

# ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

## Advances in the Management of Fungal Infections



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### H&O What are the most common fungal infections among patients with hematologic malignancies?

**MM** We are increasingly forced to confront this issue because some treatments of hematologic malignancies raise the risk for invasive fungal infection. Fungal infections can be divided into 3 broad categories: yeast infections, mold infections, and thermally dimorphic fungal infections. In clinical practice, most cases involve yeast or mold. Among the yeast infections, the most common is *Candida* species. At my center in New York and in the surrounding area, there has been an alarming rise in *Candida auris*, which can be resistant to the 3 major classes of antifungal agents: triazoles, echinocandins, and polyenes. The 2 classic mold infections are aspergillosis and mucormycosis, both of which can be aggressive and associated with substantial morbidity and mortality. Depending on the geographic location, thermally dimorphic fungi are relatively rare. When treating patients with hematologic malignancies, I am always on the lookout for *Candida* species, aspergillosis, mucormycosis, and the mold species *Fusarium*. In patients with hematologic malignancies, positive blood cultures and new skin findings make me think of *Fusarium*.

### H&O Which patients are at higher risk?

**MM** When evaluating a patient with a hematologic malignancy and an infection, the first question is the level of immunosuppression. Is the patient profoundly or marginally immunocompromised, or is the immune

system nearly intact? The level of immunosuppression is used to help risk-stratify patients to identify the most likely infectious agent, which is crucial for the diagnosis and appropriate treatment of fungal infections. My mentor, Thomas J. Walsh, MD, is fond of saying that the best antifungal agent ever created is the neutrophil. When we treat hematologic malignancies with medications that wreak havoc on the immune system, we predispose these patients to fungal infections.

### H&O Why are these infections difficult to treat?

**MM** One of the biggest challenges is the appropriate initiation of therapy. The diagnosis can be difficult. For example, a blotch on a chest X-ray or computerized axial tomography (CAT) scan might be incorrectly diagnosed as bacterial pneumonia. The patient might then receive treatment with typical antibiotics, such as vancomycin with piperacillin/tazobactam or ceftriaxone with azithromycin. During such treatment, the fungus continues to reproduce, and it can spread to other parts of the body. I have been involved in research evaluating what happens when pulmonary aspergillosis gets into the blood and starts traveling throughout the body. It can reach the brain and cause strokes and other severe complications. This scenario can be avoided if the patient begins treatment with appropriate antifungal agents instead of unnecessary antibiotics.

Molecular diagnostic tests for fungal infections are lacking. It is often necessary to wait for fungi to grow in a microbiology laboratory before a diagnosis can be made. This delay in the initiation of antifungal therapy

leads to worse outcomes. Of course, clinicians should not just assume that a fungal infection is present and initiate treatment. Many of the antifungal agents are associated with significant toxicity. Improved diagnostic assays that can rapidly and reliably diagnose conditions such as aspergillosis are needed.

### H&O How is invasive aspergillosis currently diagnosed?

**MM** The gold standard method of diagnosis consists of a direct histopathologic examination involving a biopsy from a bronchoscopy to view the hyphae under a microscope. However, this approach takes time and manpower. The *Aspergillus* galactomannan assay can strongly support the diagnosis, when positive in the

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right population of immunocompromised patients. The sensitivity and specificity of this test are good, though not superb.

A polymerase chain reaction (PCR) assay testing for *Aspergillus* is another approach, but most centers in the United States do not use it. The European *Aspergillus* PCR Initiative and other groups are working to develop a cheap and reliable PCR assay for *Aspergillus*. However, it is not necessary to perform an *Aspergillus* PCR on every patient who has a cough or shortness of breath. It will be necessary to create guidelines on how to best use the PCR assay in these patients.

In clinical practice, we use matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF), which incorporates mass spectrometry, to help identify species. Certain species of *Aspergillus* are resistant to various treatments. For example, *Aspergillus terreus* is classically resistant to amphotericin.

