

# CASE STUDIES in the ANTIFUNGAL TREATMENT of HIGH-RISK PATIENTS

## Zygomycosis in a Stem Cell Transplant Recipient

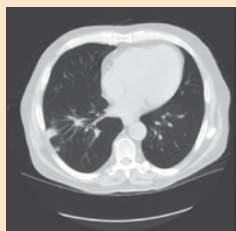
### CASE PRESENTATION:

#### Zygomycosis in a Stem Cell Transplant Recipient

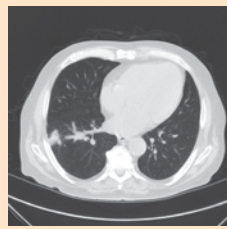
The patient is a 66-year-old man with acute myelogenous leukemia who received a 9 out of 10 HLA-matched stem cell transplant from his brother. The conditioning regimen consisted of busulfan, fludarabine, and antithymocyte globulin. He was initiated on anti-infective prophylaxis consisting of acyclovir and dapsone. The patient was considered at high risk for acquiring invasive aspergillosis because of the intensity of his conditioning and anti-graft versus host disease (GVHD) regimens. Consequently, he was given voriconazole prophylaxis at a dosage of 200 mg orally twice daily.

Five months after receiving the transplant, the patient developed cough, nasal stuffiness, and nasal drainage, and he was admitted to the inpatient transplant unit. Examination revealed crackles and dullness at the right base. There was no evidence of GVHD. A computed tomography (CT) scan showed consolidation with nodularity in the right lower lobe (Figure 1). Respiratory syncytial virus was detected in samples from fiberoptic bronchoscopy, and he was treated with 7 days of inhaled ribavirin. However, the patient worsened clinically, and a repeat CT scan showed that the consolidation had worsened with more prominent nodularity (Figure 2). A clinical diagnosis of invasive fungal pneumonia was made based on the characteristic appearance of his chest CT scan. Because he was taking voriconazole, this patient was considered at increased risk for infection with a non-*Aspergillus* mold such as *Zygomycetes*. Voriconazole was discontinued, and treatment with amphotericin B lipid complex (ABLC) 7.5 mg/kg/day was initiated. The patient improved on the lipid formulation of amphotericin B and was discharged on daily ABLC to complete a planned prolonged course of therapy. Treatment duration would be guided by radiographic and clinical response.

**Figure 1.**  
The initial computed tomography scan showed consolidation with nodularity in the right lower lobe.



**Figure 2.**  
A repeat computed tomography scan showed that the consolidation had worsened with more prominent nodularity.



The patient was readmitted 2 weeks later for a new fever that was later ascribed to a coagulase-negative staphylococcal infection cultured from an indwelling central venous catheter. During this hospital stay, a routine repeat chest CT showed no progression of the right lower lobe consolidation but showed no improvement either. He underwent a repeat fiberoptic bronchoscopy with biopsy under CT guidance because his first bronchoscopy had failed to culture the suspected mold pathogen. However, microbiologic and pathologic testing from this repeat bronchoscopy also failed to identify a fungal pathogen. Miconazole (100 mg/day) was added for combination antifungal therapy with ABLC.

A follow-up CT scan 3 weeks later showed persistent nodules in the superior segment of the right lower lobe with no extension of disease and some improvement of the infiltrate associated with the right lower lobe nodules. Because the patient had improved clinically on ABLC therapy, he underwent a thoracoscopic wedge resection of the infected right lower lobe segment to debulk residual pneumonia and to make a definitive diagnosis. Histologic examination showed multiple areas with hyphae consistent with a mold infection. However, the genus of the mold could not be determined from histologic appearance because the hyphae were deformed and fragmented, consistent with an antifungal treatment effect. One colony of *Rhizopus arrhizus* grew after 2 weeks of culture. Miconazole was discontinued, and the patient continued on ABLC for a total of 2 months of therapy. He was subsequently switched to the antifungal posaconazole for another 2 months of treatment. A repeat chest CT scan revealed no residual fungal pneumonia. The patient has shown no evidence of relapsed fungal infection after 6 months without antifungal treatment.

