

CASE STUDIES IN SERIOUS FUNGAL INFECTIONS*

John Perfect, MD[†]ABSTRACT

The cases presented here illustrate several important points regarding invasive fungal infections. In the first case study, we review the importance of accurate diagnosis and discuss why biopsies should always be performed, even in the setting of "obvious" risk factors for a particular organism. There may be multiple organisms at play, and the presence of these organisms can change over the course of treatment, so multiple biopsies are usually necessary. In the second case study, we see "the good, the bad, and the ugly" of immune modulation. It can prevent infections in those with immunity, but can become overwhelming and cause damage to the host, at the same time mimicking a treatment-refractory infection. We also discuss evidence to support combination therapies for some fungal infections. With advances in diagnostic technology and antimicrobial agents, clinicians do not commonly lose a patient to a fungal infection; rather, fatalities are often due to the underlying disease. (*Adv Stud Med.* 2006;6(6C):S531-S537)

CASE STUDY 1: THE HUMAN PETRI DISH*CHIEF COMPLAINT*

JM is a 58-year-old man with known myeloblastic leukemia, status postchemotherapy and chronic neutropenia, who presents with nonpainful, ulcerative skin lesions on his arms, which arose over several days.

PAST MEDICAL HISTORY

JM has a history of rheumatoid arthritis, treated with cyclophosphamide, methotrexate, prednisone, and adalimumab. He developed pancytopenia with 50% blast cells, was diagnosed with myeloblastic leukemia, and was treated with induction chemotherapy (cytarabine/daunorubicin). He had a suboptimal response and required reinduction with cytarabine/mitoxantrone. Several weeks before this presentation, JM was treated for an episode of febrile neutropenia with vancomycin/ceftazidime. Before admission, he had been working in cotton fields picking weeds with a short-sleeved shirt.

PHYSICAL EXAMINATION

Erythematous, crusted skin lesions are present on both arms (Figure 1).¹

MANAGEMENT

The lesions were biopsied and grew *Rhizomucor* species, with the expected ribbon-shaped, nonseptated hyphae seen on histopathology (Figure 2). JM was started on amphotericin B lipid complex (ABLCL) at 5 mg/kg/day, with granulocyte colony-stimulating factor (G-CSF) to bolster his white blood cell counts. Despite this treatment, he remained febrile and neutropenic. A computed tomography (CT) scan of his chest showed nodular infiltrates, suggesting that the fungal infection may have spread or originated in the lung. Seven days into the treatment plan, a new skin lesion developed on his arm, while the original lesions regressed (Figure 3).¹

The new lesion was biopsied and grew *Aspergillus flavus*, with a minimum inhibitory concentration

*This article is based on a satellite symposium held in conjunction with the Interscience Conference on Antimicrobial Agents and Chemotherapy Annual Meeting in Washington, DC, on December 17, 2005.

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(MIC) for amphotericin B of 2 µg/mL. For this new lesion, voriconazole 200 mg twice daily was added to the ABLC treatment for 7 days. On a follow-up chest CT, the nodular infiltrates had enlarged. At this point, ABLC and voriconazole were discontinued.

JM was then treated with posaconazole 400 mg twice daily for 1 month. His skin lesions cleared and he experienced no respiratory symptoms. After 2 months, JM remained free of fever, skin lesions, and respiratory symptoms, but pancytopenia continued with blast cells in the peripheral smear. He entered hospice care and died from his underlying disease (with no evidence of skin lesions or respiratory symptoms) 4 months after diagnosis of the fungal infection.

DISCUSSION

JM is a good example of “the concept of a Human Petri dish,” in which a severely immunosuppressed host has infection caused by multiple organisms. When JM initially presented with skin lesions, it may have been tempting to skip the biopsy and predict the causative organism based on his history of immunosuppression and his outdoor occupation. For example, it may have been reasonable to postulate that the lesions were caused by infection with *Scedosporium prolificans*, *Aspergillus fumigatus* disseminated from a pulmonary infection, *Fusarium* species, or *Cryptococcus neoformans*. However, in immunocompromised patients, it is absolutely essential to biopsy the lesion for histopathology and culture. There is no place for empirical treatment.