### H&O What are the options for antifungal prophylaxis?

**MM** There are several options. Fluconazole protects against most of the yeast pathogens, but not against some of the molds, such as *Aspergillus* or *Mucorales*. Posaconazole (Noxafil, Merck) protects against these mold infections. The US Food and Drug Administration (FDA) approved posaconazole as prophylaxis based on a trial that compared it with fluconazole or itraconazole in patients with neutropenia caused by chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome. The study randomly assigned 304 patients to posaconazole, 240 to fluconazole, and 58 to itraconazole. Posaconazole prevented invasive fungal infections more effectively than fluconazole or itraconazole, and it also improved overall survival.

Strategies may differ by institution. There is some variability with the type of prophylaxis. For example, patients with hematologic malignancies who undergo stem cell transplant are often treated with levofloxacin as bacterial prophylaxis. However, levels of resistance to levofloxacin are rising, so a different agent may be needed. The same is true with the fungal infections. Changes in the epidemiology and pattern of resistance can require a switch to another prophylactic agent.

### H&O When is prophylaxis initiated?

**MM** Some facilities initiate posaconazole immediately after stem cell transplant. Isavuconazonium sulfate (Cresemba, Astellas), a prodrug for isavuconazole, is an oral formulation, which is appealing for prophylaxis. The fungal infections that posaconazole and isavuconazole do not treat will likely assume a greater relevance in patients with hematologic malignancies.

### H&O What are the treatment options for invasive aspergillosis?

**MM** There are increasingly better options for the management of patients with invasive aspergillosis. Currently, the recommendation for pulmonary aspergillosis is voriconazole. In March 2015, the US Food and Drug Administration approved isavuconazole based on 2 very small, controversial studies. There is controversy regarding whether isavuconazole should be considered first-line therapy for aspergillosis and mucormycosis.

Combination therapy is another approach. The combination of therapies such as voriconazole or isavuconazole with an additional agent, often an echinocandin, could improve morbidity and mortality. Our laboratory has explored the role of 2 agents to treat invasive pulmonary aspergillosis, at both the in vitro level and in vivo with rabbits. For example, our in vivo rabbit studies of the combination of isavuconazole with

an echinocandin have evaluated outcomes such as fungal burden, fungal architecture, and response to treatment. The precise interaction cannot be predicted, so studies of synergy and antagonism are needed. For example, voriconazole and amphotericin each have activity against *Aspergillus*, but they will not necessarily work better together. Experiments are necessary to see which combinations are effective. Too many patients have poor outcomes. However, improvements are expected with new approaches to diagnosis and management.

### H&O Is early initiation of antifungal therapy associated with a better outcome?

**MM** In hindsight, it is easy to say that a patient's outcome would have been better if antifungal therapy had been administered earlier. The decision of when to initiate treatment is challenging.

### H&O When is treatment stopped?

**MM** There is not a one-size-fits-all approach to duration of therapy. It can be challenging to know when to stop treatment. One approach is based on symptoms and imaging findings. For example, in a patient with pulmonary aspergillosis, treatment might continue until radiographic resolution of the imaging abnormality. Treatment can also be administered until symptoms resolve completely, but that assessment varies according to the physician.

### H&O Do infections recur?

**MM** Unfortunately they do, especially in patients who require further chemotherapy or who are treated with immunosuppression later in life. These patients are at risk for recurrence of infection, which makes prophylaxis all the more important.

### H&O Is the use of antifungal therapies impacting the epidemiology of infections?

**MM** Studies have shown that the use of prophylactic agents for mold infections is changing the epidemiology of the infections seen in patients with hematologic malignancies. For example, the mold *Lomentospora prolificans* can be resistant to all available antifungal agents. This mold was previously a rare cause of infection in patients with hematologic malignancies. However, I anticipate that more cases will be seen with the increased use of posaconazole and other triazoles that are used to protect against certain types of infection, especially in high-risk patients such as those who have undergone stem cell transplant.

#### Disclosure

Dr McCarthy serves on Allergan's Gram Positive Advisory Board.

### Suggested Readings

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