

CASE STUDIES in the ANTIFUNGAL TREATMENT of HIGH-RISK PATIENTS

Ocular Infection in an Orthotopic Liver Transplant Recipient

Dear Colleague:

Aspergillus endophthalmitis is a catastrophic, sight-threatening infection, often associated with death due to disseminated infection. Unlike posttraumatic or postsurgical endophthalmitis where bacterial pathogens predominate, fungi (*Candida* and, less commonly, *Aspergillus*) are frequently seen in the endogenous form of endophthalmitis encountered in immunocompromised hosts and intravenous drug users. Opportunistic ocular infections in the liver transplant recipient are due to viruses (herpes simplex virus, cytomegalovirus, and varicella-zoster virus), usually occurring late, and due to fungi, usually occurring early, after transplantation; among the fungi, *Aspergillus* appears to have a predilection for the eye. Therapy for *Aspergillus* endophthalmitis calls for prompt and aggressive measures, combining pars plana vitrectomy (to remove inflammatory debris and the load of fungal organisms) and antifungal drug(s). The intravenous route of amphotericin B may be inadequate because the drug penetrates poorly into the eye, so intravitreal instillation is preferred. Voriconazole shows promise in anecdotal case reports. Echinocandins given intravenously do not achieve adequate levels in the vitreous; hence, they are not recommended. Despite timely surgical intervention and prolonged antifungal therapy, the vision of the patient in the case study presented here could not be preserved, and the eye eventually required enucleation; the fact that the organisms were still seen in the enucleated eye is sobering, reminding us of the destructive and persistent nature of the pathogen.



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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

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CASE PRESENTATION:

Ocular Infection in an Orthotopic Liver Transplant Recipient

A 33-year-old African American woman was transferred from another hospital with acute hepatic failure due to autoimmune hepatitis. She was treated with methylprednisolone 40 mg intravenously (IV) q12h for 1 week, as well as plasmapheresis. She continued to deteriorate and received an orthotopic liver transplant. Immunosuppressive therapy consisted of tacrolimus, mycophenolate mofetil, thymoglobulin, and high-dose corticosteroids. Antimicrobial prophylaxis included piperacillin/tazobactam (4.5 g IV immediately prior to surgery and q8h for 24 hours) and amphotericin B deoxycholate 10 mg IV per day for 10 days. The transplant failed to function, and she received a second liver transplant 8 days after the initial procedure. Antimicrobial prophylaxis was similar to that given for the first operation. A liver biopsy performed 9 days later showed acute cellular rejection, and she was treated with methylprednisolone 1 g IV per day for 3 days. Her liver function tests did not improve; therefore, muromonab-CD3 (OKT3) was started.

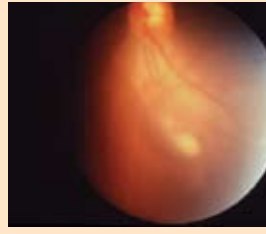
On the 14th day after receiving the second transplant, the patient developed fever, left eye pain, and blurry vision. On physical examination, her temperature was 38.7°C, pulse 131 bpm, respirations 20 per minute, and blood pressure 116/65 mm Hg. She was alert and oriented. The conjunctiva of her left eye showed erythema and chemosis; fundoscopic examination revealed yellow-white retinal lesions (Figures 1 and 2). Examination of the right eye was normal. The lungs and heart were normal on auscultation. The abdomen was soft, nontender and without organomegaly, and bowel sounds were normal. Neurologic examination was normal.

Ophthalmologic and infectious diseases consultations were obtained. Because of worsening ocular signs and symptoms, a vitrectomy was performed. Wet mount of the vitreous fluid demonstrated septate hyphae, and

Figure 1.
External appearance of the left eye showing conjunctival erythema and chemosis.

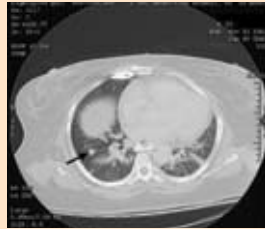


Figure 2.
Fundoscopic examination showing yellow-white retinal lesions and cloudy vitreous.



the cultures later grew *Aspergillus fumigatus*. Therapy was initiated with amphotericin B lipid complex (ABLC) 6.35 mg/kg IV per day. She was also given intravitreal injections of amphotericin B 3 times. A chest x-ray showed a right lower lobe infiltrate. Computed tomography (CT) of the chest revealed new bilateral pulmonary nodules and bibasilar air space disease (Figure 3). Bronchoalveolar lavage was performed. The wet mount of the fluid was negative for fungal elements, but the culture grew 1000 CFU/mL of *A fumigatus*. A lung biopsy was not performed. A CT of the paranasal sinuses was negative.

