ISSUE 2 CME/CE Newsletter

Preventing & Managing IFIs in the 21st Century

From Pre-Emptive to Salvage Antifungal Therapy: Achieving Successful Outcomes

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IN THIS ISSUE . . .

With the development of new diagnostic techniques and the availability of novel and next-generation antifungal agents, patient management strategies have been constantly evolving based on the latest research findings. One area under consideration is the trend of moving away from empiric therapy and the adoption of pre-emptive approaches for initiating antifungal treatment. Evidence supporting a pre-emptive strategy is still limited, though in theory it should provide some important advantages compared to empiric therapy.

Regardless of the strategy to initiate antifungal therapy, a significant proportion of high-risk patients will unfortunately not respond favorably to treatment. In these cases, it will be critical to understand the reason for clinical failure before attempting alternate management strategies. The next steps must also be based on recognizing factors related to the host, pathogen and drug. In this newsletter, the areas of empiric versus pre-emptive therapy and strategies for salvage treatment will be discussed based on the latest research findings to help guide clinicians when managing these difficult-to-treat infections.

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Knowledge-based and competence-based

TARGET AUDIENCE
This activity has been developed for clinical pharmacists, infectious diseases physicians, hematologists/oncologists, and transplant physicians responsible for the management of IFIs.

PURPOSE STATEMENT
The purpose of this activity is to educate physicians and pharmacists involved in the management of patients at risk of invasive fungal infections (IFIs) on treatment of IFIs. With this knowledge, healthcare professionals will be able to select appropriate antifungal therapy at various stages of infection—from pre-emptive to salvage therapy.

LEARNING OBJECTIVES
At the conclusion of this activity, learners should be able to

- Distinguish between the advantages of a pre-emptive strategy and empiric treatment when managing patients with IFIs
- Identify the causes of treatment failure and recognize options for salvage therapy

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ACCREDITATION
Physicians

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Off-label Disclosure Statement

During this activity, off-label use of the following antifungal agents will be discussed: fluconazole (for empiric therapy in febrile neutropenic patients), itraconazole (for empiric therapy in febrile neutropenic patients), voriconazole (for empiric therapy in febrile neutropenic patients and for refractory infections caused by *Aspergillus, Candida*, and *Cryptococcus*); caspofungin (for refractory infections caused by *Candida*); posaconazole (for refractory infections caused by *Aspergillus*, *Fusarium*, and *Cryptococcus*); liposomal amphotericin B (at a dose of 10 mg/kg); voriconazole/caspofungin combination therapy (for treatment of invasive aspergillosis).

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The topic of empiric versus pre-emptive antifungal therapy has garnered much attention recently given the new diagnostic techniques that allow for screening and early detection of invasive fungal infections (IFIs). In order to understand the differences of these two management strategies, it is important to first define each of them. In both cases, the patient is beyond antifungal prophylaxis and an IFI has entered the differential at some level of clinical suspicion. *Empiric therapy* is treatment with an antifungal agent when a fungal infection is suspected, but not yet confirmed. Patients with febrile neutropenia who are likely to have an infection even though no markers for an IFI are evident are often given antifungal empiric therapy.

The term *pre-emptive therapy* is used to describe a more targeted approach of antifungal therapy, when a patient is suspected of having an IFI and has at least one positive marker through a diagnostic test that suggests a fungal infection. Common diagnostic tools used for pre-emptive therapy include serum assays (such as β-D-glucan assay and galactomannan assay) or a high-resolution CT (HRCT) scan, which were described in greater detail in the first newsletter of this series. A pre-emptive approach has the benefits of treating a smaller number of patients suspected of IFIs, thereby reducing the risk of adverse events and drug-drug interactions associated with antifungal agents. This approach also has the added side benefit of decreasing pharmacy costs.

