Exogenous Fungal Endophthalmitis: Microbiology and Clinical Outcomes

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Objective: To report the fungal isolates, treatment strategies, and clinical outcomes for a large series of patients with exogenous fungal endophthalmitis.

Design: Retrospective, single institution, consecutive case series.

Participants: All patients treated at Bascom Palmer Eye Institute between January 1, 1990, and June 30, 2006, for culture-proven exogenous fungal endophthalmitis.

Methods: Microbiologic and medical records were reviewed for all patients with intraocular cultures positive for fungal organisms and clinically diagnosed exogenous endophthalmitis.

Main Outcome Measures: Fungal isolates, treatment strategies, visual acuity, and rate of enucleation.

Results: Culture-positive exogenous fungal endophthalmitis occurred in 41 eyes, including 18 cases (44%) associated with fungal keratitis, 10 cases (24%) occurring after penetrating ocular trauma, and 13 cases (32%) after intraocular surgery. Filamentous fungi (molds) accounted for 35 cases (85%), and Candida species (yeasts) accounted for 6 cases (15%). Although most keratitis cases were caused by Fusarium (13 of 18; 72%), Aspergillus was the most common isolate in postoperative cases (5 of 13; 38%). Open-globe cases were caused by a broader spectrum of fungi. As initial treatment, 30 (73%) patients received intraocular amphotericin B, but at least 3 antifungal agents were used in 24 (59%) cases. At least 1 pars plana vitrectomy was performed in 25 (61%) eyes, and 29 (71%) eyes underwent 3 or more procedures, including surgeries and intraocular injections. Although a final vision of 20/400 or better was achieved in 22 (54%) eyes, all but 1 of these were either in the keratitis (11 of 18) or the postoperative (10 of 13) groups. Conversely, although 10 (24%) of 41 eyes were enucleated, 7 of these were among the open-globe patients.

Conclusions: This report highlights the differences between the clinical categories of exogenous fungal endophthalmitis. Although 85% of all cases were caused by molds, most commonly Fusarium and Aspergillus, the most common fungal genera varied by clinical category. Amphotericin B was the most commonly used antifungal agent, but most cases were treated with at least 3 different antifungal agents. Final visual outcomes were variable, with the open-globe–associated patients having the poorest outcomes. Overall, 44% of patients achieved a final visual acuity of 20/80 or better.

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Exogenous fungal endophthalmitis was first reported in 1902 when Romer[1] cultured *Aspergillus fumigatus* from the vitreous of a blind painful eye enucleated 9 days after penetrating trauma. Since then, many other fungi have been reported to cause exogenous fungal endophthalmitis, and the clinical outcomes of such infections in the context of preceding fungal keratitis,[2–4] trauma,[5–11] and intraocular surgery[6,12–19] have been described. However, few reports have examined all clinical categories of exogenous fungal endophthalmitis,[20–22] making generalizations about diagnostic strategies, management approaches, and visual prognosis challenging systematically. The current report represents a large consecutive series of patients treated at a single medical center for exogenous fungal endophthalmitis and includes fungal isolates, treatment strategies, and clinical outcomes.

Patients and Methods

The study protocol was approved by the Institutional Review Board of the University of Miami Miller School of Medicine Sciences Subcommittee for the Protection of Human Subjects (protocol number 20061106). Microbiologic and clinical records were reviewed of all patients treated at Bascom Palmer Eye Institute between January 1, 1990, and June 30, 2006, for culture-proven fungal endophthalmitis (n = 111). Cases of definite endogenous fungal endophthalmitis (n = 51) were excluded. Of the remaining 60 cases, 19 were excluded because most of their care was provided at an outside office or facility. Six cases were reported previously (cases 2, 6, 10, 14, 33, and 40).[2,3,16,17]

Intraocular fluids were plated directly onto chocolate agar, 5% sheep blood agar, and Sabouraud agar. Chocolate and blood agars were incubated at 35° C for up to 2 weeks. Sabouraud agars were incubated at 35° C for 72 hours and then at 25° C for up to 2 weeks. Plates were examined daily for detection of fungal growth.