Similarly, when JM developed a new lesion while the original lesions were healing, several explanations were possible. The new lesion could also have been the result of immune reconstitution due to the GCSF or the progression of *Rhizomucor* infection due to sub-therapeutic doses of ABLC. The new lesion could have been a bacterial infection, such as *Pseudomonas*. It could have simply been the natural history of his *Rhizomucor* infection, or, as was the case, it could have been a secondary fungal infection. We performed a second biopsy on the new lesion to determine the cause. In immunocompromised patients, the clinician must biopsy new lesions in patients on appropriate therapy. These patients can develop one infection after another. In JM’s case, his biopsy grew *A flavus*, with an MIC to amphotericin B of 2 µg/mL, which suggests resistance to the polyene treatment.

We chose to add posaconazole to treat the

Aspergillus infection along with the *Zygomycetes*. Posaconazole has activity against both organisms, and a recent study suggests that it can be effective in up to 60% of patients with refractory *Zygomycetes* infections and could be used as a single agent.^{2,3} However, posaconazole is only available for compassionate use in the United States.

Another option would have been to continue ABLC treatment but at higher doses. How effective is ABLC against *Zygomycetes*? Larkin and Montero assessed the efficacy and renal safety of ABLC in the treatment of

Figure 1. Presentation



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Figure 2. Histopathology

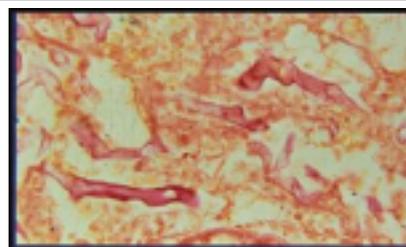


Figure 3. Previous Skin Lesions (Improved) and New Skin Lesion



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patients with invasive fungal infections caused by non-*Aspergillus* species.⁴ In patients from the Collaborative Exchange of Antifungal Research database, the overall favorable clinical response to ABLC (defined as cured, improved, and stable) for all underlying conditions was 72% (46/64 patients). A total of 8 patients were cured (13%), 25 improved (39%), and 13 were stable (20%). Of 35 patients who received ABLC as second-line therapy (ie, refractory to or intolerant of prior antifungal therapy), 24 (69%) had a favorable response. For those patients who received ABLC as primary therapy, 80% (8/10) responded favorably.^{4,5}

The high MIC in *A flavus* to ABLC is not entirely surprising, but the vast majority (95.6%) of *Aspergillus* species has MICs that are less than 2 µg/mL. However, Garcia-Martos et al have shown that *A flavus*, *Aspergillus versicolor*, *Aspergillus ustus*, *Aspergillus ochraceus*, *Aspergillus sclerotiorum*, *Aspergillus reptans*, and *Aspergillus terreus* can have MICs to amphotericin B of at least 2 µg/mL.⁶ It may also be important to determine MICs in difficult cases because cross-resistance between azoles can occur, although it is infrequent.⁷

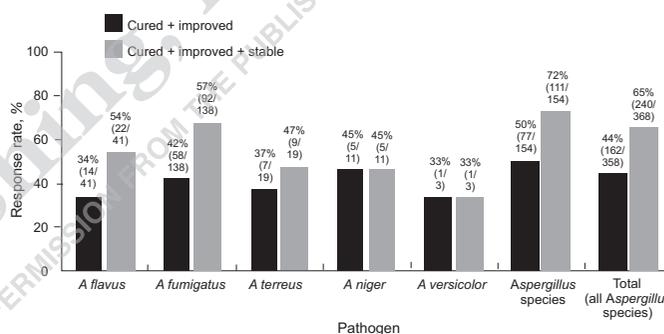
However, it is important to remember that humans are imprecise animals and MICs do not always predict clinical outcome. We performed an analysis of voriconazole use in 273 patients with refractory and treatment-intolerant fungal infections and 28 patients receiving primary voriconazole treatment for infections for which there is no approved therapy. We found no correlation between voriconazole MIC (above or below 2 µg/mL) and outcome of *Aspergillus* infection, thus each individual case will need interpretation of all results in context of the clinical situation.⁸

