Endogenous Aspergillus Endophthalmitis
Clinical Features and Treatment Outcomes

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Objective: This study evaluated the clinical features and treatment outcomes in patients with endogenous Aspergillus endophthalmitis.

Design: The study design was a multicenter retrospective chart review.

Participants: Ten patients (12 eyes) with culture-proven endogenous Aspergillus endophthalmitis treated by 1 of the authors were studied.

Intervention: Intravitreous amphotericin B injection, pars plana vitrectomy, systemic amphotericin B therapy, and oral anti-fungal therapy were performed.

Main Outcome Measures: Elimination of endogenous Aspergillus endophthalmitis and Snellen visual acuity, best corrected, were measured.

Results: All patients had a 1- to 3-day history of pain and marked loss of visual acuity in the involved eyes. Varying degrees of vitritis was present in all 12 eyes. In 8 of 12 eyes, a central macular chorioretinal inflammatory lesion was present. Four patients (six eyes) had associated pulmonary diseases and were receiving concurrent steroid therapy. One of these patients with chronic asthma also was abusing intravenous drugs. Overall, six patients (six eyes) had a history of intravenous drug abuse, whereas a seventh patient (one eye) was suspected of abusing intravenous drugs. Blood cultures and echocardiograms were negative for systemic aspergillosis. Management consisted of a pars plana vitrectomy in 10 of 12 eyes. Intravitreous amphotericin B was administered in 11 of 12 eyes. Systemic amphotericin B therapy was used in eight patients. One patient was treated with oral antifungal agents. In three eyes without central macular involvement, final visual acuities were 20/25 to 20/200. In eight eyes with initial central macular involvement, final visual acuities were 20/400 in three eyes and 5/200 or less in four eyes. Two painful eyes with marked inflammation, hypotony, and retinal detachment were enucleated.

Conclusions: Endogenous Aspergillus endophthalmitis usually has an acute onset of intraocular inflammation and often has a characteristic chorioretinal lesion located in the macula. Although treatment with pars plana vitrectomy and intravitreous amphotericin B is capable of eliminating the ocular infection, the visual outcome generally is poor, especially when there is direct macular involvement. Ophthalmology 1998; 105:57-65

Aspergillus species are ubiquitous saprophytic molds, commonly growing in soil, stored hay, and decaying vegetation. The conidia (spores) can become airborne and may enter pulmonary alveoli and paranasal sinuses. Even though exposure to Aspergillus is universal, infection in humans is uncommon. The most common pathogen is Aspergillus fumigatus, perhaps because its smaller spores facilitate easier transport into the alveoli, but A. flavus, A. niger, A. nidulans, and A. terreus also have been described as causing human disease. There are strain differences in growth rate, conidia size, and virulence that affect pathogenicity. Host predisposing conditions also affect pathogenicity as the type and probability of invasiveness, dissemination, risk of mortality, and role for systemic treatment are modified.

Endogenous Aspergillus endophthalmitis (EAE) is a rare but devastating infection usually associated with disseminated aspergillosis or with intravenous drug abuse (IVDA). Based mainly on individual case reports, the management of this ocular infection remains controversial. To better define the clinical features, current treatment regimens, and visual acuity outcomes of EAE, we report the largest number of these patients undergoing treatment and follow-up for this infection.
Patients and Methods

Patients with culture-proven EAE were identified retrospectively from the Microbiology Department records at the Bascom Palmer Eye Institute between January 1980 and April 1995. All were included in this study. The cultures were obtained from vitreous aspirates or vitrectomy specimens, placed on blood agar, chocolate agar, thioglycolate broth at 37°C, and Sabouraud’s glucose agar at 25°C. A positive culture was defined as the growth of the same organism on two or more solid media, or semiconfluent growth on a single culture medium.

Patients with a history of recent ocular surgery, ocular trauma, external infection, or scleritis were excluded. Three patients with EAE were thus identified from the Bascom Palmer Eye Institute records (patients 1, 4, and 5). One patient (patient 1) with systemic aspergillosis had sequential bilateral endophthalmitis with a positive vitreous aspirate culture from only one eye. The fellow eye with similar clinical findings is included in this series.

Seven other patients (one with bilateral involvement) with endogenous Aspergillus endophthalmitis, defined in an identical manner, are included in this series. The patients were diagnosed and treated by five vitreoretinal specialists (coauthors CCB, JGG, CEM, WCM, JHK). Information obtained from the patient’s medical record included age; gender; medical history, including predisposing systemic risk factors; duration and type of symptoms; presenting systemic and ophthalmic examination and diagnostic workup; systemic and ocular treatment; and final visual outcome. A total of 12 eyes in 10 patients with EAE were identified for the current study. Treatment and management decisions were made by the individual treating physician without a defined study protocol.