Figure 3.
Computerized tomography of the chest showing pulmonary nodule (arrow).



After 10 weeks, the patient's serum creatinine was 2.0 mg/dL, and ABLC was discontinued. She was started on oral itraconazole solution 200 mg twice daily for 4 weeks; however, the patient was intolerant to this medication (nausea, vomiting), and she was therefore switched to the IV preparation (200 mg/day), which she tolerated well. After 16 weeks, she was switched to oral voriconazole 200 mg twice daily.

Eleven months after receiving the second transplant, the patient underwent enucleation of the left eye because of severe ocular and facial pain. The histopathology of the enucleated eye showed severe granulomatous endophthalmitis. The Grocott-Gomori methenamine–silver nitrate stain demonstrated organisms with morphology consistent with *Aspergillus* spp. The patient is currently alive 4.5 years after transplantation. Her follow-up CT scan of the chest is clear. Her most recent serum creatinine level is stable at 1.8 mg/dL. She is scheduled to continue treatment with oral voriconazole indefinitely.

Question & Answer

What is the role of antifungal prophylaxis in the setting of liver transplantation?

Among solid organ transplant recipients, liver transplant recipients have the highest risk for invasive fungal infections (IFIs). The reported incidence of IFIs following orthotopic liver transplantation (OLT) ranges from 5% to 42%.¹ *Candida* spp are responsible for 62% to 91% of these infections, with mortality rates of 10% to 75%; *Aspergillus* infections account for less than 10% of IFIs, although mortality rates are much higher, ranging from 80% to 100%.²

Antifungal prophylaxis can reduce the incidence of IFIs in liver transplant recipients. Among the antifungal agents, the most convincing experience is with fluconazole.³ In a large study, fluconazole was given at a dosage of 400 mg/day for 10 weeks after transplantation. Smaller studies with other antifungals, including low-dose amphotericin B deoxycholate (10-20 mg/day),^{4,5} liposomal amphotericin B (1 mg/kg/day),⁶ amphotericin B lipid complex (ABLC) (5 mg/kg/day),^{2,7} and itraconazole^{8,9} have also shown benefit in liver transplant recipients.

A recent systematic review and meta-analysis found that fluconazole prophylaxis decreased the rate of IFIs by about 75%.¹⁰ Review of limited studies with other antifungals, including itraconazole and liposomal amphotericin B, suggested similar efficacy. The doses, routes of administration, and duration of therapies were not well defined because of the lack of data, although higher doses of fluconazole and longer durations of therapies tended to result in greater efficacy. Given the potential selection of resistant pathogens, the authors did not recommend a universal approach to prophylaxis but rather that fluconazole prophylaxis be instituted in liver transplant recipients who are at an increased risk in the early postoperative period.

Newer agents such as the echinocandins (ie, caspofungin, micafungin, anidulafungin), voriconazole, and posaconazole offer the advantage of broader spectrum

compared with that of fluconazole, especially against *Aspergillus* and fluconazole-resistant *Candida* spp. However, to date, there are no published studies evaluating their prophylactic efficacy in the liver transplant setting. Rates of invasive aspergillosis are higher among liver transplant recipients requiring dialysis (14%-31%) and those undergoing retransplantation (up to 46%).^{2,7} Based on a few studies, the use of ABLC may provide cost-effective prophylaxis in these high-risk patients.^{2,7}

What are the risk factors for IFIs in liver transplant recipients? Are there certain patient characteristics that differentiate a high-risk patient from a low-risk patient?

The most significant risk factors for IFIs in liver transplant recipients include preoperative creatinine level >3.0 mg/dL, length of transplant operation ≥11 hours, retransplantation, early *Candida* colonization, abdominal or intrathoracic reoperations, choledochojejunostomy anastomosis, intraoperative requirement of ≥40 units of cellular blood products, and cytomegalovirus infection.^{1,11} In one study, the first 4 variables were incorporated into a predictive model for risk stratification. The incidence of IFI was 1% in patients with no predictors, 20% in patients with 1 predictor, and 67% in patients with 2 or more predictors.¹

Another study identified liver transplant recipients at high risk for IFI if they had 2 or more of the following risk factors: retransplantation, preoperative creatinine ≥2.0 mg/dL, intraoperative transfusion of ≥40 units of cellular blood products, choledochojejunostomy anastomosis, *Candida* colonization within 48 hours of OLT, and reoperation (laparotomy) for reasons other than bleeding within 5 days of OLT. Patients with fewer than 2 factors were considered to be at low risk of IFI and not likely to benefit from systemic antifungal postoperative prophylaxis.¹¹

Specifically, for invasive aspergillosis, the most important risk factors are transplantation for fulminant hepatic failure, need for hemodialysis, poor allograft function, and retransplantation.^{2,7,12} Nearly all liver transplant recipients with invasive aspergillosis have had evidence of significant hepatic and/or renal dysfunction.¹²

What are the clinical manifestations of IFIs in liver transplant recipients, and how do they differ from those in other solid organ transplant recipients?