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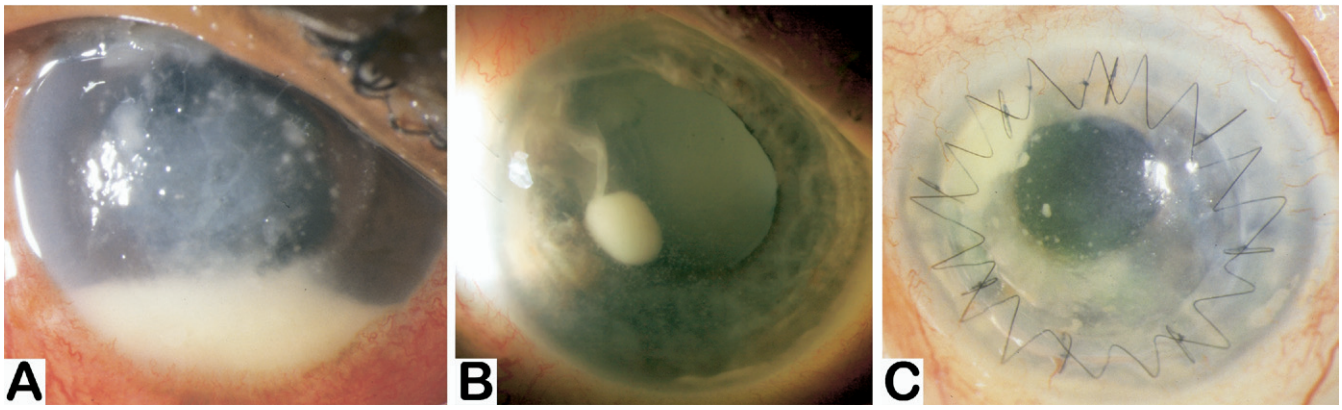

Figure 1. **A**, Photograph demonstrating *Fusarium oxysporum* endophthalmitis which developed 27 days after minor trauma with organic matter to the right eye. A hypopyon and anterior chamber fungal infiltrates are seen in the setting of a multifocal, feathery-edged corneal infiltrate. **B**, Photograph demonstrating Acremonium endophthalmitis which developed 4 months after penetrating trauma to the right eye. An anterior chamber fungal infiltrate, a small hypopyon, and 3 interrupted sutures from prior closure of the ruptured globe are seen. **C**, Photograph demonstrating *Candida albicans* endophthalmitis which developed 3 months after a penetrating keratoplasty with intraocular lens exchange in the left eye. A multifocal anterior chamber fungal infiltrate adherent to the corneal endothelium is seen in the superior temporal quadrant.

Colonies suggestive of fungal growth were evaluated by Giemsa, Calcofluor white, and slide culture to detect microscopic morphologic features and characteristic conidiation. Microscopic identification was supplemented with colony macroscopic characteristics (color, texture) and time to detection and was compared with standard mycology keys and textbooks.[23,24] Unusual isolates were sent to the Fungus Testing Laboratory (San Antonio, Texas) for identification. Culture and identification techniques did not change during the study period (1990–2006).

Culture results were considered positive when there was growth of the same organism on 2 or more solid media at the inoculation site, or when the organism grew on 1 culture media and was noted on a stained smear (gram, Giemsa, or Gomori methenamine silver).[25] To classify a fungal keratitis as endophthalmitis, 4 criteria were required to be fulfilled: positive corneal culture results; positive aqueous or vitreous culture results, or both, for the same organism; clinical evidence of endophthalmitis; and treatment with either systemic or intraocular antifungal agents. The sensitivity data for the isolates in the present study are not available.

Final visual acuity for eyes that were not enucleated was obtained between 1 and 3 months after initiation of treatment for exogenous fungal endophthalmitis in 5 (16%) of 31 eyes (cases 10, 20, 24, 29, and 39), between 3 and 6 months in 5 (16%) of 31 eyes (cases 8, 13, 15, 21, and 31), and between 6 and 12 months in 21 (68%) of 31 eyes (all other cases). The precise month at which the final vision was measured is presented.

All statistical analyses were performed using SPSS software version 15.0 for Windows (SPSS, Inc., Chicago, IL). The Pearson chi-square test with Yate's correction was used for enucleation comparisons among the different diagnostic groups and fungal organisms. The analysis of variance and Student *t* test were used for visual acuity comparisons among fungal organisms and corticosteroid use, respectively.

All previous peer-reviewed, published reports of exogenous fungal endophthalmitis as identified through a search of all articles in the Medline database identified using the terms *exogenous*, *fungal*, and *endophthalmitis* were reviewed. The present data are compared with those reported in other series of exogenous fungal endophthalmitis, with an emphasis on the larger series.