Results

The clinical features of the patients are summarized in Table 1. The patients ranged in age from 24 to 91 years. In three patients with chronic obstructive pulmonary diseases (COPD), the average age was 74 years. In the six patients with a history of IVDA and one with a history of both IVDA and asthma, the ages ranged from 24 to 40 years, with an average of 33 years.

There were 7 males and 3 females. The left eye was involved in 8 of 12 cases. The follow-up time after the initial diagnosis ranged from 2 to 23 months (mean, 9 months).

The visual acuities of the involved eyes on initial examination were count-fingers in five, hand motions in four, and light perception in one. When suspected EAE developed in the second eye in two patients, the initial visual acuities were 20/40 and 20/200, respectively.

The associated systemic conditions are summarized in Table 1. In this study, the two main disease categories of patients in whom EAE develop are those with chronic pulmonary diseases and those with a history of IVDA. One patient had both predisposing conditions. The patient characteristics, with the exception of age, treatment, and outcome, are quite similar within each group.

Four patients had chronic pulmonary diseases. Three of the four had typical COPD. The fourth (patient 4) had a history of chronic asthma and abuse of intravenous cocaine. Three patients had been treated with high-dose corticosteroid therapy over a long time course. All four patients had been hospitalized recently with severe exacerbations of their pulmonary disease, two with a new infiltrative pneumonia. During hospitalization, all four received intravenous antibiotics and high-dose intravenous corticosteroids.

In the COPD category of patients, the onset of ocular signs and symptoms began days to weeks after hospitalization. In each of the four patients, severe visual loss and pain developed rapidly in the involved eye. Presentation to an ophthalmologist usually was within 1 to 3 days of onset of visual loss. Each involved eye had anterior segment inflammation ranging from mild aqueous cells to marked aqueous cells and hypopyon formation. A moderate-to-dense vitritis was present in all four eyes, precluding a fundus view in two eyes. In the remaining two eyes, ophthalmoscopy showed confluent, yellow macular lesions.

Two patients (Tables 1, 2; patients 1, 2) with COPD had second eye involvement develop at 1 and 7 weeks, respectively, after diagnosis and treatment of EAE in the first eye. Both of these patients had documented systemic aspergillosis. Patient 1 had pulmonary aspergillosis with positive sputum cultures. Patient 2 had an initial diagnosis of severe uveitis and was treated with topical and periocular steroids. Five weeks later, this patient had disseminated subcutaneous nodules developing in the chest, abdomen, and thighs. After a skin biopsy confirmed aspergillosis, systemic amphotericin B was initiated. On the day after systemic amphotericin B was initiated, mild vitritis and a focal chorioretinitis temporal to the fovea developed in the second eye.

In the IVDA category of patients, (Tables 1, 2; patients 4–10) six of seven patients confirmed a history of IVDA. The seventh patient (patient 10) denied IVDA. Despite clinical suspicion of IVDA, no drug screens were performed on this patient. Each patient with a history of IVDA had a 1- to 2-day history of severe visual loss (<1/200) and moderate-to-severe pain in the involved eye. Two patients initially had conjunctival injection, but all seven patients had significant anterior chamber cells develop; a hypopyon developed in two patients. Mild vitritis became progressively dense. All seven had a visible inflammatory chorioretinal lesion.

Regardless of the predisposing systemic disease category, ocular findings were quite similar at presentation. All patients (except patient 3) had significant anterior chamber cells develop with or without a hypopyon. All patients had a vitritis varying from mild to severe. In three eyes (patients 1 and 2, left eye), dense vitritis precluded a view of the posterior pole. The right eye of patient 1 had no macular lesion when viewed at pars plana vitrectomy at 2 weeks post-treatment. The other nine eyes had chorioretinal inflammatory lesions that were located centrally in the macula in seven patients or isolated to the temporal macula in two patients (right eye of patients 2 and 3). The macular lesions were confluent yellowish chorioretinal infiltrates with poorly defined borders. Intraretinal hemorrhages were noted in seven eyes (patients 2, right eye, 3, 5, 6, 8–10) (Figs 1, 2). A subretinal hypopyon representing layered inflammatory cells between the neurosensory retina and the RPE was present in four eyes (patients 5, 6, 9, and 10). A subhyaloid hypopyon was present in four patients (patients 3, 6, 9, and 10) (Figs 1, 2). After resolution of the infection, the resulting chorioretinal scar appeared atrophic and fibrotic. The retinal vessels overlying the macular scar remained intact (Figs 1, 2).