Like other immunosuppressed patients, liver transplant recipients may present with few signs and symptoms of IFI because of the lack of an inflammatory response. Thus, these patients may not exhibit many clinical manifestations, and yet they have advanced disease. Importantly, the clinical manifestations of IFI will depend on the causative organism as well as the organs involved, but, for the most part, they are similar to those seen with other solid organ transplant recipients. There are a few notable differences, however. Liver transplant recipients frequently have intra-abdominal infections such as liver abscesses, cholangitis, peritonitis, and abdominal abscesses. In addition, aspergillosis in liver transplant recipients often disseminates beyond the lung and involves the central nervous system much more frequently than it does in other solid organ transplant recipients. Disseminated disease has been reported to occur in approximately 50% to 60% of liver transplant recipients compared with 15% to 20% in lung transplant, 20% to 35% in heart transplant, and 9% to 36% in kidney transplant recipients.¹²

What is the prevalence of ocular infections in patients undergoing OLT? How is the diagnosis of fungal endophthalmitis established?

Ocular infections following OLT are relatively uncommon. In a study of 684 liver transplant recipients, only 9 (1.3%) patients developed ocular infections.¹³ Ocular fungal infections were less common than were viral infections: *Candida albicans* endophthalmitis (2 patients), *Aspergillus fumigatus* endophthalmitis (1), cytomegalovirus retinitis (4), herpes simplex virus keratitis (1), and varicella-zoster virus panophthalmitis (1). However, fungal infections tended to appear earlier than viral infections. The mean time from OLT to ocular symptoms was 42 days (range, 13-60 days) for patients with fungal infections, whereas it was 128 days (range, 47-240 days) for patients with viral infections.

Most cases of fungal endophthalmitis are due to *Candida* spp and, less frequently, *Aspergillus* spp. *Candida* endophthalmitis is usually endogenous, secondary to hematogenous

spread from a distant site of infection. In contrast, *Aspergillus* endophthalmitis is usually exogenous, whereby organisms are introduced as a result of surgery or trauma.

Riddell et al reviewed 86 cases of endogenous *Aspergillus* endophthalmitis.¹⁴ The most frequent underlying conditions were corticosteroid use (43%), intravenous drug use (27%), and receipt of a solid organ transplant (23%). The most common ocular symptoms were blurry vision (84%), eye pain (44%), and eye redness (24%). Other less common symptoms included eye swelling, photophobia, floaters, and headache.

Specifically, in liver transplant recipients, *Aspergillus* endophthalmitis is a rare complication. In 3 studies, which together included a total of 2307 patients who underwent OLT, 48 patients (2%) had invasive aspergillosis, but none had evidence of *Aspergillus* endophthalmitis.¹⁵⁻¹⁷ However, this infection may be underdiagnosed. In an autopsy series of 85 patients who underwent OLT, invasive aspergillosis was present in 14 (16.5%) patients, and, of these, 6 (43%) were diagnosed with *Aspergillus* endophthalmitis.¹⁸

The diagnosis of endogenous *Aspergillus* endophthalmitis is difficult and frequently delayed. In the literature review described previously, diagnosis was made only after enucleation or at autopsy in 44 of 86 (51%) patients.¹⁴ Diagnosis was established by microscopy with appropriate stains and culture of the vitreous fluid. The highest yield was obtained from vitrectomy specimens (90%) compared with vitreous aspirate specimens (50%) and anterior chamber aspirates (8.3%).¹⁴ Use of newer techniques such as polymerase chain reaction in the diagnosis of fungal endophthalmitis appears to be promising, although the clinical experience is limited.¹⁹ In contrast to those in endogenous *Candida* endophthalmitis, blood cultures are almost always negative in *Aspergillus* endophthalmitis.¹⁴ However, histopathology and cultures of other sites of infection, such as the lung, brain, and skin, should be obtained. Isolated eye involvement in invasive aspergillosis is rare, except in intravenous drug users.¹⁴

How is fungal endophthalmitis managed?