In this case report of an allogeneic stem cell recipient with zygomycosis, the absence of well-established risk factors for invasive fungal infection (IFI) (ie, neutropenia, graft versus host disease, and use of systemic corticosteroids) is striking. Older age, donor/recipient mismatch, and, most important, a nonmyeloablative yet profoundly immunosuppressive conditioning regimen contributed to the development of the IFI. This patient underwent a “mini-transplant”; the risk for IFI is by no means “mini” but similar to that seen with conventional myeloablative transplantation.

Prevention of invasive aspergillosis is a priority in transplantation since diagnosis of the infection is difficult to make and often missed, and the mortality remains high. Consequently, prophylactic use of voriconazole is on the increase. This case study echoes recent reports citing that emergence of zygomycosis is on the rise, particularly among voriconazole recipients. Reports suggest a continued increase in filamentous fungal infections in stem cell transplant recipients. Clinical and radiologic features cannot distinguish invasive aspergillosis from other filamentous fungal infections, and as current noninvasive diagnostic abilities are limited, the clinicians need to consider many etiologic possibilities while making decisions regarding empiric/preemptive therapy. In this case study by Michael Kleinberg, MD, PhD, appropriate therapeutic approach in the absence of microbiologic confirmation resulted in a satisfactory outcome for an infection that usually carries a high mortality rate.



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## Educational Objectives

- Determine how therapeutic choices for invasive fungal infections can be most appropriately employed in high-risk patients
- Explore methods to improve patient outcomes, considering antifungal efficacy, spectrum of activity, safety, and cost-effectiveness
- Compare and understand the clinical uses of available antifungal agents

## CME Information

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 Wayne State University School of Medicine and The MedEd Group, LLC.

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## Question & Answer

### Which fungal organisms are most commonly involved in hematopoietic stem cell transplant (HSCT) recipients? How common are Zygomycetes infections in this population?

*Candida* spp and *Aspergillus* spp remain the principal causes of invasive fungal infections (IFIs) in HSCT recipients, but infection patterns have changed in recent years. With the adoption of fluconazole prophylaxis, the incidence of candidal infections has declined substantially in the pre-engraftment period. However, there is an increase in the rates of opportunistic mold infections, especially with *Aspergillus*, in the postengraftment period.<sup>1</sup>

Mycoses due to less common opportunistic pathogens, such as Zygomycetes and *Fusarium*, are also being seen with increasing frequency.<sup>1,2</sup> Zygomycetes spp are responsible for up to 12% of filamentous mold infections.<sup>3,4</sup> Within the Zygomycetes class, the organisms responsible for most cases of human infection include *Rhizopus* spp, *Mucor* spp, and *Cunninghamella bertholletiae*.<sup>5</sup> These infections can be acquired by inhalation and typically present as sinusitis, rhinocerebral infection, or pneumonia.<sup>6</sup> Zygomycosis is an angioinvasive infection resulting in rapid necrosis of surrounding tissue. Mortality rates for invasive zygomycosis in patients with hematologic malignancies can exceed 60% despite treatment with active antifungals.<sup>7</sup>

Newer modalities for transplantation and more potent immunosuppressive therapies contribute importantly to the changing epidemiology of invasive mycoses (Table).<sup>8</sup> Today, more and more IFIs are seen at 3 months or more following transplantation.<sup>1</sup>

### Which antifungal treatments are effective for Zygomycetes infections? What are the clinical data?

ABLC and posaconazole are the only antifungal agents with adequate clinical data to support their use in treating zygomycosis. Both of these antifungals have had extensive case series of patients analyzed retrospectively. Almost all of the patients were pretreated with another antifungal drug initially, many times because antifungal therapy was started before the diagnosis of zygomycosis was made. Data with other antifungal drugs are scant and consist mostly of collections of case reports.<sup>5</sup>