In the systemic work-up (Table 2), acute or chronic abnormalities were present on a chest x-ray in all four patients with COPD. In one patient, these abnormalities were suggestive but not diagnostic of aspergillosis. Sputum specimens were positive in the IVDA category of patients. In three of the four patients, Five of the seven patients with a history of IVDA had normal chest x-ray examinations. Echocardiograms in seven patients were normal. A
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Table 1. Clinical Characteristics of Patients with Endogenous Aspergillus Endophthalmitis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)/Sex</th>
<th>Eye</th>
<th>Predisposing Condition</th>
<th>Time from Onset of Symptoms to Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>91/M</td>
<td>OS</td>
<td>Hospitalized for COPD and pneumonia; pulmonary Aspergillosis; chronic corticosteroids</td>
<td>2 days</td>
</tr>
<tr>
<td>1b</td>
<td>91/M</td>
<td>OD</td>
<td>Same</td>
<td>1 day; 7 days after OS</td>
</tr>
<tr>
<td>2a</td>
<td>68/M</td>
<td>OS</td>
<td>Hospitalized for COPD; use of chronic corticosteroids; cutaneous nodular Aspergillosis at 5 wks</td>
<td>3 days post hospitalization; diagnosis at 5 wks</td>
</tr>
<tr>
<td>2b</td>
<td>68/M</td>
<td>OD</td>
<td>Same</td>
<td>1 day; 6th wk after OS onset</td>
</tr>
<tr>
<td>3</td>
<td>63/F</td>
<td>OS</td>
<td>COPD, use of chronic corticosteroids, recent hospitalization</td>
<td>2 days</td>
</tr>
<tr>
<td>4</td>
<td>31/F</td>
<td>OS</td>
<td>IVDA; hospitalized for asthma; high dose corticosteroids</td>
<td>2 days</td>
</tr>
<tr>
<td>5</td>
<td>39/M</td>
<td>OD</td>
<td>IVDA</td>
<td>2 days</td>
</tr>
<tr>
<td>6</td>
<td>40/M</td>
<td>OS</td>
<td>IVDA</td>
<td>2 days</td>
</tr>
<tr>
<td>7</td>
<td>32/M</td>
<td>OS</td>
<td>IVDA</td>
<td>4 days</td>
</tr>
<tr>
<td>8</td>
<td>24/F</td>
<td>OS</td>
<td>IVDA</td>
<td>2 days</td>
</tr>
<tr>
<td>9*</td>
<td>32/M</td>
<td>OS</td>
<td>IVDA</td>
<td>1 week</td>
</tr>
<tr>
<td>10</td>
<td>33/M</td>
<td>OD</td>
<td>Presumed IVDA</td>
<td>Same day</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; IVDA = intravenous drug abuse; OD = right eye; OS = left eye; F = female; M = male.
* Patient 9 previously published in Gross.*

Table 2. Clinical Characteristics of Patients with Endogenous Aspergillus Endophthalmitis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial VA</th>
<th>Anterior Segment</th>
<th>Posterior Segment</th>
<th>Systemic Workup</th>
<th>Systemic Cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>HM</td>
<td>Hypopyon OS, cataract</td>
<td>Dense vitritis</td>
<td>CXR: abnl COPD</td>
<td>(+) sputum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Echo CV: nl</td>
<td>(−) blood, urine</td>
</tr>
<tr>
<td>1b</td>
<td>20/200</td>
<td>Hypopyon OD, cataract</td>
<td>Dense vitritis</td>
<td>CXR: abnl COPD</td>
<td>(+) skin nodules; (−) blood, urine</td>
</tr>
<tr>
<td>2a</td>
<td>LP</td>
<td>2+ cell, iris nodules, cataract</td>
<td>Dense vitritis</td>
<td>CXR: abnl COPD</td>
<td>(−) blood</td>
</tr>
<tr>
<td>2b</td>
<td>20/40</td>
<td>Normal</td>
<td>Vitritis, temporal chorioretinitis</td>
<td>CXR: abnl COPD</td>
<td>(−) sputum, blood</td>
</tr>
<tr>
<td>3</td>
<td>HM</td>
<td>2+ cell</td>
<td>Vitritis, temporal chorioretinitis, pseudohypopyon</td>
<td>CXR: abnl asthma</td>
<td>(−) sputum, blood</td>
</tr>
<tr>
<td>4</td>
<td>HM</td>
<td>2+ cell, herpetic dendrites</td>
<td>Vitritis, macular chorioretinitis</td>
<td>CXR: abnl COPD</td>
<td>(−) blood</td>
</tr>
<tr>
<td>5</td>
<td>HM</td>
<td>Conjunctival injection</td>
<td>Vitritis, macular chorioretinitis, pseudohypopyon</td>
<td>CXR normal, Echo CV: nl</td>
<td>(−) blood</td>
</tr>
<tr>
<td>6</td>
<td>1/200</td>
<td>4+ cell</td>
<td>Vitritis, macular chorioretinitis</td>
<td>CXR, Echo CV, CT brain: nl</td>
<td>(−) blood</td>
</tr>
<tr>
<td>7</td>
<td>1/200</td>
<td>4+ cell</td>
<td>Vitritis, macular chorioretinitis</td>
<td>CXR, Echo CV, CT brain: nl</td>
<td>(−) blood</td>
</tr>
<tr>
<td>8</td>
<td>1/200</td>
<td>Hypopyon</td>
<td>Vitritis, macular chorioretinitis</td>
<td>CXR, Echo CV, CT brain: nl</td>
<td>(−) blood</td>
</tr>
<tr>
<td>9</td>
<td>1/200</td>
<td>Hypopyon</td>
<td>Vitritis, macular chorioretinitis</td>
<td>CXR, Echo CV: nl, HIV neg</td>
<td>(−) blood</td>
</tr>
<tr>
<td>10</td>
<td>2/200</td>
<td>1+ cell</td>
<td>Vitritis, macular chorioretinitis, pseudohypopyon</td>
<td>CXR: nl</td>
<td>(−) blood</td>
</tr>
</tbody>
</table>

