe fluconazole, which is an appropriate choice of therapy in confirmed cases of *C. albicans*, instead of the more expensive echinocandin therapy. Likewise, he added, fluconazole susceptibility testing can be used to guide therapy and control costs. He noted that an upcoming publication supports this concept; its authors found that routine in-house fluconazole susceptibility testing in patients with confirmed infection with *C. glabrata* was more cost-effective than either (1) prescribing echinocandin therapy to every patient or (2) sending out selective samples for testing.

Dr. Pfaller went on to note that many of the available diagnostic tests are not used effectively in clinical practice. While a galactomannan enzyme immunoassay is available to identify the presence of *Aspergillus* mould species, its use is highly variable in practice. Dr. Pfaller cited one study of galactomannan testing in University of North Carolina Hospitals, where researchers reported that 67% of patients received only one galactomannan test, suggesting a wide variability in the use of this diagnostic tool. Meanwhile, of nine patients with biopsy-confirmed invasive aspergillosis, six had not been tested with the galactomannan immunoassay.<sup>14</sup> “These data show that galactomannan testing is often misused in a similar manner as other serologic tests, with only one test performed.” He emphasized that, to the contrary, it is best to perform galactomannan immunoassay tests serially to prospectively follow patients at risk. Furthermore, he contended that beta-glucan tests could be potentially used in a similar fashion to monitor for candidiasis in patients at risk.

Dr. Pfaller noted that this test is also underutilized in clinical practice, based on his

experience. He also cited the use of polymerase chain reaction (PCR) molecular diagnostic tests to detect fungal infection, although he emphasized that these tests are not standardized and experts fail to agree on the utility of PCR. In surveys of US clinical microbiology laboratories, only 20% used molecular diagnostics for any infectious agent and only 5% of laboratories employed PCR for mycology testing,<sup>15</sup> noted Dr. Pfaller. Meanwhile, this low uptake of molecular testing is compounded by a lack of clinical mycologists and likewise, a lack of continuing education devoted to clinical mycology, according to Dr. Pfaller. He noted a review that highlighted the need for advanced medical mycology training,<sup>16</sup> concluding, “This represents a looming crisis for diagnostics in mycology that will not be ameliorated by the ability to develop more sophisticated diagnostic capabilities.”

Dr. Perfect agreed and requested that Dr. Marr expand on the discussion of assays that are currently approved by the Food and Drug Administration [FDA], including the beta-glucan and galactomannan immunoassays. He asked the panel, “In your opinion, what are the issues that limit the uptake and utility of galactomannan testing in clinical practice? Is there a message that needs to get out to the clinicians who treat these patients?”

“Galactomannan testing has been around for some time and is FDA-approved, but some important questions still need to be answered,” replied Dr. Marr. She noted that the use of antifungal therapy prior to sampling lowers the sensitivity of the assay, and that researchers have not entirely clarified which fluids, such as bronchoalveolar lavage

“It is important to emphasize that we cannot depend on an agent to cover all eventualities, and an etiologic diagnosis should be made whenever possible.”

—Dr. Pfaller

[BAL] fluid, serum, or urine can be tested reliably. “The ability to reliably test concentrated urine would be useful and would reinforce the available data that demonstrates the utility of galactomannan testing of BAL. These applications may be more promising than the ability to test serum,” stated Dr. Marr. She also observed that the kinetics of galactomannan levels have not been well described, and these factors may impact the reliability of the assay. “Therefore, basic questions about the galactomannan assay have not been entirely answered, which can frustrate clinicians who are trying to manage a very complicated patient population and this can lead them to reject this diagnostic tool. To compound this frustration, funding is not easily available to facilitate further research in this area,” she concluded.

“The underutilization of both galactomannan and beta-glucan testing demonstrates the fact that we clinicians may be more comfortable just initiating therapy instead of using these tools in a serial fashion to guide therapy,” offered Dr. Pappas. “This is a culture of ‘treat first and ask questions later,’ and this mindset clearly needs to be overcome. The underutilization of beta-glucan testing may be more complicated than the challenges surrounding galactomannan testing, because many institutions need to send samples out to be analyzed with the beta-glucan assay.”

“I am concerned about the reliability of these tests, though, especially in complicated patients,” countered Dr. Pfaller. He noted at least one report of beta-glucan testing in intensive care unit [ICU] patients in which the test was very sensitive in patients with documented candidemia, and was very specific in patients without any infection. However, in patients with bacteremia—most often due to Gram-positive organisms—a number of false positive results arose that were not easily explained.<sup>17</sup> “It may be that the test is not easy to perform. It does need to be conducted very scrupulously and in replicate, and is subject to contamination. In these critically

ill patients, there could be a variety of issues that may result in confusing data,” explained Dr. Pfaller.

Dr. Drew added, “Antifungal therapy, including prior therapy, does have the potential to cause false positives with the beta-glucan assay, as Dr. Marr noted. Also, it is possible that beta-lactam antibiotics can cause the same issues, especially piperacillin/tazobactam beta-lactam therapy.”

“I agree,” said Dr. Pfaller. “New reports of sources for beta-glucan and galactomannan false positives are always appearing in the literature, including a recent letter published in the *Journal of Clinical Microbiology*.<sup>18</sup> One report noted false-positives with a *Trichosporon*-like organism; this may not be entirely troublesome, as it still suggests that an infection is present. Ultimately, I agree with Dr. Marr’s point that there are many variables with the beta-glucan and galactomannan tests that have yet to be investigated.”