For example, for the individual patient, MIC testing can provide important information. Dannaoui et al showed an important in vivo-in vitro correlation in a patient with *A fumigatus* infection.⁹ Isolates were recovered at 4 different time points, showing that the MIC increased dramatically from 0.5 µg/mL (pretreatment) to greater than 16 µg/mL after 4 months of itraconazole therapy. The isolates were used in a murine model of disseminated aspergillosis and each isolate had the same trend in sensitivity/resistance to itraconazole. Random amplified polymorphic DNA typing showed that the strains were identical, suggesting that the same strain was recovered over time and had acquired resistance to itraconazole.⁹

Clinical outcomes may also depend on the

species of *Aspergillus*. A retrospective cohort study of invasive *A terreus* infections over a 5-year period showed that this species is more resistant to polyenes than voriconazole. In this study, mortality rates were 55.8% (19/34) with voriconazole and 73% (36/49) with a polyene.¹⁰ Similarly, Chandrasekar and Ito showed that the response rate to ABLC was 33% to 50%, depending on the specific *Aspergillus* species (Figure 4).¹¹ Further, apparent antagonism was observed when ABLC was followed by therapy with itraconazole (Table 1).¹¹

Figure 4. Response to ABLC Depends on *Aspergillus* spp



The efficacy and renal safety of amphotericin B lipid complex (ABLC) were assessed in 398 patients with invasive aspergillosis. The most common underlying conditions were hematopoietic stem cell transplantation (101/398 [25%]), hematologic malignancy (101/398 [25%]), and solid-organ transplantation (109/398 [27%]).

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Table 1. Clinical Response to Therapy with ABLC by Sequential, Combination, or Continued Use of Itraconazole

Clinical Response	Sequential Itraconazole (%) [*]	Combination Itraconazole (%) [†]	Continued Itraconazole (%) [‡]
Cured/improved	27/54 (50)	21/57 (37)	9/33 (27)
Cured/improved/stable	36/54 (67)	31/57 (54)	21/33 (64)

Data are number of patients with clinical response/number of patients evaluated (%).

^{*}Defined as prior therapy with itraconazole that was stopped prior to start of therapy with ABLC.

[†]Defined as no prior therapy with itraconazole but started concomitantly with therapy with ABLC.

[‡]Defined as prior therapy with itraconazole and continued after start of therapy with ABLC. ABLC = amphotericin B lipid complex.

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Thus, the “Human Petri Dish” reminds us that biopsies should always be performed, even in the setting of “obvious” risk factors for fungal infections. Multiple fungi may be at play, and the presence of these fungi can change over the course of treatment, thus multiple biopsies are usually necessary.

CASE STUDY 2: THE GOLDILOCKS SYNDROME

CHIEF COMPLAINT

CR is a 22-year-old woman who presents with 2 weeks of headaches, nausea, and vomiting.

PAST MEDICAL HISTORY

CR had received a kidney transplant 4 years ago; 3 months before she developed severe headaches, she developed acute rejection of the kidney transplant and was treated with high-dose steroids and muromab-CD3. She is currently on tacrolimus, mycophenolate mofetil, and prednisone.

PHYSICAL EXAMINATION

She is afebrile, and her mental status is normal. She has bilateral papilledema and ankle clonus.

LABORATORY STUDIES

Her complete blood count is normal. Her creatinine is 4.0 mg/dL. Lumbar puncture is performed: opening pressure is 400 mm H₂O.

Cerebrospinal fluid (CSF) analysis reveals:	
White blood cells (WBC)	100 cells/mm ³
Glucose	43 mg/dL
Protein	79 mg/dL
India ink	(+)
CSF <i>Cryptococcal</i> antigen	1:256
Serum <i>Cryptococcal</i> antigen	>1:1024
Culture for <i>Cryptococcus neoformans</i>	(+)

Magnetic resonance imaging (MRI) of the brain is consistent with basilar meningitis.

MANAGEMENT

CR was diagnosed with *Cryptococcal* meningitis and treated with ABLC 5 mg/kg/day for 20 days, flucytosine for 14 days, then fluconazole 200 mg/day. Immunosuppressants were continued during this time.