VA = visual acuity; OD = right eye; OS = left eye; HM = hand motions; LP = light perception; CXR = chest x-ray; Echo CV = echocardiogram; CT = computed tomography; abnl = abnormal; nl = normal; neg = negative; HIV = human immunodeficiency virus.
computed tomographic brain scan was normal in four patients, none of whom had neurologic abnormalities. Blood cultures were uniformly negative in all patients, even in the two with documented disseminated aspergillosis. A human immunodeficiency virus test was negative on all patients with a history of IVDA.

An anterior chamber aspirate showed no growth in the three patients tested. Vitreous needle aspirates were positive for Aspergillus in two of four patients. Nine of 12 eyes had initial diagnostic pars plana vitrectomies performed at 1 to 6 days after presentation. Cultures of the vitrectomy specimens were positive in eight of nine eyes. However, in the right eye of case 2, intravenous amphotericin B had been initiated 1 day before onset of a focal retinitis. At the time of vitrectomy 6 days later, the cultures were negative.

The Aspergillus species identified were *A. fumigatus* in the COPD category of patients and *A. flavus, A. glaucus, and A. terreus* in the IVDA category of patients (Table 3).

Intravitreous amphotericin B was used in 11 of the 12 eyes. In the initially involved eye of patient 2, topical and sub-Tenon's corticosteroids were administered for severe uveitis. By 5 weeks, however, the patient had light perception vision, iris nodules, and severe endophthalmitis. The correct diagnosis eventually was made after the patient had systemic aspergillosis develop confirmed by biopsy of subcutaneous nodules. At the time of enucleation 5 months later, results from the pathology report showed diffuse inflammation and aggregates of fungal hyphae.

The intravitreous treatment consisted of amphotericin B with initial dosages of 5 μg in seven eyes, 10 μg in three eyes, and 20 μg in one eye. Intravitreous dexamethasone 400 to 800 μg was combined with the amphotericin B in three eyes (Table 3, patients 1 and 5). Repeat intravitreous amphotericin B injections were given in eight eyes. The timing of reinjections varied from 2 days to 6 weeks, with an average interval of 1 week. A maximum total dose of 30 μg was given in two eyes over an interval of 2 months (patients 4 and 5). There was no visible toxicity in these two eyes. An indication for reinjection was the suspicion of persistence of fungal organisms, based on increasing or slow resolution of intraocular inflammation, or persistent vitritis.

Adjunctive subconjunctival therapy consisted of corticosteroids in two eyes and varying dosages of miconazole or amphotericin B in five eyes. Two eyes received topical amphotericin B 0.2% drops; one received topical natamycin drops.

Nine of ten patients received systemic antifungal therapy. Intravenous amphotericin B was started in eight patients (Table 3). It was discontinued after 6 days in a 91-year-old patient.
### Table 3. Surgical Management, Antifungal Therapy, Visual Results