Dr. Drew noted that in a recent study of the beta-glucan immunoassay in a population of patients with high-risk neutropenia, the outcome benefit demonstrated with the use of the test was the avoidance of antifungal therapy. Patients with neutropenia were screened with a galactomannan enzyme immunoassay and underwent a diagnostic evaluation that included thoracic computed tomography [CT] scanning and bronchoscopy with lavage. Amphotericin B was administered only to patients who were seropositive, had a positive microbiologic test result, and had radiological findings consistent with invasive fungal infection. This strategy reduced the rate of amphotericin B use by 78% and resulted in early initiation of antifungal therapy in 10 cases that were not clinically suspected as being invasive fungal infection.<sup>19</sup> “In that sense, the test does have the ability to demonstrate an outcome benefit,” he explained.

“I do want to make one final point: we may be asking too much of these diagnostic tests,” offered Dr. Marr. “These are, by definition, not real pathogens. This is not like

testing someone for HIV infection, for instance, and a positive test does not necessarily mean disease. We should carefully analyze the probability of disease in specific hosts. Overall, there needs to be a shift in the way we think about these diagnostic tools.”

### *Epidemiology of Drug Resistance*

“We are now going to address the issue of drug resistance, which is becoming more important to consider as newer agents are being introduced,” stated Dr. Perfect. “Dr. Pfaller, as an expert on the *in vitro* testing of drug resistance epidemiology, what is your overall impression of drug resistance with antifungal agents in daily clinical practice?” he asked.

Dr. Pfaller replied that in his recent analysis from the ARTEMIS Antimicrobial Resistance Program that conducted surveillance efforts of candidemia and susceptibility against azoles between 1997 through 2003, susceptibility to fluconazole did not change for *C. albicans*, *C. parapsilosis*, *C. tropicalis*, or *C. krusei*. Meanwhile, the newer azole agent voriconazole was more active than fluconazole against *C. glabrata*.<sup>20</sup> Dr. Pfaller reported another analysis of *Candida* isolates performed from 1992 and 2001 by the International Fungal Surveillance Participant Group, concluding that little variation occurred in fluconazole susceptibility *C. parapsilosis*, *C. tropicalis*, or *C. krusei* during this period, while fluconazole susceptibility in *C. glabrata* was highly variable.<sup>21</sup> Dr. Pfaller noted that since laboratories have been encouraged to identify the species of yeast isolates in cases of invasive infection, clinicians have seen a number of new species emerge. For instance, in his studies, 22 different *Candida* species have been reported as causing invasive disease worldwide.<sup>22</sup> While five *Candida* species (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei*) still account for over 95% of all *Candida* infections, Dr. Pfaller predicted that other organisms, including noncandidal species, would become more prominent in the future. He explained that

patients who are already sick would be most vulnerable to developing some of these atypical infections, and they will likely already have received fluconazole. These atypical isolates are likely to be resistant to fluconazole and, in addition, are likely to develop cross-resistance to other azoles. Atypical, noncandidal yeast isolates will become more prominent in the future, he predicted. This has important therapeutic implications, he noted, because these organisms are not susceptible to echinocandins, are less susceptible to triazoles, and are variably susceptible to amphotericin B. “Beyond the top five most common *Candida* species, the noncandidal organisms are the ones that we should start looking at now. I think that we will be seeing them in our patients in the future,” he concluded.

“Dr. Pfaller has offered the larger perspective of new isolates appearing on the horizon,” noted Dr. Perfect. “Dr. Marr, how do you manage severely immunosuppressed patients, especially based on your observations of moderate levels of azole resistance as well as lower levels of echinocandin resistance in clinical practice? What is your clinical perspective on the magnitude of echinocandin resistance in severely immunosuppressed patients?”

“We have had several patients in our institution break through with disseminated candidiasis caused by *C. albicans* and *C. krusei* while receiving caspofungin therapy,” responded Dr. Marr. “We subsequently confirmed that the organisms were resistant to caspofungin. It is interesting to note that caspofungin dosing had been reduced in these patients due to poor hepatic function caused by graft versus host disease. It is difficult to determine if this was just a coincidence, but we have observed this phenomenon.” Dr. Marr noted research by David Perlin et al. that described a mutation in the Fks1p subunit of the glucan synthase gene that confers reduced susceptibility in *Candida* species and noncandidal yeast species.<sup>23</sup> “With these initial mechanisms identified, we might be in the early

stages of appreciating the microbial adaptations that can occur when patients are exposed to the agents for a long period of time,” concluded Dr. Marr.

“Dr. Pfaller, have you seen a higher prevalence of drug resistant strains in your research?” asked Dr. Perfect.

