

Treatment of Endogenous Fungal Endophthalmitis: Focus on New Antifungal Agents

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Endogenous fungal endophthalmitis, involving only the chorioretinal structures or extending to involve the vitreous (vitritis), is a sight-threatening infection requiring early appropriate therapy. Endophthalmitis is a relatively frequent complication of candidemia and less commonly occurs in patients who have invasive aspergillosis. Because the eye is a protected compartment, penetration of systemically administered antifungal agents is highly variable. In the posterior segment of the eye, amphotericin B (AmB) achieves very poor concentrations, but fluconazole concentrations are high. Among newer antifungal agents, voriconazole shows the most promise, because therapeutic concentrations for most *Candida* and *Aspergillus* species are achieved in the vitreous, and its antifungal activity is broad. In contrast, neither posaconazole nor the 3 echinocandins achieve adequate therapeutic concentrations in the vitreous. For sight-threatening macular involvement and vitritis, intravitreal injection of either AmB or voriconazole is helpful to achieve high local antifungal activity as quickly as possible. We review the available evidence regarding the most appropriate use of antifungal agents for endogenous fungal endophthalmitis, with the emphasis on treatment of infections due to *Candida* species.

Intraocular fungal infections originate either exogenously, as occurs with penetrating trauma and postoperative infections, or endogenously from hematogenous spread. Endogenous infections range from isolated chorioretinitis to chorioretinitis with extension into the vitreous. For the purposes of this article, the term fungal endophthalmitis refers to chorioretinitis with or without associated vitritis.

Current Infectious Diseases Society of America (IDSA) guidelines for the management of endogenous *Candida* endophthalmitis recommend intravenous AmB deoxycholate (AmB-d) and oral flucytosine, possibly with vitrectomy and intravitreal AmB-d, as therapy for

patients with sight-threatening infections, and fluconazole for less severe cases [1]. These recommendations are based on animal data and clinical experience reported almost entirely before the introduction of the extended spectrum triazoles, voriconazole and posaconazole, and the echinocandins. Based on a few case reports, most of which deal with keratitis and not endophthalmitis, the IDSA guidelines for the management of invasive eye infection caused by *Aspergillus* suggest voriconazole, given either systemically or by intravitreal injection, as an alternative treatment to intravenous and intravitreal AmB-d [2]. We sought to determine the role for the use of newer antifungal agents for the more common *Candida* endogenous endophthalmitis and for the less common *Aspergillus* endogenous endophthalmitis. Much of the data on the use of new agents for the treatment of endophthalmitis are reported in the ophthalmic literature that is not routinely perused by infectious diseases specialists. We confined our review to reports dealing with endogenous *Candida* or *Aspergillus* endophthalmitis and only

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included those reports of keratitis or exogenous endophthalmitis that included data on intraocular concentrations of antifungal agents.

Implicit in the approach to treatment of endogenous endophthalmitis is the assumption that achieving adequate concentrations of antifungal agents in the infected tissues is crucial to success. The choroid and retina are highly vascular compared with the vitreous, and the vascular compartments are separated from intraocular structures by the blood-ocular barrier. Thus, infection localized to the chorioretinal layers, which are not protected by this barrier, can be treated with systemic antifungal agents, but treatment of other intraocular infections requires penetration of the antifungal agent through this relatively impermeable barrier. Chorioretinal lesions outside of the macula are often treated solely with systemic antifungal agents. However, sight-threatening lesions in the macula and chorioretinitis with vitritis usually necessitate intravitreal injection of antifungal agents, with or without vitrectomy. The available clinical data support this approach but have not been rigorously tested; most of the data are derived from reports of small case series that generally focus on a single approach.

The second assumption in treating endogenous endophthalmitis is that an examination has been performed by an ophthalmologist familiar with fungal endophthalmitis soon after the diagnosis of candidemia or the occurrence of ocular symptoms. If endophthalmitis is found, follow-up examinations should be routinely performed to evaluate the response to therapy and the development of complications.