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Time to Treatment</th>
<th>Initial Ocular Diagnosis</th>
<th>Ocular Culture</th>
<th>Antifungal Therapy</th>
<th>Systemic</th>
<th>Reoperative</th>
<th>Repeat Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Day 2</td>
<td>Vit asp (+)</td>
<td>A. fumigatus</td>
<td>Amphotericin B 5 µg x 2 Decadron 400 µg</td>
<td>None</td>
<td>Amphotericin B (1 wk); fluconazole</td>
<td>Vit asp (3 wks) Negative</td>
</tr>
<tr>
<td>1b</td>
<td>Day 1</td>
<td>Vit asp (-)</td>
<td>Neg</td>
<td>Amphotericin B 5 µg x 3 Decadron 400 µg x 3</td>
<td>None</td>
<td>Same</td>
<td>PPV, PPL (2 wks) Negative</td>
</tr>
<tr>
<td>2a</td>
<td>6 wks</td>
<td>Skin nodule biopsy (5th wk)</td>
<td>Asp. sp (+) Skin</td>
<td>None sc/top steroids at onset</td>
<td>Amphotericin B* 1545 mg (0.6 mg/kg x 6 wks)</td>
<td>None Enuc (5 mos) (+) vitreous hyphae</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>Day 6</td>
<td>PPV (-)</td>
<td>Amphotericin B 5 µg</td>
<td>None</td>
<td>Amphotericin B* started 1 day prior to PPV</td>
<td>PPV, PPL (6 mos); AC IOL (18 mos) (+) lens vitreous</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Day 1, 4 hrs</td>
<td>PPV (+)</td>
<td>Asp. sp</td>
<td>Amphotericin B 10 µg (repeat 6 mos x 2)</td>
<td>None</td>
<td>Amphotericin B 716 mg; fluconazole; itraconazole</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>Day 2</td>
<td>PPV (+)</td>
<td>A. fumigatus</td>
<td>Amphotericin B 10 µg x 3 Miconazole sc</td>
<td>None</td>
<td>Ketoconazole; fluconazole; itraconazole</td>
<td>PPV, PPL (1 mo); MP, SBP (2 mos); Enuc (8 mos) Negative</td>
</tr>
<tr>
<td>5</td>
<td>Day 6</td>
<td>PPV (+)</td>
<td>A. glaucus</td>
<td>Amphotericin B 10 µg x 3 Decadron 800 µg</td>
<td>None</td>
<td>Amphotericin B 400 mg; fluconazole</td>
<td>None None</td>
</tr>
<tr>
<td>6</td>
<td>Day 2</td>
<td>PPV (+)</td>
<td>A. flavus</td>
<td>Amphotericin B 20 µg</td>
<td>None</td>
<td>Amphotericin B 350 mg; fluconazole</td>
<td>None None</td>
</tr>
<tr>
<td>7</td>
<td>Day 1</td>
<td>AC tap (-); Vit asp (+); PPV (+) (day 3)</td>
<td>A. flavus</td>
<td>Amphotericin B 5 µg x 2</td>
<td>None</td>
<td>Amphotericin B 275 mg; fluconazole</td>
<td>PPV, SBP (3 wks) Negative</td>
</tr>
<tr>
<td>8</td>
<td>Day 2</td>
<td>AC tap (-), vit asp (+); PPV (+) (day 4)</td>
<td>A. flavus</td>
<td>Amphotericin B 10 µg x 3 Miconazole sc; Amphotericin B top</td>
<td>None</td>
<td>Amphotericin B 275 mg; Fluconazole</td>
<td>None None</td>
</tr>
<tr>
<td>9</td>
<td>1 wk</td>
<td>AC tap (-); PPV (+) (day 4)</td>
<td>A. terreus</td>
<td>Amphotericin B 5 µg x 2 Amphotericin B 0.2 mg x 4 sc</td>
<td>None</td>
<td>None</td>
<td>None None</td>
</tr>
<tr>
<td>10</td>
<td>Day 2</td>
<td>PPV (+)</td>
<td>A. flavus</td>
<td>Amphotericin B 5 µg</td>
<td>None</td>
<td>Amphotericin B 0.5 mg/kg x 3 wks</td>
<td>None None</td>
</tr>
</tbody>
</table>

AC = anterior chamber; Amphotericin B = amphotericin B; Amphotericin B* = liposomal encapsulated form of amphotericin B; cat = cataract; cult = culture; Enuc = enucleation; IOL = intraocular lens; MP = membrane peeling; PPL = pars plana lensectomy; PPV = pars plana vitrectomy; SBP = scleral buckle procedure; sc = subconjunctival; top = topical; Vit asp = vitreous aspirate.

(Table 3, patient 1) because of emesis and renal failure. When the patient died 6 weeks later, no autopsy was permitted. In patient 4, intravenous amphotericin B was associated with severe emesis and dehydration. Seven of eight patients completed a 3- to 6-week course of systemic amphotericin B. Dosages ranged from 0.5 to 0.6 mg/kg, with a total dosage of 275 to 1545 mg. Two of these patients (patients 2 and 3) were treated with Amphocil, the liposomal encapsulated form of amphotericin B. In patients 2 and 3, Aspergillus endophthalmitis persisted or recurred despite systemic treatment. In three of the six patients (Table 3, patients 6–8), fluconazole (500 mg four times daily for 3 weeks) was given in combination with the intravenous amphotericin B.

The azole compounds were given to three patients (patients 1, 4, and 5). Patient 1 received fluconazole after intravenous amphotericin B was discontinued. Because of suspected persistent endophthalmitis, patient 4 was treated with fluconazole, then itraconazole after amphotericin B was discontinued. One patient (patient 5) received oral ketoconazole followed by fluconazole. In patient 9, only intravitreal and subconjunctival amphotericin B treatment was used.