“In our surveys, more than 99% of clinical isolates of *Candida* species are still fully susceptible, meaning that they have a minimum inhibitory concentration [MIC] of less than 2 micrograms per milliliter to all three of the available echinocandins. In clinical practice, echinocandin resistance is likely going to be a rare event for some time,” hypothesized Dr. Pfaller. “However, a common theme is appearing in cumulative case reports and case series of very sick patients who have been in the hospital for an extended period of time and have been exposed to a wide range of agents. These patients have a persistent focus of infection with organisms that have already been challenged with other classes of antifungal agents and survived. The echinocandins are still active, but a greater drug exposure may be required to address the infection. Consequently, the phenomenon that Dr. Marr described in which patients with a dose de-escalation of echinocandin therapy developed clinical resistance does not surprise me. I believe that we should think about these agents in the same way that we think about fluoroquinolones and bacterial resistance—resistance in organisms such as *Streptococcus pneumoniae* is rare, but certain levels of drug exposure will result in the emergence of resistance mutations. We should remember that point mutations in the Fks1p gene are needed to reach a high level of echinocandin resistance, which is analogous to bacterial resistance to fluoroquinolones. As a consequence, resistance will occur in certain clinical settings—these patients have exhausted all other clinical options because they are already resistant to multiple drugs.”

“In my experience, I occasionally have patients with candidemia who break through

on echinocandin therapy or exhibit persistent infection, but the isolates that we have evaluated in these patients continue to have relatively low MICs,” noted Dr. Perfect. “We usually think of persistent infection as being related to neutropenia in the patient, or a complication of a catheter line or other device. Dr. Pappas, what is your experience in this area?”

Dr. Pappas agreed with Dr. Perfect’s observation, stating, “In most of the patients that we see with persistent candidemia despite what should be effective echinocandin therapy, the cause is typically a mechanical problem with a retained prosthetic device, such as a prosthetic heart valve that is persistently infected, or an IV catheter.” He reported that he has treated some patients in whom he could not clear the candidemia despite the administration of what he thought should have been effective therapy. “At our institution, we do not analyze isolates for echinocandin susceptibility on a regular basis, so it is impossible to say if the causative organisms had higher MICs, but they were certainly clinically resistant.” Fortunately, he noted, resistance to echinocandins has been uncommon in his clinical experience. “However, if a patient is failing therapy despite the use of an echinocandin, I would immediately investigate the management of the IV catheter, and consider an echocardiogram to assess possible valvular involvement in selected patients.”

“Do you think that any issues exist with respect to proper dosing of echinocandins?” queried Dr. Perfect. “Do you worry about needing to administer progressively higher doses in some patients, and the resistance issues that could potentially ensue?”

“Some *in vitro* data do exist that fungicidal activity decreases at high levels of caspofungin, but this was not replicated in an animal model of infection,” replied Dr. Pappas. He further explained, “Meanwhile, recent data with micafungin that has yet to be published demonstrated better, but not statistically different, efficacy at a dose of 100 mg

than 150 mg, which one may not necessarily expect. It is difficult to know for sure, but in the vast majority of patients the doses that we use are appropriate and we are not likely to see a greater benefit by increasing the dose.”

Dr. Pfaller summarized, “At this point, we are certainly not at a crisis point with respect to any antifungal resistance issues. Institutions with high levels of *C. glabrata* and consequent azole resistance may benefit from the decreased use of azoles and a temporary increase in echinocandin use, even though this may increase the overall expense of therapy. This is the most common resistance issue with respect to antifungal therapy.” He said that excellent means exist for performing fluconazole susceptibility testing to predict whether an organism will respond to other azoles, “and this strategy will allow us to use the lower cost azoles in susceptible organisms, as opposed to the more expensive echinocandins.”

## Clinical and Pharmacologic Issues

### *Pharmacologic Issues in Antifungal Therapy for Invasive Disease*

Important pharmacologic issues are present in the management of invasive fungal infections due to the potential toxicity of antifungal agents and the amount of concomitant therapies that most patients are receiving. Dr. Perfect requested that the panel discuss these issues, asking, “What are the most important interaction issues in patients receiving multiple concomitant drugs with these antifungal agents? Do these issues affect the choice of antifungal therapy? Overall, what are the most important safety issues to consider, and what is the role of therapeutic monitoring?”

Dr. Drew responded, “Multiple sources of interactions can occur with these agents, including drug-drug and drug-food interactions. Absorption is an important issue with azole drugs that can be affected by food in-

take. Oral posaconazole, for example, should ideally be taken with a full, high-fat meal. So, the first step to ensure drug efficacy is to be aware of the optimal conditions for administering the drug with the perspective of food intake.” This is not an issue with IV administration. From the perspective of drug-drug interactions, he explained, the most important issues are interactions in the cytochrome P450 system, especially with azole antifungal therapy. “However, any interactions between antifungal agents and concomitant immunosuppressive agents are obviously going to be of great clinical significance. Clinicians need to be aware of the potential for these interactions in susceptible patients, as well as the steps that can be taken to resolve issues that could arise. Ultimately, I would suggest that clinicians should closely monitor immunosuppressive therapy in patients receiving any azole therapy.”

“How effective are physicians in identifying the potential for these drug interactions? Can this be a source of medical error when potential interactions are not properly identified?” asked Dr. Perfect.

“Yes, the potential does exist for medical error, but the risk can be reduced with effective frontline personnel who have extensive experience with the patient population and the strategies for dealing with potential drug interactions, whether they be physicians, pharmacists, or nurse clinicians,” said Dr. Drew. He added, “Automated systems are useful for raising potential red flags, but they do not address the clinical relevance of potential interactions or the steps that can be taken to monitor or manage drug interactions.”

“I want to emphasize the importance of having regular access to a hospital pharmacist who can help identify and manage potential drug interaction issues,” Dr. Pappas interjected. “Unfortunately, the automated systems designed to identify potential problems are easily ignored.”