Results

Demographics, Clinical Features, and Culture Data

Of the 41 eyes from 41 patients who met study inclusion criteria, 20 were right eyes. Twenty-three patients (56%) were men, and the mean age was 58.7 years, with a range of 19 to 90 years (Table 1; available at http://aaojournal.org). Twenty-one patients (51%) identified themselves as white, 13 (32%) as Hispanic, 6 (15%) as black, and 1 (2%) as Asian. Four patients had a diagnosis of diabetes mellitus at the time of presentation (cases 5, 23, 24, and 32), 1 had systemic sarcoidosis (case 9), and 1 was undergoing treatment for leukemia (case 38).

Fungal endophthalmitis developed by contiguous spread in 18 patients with advanced fungal keratitis (Fig 1A). Risk factors for the development of keratitis were contact lens use (5 cases: cases 2, 3, 11, 13, and 14), trauma with organic matter (5 cases: cases 6, 7, 10, 15, and 17), LASIK (2 cases: cases 4 and 16), a neurotrophic ulcer with desmetocele (1 case: case 1), and unknown (5 cases). Endophthalmitis was suspected from 4 days to 6 months after the initial corneal infiltrate was diagnosed (mean, 1.7 months; standard deviation [SD], 1.7 months; median, 1 month). In 3 patients, endophthalmitis developed after a penetrating keratoplasty for corneal perforation or impending perforation in the setting of culture-proven fungal keratitis from the same organism (cases 1, 5, and 13). Topical corticosteroids were used before the diagnosis of endophthalmitis in 14 (78%) of 18 cases. Visual acuity at presentation with endophthalmitis was 20/400 or better in 2 (11%) of 18 cases, a hypopyon was present in 11 (61%) of 18 cases, and an intraocular fungal infiltrate was visualized on examination in 9 (50%) of 18 cases. Fusarium species accounted for 13 (72%) of 18 of the causative organisms (Table 1; available at http://aaojournal.org).

Ten cases of fungal endophthalmitis occurred after open-globe injury (Fig 1B). The onset of symptoms was from 1 day to 6 months after the injury (mean, 1.8 months; SD, 2.0 months; median, 1 month). The penetrating object was organic in 3 cases (30%; cases 19, 25, and 27), metal in 6 (60%; cases 20, 21, 22, 23, 26, and 28), and unknown in 1 (case 24). Topical corticosteroids were used before the diagnosis of endophthalmitis was made in 8 (80%) of 10 cases. Visual acuity at presentation was worse than

20/400 in all patients, a hypopyon was present in 8 (80%) of 10 cases, and an intraocular fungal infiltrate was visualized on examination in 6 (60%) of 10 cases. There was no single predominant causative fungal genus, with 2 (20%) of 10 cases the result of Candida species and 2 (20%) of 10 cases the result of *Aspergillus* species (Table 1; available at http://aaojournal.org).

Fungal endophthalmitis developed in 13 patients after intraocular surgery, including 9 after cataract surgery with intraocular lens implantation and 3 after penetrating keratoplasty (Fig 1C). In 1 patient, endophthalmitis developed in the setting of blebitis 24 months after glaucoma filtering surgery (case 41). The onset of symptoms was from 10 days to 24 months after surgery (mean, 5.6 months; SD, 8.2 months; median, 3 months). All 13 of these eyes received topical corticosteroids before the diagnosis of endophthalmitis. Visual acuity at presentation was 20/400 or better in 8 (62%) of 13 patients, a hypopyon was present in 1 patient, and an intraocular fungal infiltrate was visualized on examination in 7 (54%) of 13 patients. Aspergillus species accounted for 5 (38%) of 13 isolates, and Candida species accounted for 3 (23%) of 13 isolates (Table 1; available at http://aaojournal.org). Intraocular cultures from the blebitis-associated case identified *Lecythophoria mutabilis.*

Intraocular culture results were positive in all patients (n = 41), and 14 patients had both a vitreous and an anterior chamber sample cultured (Table 1; available at http://aaojournal.org). Of these 14 patients, vitreous samples were positive in 8 and anterior chamber samples were positive in 10, yielding a double-positive culture rate of 29% (4 of 14). In total, vitreous cultures were obtained from 32 patients, including 10 of 18 cases associated with fungal keratitis, 10 of 10 cases associated with an open-globe injury, 11 of 12 cases associated with intraocular surgery, and the case associated with blebitis. The vitreous culture results were positive in 26 (81%) of 32 cases. Aqueous cultures were obtained from 24 patients, including 13 of 18 cases associated with fungal keratitis, 5 of 10 cases associated with an open-globe injury, 6 of 12 cases associated with intraocular surgery, and the case associated with blebitis. The aqueous culture was positive in 20 (83%) of 24 cases.