Eight eyes had secondary ocular procedures and repeated intravitreal cultures after initial diagnostic and antifungal therapy (Table 3). A pars plana vitrectomy was repeated in six patients. Patient 4 also had a retinal biopsy. In seven eyes, fungal organisms were not reisolated. However, in patient 3, EAE initially presented with dense vitritis and a subhyaloid hypopyon. At pars plana vitrectomy, a small temporal chorioretinal lesion was found. After systemic and intravitreal amphotericin B therapy, this lesion healed by 1 month. At 6 months, recurrent vitritis with fungal balls on the posterior lens surface developed. Aspergillus species grew from the vitreous and lens cultures. The previously healed temporal chorioretinal lesion was unchanged. In one additional case, the right eye of patient 2, chronic inflammation persisted for 5 months after systemic therapy. This eye was enucleated with pathology, showing vitreous hyphae typical of Aspergillus species.

The final visual outcomes are listed in Table 4. The three
eyes presenting without central macular chorioretinal lesions achieved favorable final visual acuities. Two of these eyes were the fellow eyes with smaller initial lesions and prompt diagnosis and treatment. The fellow right eye of patient 2 had 20/40 visual acuity, and a temporal chorioretinal lesion maintained 20/40 visual acuity. After a cataract developed, visual acuity was 20/80 at last follow-up. The other fellow eye in this study, the right eye of patient 1, remained at 20/200 visual acuity until the patient died of systemic aspergillosis and multiple end organ failure. One eye (patient 3) that had hand motions visual acuity improved to 20/25 visual acuity at the last examination. In this eye, the chorioretinal lesion was confined to the temporal macula.

Of the eight eyes with central macular chorioretinal lesions, seven were directly visible at presentation (patients 4–10). One patient (left eye of patient 1) had macular involvement identified by echography. Initial visual acuities ranged from 20/200 to hand motions. Final visual acuities were 20/400 or worse in four eyes with one eye (patient 4) under-}

### Table 4. Visual Outcomes of Patients with Endogenous Aspergillus Endophthalmitis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Eye</th>
<th>Initial VA</th>
<th>Location of Chorioretinal Lesion</th>
<th>Final VA</th>
<th>Follow-up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>OS</td>
<td>20/200</td>
<td>Macular (by echography)</td>
<td>20/200</td>
<td>1.5 (death)</td>
</tr>
<tr>
<td>1b</td>
<td>OD</td>
<td>1/200</td>
<td>No macular lesion at PPV (2 wks)</td>
<td>1/200</td>
<td>1.5 (death)</td>
</tr>
<tr>
<td>2a</td>
<td>OS</td>
<td>20/40</td>
<td>No view</td>
<td>20/80</td>
<td>5 (enucleation)</td>
</tr>
<tr>
<td>2b</td>
<td>OD</td>
<td>20/25</td>
<td>Temporal macula</td>
<td>20/20</td>
<td>10 (20/40 at 5 mos)</td>
</tr>
<tr>
<td>3</td>
<td>OS</td>
<td>HM</td>
<td>Temporal macula</td>
<td>20/25</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>OS</td>
<td>HM</td>
<td>Central macular</td>
<td>Enucleation</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>OD</td>
<td>HM</td>
<td>Central macular</td>
<td>3/200</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>OS</td>
<td>1/200</td>
<td>Central macular</td>
<td>20/400</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>OS</td>
<td>1/200</td>
<td>Central macular</td>
<td>HM</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>OS</td>
<td>1/200</td>
<td>Central macular</td>
<td>1/200</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>OS</td>
<td>1/200</td>
<td>Central macular</td>
<td>20/400</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>OD</td>
<td>2/200</td>
<td>Central macular</td>
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VA = visual acuity; OD = right eye; OS = left eye; HM = hand motions; LP = light perception.

In the absence of localized systemic symptoms in these patients with EAE, the diagnostic yield of blood cultures, pulmonary radiographic studies, and echocardiograms is low. Even in patients who are immunosuppressed with definite dissemination, blood cultures are almost always negative.17 In this series, seven patients with EAE with suspected or confirmed IVDA underwent systemic evaluation, but clinical testing did not show any additional sites of Aspergillus infection. Michelson et al18 reported one case in which a second systemic focus of Aspergillus osteomyelitis accompanied EAE in an intravenous drug abuser. Although there are no currently reported cases of EAE in patients with AIDS, the frequency of AIDS in intravenous drug abusers may warrant human immunodeficiency virus testing. Aspergillus has been documented in patients with AIDS.19-21 When a negative history includes denial of drug abuse, clinical suspicion and drug screening may be helpful in ruling out this possibility.