“The issue of drug interactions can be very complicated, especially in organ or stem

cell transplant recipients with graft versus host disease,” Dr. Marr added. “Physicians know that they need to decrease the dose of cyclosporine with invasive infection, but they do not want to adjust the dose to the point that they may be at risk for organ rejection. Consequently, they may be more likely to increase the dose of antifungal therapy or cycle through different antifungal therapies, which raises the issue of cycling toxicities and the potential for resistance.”

Dr. Drew agreed, emphasizing the importance of knowing how to manage antifungal therapy with azole agents when interactions with immunosuppressive therapy arise.

“In my experience,” submitted Dr. Perfect, “the issue of drug interaction extends beyond immunosuppressive agents to include cardiovascular therapies and drugs to manage a host of comorbidities that present in these patients. In some patients, the potential for cardiac complications such as prolonged QT interval and torsades is a major concern to me. Even though the echinocandins are associated with some interactions, they may be more attractive than the azoles due to these issues of drug interactions, especially with respect to the cytochrome P450 enzyme system.”

“In terms of safety issues, it is well established that the patients we are treating for invasive fungal infections are very ill, and their reserves are low. Many of these patients have already undergone chemotherapy or immunosuppressive therapy, and they have already confronted considerable safety issues with other agents, including nephrotoxicity and hepatotoxicity,” said Dr. Drew. He explained that the decreased potential for safety issues makes echinocandins attractive, especially relative to amphotericin B. While infusion reactions have been noted with the use of echinocandins, these can be managed in most patients by slowing the infusion or making other adjustments, according to Dr. Drew. He emphasized, “Overall, the echinocandins are a much friendlier class of drugs, especially compared with amphotericin B. However, I do not think that it would be wise

to become complacent about monitoring echinocandins and the safety issues that may arise, because these agents are still associated with a low risk of hepatotoxicity.”

Dr. Perfect next asked the panel to discuss the clinical significance of therapeutic monitoring of patients being treated with azoles.

Dr. Drew explained that the concentrations of older drugs such as flucytosine were monitored due to potential toxicity issues. Meanwhile, patient-to-patient pharmacokinetic differences and the potential for exposure variability have also been observed with select azole compounds. “We have wanted to monitor some of the azole compounds for a number of reasons. With itraconazole therapy, we were documenting drug absorption. Efficacy and safety data are still emerging on the newer azoles, including voriconazole and posaconazole, and there may be some safety issues with voriconazole, at least at high serum concentrations.” Finally, genetics may also play a role in the metabolism of voriconazole. Echinocandins are not generally associated with these issues, he noted, so there has been no real clinical impetus to monitor these agents. “Ultimately, it is important to note that in these very sick patients, exposure to antifungal therapy may be one of the few factors that physicians can reliably control,” he emphasized. Dr. Drew added, “If exposure to azole drugs has the potential to be highly variable, then perhaps serum concentration monitoring is warranted in select situations, as some have proposed.”

“But you may be asking for too much to say that we need more outcomes data to determine the need for therapeutic drug monitoring,” countered Dr. Marr. “Outcomes data in these invasive fungal infections are incredibly difficult to gather in the face of multiple confounding clinical factors. Asking to experimentally demonstrate that outcomes are different based on drug levels may be unreasonable.”

Dr. Drew cited evidence that suboptimal outcomes with voriconazole levels of less than 2 µg/mL, and toxicity with levels of

more than 6 µg/mL. He asked Dr. Marr, “Should the therapeutic level for voriconazole be defined as being from 2 µg/mL to 6 µg/mL?”

“That does seem to be a reasonable interval, although the high end of 6 µg/mL was identified in phase I studies with healthy volunteers, and I think that it would be a mistake to use the same cutoff value in such a complicated patient population,” answered Dr. Marr.

Dr. Pfaller offered, “I wanted to note that the draw times for blood samples in previous studies were subject to a certain degree of randomness. If we are going to analyze drug levels and link these with outcomes, we need to standardize the draw time, which I propose as being during trough drug levels. I also suggest that the target trough level should be 1 µg/mL, to encompass the vast majority of organisms that are being addressed.”

Dr. Perfect cited recently published data of his own from a case-control study that investigated the efficacy and safety of posaconazole 800 mg/day in patients with invasive aspergillosis or other mycoses who were refractory to standard antifungal therapy; outcomes in these patients were compared with a retrospectively analyzed, matched control group. The overall success rate of posaconazole was 42% compared to 26% in the matched control group, but there was some suggestion that patients with low levels of drug exposure had poorer outcomes.<sup>24</sup> “I do think we need to pay attention to drug exposure and absorption, especially with oral drugs,” concluded Dr. Perfect.

“I agree that it is usually easiest to deliver a drug intravenously, which is not possible in the case of posaconazole,” declared Dr. Drew. “We need to understand, however, that we have been investigating the majority of these drugs in prophylaxis trials, and a high number of the patients enrolled are not sick to begin with. However, there are some data with salvage therapy, and Dr. Marr would be the one with the most experience with this pop-

ulation.” One trial reported the utility of posaconazole as a salvage therapy in patients requiring surgery for invasive fungal infection,<sup>25</sup> while another trial reported its use as salvage therapy in zygomycosis.<sup>26</sup>

## Clinical Issues in Invasive Fungal Disease

“Let’s move on to discuss clinical issues in the management of invasive fungal disease,” suggested Dr. Perfect. “When treating invasive candidiasis, how does the clinician choose an agent by class and what is your ranked preference of each class for invasive candidiasis?”