Empiric Therapy

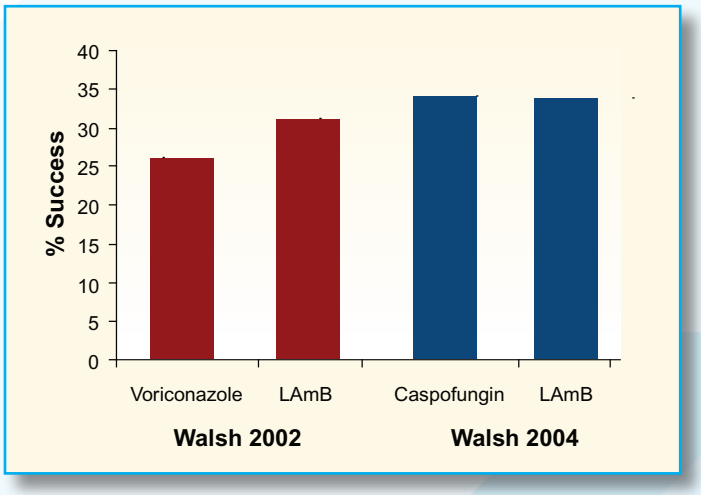
Studies have consistently shown increased mortality rates when effective antifungal therapy has been delayed.[1-3] Therefore, empiric therapy can be imperative in initiating treatment at the first signs of an infection, particularly in high-risk populations such as oncology and transplant patients. Empiric therapy is driven by evidence-based guidelines, such as those released by the National Comprehensive Cancer Network (NCCN) and the Infectious Diseases Society of America.[4, 5] For neutropenic patients, NCCN recommends considering antifungal therapy with activity against molds in patients with fever for 4 or more days of empiric broad-spectrum antibacterial therapy.[4] In addition to national guidelines, many institutions have adopted local guidelines that dictate the timing of initiation and selection of a specific agent based on the local epidemiology of infection.

Choosing an Agent for Empiric Therapy

Several studies have evaluated the use of different antifungal classes for empiric therapy of neutropenic patients. Early studies demonstrated the effectiveness of amphotericin B deoxycholate (AmBd) for empiric therapy, and these studies were the basis of using amphotericin B for empiric therapy for subsequent years.[6, 7] However, AmBd has several toxicities associated with its use, including nephrotoxicity and infusion-related reactions.[8] The lipid formulations of amphotericin B (LFAmB) offer similar efficacy as AmBd with fewer adverse events.[9] Head-to-head comparisons of the lipid formulations tend to show no difference in efficacy and no definitive differences in the safety profile of these agents.[10, 11]

Among the azoles, fluconazole, itraconazole, and voriconazole have all been shown to offer benefit to patients with febrile neutropenia.[12-15] However, it is important to note that fluconazole does not exhibit activity against *Aspergillus*, which should be considered in patients at risk of molds infections. A comparative study of voriconazole versus liposomal amphotericin B (LAmB) showed a lower success rate with voriconazole (26% vs. 31%)**(Figure 1)**.[15] However, significantly fewer patients receiving voriconazole experienced breakthrough infections (1.9% vs. 5%; $P<.05$). Although it is not FDA approved for empiric therapy in neutropenic patients, voriconazole offers an alternative to amphotericin B that has fewer toxicities and provides the option for oral administration.

Figure 1. Success rates of empiric antifungal therapy in febrile neutropenia patients[15, 16]



The echinocandins are generally well tolerated with few drug-drug interactions. Though only available in IV formulations, the echinocandins exhibit activity against yeasts and molds, with the most significant exceptions being *Cryptococcus* and the Zygomycetes. In a randomized, double-blind trial, caspofungin was compared LAmB in febrile neutropenic patients (N=1095) and showed similar efficacy between the two treatments (33.9% for caspofungin and 33.7% for LAmB) **(Figure 1)**.[16] Caspofungin did show a benefit in survival at the 7-day follow-up (92.6% vs. 89.2%; *P*=.05).