OLDER ANTIFUNGAL AGENTS

Amphotericin B

The greatest clinical experience has been accrued with AmB-d. Early studies noted minimal or no penetration of AmB-d into the vitreous in rabbits or humans [3–5]. More recent studies have confirmed the poor penetration of both AmB-d and lipid formulations of AmB into the vitreous in noninflamed rabbit eyes. However, multiple-dose studies over 7 days in rabbits with endotoxin-induced uveitis, which presumably compromises the blood-ocular barrier, showed that higher levels could be achieved with liposomal AmB ($.47 \pm .21 \mu\text{g/mL}$) than with AmB-d ($.16 \pm .04 \mu\text{g/mL}$) [6]. Although patients have been successfully treated with systemic AmB-d, failures are common, and the toxicity of the drug is well known [7–9].

Because of the low intraocular levels attained with systemic administration, AmB-d has been injected directly into the vitreous for treatment of severe endophthalmitis. Early studies demonstrated retinal toxicity in rabbits with doses $>10 \mu\text{g}$ [10]; however, others noted histopathologic evidence of focal retinal damage at doses as low as $1 \mu\text{g}$ [11]. Injection

directly adjacent to the retina increased the risk of damage. Ganglion cell damage and retinal detachment were thought to be secondary to increased membrane permeability induced by AmB-d [10].

In rabbits, lipid formulations of AmB have been compared with AmB-d [12, 13]. Dose-related toxicity involving the retinal ganglion cells was found with all formulations but was less with liposomal AmB than with AmB lipid complex and AmB-d [12]. A study in primates suggested reduced toxicity when liposomal AmB was administered intravitreally and minimal toxicity when $<30 \mu\text{g}$ of AmB-d was used [14]. After intravitreal injection in normal rabbit eyes, the intraocular half-life of AmB-d was 7–15 days, compared with only 1.8 days in vitrectomized eyes [15].

The reported clinical experience of intravitreal injection of AmB-d in humans is limited to case reports and small case series. Doses from 20 to $100 \mu\text{g}$ have been administered without toxicity [16–19]. However, the dose typically administered ranges from 5 to $10 \mu\text{g}$. A total of 30 eyes were injected with AmB-d in this dosage range in 2 case series without the occurrence of significant toxicity [18, 20]. Intravitreal AmB-d has been used as sole treatment for endogenous *Candida* endophthalmitis to avoid systemic toxicity [21], but this approach cannot be recommended. Intravitreal AmB-d is used as adjunctive therapy along with systemic antifungal agents in patients who have sight-threatening endophthalmitis caused by *Candida* species and in most cases of *Aspergillus* endophthalmitis.

Flucytosine

Flucytosine is an adjunctive agent that can be used in combination with AmB for the treatment of *Candida* endophthalmitis [1]. It is synergistic with AmB in killing *Candida* and achieves high levels in all intraocular compartments in rabbits and humans [3, 22, 23]. Minimal additional benefit was noted when flucytosine was added to fluconazole in a study in rabbits with endophthalmitis [23]. It is not known whether this combination might be helpful in humans.

Fluconazole

Clinical experience using fluconazole for *Candida* endophthalmitis has increased over the last 20 years. Experimental data in rabbits show that the levels achieved in the vitreous are approximately 50% of peak plasma levels and 150% of trough plasma levels [24]. In one study, higher concentrations were achieved in the vitreous than in the aqueous humor [25], and somewhat higher levels have been noted in inflamed eyes [26]. Fewer data are available in humans, but it appears that vitreous concentrations are approximately 70% of those in plasma [27, 28]. The drug is well tolerated when injected intravitreally [28]; however, few studies have examined intravitreal fluconazole use, most likely because vitreous levels are high with systemic administration.