“The only agents that should be considered as initial therapy in the setting of invasive candidiasis are fluconazole, the echinocandins, and rarely, amphotericin B,” Dr. Pappas asserted. If the patient is at increased risk, has proven or suspected invasive candidiasis, and is being managed in the ICU, he would choose to start therapy with an echinocandin. Personally, he believes that choosing between the three echinocandins is not important. “So, from my perspective, initial therapy in the vast majority of my patients with proven or suspected candidiasis is going to be with an echinocandin. I may, however, consider fluconazole initially in a patient who is normotensive, only modestly febrile, and has had no prior fluconazole exposure. At some level, we all have to make an assessment as to the level of illness for an individual patient, and there are some patients in whom fluconazole as primary therapy is appropriate. Unfortunately, most of them do not reside in the ICU.” He noted, however, that echinocandins are not practical in resource-strapped environments, in which case amphotericin B is often used due to its considerably lower price. Where echinocandins are feasible, however, amphotericin B has been largely supplanted due to the risk of renal dysfunction and the ensuing higher mortality risk

and associated costs stemming from this complication.

“If you knew, though, that over 70% of your candidemia cases over the past three years were due to *C. albicans*, would this change your choice of initial therapy?” posed Dr. Pfaller.

“If you are at an institution that uses lots of fluconazole, then you do need to consult with your hospital epidemiologist and have causative organisms identified to the species,” Dr. Pappas replied. “If susceptibility testing is not routinely performed—and our previous discussion suggests that it is not—then you must identify the causative organism to the species level. These findings can determine your therapeutic choice.” Dr. Pappas did contend that overall, echinocandins have demonstrated success rates approaching 85% for invasive candidiasis due to *Candida albicans*. “The consistent superiority of echinocandins cannot be ignored. If I have a patient that I have identified as being very ill, I start with an echinocandin and then transition to fluconazole when appropriate, meaning when the patient is afebrile and normotensive, and I have identified the organism,” concluded Dr. Pappas.

Dr. Marr offered, “I think that fluconazole is a good alternative to amphotericin B due to its lower toxicity, and now we have the echinocandins that take this a step further. However, I disagree with Dr. Pappas’ comment that all three of the echinocandins are indistinguishable from each other, and I think we may find in the future that each agent has notable differences, and that each may perhaps work differently from a microbiologic perspective,” countered Dr. Marr.

Dr. Pappas responded, “I agree that the drugs are each going to behave differently, but I am doubtful that a clinically relevant difference will be detected without an enormous clinical trial.”

“Eventually, the drug-resistant organisms will help demonstrate the differences between the echinocandins in the clinical setting,” responded Dr. Marr.

Dr. Pappas conceded, “Yes, I agree.”

Then Dr. Drew turned to Dr. Pappas, asking, “Could I pose a follow-up question with regard to *C. glabrata* and dose-dependent susceptibility? In smaller community hospitals, we are often unable to routinely use echinocandins due to cost issues, and fluconazole is still the most common choice. Also, fluconazole is still common in the surgical ICU, where *C. albicans* remains the predominant causative fungal species. For clinicians practicing in these settings, which dose of fluconazole is optimal in patients with normal renal function?”

Dr. Pappas cited a randomized, blinded, multicenter study by Rex et al. from the National Institute of Allergy and Infectious Diseases Mycoses Study Group which compared fluconazole to fluconazole plus amphotericin B in the treatment of non-neutropenic patients with candidemia. He explained, “When the trial was conducted, no new agents were available, including the echinocandins, so we increased the dose of fluconazole to 800 mg per day, especially because an increase in fluconazole MICs in *C. glabrata* had been observed. Success rates with the 800 mg fluconazole monotherapy regimen were 56%, while the combination regimen resulted in a success rate of 69%.<sup>27</sup> So the argument for a higher initial dose, other than a loading dose, has not been supported by recent studies.”

“Recent studies have reported that a lower level of drug exposure relative to MIC was a predictor of mortality in candidemia in a four-hospital study,” noted Dr. Pfaller. Investigators noted the dose-dependent properties of fluconazole, and concluded that underdosing of fluconazole in the presence of less-susceptible *Candida* isolates could potentially increase mortality risk due to candidemia.<sup>28</sup> He added, “It is important to understand that the investigators looked at weight-based dosing, and evaluated both the area under the concentration curve to MIC ratio as well as the dose to MIC ratio.”

Dr. Pfaller also cited data from two studies published by Andes et al. in *Antimicrobial Agents in Chemotherapy*, which reported that drug resistance occurred in animal models and *in vitro* models of prolonged, sub-MIC exposure to fluconazole.<sup>29,30</sup> “There are a number of data sources that support optimal dosing, but we still have not discovered the optimal dose to MIC ratio,” concluded Dr. Pfaller.

Dr. Drew concurred, “We still do not have bedside MIC data for these patients. Meanwhile, the clinician is trying to decide between a dose of 400 mg and 800 mg. The easy answer is to use the highest dose that is safe. Surgeons, in fact, have moved to the 800 mg dose quite readily.”