Lumbar puncture was performed again after 14 days of treatment, and the results were consistent with an excellent response:

Opening pressure	140 mm H ₂ O
WBC	28/mm ³

India ink	(-)
CSF <i>Cryptococcal</i> antigen	1:256
Culture for <i>C. neoformans</i>	(-)

CR remained on fluconazole and did very well until approximately 4 months later, when she developed severe headaches and photophobia. An MRI scan revealed supra- and infratentorial leptomeningeal enhancement. The CSF WBC count reverted back to 100 cells/mm³, but the *Cryptococcus* antigen titer in the CSF dropped to 1:16 and CSF culture for *Cryptococcus* was negative.

CR was initially treated with 2 weeks of ABLC, but there was no clinical improvement. CSF cultures remained negative. At that point, dexamethasone was started to reduce the central nervous system (CNS) inflammation, with the thought that the patient's symptoms were due to immune reconstitution syndrome. The patient improved dramatically with the steroid treatment. Fluconazole was continued and dexamethasone was tapered over 6 weeks. Tacrolimus and mycophenolate mofetil were discontinued and dialysis started.

One week after steroid discontinuation, CR's severe headaches returned. Cryptococcal cultures and antigen titer from a lumbar puncture were negative; the MRI showed improvement but CR still had meningeal enhancement. We considered immune reconstitution syndrome and too rapid of steroid taper the most likely cause. We decided to administer steroids again and taper over 4 months. Presently, she is asymptomatic and off steroids without relapse at more than 1 year.

DISCUSSION

CR had 2 acute concerns: her intracranial pressure and an infection with *C. neoformans*. Therefore, we had to approach both problems simultaneously.

Managing intracranial pressure

Because CR had such high intracranial pressure on initial presentation (400 mm H₂O) it was important to initially address it. The Infectious Diseases Society of America (IDSA) has published guidelines for the diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis.¹² The IDSA guidelines recommend daily removal of CSF with lumbar puncture sufficient to reduce pressure to less than 200 mm H₂O or 50% of initial opening pressure and daily opening pressure to less than 250 mm H₂O. Lumbar puncture after 2

weeks of treatment is also recommended to assess the efficacy of the patient's therapy.¹² Following these guidelines can have important implications on patient outcomes. One study showed that patients with pressures of 250 mm H₂O or greater also had higher titers of cryptococcal capsular polysaccharide antigen in the CSF, more frequent headaches, meningismus, papilledema, and pathologic reflexes (all of which CR had), in addition to hearing loss. Patients with higher intracranial pressures are also at higher risk for decreased short-term survival.¹³ Shoham et al retrospectively analyzed 39 consecutive cases of culture-proven, cryptococcal meningitis, of whom 26 had *C neoformans*.¹⁴ Measurement of opening pressure was only performed on 50% of the patients with *C neoformans*, and major deviations from the IDSA guidelines for managing intracranial pressure were observed in more than 50% (54%). Importantly, of those patients who did not receive guideline-specified care, 50% developed cranial neuropathies during therapy, compared to 20% of those whose care followed the guidelines closely (or with minor deviations; $P = .024$).¹⁴

Removing CSF can relieve intracranial pressure in the short-term, but other treatments may be necessary to have a long-term impact. Acetazolamide and mannitol are not useful for treating intracranial pressure.¹⁵ The usefulness of steroids is unclear with both success and failures.¹⁴ Surgical procedures (eg, lumbar drains, ventriculostomy, or ventricular shunt) may be effective in certain circumstances. Thus, controlling intracranial pressure is not an exact science, but one that needs to be adjusted in concert with the patient's clinical status, and one that can have a tremendous impact on the patient's outcome. In fact, despite high opening pressure, this patient improved on antifungal therapy and did not require CSF withdrawal.

Treating the infection

We chose combination induction therapy for CR (amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day) for 2 weeks. Brouwer et al compared 2-week courses of various treatments in 64 patients to a first episode of HIV-associated cryptococcal meningitis: amphotericin B (0.7 mg/kg daily); amphotericin B plus flucytosine (100 mg/kg daily); amphotericin B plus fluconazole (400 mg daily); or triple therapy with amphotericin B, flucytosine, and fluconazole.¹⁶ The results showed (Table 2) that amphotericin B plus flucytosine had higher fungicidal activity than amphotericin alone,

amphotericin B plus fluconazole, or triple therapy with amphotericin B, flucytosine, and fluconazole.¹⁶