The data in rabbits with experimental *Candida* endophthalmitis are conflicting. Some studies have shown success with fluconazole, even when treatment was delayed for 5 days [29]; others have shown success when treatment was started within 24 h of infection but failure when it was delayed for 7 days [26]. In a rabbit model of disseminated candidiasis, AmB-d performed better than fluconazole in eradicating organisms from the vitreous in one study [30], but opposite results were noted in another study [23].

Studies in humans have shown response rates >90% [20, 28, 31], but the data are somewhat obfuscated because some patients had vitrectomy and intravitreal AmB-d, in addition to systemic fluconazole. Failure of fluconazole also has been reported [32–34]. Because of its excellent intraocular concentrations and safety, fluconazole has become a preferred therapy that is used by many physicians for susceptible organisms. It is usually given as the sole agent for chorioretinitis and combined with intravitreal therapy and/or vitrectomy for more advanced disease with vitreal involvement.

NEWER ANTIFUNGAL AGENTS

Voriconazole

After the large outbreak of *Fusarium* keratitis in contact lens wearers in 2005, interest in voriconazole to treat fungal eye infections increased among ophthalmologists, who realized the benefits of this broad-spectrum triazole agent in treating that difficult problem. Many studies on the distribution of voriconazole within ocular compartments were performed during treatment of complicated *Fusarium* keratitis, and, in contrast to fluconazole, most of the literature on voriconazole is from humans, rather than from experimental animals.

Penetration of voriconazole into the eye was studied in 14 patients who had noninflamed eyes and who were undergoing elective pars plana vitrectomy. Two doses of 400 mg voriconazole were given orally 12 hr apart on the day before surgery, and voriconazole concentrations were measured in blood, aqueous humor, and vitreous 3 h after the second dose of voriconazole [35]. The mean voriconazole concentrations achieved were $2.13 \pm .93$ µg/mL for plasma, $1.13 \pm .57$ µg/mL for aqueous humor, and $.81 \pm .31$ µg/mL for vitreous (38% of plasma). In a single patient receiving systemic voriconazole for infection other than endophthalmitis, voriconazole levels 8 h post mortem were 1.52 µg/mL in the aqueous humor and 1.12 µg/mL in the vitreous [33].

There is a growing body of data on intravitreal injection of voriconazole. An in vitro study using human retinal pigment epithelium cells exposed to voriconazole at concentrations from 25 up to 10,000 µg/mL showed that concentrations <250 µg/mL had no toxic effects [36]. Rats underwent a single intravitreal injection of voriconazole to achieve concentrations that ranged

from 5 to 500 µg/mL [37]. Three weeks later electroretinographic studies showed no toxic effects at any dosage level, and histologic examination showed focal necrosis in the outer retina only in those eyes in which the concentrations were ≥ 50 µg/mL. Thus, it is suggested that voriconazole concentrations of up to 25 µg/mL in the vitreous are safe. When an injection of 100 µg is given into the vitreous, which has a volume of approximately 4 mL, the voriconazole concentration will be 25 µg/mL. The concentration of voriconazole given by intravitreal injection in normal rabbit eyes was found to exhibit exponential decay, and the half-life was 2.5 h [38]. Whether this process is similar in humans is not known. The rationale for the injection of voriconazole is that it may be safer than AmB-d and that it immediately achieves high levels of the drug in the vitreous, whereas serum levels from systemic administration are gradually reaching a steady state.

Clinical efficacy of systemic voriconazole has been reported in a small number of patients who had *Candida* endophthalmitis and more who had mold endophthalmitis [33, 34, 39, 40]. Of 7 patients with *Candida* endophthalmitis treated with voriconazole (200 mg twice daily in most patients), 6 survived, and visual acuities at the end of therapy ranged from 20/20 to 20/100. One of these patients also received an intravitreal injection of voriconazole, several were given caspofungin, and 1 received intravitreal AmB-d, so it is difficult to evaluate the efficacy of voriconazole alone. In our practice, we have noted that systemic voriconazole, with or without intravitreal injection, seems to lead to a more rapid response than other antifungal agents.