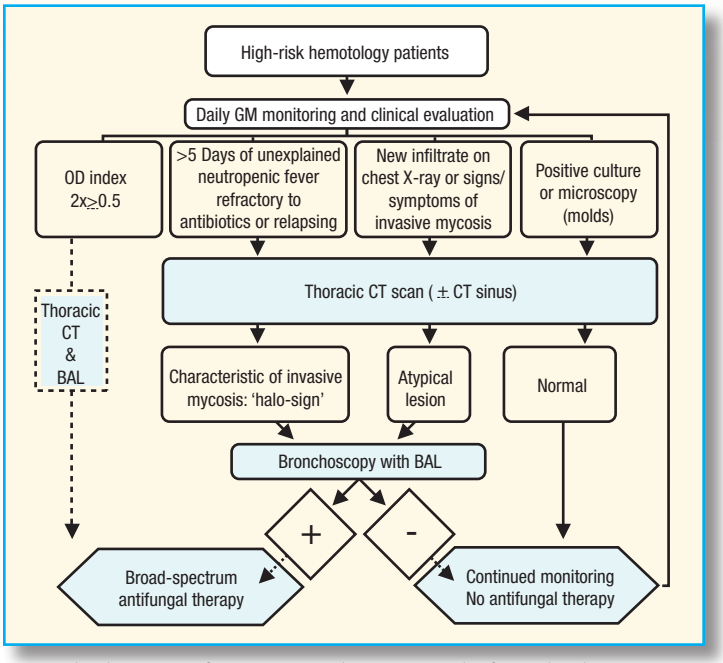
Based on multiple studies completed within the past decade for candidemia the IDSA has released updated guidelines for the treatment of invasive candidiasis.[5] For neutropenic patients with presumed invasive candidiasis, the preferred first-line agents include a LAmB, voriconazole, or caspofungin. Fluconazole or itraconazole can be considered as alternative agents. An important consideration is to avoid using empiric azole therapy in patients that have a significant recent azole exposure for prophylaxis. Additionally, AmBd is not routinely recommended due to toxicity concerns.

Pre-Emptive Therapy

A pre-emptive approach relies on the presence of a surrogate marker to indicate the presence of an active fungal infection. This strategy typically targets individuals at high risk of infection for screening purposes. Given the costs associated with continuous screening, it will be important to determine which patients should be targeted to maintain cost-effectiveness. Additionally, studies are needed to determine which diagnostic approach is most effective for screening as well as which agent should be used for initial therapy.

To test the utility of a pre-emptive approach, one study developed an algorithm that combined the galactomannan assay and HRCT scanning with traditional radiology and cell culture techniques to identify high-risk patients most likely to benefit from antifungal therapy **(Figure 2)**.[17] Neutropenic patients were given therapy only if they were seropositive (≥2 consecutive positive galactomannan assay results), or had a positive microbiological result, and exhibited supportive radiological findings of an infection. A total of 136 treatment episodes from 88 patients were investigated. Neutropenic fever developed in 117 episodes, of which at least 41 episodes (35%), in retrospect, would have qualified for empiric therapy according to existing national guidelines. However, applying the study algorithm limited the use of antifungals to only 7.7% of these episodes of neutropenic fever. No undetected cases of aspergillosis were identified, though one case of zygomycosis was missed. The overall 12-week survival rate was 63.6%, and 63.1% for invasive aspergillosis. The use of a pre-emptive approach reduces the use of costly agents and minimizes the risk of adverse events.

Figure 2. Pre-emptive approach to initial antifungal therapy[17]



Comparing Empiric versus Pre-Emptive Therapy

Dr. Elizabeth Dodds Ashley

A growing body of evidence is beginning to emerge in the literature that compares pre-emptive strategies with empiric therapy. In a study by Hebart and colleagues, allo-SCT patients were randomized to receive either PCR-based pre-emptive therapy or liposomal amphotericin B empiric therapy.[18] In the pre-emptive group, patients received therapy after one positive PCR result or 120 hours of febrile neutropenia refractory to broad-spectrum antibacterial therapy. In the empiric group, patients received LAmB after 120 hours of febrile neutropenia. In the pre-emptive group, 57.1% (112 of 198) received antifungal therapy, while 36.7% (76 of 211) in the empiric therapy group received antifungal therapy. The pre-emptive group had a better 30-day survival rate (1.5% mortality rate compared to 6.3%; *P*=.015), though there was no difference in survival or incidence of IFIs at Day 100.

(Continued on page 5)

Antifungal Drug Resistance

Despite clinicians' attempts to provide early appropriate antifungal therapy, treatment failure to the initial drug occurs all too frequently. One potential cause of ineffective treatment is due to resistance by the organism against the antifungal agent being used. Drug resistance can be divided into two categories: primary (or intrinsic) resistance and secondary (or acquired) resistance.