“We do know that the MIC90 drug concentration required to inhibit 90% of all isolates tested for *C. albicans*, *C. parapsilosis*, or *C. tropicalis* is 1, and the MIC90 for *C. glabrata* is in the range of 16 to 32,” added Dr. Pfaller. “If one does the math, it clearly shows that the vast majority of patients infected with *C. glabrata* species will be sub-optimally dosed at levels below 800 mg. A dose of 400 mg would be safe for all other species that are effectively treated with fluconazole. This is all that we know at this point.”

“To touch base on some other important management issues, how would you manage breakthrough fever in high-risk patients receiving prophylaxis with the extended-spectrum azoles that have activity against both yeast and moulds?” asked Dr. Perfect.

Dr. Marr replied, “I would either give the safest drug possible or do nothing at all. We should really take pause and try to determine the cause of the fever with the agents on board before reflexively reaching for another broad-spectrum agent. For instance, in a high-risk transplant recipient, we are worried about moulds and perhaps *C. glabrata* breaking through azole therapy.” However, the likelihood that one of these organisms is the cause of the fever is exceedingly small, and Dr. Marr noted that “Sometimes clinicians try to cover any potential cause of the

fever with the addition of more extended-spectrum azoles at the expense of the patient’s organ function in terms of interaction with immunosuppressive therapy or hepatic toxicity. Otherwise, we administer polyenes such as amphotericin B that can cause renal insufficiency. Overall, we spend a large amount of money treating fever during neutropenia, but we are actually preventing and treating few infections in this setting. Therefore, I think that we should sit back and consider the best tools to diagnose the cause of the fever, and then prescribe the safest drugs possible—in this case echinocandins—when necessary.”

Pressing further, Dr. Perfect asked, “If you would give an echinocandin first, would you worry about coverage for moulds?”

“I would likely give an echinocandin and follow this up with a CT scan of the chest to rule out an invasive mould infection of the lungs,” Dr. Marr responded. “Obviously, if there is evidence of invasive aspergillosis or zygomycosis, then I would rearrange my therapeutic plan accordingly.”

“Your emphasis on pausing in the presence of fever to perform some diagnostic tests, including the CT scan, biomarkers, BAL, and other tools is something important that I think should be emphasized,” noted Dr. Perfect.

“Yes, but I should mention the large caveat that it is easy to sit among my fellow panelists and discuss withholding therapy in the absence of identification of the cause of a fever,” responded Dr. Marr, “but it is much harder to watch a patient remain febrile for a long period of time when you know that it could be due to an underlying infection that you have not treated. This is common right now, evidenced by standard practices that have been defined by our clinical studies. More often than not we are practicing medicine with litigious issues in mind, frankly. One of the most important clinical trial needs in this area is a large-scale outcomes study that addresses our current strategy of treating fever with empiric therapy.”

“I support these ideas,” concurred Dr. Perfect. “We must be very cautious in handling a fever of unknown etiology, and should recognize that the fever alone may not be an important issue from a clinical standpoint. However, if the fever is due to an underlying fungal infection, clinical experience has shown us that we need to address that fungal infection as soon as possible to prevent adverse outcomes. Ultimately, we need consistent strategies to approach fever in these high-risk patient populations,” he concluded. “And, as we complete this discussion of management issues, I would like to address the final point of the utility of combination antifungal therapy to treat mould infections.”

“Honestly, it is difficult to predict where this therapeutic strategy is heading,” Dr. Marr declared. “Studies still need to be performed in a way that will allow us to most efficiently answer the right questions to adopt this strategy in clinical practice.” Based on limited animal studies, *in vitro* studies, and Dr. Marr’s own anecdotal experience in clinical practice, she believes that a combination regimen appears to not cause harm. For instance, adding an echinocandin to voriconazole in aspergillosis does not cause overt adverse effects, but it may be an unnecessary waste of drugs and resources. “Right now, in the absence of randomized clinical studies, I think that it is best to evaluate each patient for their overall risk, underlying disease, stage of disease, potential duration of neutropenia, and the level of other immunosuppressants, such as steroids, needed to treat graft versus host disease.” One review of the literature concluded that a combination strategy may be beneficial in carefully selected high-risk patients, but likewise highlighted the need for randomized clinical studies.<sup>31</sup>

Dr. Pappas agreed, “I am agnostic about the issue of combination therapy as well, but I do not see any harm in administering a second agent. In our institution, we are a little

less aggressive, and it is common to begin with monotherapy. I think it is also critical to realize the limitations of anecdotal evidence from one center when making treatment decisions,” and he noted that the choice of therapy and subsequent outcomes may reflect inherent biases of the center as well their specific patient composition, the extent of their underlying disease, and other factors. “The only way to definitely address our concerns surrounding combination therapy is to conduct a well-controlled clinical trial. If we are interested in the answer to this important clinical and therapeutic question, then we will need to participate and enroll patients in a well-designed prospective study.”

Dr. Perfect noted that cryptococcal meningitis is an example of an infection that is historically treated with combination therapy. He then asked the panel to share how they would address this sample infection.