One added advantage of voriconazole over fluconazole is that it has activity against *Aspergillus* species and fluconazole resistant *Candida* species, such as *Candida glabrata* and *Candida krusei*. *Aspergillus* endophthalmitis often involves the macula and is especially difficult to treat [18, 20]; response rates for AmB-d (intravitreal and systemic) have been as poor as 8% [41]. There are a few cases reports in which voriconazole was used; most reports were of exogenous *Aspergillus* endophthalmitis, but one documented resolution of endogenous *Aspergillus terreus* endophthalmitis [42]. Although it seems appropriate to use voriconazole for *Aspergillus* endophthalmitis, the true response rate is not known.

When voriconazole is used to treat endophthalmitis, serum levels should be monitored, because of their high variability among patients. Trough levels between 2 and 5 µg/mL are the goal. Serum levels within this range have been associated with a better outcome in invasive mold infections [43, 44]. Higher levels are associated with increasing toxicity [44].

Posaconazole

Very few data are available regarding the use of posaconazole for ocular infections. No animal data have been published regarding intraocular concentrations of oral posaconazole. One patient,

who had *Fusarium* keratitis and endophthalmitis, was successfully treated with oral posaconazole (200 mg 4 times daily) plus topical posaconazole and vitrectomy. Sampling at the time of surgery yielded a posaconazole concentration of .25 µg/mL in the vitreous, and .9 µg/mL in the aqueous humor [45]. Another report demonstrated resolution of *Fusarium* endophthalmitis in 2 patients in whom voriconazole treatment had failed [46].

At this time, there are too few data to suggest that posaconazole should be considered for the treatment of endophthalmitis, although it might possibly be an alternative option in cases of intolerance to other antifungal agents. It cannot be recommended because of its relatively poor penetration into ocular structures combined with the variable absorption of the oral suspension, which is currently the only available formulation.

Echinocandins

The echinocandins, micafungin, caspofungin, and anidulafungin, penetrate ocular compartments poorly [47–49]. In studies in experimental animals, it has been shown that concentrations of micafungin in the vitreous in noninflamed eyes are very low, ranging from undetectable to .034 µg/mL [48]. Anidulafungin levels in the vitreous have ranged from undetectable to .184 µg/mL when very high dosages were used [49]. A rabbit uveitis model was used to evaluate caspofungin penetration into various ocular compartments. At a dose of 1 mg/kg/day, no drug was detectable in the vitreous of inflamed eyes at any time point during the study [50]. In rabbit models of disseminated candidiasis and *Candida* meningitis, micafungin reduced the fungal burden in the vitreous, but only when doses higher than those used clinically were given [51, 52]. In rabbits, intravitreal injection of 15 µg micafungin was nontoxic [53]; intravitreal echinocandin use has not been reported in humans.

A single case report of possible *Candida* endophthalmitis in a patient who appeared to have mild vitritis noted success with caspofungin therapy [54], but others have documented failure with caspofungin and found undetectable levels in the vitreous [55]. Review of the 5 randomized controlled treatment trials that studied echinocandins for candidemia and invasive candidiasis revealed that 21 of the 1028 patients who received an echinocandin were noted to have endophthalmitis [56–60]. Among these 21 patients, 12 were said to have had resolution of their eye infection. However, these data are not terribly useful, because the studies were designed to exclude patients who had known endophthalmitis, the reports did not differentiate between those who had vitritis and those who had only chorioretinitis, and only scant data were provided on individual cases.

It is difficult to draw any conclusions about the efficacy of systemic echinocandins for the treatment of endophthalmitis. It is possible that isolated chorioretinitis without vitreous extension could respond to echinocandin therapy, but there are no

firm data to verify this hypothesis. At this time it seems prudent to not use echinocandins for treatment of endophthalmitis.