With CR, we followed this induction therapy with fluconazole 200 mg/day (the dose was low because of her low creatinine clearance). Mussini et al have shown that discontinuation of maintenance therapy for cryptococcal meningitis in HIV-infected patients is safe if the CD4⁺ cell count is more than 100 cell/mm³ while receiving highly active antiretroviral therapy (HAART) and generally after 2 years of treatment and stable clinical course.¹⁷ However, in solid-organ transplant recipients, maintenance therapy often continues for longer than 6 months (55% of patients) and sometimes for longer than 1 year (25% of patients). The relapse rate in 1 study (of solid-organ transplant recipients) was only 1.3% (1/79). Amphotericin B was used more frequently than fluconazole in most patients as initial therapy: CNS infection (69% vs 16%; $P = .00001$), disseminated infection (82.7% vs 20%; $P = .00001$), fungemia (29% vs 8%; $P = .046$), and infection limited to the lungs (14% vs 64%; $P = .00002$).¹⁸

The Goldilocks syndrome: immune reconstitution

CR showed signs of immune reconstitution syndrome during her first course of treatment with advent of new symptoms: headaches, nausea, vomiting, photophobia, and increased inflammation in the CNS by NMR but reduced antigen titers and negative CSF cultures. In some HIV-infected patients, HAART is associated with the development of a marked inflammatory response against previously identified or sub-clinical infections.¹⁹ This has been termed "immune restoration disease" or "immune reconstitution inflam-

Table 2. Combination Induction Therapy for *Cryptococcus neoformans* Meningitis

Treatment Regimen	Difference in Log CFU Daily Compared to Amphotericin B plus Flucytosine	95% Confidence Interval	<i>P</i>
Amphotericin B	0.23	0.10–0.36	.001
Amphotericin B plus fluconazole	0.15	0.01–0.29	.03
Triple therapy	0.17	0.04–0.3	.01

CFU = colony-forming units.
Data from Brouwer et al.¹⁶

matory syndrome" (IRIS). This syndrome occurs in approximately 30% of patients who are receiving HAART and become infected with *Cryptococcus*.^{20,21} Patients with IRIS had higher CSF opening pressures, higher glucose levels, and higher WBC counts than those with typical *C. neoformans* meningitis.²⁰ They were also more likely to have initiated HAART nearer to the time of diagnosis of their opportunistic infection ($P < .001$), to have been antiretroviral naive at time of diagnosis of their opportunistic infection ($P < .001$), and to have a more rapid initial fall in HIV-1-RNA level in response to HAART ($P < .001$) compared to those who did not develop IRIS.²¹

Immune reconstitution syndrome is common in, but certainly not unique to, AIDS. Immune reconstitution syndrome occurs in other patients with rapid changes in immune status, such as transplant recipients, although it is usually not as common as in patients with AIDS. Singh et al followed a cohort of 83 consecutive organ transplant recipients with *Cryptococcus* infection for a median time of 2 years.²² An "IRIS-like entity" was observed in 5% of the patients a median of 5.5 weeks after antifungal treatment was initiated. Importantly, the patients experienced worsening symptoms, despite negative cultures. Patients who developed this "IRIS-like entity" were more likely to have received tacrolimus, mycophenolate mofetil, and prednisone as immunosuppressive therapy ($P = .007$).²² The investigators also subsequently showed that the probability of allograft survival was significantly lower in the patients with IRIS compared to those who did not experience IRIS.²³

Clinicians often become immersed in dealing with the disease without determining the true cause. In some cases, the infectious organisms may not be directly causing disease, and, in fact, the pathogen may be dead. The overstimulated host may be causing disease, as is indicated in this case study with IRIS. (With advances in diagnostic technology and antimicrobial agents, clinicians do not commonly lose a patient to a fungal infection; rather, fatalities are often due to the underlying disease.) Therefore, although steroids play an essential role in immunosuppression and causing fungal infections, they can also be used to treat the disease when immunity is overstimulated. As suggested by the title, in patients experiencing IRIS, at times immunity is "too hot" causing IRIS, but is also "too cold" due to our need to treat a patient's comorbid conditions. Our job, in prevention and treatment of these fungal infections, is to get immunity "just right."

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