Primary resistance occurs when the fungal organism is resistant to a drug prior to any exposure. Some important examples of this are included in **Table 1.**

Table 1. Primary resistance to drug by fungal organism

Fungal Organism	Resistant to Drug
Candida krusei	**fluconazole**
Aspergillus terreus	**amphotericin B**
***Scedosporium* species**	**amphotericin B**
Cryptococcus neoformans	**echinocandins**
***Trichosporon* species**	**echinocandins**

Secondary resistance occurs after exposure to a drug over a given amount of time. This type of resistance is commonly observed with antibacterials and can also occur, though less often, with antifungal agents, particularly with long exposures to the drug. This type of resistance is observed with *Candida albicans* and *Cryptococcus neoformans* that develop resistance to fluconazole. Secondary resistance to flucytosine is also common and it is generally recommended to use this product in combination with another antifungal agent to limit resistance development. Fortunately, because of its mechanism of action, secondary resistance to amphotericin B is very rare.

Clinical Resistance

Before attempting to determine the best course for a patient who fails initial antifungal therapy, it will be important to understand the cause of failure, or the reason for clinical resistance. **Table 2** lists the most common reasons for failure and it is important for clinicians to keep these in mind when considering salvage therapy.[20]

Table 2. Principle factors for antifungal failure[20]

Factor	Implication
Wrong diagnosis	Weak diagnostics and/or IRIS
Net state of immunosuppression	Improvement in immunity of host is essential
High burden of fungus at initiation of treatment	Earlier treatment intervention improves outcome
Strain acquisition of increased virulence	Probably less of a problem than host factors but can be measured
PK and/or PD	Drug toxicity, drug levels, drug-drug interaction
Site of infection	Drug penetration, tissue necrosis, foreign body
Length of treatment and/or compliance	Precision is not certain; patient and clinican may lose focus on long-term drug administration
Underlying disease	Final arbitrator in most invasive mycoses

(Continued from page 4)

Another randomized controlled trial by Cordonnier and colleagues compared empiric and pre-emptive approaches in neutropenic patients.[19] Empiric therapy was defined as treatment of patients with persistent or recurrent fever. Pre-emptive treatment was defined as treatment of patients who have clinical, imaging, or galactomannan-antigen-assay evidence suggesting fungal infection. First-line therapy was with AmBd or LAmB. Survival was similar between the two groups (97.3% for empiric and 95.1% for pre-emptive), though proven or probable IFIs were more common with pre-emptive therapy (9.1% vs. 2.7%; $P<.05$). Pre-emptive therapy decreased the cost of antifungal drugs by 35%. These studies emphasize the need for additional studies to evaluate the benefits of pre-emptive versus empiric therapy, with particular emphasis on how outcomes can be impacted by different patient populations, diagnostic approaches, and antifungal agents used.

Wrong Diagnosis

Though recent developments have greatly improved the diagnostics of IFIs, there are still significant limitations in reaching an accurate and timely diagnosis. Tissue samples can be invaluable in making a diagnosis. However, in some patients, tissue samples would be difficult to obtain due to underlying conditions. Biomarkers for serology tests may not be robust enough for detection in some patients. Culture techniques are relatively poor for fungal pathogens and this can make it difficult to determine the presence of a fungal infection. Because of this, it is important for clinicians to be suspicious of fungal infections in high-risk patients and to use multiple diagnostic tools for detection and verification of the presence of an IFI.

In immunosuppressed patients, a patient's condition may inexplicably worsen and develop signs such as unexplained fever, intracranial pressure, or have abnormal chest X-rays. Though these signs may indicate an uncontrolled fungal infection, they can also be caused by inflammatory reactions. It is important to consider the cause to be an immune modulation issue, such as immune reconstitution inflammatory syndrome (IRIS). In these cases, the patient transitions rapidly back and forth from immune stimulation to immune suppression. Though the signs may mimic a fungal infection, it is actually due to the patient's immune system and clinicians must recognize this to understand what is causing the disease process.

Net State of Immunosuppression

Frequently patients at high risk of fungal infections are immunocompromised and the net state of immunosuppression is critical when trying to defend against an infection. It is important to try to restore the white blood cell count in neutropenic patients as it will be difficult to have a successful outcome in the absence of the body's defense mechanisms with the use of antifungal agents alone.