The clinical features of EAE in this study are consistent with descriptions of similar patients in the literature.22 Regardless of predisposing or associated systemic conditions, the ocular presentation and findings often are characteristic and provide possible diagnostic utility. Acutely, patients present with rapid onset of pain and severe visual loss. Often, the central macula is involved. A confluent, yellowish macular infiltrate begins in the choroid and subretinal space. An inferior gravitational layering of in-

### Discussion

Endogenous Aspergillus endophthalmitis initially was reported by Dimmer3 in 1913 in a patient with arthritis. Naidoff and Green6 in 1975 reported a case occurring after renal transplantation and reviewed the early literature noting the lack of beneficial treatment with intravenous amphotericin B. Endogenous Aspergillus endophthalmitis since has been reported in immunocompromised patients with heart transplants,7 endocarditis,8 lung and liver transplants,9,10 and leukemia.11,12 It has been reported in a patient with allergic bronchopulmonary aspergillosis after treatment with corticosteroids.13 Like the majority of patients in this study, EAE also has been reported in intravenous drug abusers.14-15 Predisposing systemic conditions may modify the probability of dissemination, risk of mortality, and role for systemic treatment. The mortality of invasive, disseminated aspergillosis remains high.16 Endogenous Aspergillus endophthalmitis during systemic aspergillosis usually requires more than systemic treatment to achieve resolution of the ocular infection.

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flammary exudate may occur in either or both the subhyaloid and subretinal space (Fig 2). Although these signs are not specific, they are frequent enough to suggest EAE.

The severity of retinal involvement in EAE may range from subretinal or subhyaloid infiltrates to vascular occlusion and full-thickness retinal necrosis. Intraretinal hemorrhages are frequent. It is presumed that after hemogenous dissemination, an initial choroidal lesion occurs. The infection spreads to involve the overlying retina with progressive abscess formation. Eventually, the vitreous is invaded, and finally the anterior segment becomes involved.

Diagnosis of EAE by anterior chamber or vitreous aspirates alone is unreliable. In this series, two of four vitreous needle aspirates were positive. Pars plana vitrectomy specimens assisted by Gram or Giemsa stains have the highest yield of positive cultures for Aspergillus. In this series, eight of nine previously untreated eyes had a positive culture from the vitrectomy specimen.

The visual outcome in these patients is influenced primarily by the propensity of Aspergillus for initial macular choroidal involvement. In this series, two of three eyes recovered excellent visual acuities of 20/40 and 20/25 because the initial lesions were temporal to the fovea and treatment was prompt. By contrast, only three of eight eyes with macular involvement achieved 20/400 visual acuities.

The antifungal agent used most often for treatment of systemic aspergillosis is amphotericin B. In vitro sensitivities to amphotericin B are problematic, depend on methodology, and can be variable with minimum inhibitory concentrations (MICs) ranging from less than 0.5 to 8 µg/ml. There are significant phenotypic differences in susceptibility between different Aspergillus isolates, pathogenic versus laboratory strains, and between species. In vivo responses to amphotericin B are even more unpredictable and may not compare with in vitro sensitivity studies. Without host immune competence, treatment rarely is effective. Although the definition of a “complete” treatment of amphotericin B is controversial, systemic dosage regimens range from 0.5 to 1.0 mg/kg per day for a duration of 4 to 6 weeks or until resolution of the infection. To reduce the significant toxicity and enhance the efficacy of intravenous amphotericin B, alternatives such as liposome-encapsulated amphotericin B or combinations with 5-fluorouracil and azole compounds have been used. Further discussion of the use of intravenous amphotericin B in the management of extraocular aspergillosis is reviewed by Denning et al and Georgiev. An infectious disease specialist should be consulted in the systemic treatment of patients with EAE.

Because of the effectiveness of vitrectomy and intravitreous amphotericin B, the systemic use of intravenous amphotericin B may have minimal utility in the treatment of EAE. For documented or suspected extraocular foci, systemic treatment may be indicated. Penetration of intravenous amphotericin B into the vitreous cavity of the normal or inflamed eye is poor. In an animal study, there was negligible penetration of amphotericin B in the aqueous and vitreous of noninflamed eyes and poor penetration in experimental uveitis eyes. One human study showed erratic intravitreous penetration in inflamed eyes.

Other systemic agents used for extraocular aspergillosis have limited efficacy in the treatment of endophthalmitis. 5-fluorouracil shows synergism with amphotericin B and has good CNS and ocular penetration. There is a risk of bone marrow and gastrointestinal toxicity. Theazole compounds with the possible exception of itraconazole are not recommended as sole therapy for systemic aspergillosis. Ketoconazole lacks consistent anti-Aspergillus efficacy. The majority of Aspergillus isolates of in vitro and human studies are resistant with MICs ranging from 12.5 to 25 µg/ml. Clotrimazole and miconazole for aspergillosis also have inconsistent effectiveness.

Fluconazole has excellent penetration into the CSF and vitreous. Fluconazole shows high MICs (>100 µg/ml) and minimal efficacy compared with those of amphotericin B against Aspergillus. In one study, fluconazole in vitro did not inhibit any of 45 pathogenic strains of A. fumigatus.