“I can provide my opinion, which is largely based on data,” offered Dr. Pappas. “I address cryptococcal meningitis from a few different approaches. First, it is a safe assumption that all patients with confirmed cryptococcal meningitis should receive amphotericin B as opposed to fluconazole as first-line therapy.” Data suggest that unless the physician chooses to employ a high dose of liposomal amphotericin B of 6 mg/kg, then conventional amphotericin B is likely a better choice. “This is the one disease state for which I think conventional amphotericin B is a better choice than liposomal amphotericin B. Also, flucytosine is appropriate when available; it is convenient because it is available in an oral formulation, although it does represent some challenges in terms of monitoring. Overall, we have fallen into some problems in the management of cryptococcal meningitis as we have completely removed ourselves from our original approach of applying the standards of treating HIV patients to everyone else with the infection. While we often switch a patient from amphotericin B to oral fluconazole after two weeks if the

patient looks slightly better, this may be a mistake.” He emphasized that every patient needs to be evaluated and treated on an individual basis. While it is appropriate to evaluate the patient for progress at two weeks, Dr. Pappas expressed that it may not always be wise to then switch the patient to fluconazole, as is done in some practices. “Finally, I want to emphasize the importance of pressure management. Our ability to effectively manage pressure can impact the risk of long-term residual morbidity, if not mortality, in these patients. There is evidence from Thailand, for instance, where they manage pressure very aggressively with lumbar punctures once or twice daily until the cerebral edema subsides and this is no longer necessary. To summarize, aggressive pressure management and initial amphotericin B therapy, with or without the addition of flucytosine, is the most appropriate strategy at this point to manage cryptococcal meningitis and produce good long-term outcomes.”

## Final Thoughts

“The development of echinocandins represents one of the most important developments in mycology in recent years, and they now have a place of preeminence in the treatment of most forms of invasive candidiasis, with the exception of infections of the central nervous system,” Dr. Pappas offered as his concluding message for this *Medical Crossfire*. “The echinocandins have supplanted amphotericin B, even in infective endocarditis, although there currently exists scant data on their use in this type of infection. Finally, I would again like to emphasize the importance of effective pressure management in cryptococcal meningitis.”

“I want to underscore the importance of making an etiologic diagnosis and supporting the mission of microbiology laboratories to arrive at a definitive diagnosis, especially with respect to yeast and hopefully with

moulds, as well,” Dr. Pfaller contributed. “This is of primary importance when managing these patients, especially in high-risk patients who have already been exposed to two or more different classes of antifungal therapies. The potential for infection with an unusual organism certainly exists with these high-risk patients, and it will be impossible to treat the patient appropriately without an etiologic diagnosis. Even in the case of infection with a common organism, the potential certainly exists for mismanagement without identification of the causative organism. Although molecular diagnostics for etiologic identification are promising, the lack of personnel to perform these tests limits their utility in daily practice. I would therefore suggest that clinicians responsible for the management of these high-risk patients make every effort to support the laboratory within their respective institution.”

“I am excited about the expanding armamentarium to tackle complex infections, and their potential to advance therapy in high-risk patients,” declared Dr. Drew. “On the other hand, we need to do a better job of using the agents that are available to us. This means more effective dosing strategies and more careful risk assessment evaluations in choosing regimens for both prophylaxis and preemptive therapy. We must use the tools that we have more wisely,” he concluded.

Dr. Marr concurred with Dr. Drew, stating, “I agree that the availability of new treatments is exciting, because this gives us a starting point to discuss some of the important clinical issues that we face, even in these complicated, high-risk patients. However, I want to emphasize the fact that we are treating people, not their infections. Simultaneously, we are trying to prevent these infections in people. We should really be spending more time talking about some of the ‘off-target’ variables that are important to consider aside from the microbiologic data, especially end-organ toxicity and drug interactions, now that we have these new options to manage these complex patients.” ■

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# Optimizing Treatment of Invasive Fungal Diseases

## CME Test

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1. Cross-resistance issues between azole antifungal therapies are most common in which yeast species?
  - a. *Candida glabrata*
  - b. *Candida albicans*
  - c. *Candida krusei*
  - d. *Candida parapsilosis*
2. A clinically stable patient receiving an echinocandin could be transitioned to fluconazole if it was determined that which of the following organisms caused the invasive fungal infection?
  - a. *Aspergillus*
  - b. *C. glabrata*
  - c. *C. albicans*
  - d. *Rhizopus*
3. Which assay can be used to detect *C. albicans* in blood cultures?
  - a. beta-glucan enzyme immunoassay
  - b. nucleic acid fluorescence stains
  - c. galactomannan immunoassay
  - d. susceptibility testing
4. The following has *not* been cited as a factor that can cause false positives in beta-glucan testing:
  - a. antifungal therapy
  - b. piperacillin/tazobactam beta-lactam therapy
  - c. the presence of candidemia
  - d. the presence of a Gram-positive infection
5. The beta-glucan immunoassay has been used reliably to
  - a. rule out invasive fungal infection.
  - b. avoid unwarranted use of antifungal therapy.
  - c. allow for early initiation of antifungal therapy.
  - d. all of the above
6. Which yeast species has demonstrated the most variability in susceptibility to fluconazole?
  - a. *C. parapsilosis*
  - b. *C. glabrata*
  - c. *C. tropicalis*
  - d. *C. krusei*
7. Resistance to echinocandins has been reported in patients who exhibit which of the following qualities?
  - a. previous exposure to a wide range of antifungal agents
  - b. no previous exposure to fluconazole
  - c. colonization with *C. glabrata*
  - d. colonization with *C. albicans*
8. Which of the following is the most clinically significant drug-drug interaction issue with antifungal therapy?
  - a. interactions in the cytochrome P450 system
  - b. interactions with immunosuppressive regimens
  - c. both a and b
  - d. none of the above
9. A patient with which of the following clinical traits and evidence of invasive candidiasis would *not* be considered a good candidate for initial fluconazole monotherapy?
  - a. intensive care unit (ICU) admission due to infection
  - b. normotensive
  - c. modestly febrile
  - d. no prior fluconazole exposure
10. How should clinicians manage breakthrough fever of unknown etiology in high-risk patients receiving prophylaxis with an extended spectrum azole?
  - a. immediate switch to fluconazole
  - b. immediate switch to amphotericin B
  - c. use of another extended-spectrum azole
  - d. diagnostic workup to determine the cause of the fever