Fungal Burden

As was mentioned earlier with the goal of pre-emptive therapy, early diagnosis and treatment will significantly improve outcomes as you are attempting to fight the infection when the fungal burden is lower. If the diagnosis is delayed, the burden of fungal organisms can be too great for the host to control, leading to eventual failure.

Strains with Increased Virulence

The impact of acquiring a strain with increased virulence is still being studied and may not be as critical as host factors, but it is possible to measure its impact. Certain outbreaks of fungal infections have been attributed to strains with increased virulence, such as a cryptococcal outbreak in Vancouver, Canada.[21] Therefore, it will be important to continue surveillance of fungal pathogens to see if they are developing increased virulence.

PK/PD of Antifungal Agents

The pharmacokinetics and pharmacodynamics of antifungal agents is intimately important in clinical success as the serum drug concentration of some antifungal agents has been associated with clinical outcomes and tolerability. This will be discussed in greater detail later in this newsletter.

Site of Infection

The site of infection should help determine antifungal selection as the drug must be able to penetrate to the site of infection. For example, an ocular infection should be treated with an agent that can penetrate to the vitreous humor while central nervous system infections should use agents that penetrate to those sites. Also, certain infections cause necrotic tissue and must be surgically removed since antifungal agents cannot penetrate into those areas to eradicate the pathogen. Pathogens related to foreign bodies, such as catheters or prosthetic devices, can be particularly difficult as fungi can develop resistance to antifungal agents when they are present in biofilms. Removal of the foreign body must be considered to improve the outcome of the patient.

Length of Treatment and/or Compliance

The difficulty in treating an infection is determining the appropriate length of therapy as studies have yet to definitively determine this. Traditionally, candidemia is treated for two weeks past the last positive culture, but length of therapy is not as simple with all patients and with other pathogens, such as *Aspergillus*. The patient and the clinician must not lose focus when treating a fungal infection long-term as the severe nature of the infection must be emphasized along with the necessity for long-term treatment.

Underlying Disease

In most patients encountered in the clinical setting with IFIs, the infection can be controlled if the pathogen is identified by using one or a combination of the three antifungal classes. However, the final arbitrator is the underlying disease, which can provide serious challenges when managing these patients.

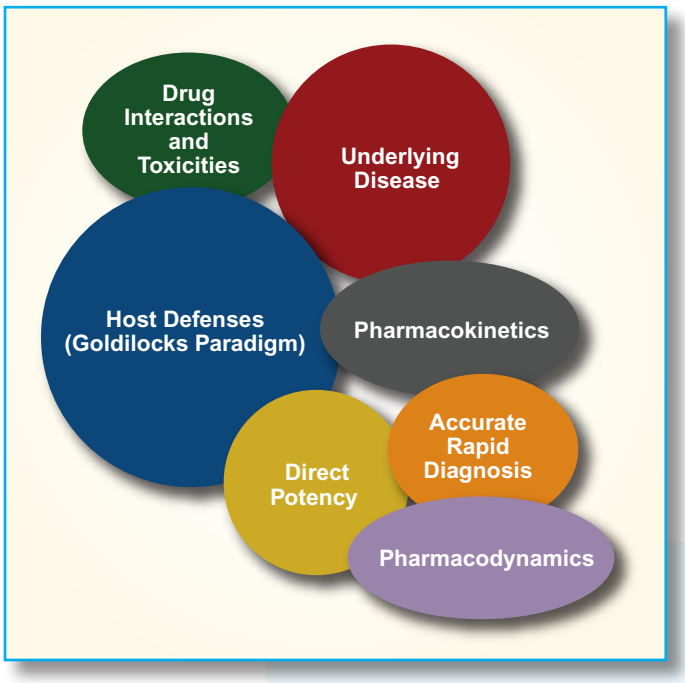
TREATMENT STRATEGIES FOR OVERCOMING REFRACTORY INFECTIONS

Patient outcomes can be affected by a number of inter-related factors: **(Figure 3)**

- **the host**
- **the pathogen**
- **the drug**

A better understanding of these factors for each individual patient can help guide clinical decision-making towards a successful outcome. When managing patients with refractory infections, a number of options can be considered. However, it is important to note that several questions remain when using these strategies and additional research is needed to fully understand how to optimize treatment in these patients.