Among various amphotericin B formulations, ABLC has the best evidence support-

ing its efficacy in treatment of zygomycosis. Larkin and Montero identified patients with zygomycosis in the Collaborative Exchange of Antifungal Research (CLEAR) registry database of patients with IFI treated with ABLC.<sup>9</sup> Outcomes of 64 patients with zygomycosis treated with ABLC were analyzed. Of these 64 patients, 27% had leukemia and 12.5% were bone marrow transplant recipients. The median daily dose of ABLC was 4.8 mg/kg, and the median duration of therapy was 16 days. The overall success rates assessed at end of therapy with ABLC were 72% (46/64 patients), including 13% complete, 39% improved, and 20% stable responses, with 28% of patients failing ABLC. Success rates were similar whether patients were treated initially with ABLC or whether ABLC was given after failure of another antifungal. Response rates were similar for invasive zygomycosis compared to local disease such as sinusitis.

Posaconazole is a broad-spectrum triazole that was recently approved by the FDA for prophylaxis against mold infections in leukemia patients and HSCT recipients. Posaconazole demonstrates good in vitro activity against Zygomycetes.<sup>10</sup> Other azoles such as itraconazole and voriconazole have little or no activity against Zygomycetes. van Burik et al reported on the compassionate use of posaconazole 800 mg/day (given as 200 mg 4 times daily or 400 mg twice daily) as salvage therapy in 91 patients with zygomycosis who had failed treatment with other antifungals.<sup>11</sup> Stem cell transplant recipients represented 27 of 91 patients. Similar to our patient, approximately half of patients received antifungal prophylaxis (20% with voriconazole) and 64 of 91 patients had surgical debridement in addition to posaconazole therapy. When assessed at 12 weeks or less after start of treatment, 60% of patients had a complete response, 46% had a partial response, 21% had stable disease, and only 17% failed posaconazole treatment. Similar to ABLC, invasive zygomycosis responded equally well to posaconazole as did local infection.

### What was the rationale for the selection/discontinuation of specific antifungal agents in this patient case?

Because of the partially mismatched donor stem cells, intensity of the conditioning regimen, and potential for GVHD, this patient was considered to be at high risk for developing a mold infection. Both GVHD itself and the drugs used to treat GVHD suppress the immune system and are risk factors for



the percentage of voriconazole-resistant non-*Aspergillus* molds like Zygomycetes that present as breakthrough IFIs.<sup>26,19</sup> Another example is that anti-graft versus host disease (GVHD) therapy with infliximab has been associated with an increased risk of mold (especially *Aspergillus*) in HSCT recipients with severe GVHD.<sup>20</sup> Unfortunately, studies focusing on fungal infections often do not distinguish between different cancer types, patient populations, immunosuppressive strategies, and other risk factors.

This patient exemplifies the difficulty in making a timely pathogen diagnosis. Antifungal therapy must be initiated as soon as there is clinical suspicion of an IFI and continued while a workup is underway. Empiric therapy should be chosen based on all the factors that contribute to the individual's risk for infection. These include risk factors, clues from diagnostic tests, the antifungal agent used for prophylaxis, and other considerations needed to estimate risk for the various fungal pathogens. In our case study, the patient worsened clinically despite voriconazole prophylaxis; therefore, this increased our suspicion that the causative organism was probably not *Aspergillus* and was more likely to be an azole-resistant fungus such as Zygomycetes.

### When should there be a clinical suspicion for the less common non-*Aspergillus* fungal infections? How should they be treated?