1. a. While cross-resistance is not really an issue for some *Candida* species such as *C. krusei*, the pathogenic yeast *C. glabrata* demonstrates cross-resistance between azole drugs, so voriconazole therapy after patient exposure to fluconazole, for instance, is not recommended.

**Locator:** Clinical Trial Updates: Treatment Trials

2. c. Dr. Pappas noted that if a clinically stable patient was receiving an echinocandin and it was subsequently determined that the causative organism was *C. albicans* or *C. parapsilosis*, it would be appropriate to transition the patient to fluconazole.

**Locator:** Clinical Trial Updates: Treatment Trials

3. b. Nucleic acid fluorescence stains are available to identify *C. albicans* directly from blood cultures. While this test is not commonly used, it may be very cost effective in a setting where up to half of candidemia cases are due to *C. albicans* and echinocandins are used broadly.

**Locator:** Diagnostic and Resistance Issues: Beta-Glucan and Galactomannan Immunoassays

4. c. In a report of beta-glucan testing in ICU patients, the test was very sensitive in patients with documented candidemia, and was very specific in patients without any infection. However, in patients with bacteremia—most often due to Gram-positive organisms—a number of false positive results arose that were not easily explained. The test does need to be performed very scrupulously and in replicate, and is subject to contamination. Antifungal therapy, including prior therapy, does have the potential to cause false positives with the beta-glucan assay. Finally, it is possible that beta-lactam antibiotics can cause the same issues, especially piperacillin/tazobactam beta-lactam therapy.

**Locator:** Diagnostic and Resistance Issues: Beta-Glucan and Galactomannan Immunoassays

5. d. In a recent study of the beta-glucan immunoassay in a population of patients with high-risk neutropenia, the outcome benefit demonstrated with the use of the test was the avoidance of antifungal therapy. Patients with neutropenia were screened with a galactomannan enzyme immunoassay and underwent a diagnostic evaluation that included thoracic computed tomography scanning and bronchoscopy with lavage. Amphotericin B was administered only to patients who were seropositive, had a positive microbiologic test result, and had radiological findings consistent with invasive fungal infection. This strategy reduced the rate of amphotericin B use by 78% and resulted in early initiation of antifungal therapy in 10 cases that were not clinically suspected as being invasive fungal infection.

**Locator:** Diagnostic and Resistance Issues: Beta-Glucan and Galactomannan Immunoassays

6. b. The International Fungal Surveillance Participant Group concluded that little variation occurred in fluconazole susceptibility in *C. parapsilosis*, *C. tropicalis*, or *C. krusei* from 1992 to 2001, while fluconazole susceptibility in *C. glabrata* was highly variable during this period.

**Locator:** Diagnostic and Resistance Issues: Epidemiology of Drug Resistance

7. a. A common theme is seen in cumulative case reports and case series of very sick patients who have been in the hospital for an extended period of time and have been exposed to a wide range of agents. These patients have a persistent focus of infection with organisms that have already been challenged with other classes of antifungal agents and survived. The echinocandins are still active, but a higher dosage of drug exposure is required to address the infection.

**Locator:** Diagnostic and Resistance Issues: Epidemiology of Drug Resistance

8. c. In terms of drug-drug interactions with antifungal therapy, the most important issues are interactions in the cytochrome P450 system, especially with azole antifungal therapy. However, any interactions between antifungal agents and concomitant immunosuppressive agents are obviously going to be of great clinical significance.

**Locator:** Clinical and Pharmacologic Issues: Pharmacologic Issues in Antifungal Therapy for Invasive Disease

9. a. If the patient is at increased risk, has proven or suspected invasive candidiasis, and is being managed in the ICU, Dr. Pappas emphasized that he would choose to start therapy with an echinocandin. Personally, he believes that choosing between the three echinocandins is not important. “So, from my perspective, initial therapy in the vast majority of my patients with proven or suspected candidiasis is going to be with an echinocandin. I may, however, consider fluconazole initially in a patient who is normotensive, only modestly febrile, and has had no prior fluconazole exposure.”

**Locator:** Clinical and Pharmacologic Issues: Clinical Issues in Invasive Fungal Disease

10. d. Dr. Marr noted, “I would either give the safest drug possible or do nothing at all. We should really take pause and try to determine the cause of the fever with the agents on board before reflexively reaching for another broad-spectrum agent. Sometimes clinicians try to cover any potential cause of the fever with the addition of more extended-spectrum azoles at the expense of the patient’s organ function in terms of interaction with immunosuppressive therapy or hepatic toxicity. Therefore, I think that we should sit back and consider the best tools to diagnose the cause of the fever, and then prescribe the safest drugs possible—in this case echinocandins—when necessary.”

**Locator:** Clinical and Pharmacologic Issues: Clinical Issues in Invasive Fungal Disease

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