Figure 3. Rings of Antifungal Failure



Accurate and Rapid Diagnosis

Misdiagnosis is a major cause of treatment failure. Therefore, it is important to use multiple diagnostic tools to confirm a fungal infection. When allowed, tissue samples can be critical in diagnosing a fungal infection and identifying the pathogen through histopathology. Serum antigen assays (such as β-D-glucan assay and the galactomannan assay) can be used in conjunction to culture in order to rapidly detect an infection and also to support radiographic evidence. When possible, in vitro susceptibility testing should be conducted, particularly in severely ill or immunocompromised patients and those who fail initial treatment.

In addition to an accurate diagnosis, antifungal treatment should be initiated as soon as possible. As discussed in the first newsletter, several studies have shown an increase in mortality rates when therapy was delayed. For patients with *Candida* infection, one study demonstrated that the mortality rate was approximately 15% when fluconazole therapy was started on the same day as the blood culture was collected.[1] The mortality rate increased to 23% if therapy was initiated one day later, and 36% if therapy started 2 days later. Similar results have been observed with *Aspergillus* and Zygomycetes infections.[22, 23] Therefore, early and accurate diagnosis along with early initiation of effective treatment is essential for improving patient outcomes.

Immune Modulation

Restoring a patient's immune system can be critical and, in some cases, a necessity in fighting these infections as antifungal agents alone will not always be effective. Clinicians must consider reducing immunosuppressive protocols to help restore the patient's immune system. Alternatively, immune systems can be boosted with the use of immunomodulatory agents, such as cytokines. Immune reconstitution has had mixed results when managing patients with IFIs. In a study with cryptococcal meningitis, the use of two doses of recombinant gamma interferon resulted in a trend of faster yeast count drop in the cerebrospinal fluid, though the difference was not significant.[24] Immune reconstitution, however, can have adverse effects as well. A small study from Italy that included aspergillosis patients suggested that a too rapid increase in white blood cell count following G-CSF therapy increased the risk of death.[25] Thus, it is important to attain a gradual return of the immune system rather than too fast.

Drug Prescription

In addition to selecting an effective antifungal agent, proper dosing of the agent is critical to ensure that an adequate concentration reaches the site of infection while maintaining tolerability. This can be challenging with the newer azoles, as they exhibit non-linear pharmacokinetics and drug concentrations can be impacted by drug-drug interactions and genetic polymorphisms (for voriconazole in particular). When dosing voriconazole, studies have indicated a higher likelihood of clinical effect is achieved with trough levels of 1-2 µg/mL.[26, 27] However, adverse events increase when levels exceed 5.5 µg/mL, and so therapeutic drug monitoring may be important for certain patients, particularly critically ill patients or those who are not responding adequately to therapy.[28] One study of HSCT recipients showed that 15% of patients receiving voriconazole had undetectable levels in their serum.[27]

Some information is becoming available on optimal dosing of other classes of agents. For the echinocandins, a dose of 50 mg/day of caspofungin is equivalent to 100 mg/day or 150 mg/day of micafungin when treating candidemia.[29] For the polyenes, a pivotal study compared a higher dose of liposomal amphotericin B (10 mg/kg) versus the standard dose (3 mg/kg) and demonstrated that efficacy was not improved with the higher dose against IFIs (mainly aspergillosis).[30] However, the higher dose was associated with increased rates of adverse events, particularly hepatotoxicity and elevation of liver enzymes, resulting in more discontinuations. So it is important for clinicians to choose the right agent at the right dose to effectively eradicate the infection while maintaining tolerability.

New Agents

The availability of newer antifungal agents has given clinicians more options when managing patients with a refractory infection. **Table 3** shows a summary from various clinical studies on success rates with these agents for salvage therapy for several types of infections.[34-40] It would be difficult to draw any conclusions from these data given the small number of patients and from the fact that these studies used a very select group of patients that may have had other underlying conditions that could affect outcomes. Yet, the success rates of generally between 40% to 60% show the difficult nature of treating these patients even with the latest antifungal agents.