This is probably the most vexing problem in management of fungal infections in immunocompromised patients. Studies of effectiveness of antifungals against various pathogens are most relevant when the infecting fungus has been identified. However, this literature is of limited usefulness when a patient is only suspected to have an IFI and where there is a long delay in identifying the pathogen, if it is identified at all. As this case exemplifies, treatment of this patient requires estimating the patient's risk for an IFI, likelihood that the patient is truly infected given that risk, and predicting which fungus is causing the infection. The risk

factors predisposing our patient to an IFI have been discussed above. We rely on high-resolution chest CT imaging for early detection of pulmonary infections. Chest CT scans are probably the most sensitive early indicators of pulmonary aspergillosis and other fungal pneumonias.<sup>21</sup> Approximately 50% of neutropenic patients with hematologic malignancies and with fevers unresponsive to broad-spectrum antibacterial agents will have abnormal CT scans that are consistent with an infection.<sup>21-23</sup>

About 50% of persistently febrile neutropenic patients with abnormal chest CT scans consistent with pneumonia are actually infected.<sup>23</sup> Using combined early chest CT scanning with bronchoalveolar lavage and polymerase chain reaction, Chopra estimated that about 20% of febrile neutropenic patients receiving broad-spectrum antibacterials (and 40% of the patients with abnormal chest CT scans) have pulmonary aspergillosis.<sup>24</sup> This should be considered a ballpark estimate at best, and it is unclear whether these estimates, if accurate, are also true in high-risk, nonneutropenic allogeneic stem cell transplant recipients, like our patient. However, it is interesting that this all-comer estimate of 20% incidence for aspergillosis is similar to that seen in the Chamilos et al autopsy series.<sup>4</sup> Returning to our patient, his chest CT scan showed presence of nodules, which are seen in more than 90% of patients with pulmonary aspergillosis<sup>25</sup>, and presumably in non-*Aspergillus* mold pneumonias as well. Therefore, we estimated that the risk of pulmonary IFI in our patient was substantial and warranted empiric treatment with antifungals and an aggressive diagnostic approach.

There are few useful studies to help predict the identity of a fungal pathogen even once a clinician has determined that his or her at-risk patient has a high likelihood of an IFI. Studies relying on a positive fungal culture to confirm an IFI grossly underestimate the true incidence of IFIs in general and individual fungal species in particular. In neutropenic patients, most infections will be caused by *Aspergillus*, but there is an approximate 25% chance that a non-*Aspergillus* infection such as infection with a Zygomycetes, *Fusarium*, or other mold is the culprit.<sup>4</sup> It is important,

therefore, for clinicians to recognize that there is a real risk for a non-*Aspergillus* infection in a persistently febrile neutropenic patient with an abnormal chest CT suggestive of a pulmonary IFI. In other words, not all IFIs are aspergillosis.

As discussed earlier, voriconazole prophylaxis in our patient increased the likelihood that his suspected IFI was not caused by *Aspergillus* but rather by another mold such as Zygomycetes. Among the antifungal agents available, amphotericin B formulations have the broadest spectrum of activity and are the preferred therapeutic choice against most non-*Aspergillus* molds, including Zygomycetes. Lipid-based amphotericin B formulations are preferred, in general, over conventional amphotericin B deoxycholate because of lower risk for renal toxicity, despite their higher drug costs.

In our case study, the patient had worsened clinically and radiologically in the setting of voriconazole prophylaxis; this increased our suspicion that the fungal infection was not due to *Aspergillus* but was likely to be due to Zygomycetes, which is the second most common infecting mold. At that point, it was extremely important to switch to an agent like ABLC with activity against Zygomycetes before the diagnosis of zygomycosis was confirmed.

In summary, this was a case of a stem cell transplant recipient who developed zygomycosis. HSCT recipients are a very high-risk group for IFIs. Although *Aspergillus* is the most common infecting mold, less common but emerging opportunistic infections, such as those due to Zygomycetes, are becoming more prevalent. The use of voriconazole prophylaxis may be contributing to this pattern. ABLC and posaconazole are antifungal agents with good clinical data supporting their use against Zygomycetes. In my view, intravenous ABLC is preferred over oral posaconazole for initial treatment of life-threatening zygomycosis to ensure adequate delivery of drug. Suspected early, zygomycosis can be treated successfully with initial treatment using lipid-based amphotericin B formulations and completed with oral posaconazole.

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