Treatment for fungal endophthalmitis includes systemic antifungal drugs, vitrectomy,

and intravitreal amphotericin B. Patients with *Candida* chorioretinitis alone or with mild vitreitis can be treated with systemic amphotericin B deoxycholate, a lipid-based formulation of amphotericin B, or fluconazole.²⁰ Duration of antifungal therapy must often be long, and consideration should be given to higher doses with fluconazole. Because the intraocular penetration of amphotericin B is poor (given its large molecular size and poor lipid solubility), in patients with moderate or marked vitreitis and in those with infection caused by fluconazole-resistant fungi, vitrectomy possibly along with intravitreal amphotericin B (5-10 µg) and systemic amphotericin B should be the approach of choice.²⁰ In the absence of fungemia or evidence of extraocular infection, systemic antifungal therapy may not be needed.^{20,21} In the literature review of 86 cases of endogenous *Aspergillus* endophthalmitis, 41 of 54 (76%) patients who received antifungal treatment were treated with intravenous amphotericin B for varying durations of time.¹⁴ Of these patients, 22 of 41 (54%) were also treated with intravitreal amphotericin B with or without vitrectomy.

Currently, the drug of choice for the treatment of invasive aspergillosis is voriconazole. Herbrecht et al showed that voriconazole was associated with better outcomes and fewer side effects than was amphotericin B.²² Voriconazole has good central nervous system and ocular penetration. Although experience is limited, case reports have shown successful use of systemic voriconazole for the treatment of fungal endophthalmitis.²³⁻²⁵ In some cases, voriconazole was combined with caspofungin.^{24,25} Some experts have recently recommended combination therapy with voriconazole and caspofungin for the treatment of severe invasive aspergillosis in solid organ transplant recipients.²⁶ Well-designed, multicenter studies are needed to clarify the use of combination therapy in these patients, however. There has also been some limited experience with the use of intravitreal voriconazole. Two recent case

reports (4 patients total) have described the favorable use of intravitreal voriconazole for the treatment of *Aspergillus* endophthalmitis.^{27,28} Given its good ocular penetration and broad spectrum of antifungal activity, voriconazole appears to be a promising agent for the treatment of fungal endophthalmitis. However, it is important to recognize that, even with adequate treatment, *Aspergillus* endophthalmitis is associated with poor visual prognosis and high mortality.

How does having a liver transplant impact the choice of antifungal therapy compared with that for patients without transplants?

The major impact is related to the drug-drug interactions that can occur between antifungal agents and the immunosuppressive drugs that are used to prevent rejection in the transplant recipient.^{29,30} The azoles (ie, fluconazole, itraconazole, voriconazole, posaconazole), to varying degrees, increase the plasma levels of the calcineurin inhibitors tacrolimus and cyclosporine, which may lead to renal toxicity. It is therefore important to adjust the dose and monitor the serum levels of the co-administered drugs. Voriconazole also substantially increases the levels of sirolimus; coadministration of these drugs is not recommended. Cyclosporine increases the serum levels of caspofungin, which in turn may cause abnormalities of liver function tests. In addition to drug-drug interactions, amphotericin B-induced nephrotoxicity can be additive to that caused by other nephrotoxic drugs such as tacrolimus, cyclosporine, and aminoglycosides.

What was the rationale for the choice of antifungal agents in this patient?

This patient had disseminated *Aspergillus* infection involving the lungs and the eye. She was initially treated with systemic ABLC. ABLC has been associated with similar efficacy and less nephrotoxicity compared with

amphotericin B deoxycholate. In addition, because of the poor ocular penetration of amphotericin B, intravitreal amphotericin B (the only antifungal agent approved for intravitreal use) was also used. Unfortunately, the patient developed amphotericin B-induced nephrotoxicity. For this reason, she was switched to oral itraconazole and then, because of gastrointestinal intolerance, to intravenous itraconazole. Voriconazole was initiated when it became commercially available. Voriconazole is better absorbed than itraconazole, and it is more effective and less toxic than amphotericin B in the treatment of invasive *Aspergillus* infection.²² In addition, it has good cerebrospinal fluid and ocular penetration. Despite prolonged antifungal therapy, the patient required enucleation. Samples of the enucleated eye revealed the persistence of intraocular *Aspergillus*, emphasizing the importance of surgical drainage in the management of invasive aspergillosis. Our patient is alive and doing well and continues on chronic suppression with oral voriconazole.

In summary, IFIs are a major cause of morbidity and mortality in liver transplant recipients. Antifungal prophylaxis should be considered in liver transplant recipients who are at increased risk in the early postoperative period, such as those requiring dialysis or retransplantation. The occurrence of ocular infections in liver transplant recipients is rare but usually indicates disseminated disease, making it critical to look for other sites of infection. *Candida* endophthalmitis is more common than *Aspergillus* endophthalmitis, but the diagnosis of the latter is especially difficult because (unlike disseminated *Candida*) blood cultures are rarely positive. Better diagnostic tools are needed, especially to establish invasive aspergillosis. The treatment of fungal endophthalmitis includes systemic antifungal drugs and, in patients with moderate to severe vitreitis, vitrectomy and intravitreal drugs.

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