VITRECTOMY

Vitrectomy is recommended for sight-threatening *Candida* and *Aspergillus* endophthalmitis with vitritis [1, 2]. Sampling the vitreous at the time of vitrectomy provides important culture data to guide treatment. Vitrectomy allows removal of loculated areas of infection that would not respond to systemic antifungal agents and decreases the overall burden of organisms. The procedure is usually combined with the administration of intravitreal antifungal agents. Outcomes for early vitrectomy combined with systemic antifungal therapy with AmB-d or fluconazole have been favorable for *Candida* endophthalmitis [61, 62]. When difficult-to-treat fungal organisms are present in a protected space in which antifungal penetration is poor, surgical resection of the involved tissue (vitreous) with intravitreal administration of antifungal agents is a logical therapeutic intervention. It is important to recognize that the half-life of antifungal agents administered directly into the vitreous at the time of vitrectomy will be shortened and that repeated administration may be necessary.

SUGGESTED RECOMMENDATIONS FOR TREATMENT OF ENDOGENOUS ENDOPTHALMITIS

For *Candida* endophthalmitis, we favor the use of systemically administered agents that are known to achieve adequate concentrations in the vitreous. Fluconazole, voriconazole, and flucytosine achieve therapeutic intravitreal concentrations, whereas the echinocandins and all formulations of AmB do not. Most experience has accumulated with fluconazole. There is less experience with voriconazole, but there are data on the efficacy and safety of intravitreal injection of this agent. Flucytosine should be used in combination with AmB and not as sole therapy. We feel that the role for echinocandins and posaconazole in the management of endogenous endophthalmitis is minimal. These suggestions differ from the IDSA guidelines in encouraging an increasing role for fluconazole and voriconazole and a decreasing role for AmB-d, and also in suggesting that echinocandins should not be used as alternative agents.

For patients who have *Candida* chorioretinitis with no vitreal involvement, systemic antifungal agents are appropriate as long as repeated examinations show no extension into the vitreous or the macula. Either fluconazole (12 mg/kg loading dose, then 6–12 mg/kg daily), or voriconazole (6 mg/kg for 2 doses, then 4 mg/kg twice daily) can be used. Initial intravenous administration seems prudent for voriconazole, and serum concentrations should be monitored carefully to ensure adequate

exposure and to prevent toxicity. No studies have defined the appropriate duration of therapy. A reasonable approach, consistent with the IDSA guidelines, is to treat for at least 4–6 weeks, with the final duration dependent on the response observed in repeated ophthalmologic examinations.

For sight-threatening macular involvement and vitritis due to *Candida* species and for all cases of *Aspergillus* endophthalmitis, in addition to systemic therapy, intravitreal injection of an antifungal agent should be performed to ensure immediate achievement of appropriate levels in the posterior segment. Either voriconazole (100 µg) or AmB-d, (5–10 µg) can be given by intravitreal injection. Voriconazole may be safer than AmB-d, but there is more experience with AmB-d, which also has the advantage of having a longer half-life after intravitreal injection. The need for repeated injections is dependent on the response to therapy noted at ophthalmologic examinations. Vitrectomy should be considered to decrease the burden of organisms and to allow the removal of fungal abscesses that are inaccessible to systemic antifungal agents.

It is important to emphasize that a team approach involving both ophthalmology and infectious diseases is essential to ensure the most efficacious treatment and preservation of visual acuity. Vitrectomy and intravitreal injection of an antifungal agent require the patient to be seen by an ophthalmologist who has experience in treating fungal endophthalmitis. The nuances of drug absorption, drug-drug interactions, and toxicity associated with the azole agents require an infectious diseases physician who has experience using these agents. Careful follow-up to assess the response to therapy is essential to detect macular or vitreal extension as early as possible and initiate aggressive therapy to preserve visual acuity.

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