Systemically administered itraconazole achieves low serum levels and poor penetration into uninflamed aqueous, vitreous, or CSF compartments. Savani et al showed that in an animal model of Candida endophthalmitis, vitreous concentration was 10% of the serum level and lacked treatment benefit. Aspergillus species were not tested in Savani’s report. In vivo, animal, and limited human trials of patients with invasive aspergillosis show low MICs and good tissue penetration. In these selective reports, therapeutic responses generally are favorable and comparable with those of Amphotericin B.

Ketoconazole, fluconazole, itraconazole, and miconazole administered simultaneously and sequentially with Amphotericin B in an in vitro study against 15 strains of A. fumigatus showed variable results. Pretreatment of amphotericin B followed by an azole drug could be synergistic, additive, or indifferent. However, the pretreatment or combination of these azole compounds with amphotericin B increased antagonistic effects.

Intravitreous injection of 5 to 10 µg of amphotericin B is a widely used treatment for fungal endophthalmitis. In an animal model, intravitreous amphotericin B at dosages between 25 and 100 µg produced severe retinal toxicity. However, slow, midvitreous injections of 5 to 10 µg of amphotericin B showed no retinal toxicity. In the current series, amphotericin B was injected during the initial treatment at a dosage of 5 µg in seven eyes, 10 µg in three eyes, and 20 µg in one eye. In this latter patient receiving 20 µg, there was no visible nor clinical evidence of retinal toxicity. The half-life of intravitreous amphotericin B administered in an animal study was 1.8 days in vitrectomized eyes but was 7 to 15 days in nonvitrectomized eyes. Based on these studies, it appears that repeat intravitreous injections may be tolerated 2 or more days after the initial vitrectomy and injection of amphotericin B 5 to 10 µg. In the current study, no visible toxicity occurred in two patients receiving a cumulative dosage of 30 µg over a 2-month period.

Subconjunctival amphotericin B injections, whereas
tolerated at low dosages, are painful and associated with subconjunctival nodules or necrosis at larger dosages.\textsuperscript{35} Because the intraocular penetration is quite low, efficacy is doubtful. Subconjunctival natamycin or miconazole also has doubtful intraocular penetration and efficacy. Topical amphotericin B is irritating with significant epithelial toxicity. Because of poor penetration, it is only indicated for superficial keratomycoses.

Intravitreous corticosteroids, although controversial, may be useful as adjunctive therapy in EAE. In a rabbit model of Candida endophthalmitis, eyes treated with adjunctive dexamethasone showed reduced inflammation, less retinal destruction, and no increase in candidal proliferation compared to eyes treated with amphotericin B only.\textsuperscript{36} Three patients were treated with intravitreous corticosteroids in this study.

In the current study, EAE occurred in patients with COPD and in patients abusing intravenous drugs. Patients with chronic pulmonary diseases combined with corticosteroid therapy are a subgroup of patients who seem to have a greater risk for systemic and endogenous aspergillosis. Identifying systemic risk factors may increase diagnostic ability and may guide the selection of appropriate intravitreous and systemic therapy. The rapid onset of characteristic ocular signs and symptoms, including vitritis, a chorioretinal abscess in or near the macula, and a subhyaloid or subretinal hypopyon were frequent features of patients with EAE in this study. The final visual outcome with endogenous Aspergillus endophthalmitis generally is poor because of frequent macular involvement.

The optimal treatment for EAE remains controversial. Our current EAE treatment recommendations are based on our experience with these ten patients and on published studies. Because pars plana vitrectomy is more likely to yield positive culture results compared with those of vitreous needle aspirates alone, we generally recommend pars plana vitrectomy when vitreous seeding is present. Vitrectomy may not be necessary in fellow eyes in which only isolated chorioretinal lesions are present and when the diagnosis can be made from evaluation of the first eye.\textsuperscript{37} Amphotericin B, 5 to 10 µg, is our recommended intravitreous antifungal treatment. The use of intravitreous dexamethasone 400 µg remains controversial, but we currently recommend using this adjunctive medication to reduce the marked intraocular inflammation in many of these eyes. The overall goal of systemic antifungal therapy is to supplement the effectiveness of intravitreous amphotericin B therapy and to treat proven or clinically suspected systemic aspergillosis. In patients with EAE with other signs of systemic infection, intravenous amphotericin B generally is recommended. In patients with isolated EAE, a less toxic systemic medication can be considered. In these patients with isolated EAE, or those patients in whom intolerance or complications with amphotericin B developed, we recommend itraconazole as the alternative systemic therapy. Because of the associated pain and lack of proven efficacy from subconjunctival amphotericin B administration, we do not currently recommend this treatment. In patients with persistent vitreous infiltrates and suspected recurrent disease after initial treatment, we recommend repeat intravitreous injection of amphotericin B, 5 to 10 µg, and possibly repeat vitrectomy.

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