Combination Therapy

Dr. John Perfect

The use of combination therapy remains a controversial topic as there is a lack of well controlled prospective clinical trials comparing combination therapy with monotherapy. Animal models suggest a benefit with combination therapy and combination therapy is suggested for cryptococcal infections (flucytosine plus amphotericin B).[31, 32] However, there are no studies to support the use of combination therapy for *Candida* infections. A study by Marr and colleagues suggested that combination therapy with voriconazole plus caspofungin provided a survival benefit when compared to voriconazole alone for patients with invasive aspergillosis who failed initial therapy with an amphotericin B formulation.[33] However, the study occurred over two separate periods of time and other factors may have impacted these results. Combination therapy may be helpful for high-risk patients or those refractory to standard treatment, though additional research is clearly needed.

Table 3. Success rates by various antifungal agents for salvage therapy[34-40]

Drug	Aspergillosis	Candidiasis	Fusariosis	Zygomycosis
Voriconazole	62/142 (44%)	50/87 (58%)	5/11 (46%)	-
AmB Lipid Complex	55/130 (42%)	28/42 (67%)	9/11 (82%)	17/24 (71%)
Caspofungin	37/83 (45%)	13/15 (87%)	-	-
Posaconazole	47/107 (42%)	-	10/21 (48%)	19/24 (79%)

Therapy Management Issues

Table 4 lists several therapeutic management issues for patients with infections caused by *Cryptococcus*, *Candida*, or *Aspergillus*.[20] Though these are primarily based on opinion, this list may help guide management strategies when confronted with a patient with a refractory infection. Though resistance may be an issue in refractory infections, it is also important to consider the patient's underlying disease and immune status as well as the pharmacokinetics and pharmacodynamics of the antifungal agents used.

Table 4. Therapy management issues for failure of treatment with specific fungal infections[20]

Cryptococcal meningitis
Acute and chronic intracranial pressure problems can cause treatment failure
Most persistently positive CSF culture results occur because of less aggressive induction therapy
Treat with 2–3 weeks of induction therapy with polyene and flucytosine
Consider microbiological failure if positive CSF culture results at 8–10 weeks of initial therapy
If culture results are still positive, test for azole susceptibility and restart with combination antifungal induction therapy
Define agent for clearance phase on the basis of susceptibility
Consider IFN-γ if culture results are persistently positive after repeated induction therapy
Consider IRIS*; cryptococcal antigen or nonviable yeasts in CSF are not necessarily biomarkers for eventual microbial failure
Candidemia
If persistent candidemia, consider removal and/or change catheters and drain abscesses
Compare initial and persistent isolates for in vitro susceptibility to azoles and candins
Identify *Candida* to species level, to predict drug susceptibility and natural history of infection
Change classes of antifungals (candins, azoles, or polyenes) with retreatment
Consider IRIS*; cryptococcal antigen or nonviable yeasts in CSF are not necessarily biomarkers for eventual microbial failure
Invasive aspergillosis
Identify fungal isolate to species level; attention to drug resistant strains, such as *Aspergillus ustus, Aspergillus terreus,* and *Aspergillus lentulus*
Check azole, polyene, and candin in vitro susceptibility
Check the diagnosis
Check antifungal drug level in serum (azoles)
Consider surgical removal of a large necrotic focus
Consider combination therapy or change in individual class of antifungal for retreatment

* immune reconstitution inflammatory syndrome

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POST TEST | EVALUATION | AND CREDIT APPLICATION

Release Date: October 10, 2009 Expiration Date: October 10, 2010 Center Serial #: CV3102-2

Select your professional title: ☐ Physician ☐ Pharmacist Other _____

Select your practice setting: ☐ Teaching hospital ☐ Community hospital ☐ LTAC ☐ Other _____

Your evaluation and suggestions will help improve the quality of future continuing education activities. Please answer the following questions and evaluate the activity. Additional space for your comments and suggestions is available. Thank you for your cooperation.

POST TEST (Please check the most appropriate answer)

1. Treatment of a patient suspected of an invasive fungal infection with at least one positive diagnostic marker is called:

☐ Prophylactic treatment ☐ Empiric treatment ☐ Pre-emptive therapy ☐ Salvage therapy

2. Which of the following agents does not exhibit in vitro activity against *Aspergillus*?

☐ Fluconazole ☐ Itraconazole ☐ Voriconazole ☐ Posaconazole

3. For neutropenic patients with presumed invasive candidiasis, the IDSA guidelines recommend all of the following agents EXCEPT:

☐ Lipid formulation of amphotericin B ☐ Amphotericin B deoxycholate ☐ Voriconazole ☐ Caspofungin

4. In a study by Maertens that evaluated the utility of a pre-emptive approach, which diagnostic tool was not included as part of the treatment algorithm?

☐ Galactomannan assay ☐ Thoracic CT scan ☐ Histology of tissue biopsy sample ☐ Cell culture

5. Which organism exhibits primary resistance to amphotericin B?

☐ *Candida glabrata* ☐ *Aspergillus flavus* ☐ *Aspergillus terreus* ☐ *Cryptococcus neoformans*

6. Which antifungal agent is generally used in combination with other agents due to the risk of secondary resistance?

☐ Fluconazole ☐ Flucytosine ☐ Voriconazole ☐ Amphotericin B deoxycholate

7. Due to its non-linear pharmacokinetics, therapeutic drug monitoring may be useful when dosing which antifungal agent?

☐ Fluconazole ☐ Amphotericin B deoxycholate ☐ Voriconazole ☐ Caspofungin

8. In a study that compared 3 mg/kg versus 10 mg/kg doses of liposomal amphotericin B for the treatment of IFIs, which of the following statements is false?

☐ The higher dose resulted in greater efficacy
☐ The higher dose resulted in greater rate of discontinuations
☐ The higher dose resulted in a greater risk of hepatotoxicity
☐ The high dose resulted in an overall increase in adverse events

LEARNING OBJECTIVES: Were the learning objectives met?	Yes	Somewhat	No
1. Distinguish between the advantages of a pre-emptive strategy and empiric treatment when managing patients with IFIs	☐	☐	☐
2. Identify the causes of treatment failure and recognize options for salvage therapy	☐	☐	☐

If you answered 'No' to any objective, please explain.

SCIENTIFIC CONTENT: Please rate	Excellent	Good	Fair	Poor
1. The scientific content of this activity was	☐	☐	☐	☐
2. The level of expertise of the authors was	☐	☐	☐	☐

OVERALL EVALUATION	Yes	Somewhat	No
1. This activity met my expectations.	☐	☐	☐
2. The content was relevant to my practice.	☐	☐	☐
3. This activity was fair and balanced.	☐	☐	☐
4. This activity was without commercial bias.	☐	☐	☐

If you answered "No" to 3 or 4, please explain.

LEARNING FORMAT	Yes	Somewhat	No
1. The format enhanced achievement of learning objectives.	☐	☐	☐
2. The format was easy to follow and understand.	☐	☐	☐

PRACTICE APPLICATION

1. What aspects of this activity were most relevant to your practice?

2. Please list one therapeutic strategy in prevention and treatment of an IFI that you learned in this activity.

3. Will you make changes to your practice based on participation in this activity? If yes, please specify.

4. What aspects of IFIs do you need to learn more about to improve your practice performance?

DO YOU HAVE (1) ANY SUGGESTIONS FOR IMPROVING THIS ACTIVITY or (2) ANY ADDITIONAL COMMENTS?

CREDIT APPLICATION (Please Print)

Name and Degree _____

Address _____

City _____ State _____ ZIP _____

E-mail _____ May we contact you by e-mail? ☐ Yes ☐ No

Type of credit requested ☐ Pharmacy CPE ☐ MD/DO *AMA PRA Category 1 Credit™*

I certify that I have reviewed *From Pre-Emptive to Salvage Antifungal Therapy: Achieving Successful Outcomes*

Signature _____ Date _____

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This Newsletter is part of the Initiative *Preventing & Managing IFIs: Progress & Promise in the 21st Century*. The first step in this Initiative consisted of 2 Live Webinars, now available as On-demand Webinars in which experts in medical mycology discuss scientific evidence. Podcasts represent the second step in this Initiative. Scientific evidence presented in the Webinars is reinforced and placed in clinical context through case discussions between physician and pharmacist experts. This approach highlights clinical considerations that both specialties should be aware of when formulating and evaluating their management approach.

To access these On-demand Webinars and Podcasts, please visit *www.vemcomeded.com* (go to CME Portal).