Eighty-eight percent of patients (36 of 41) were followed up for at least 3 months or underwent enucleation, but 5 patients had follow-up of between 1 and 3 months (cases 10, 20, 24, 29, and 39; Table 2; available at http://aaojournal.org).

Treatment Strategies

As initial management, 20 eyes underwent pars plana vitrectomy, 1 underwent anterior vitrectomy, and 10 underwent vitreous tap and inject (Table 2; available at http://aaojournal.org). Additional ocular procedures, including surgeries or intraocular injections, were performed in 36 eyes (88%), and at least 2 additional procedures were performed in 14 eyes (78%) associated with preceding keratitis, 7 eyes (70%) associated with an open-globe injury, and 8 eyes (62%) associated with intraocular surgery. At least 1 pars plana vitrectomy was performed in 25 (61%) eyes. Pars plana vitrectomy was performed most commonly among the open-globe cases (9 of 10; 90%) and least commonly performed in the keratitis-associated cases (7 of 18; 39%). A penetrating keratoplasty was performed in 94% (17 of 18) of the keratitis-associated cases, most commonly the result of severe corneal involvement or impending perforation. A penetrating keratoplasty was not performed in any open-globe–associated case and was performed in 1 postoperative patient (1 of 13; 8%; case 38).

For initial antifungal treatment, 30 (73%) of 41 patients received intraocular amphotericin B (22 of 30 intravitreally, 7 of 30 intracamerally, and 1 both intravitreally and intracamerally). Other primary antifungal treatments included intravitreal voriconazole in 3 (7%) of 41, intravitreal miconazole in 1 (2%) of 41, and a combination of oral, topical, and subconjunctival antifungal agents in 7 (17%) of 41 patients.

By the end of the treatment course, 39 (95%) of 41 patients had received at least 1 intraocular antifungal agent. Of the 2 patients not given an intraocular antifungal agent, 1 was treated with oral and subconjunctival voriconazole and 1 was given oral fluconazole. Intraocular amphotericin B was given to 36 (88%) of 41 patients (30 intravitreally and 8 intracamerally). Of the 5 patients who did not receive intraocular amphotericin B, 3 were given intravitreal voriconazole (cases 13 and 24) or miconazole (case 28). In total, voriconazole was given to 11 (27%) of 41 patients (6 intravitreally, 4 intracamerally, 8 orally, and 2 topically). Three or more antifungal agents were used in 24 (59%) of 41 patients, most commonly in the keratitis-associated patients (72%; 13 of 18; Table 2; available at http://aaojournal.org). Systemic antifungal agents were used in 34 (83%) of 41 patients, including fluconazole (20 of 34), ketoconazole (9 of 34), voriconazole (7 of 34), itraconazole (6 of 34), amphotericin B (2 of 34), miconazole (1 of 34), and combination treatment (12 of 34). Antifungal therapy was administered for less than 1 month in 5 (12%) of 41 cases, for 1 to 3 months in 28 (68%) of 41 cases, and for 3 to 6 months in 8 (20%) of 41 cases.

Clinical Outcomes

Overall, 22 (54%) of 41 cases achieved a final visual acuity of 20/400 or better and 18 (44%) of 41 achieved a final visual acuity of 20/80 or better (Table 2; available at http://aaojournal.org). All patients (41 of 41) were evaluated 1 month after the initiation of treatment for endophthalmitis, at which time the median visual acuity was counting fingers (range, 20/40–no light perception). Subsequently, 22 (67%) of 33 patients were evaluated at 6 months and 10 (31%) of 32 were evaluated at 1 year, excluding patients who were enucleated before the given follow-up period. Of these patients, the median visual acuity was 20/70 (range, 20/20–light perception) at 6 months and 20/55 (range, 20/20–no light perception) at 12 months.

The proportion of patients achieving a final visual acuity of 20/400 or better was significantly different among the clinical groups ($P = 0.014$, chi-square). Also, the difference in final mean logarithm of the minimum angle of resolution acuity was statistically significant among the 3 clinical groups ($P<0.001$, analysis of variance). Among the keratitis-associated cases, 11 (61%) of 18 achieved a final vision of 20/80 or better, whereas 6 (33%) had final vision worse than 20/400 (no light perception in 2, light perception in 2, and hand movements in 2). Similarly, 7 postoperative cases (54%) achieved a final vision of 20/80 or better and only 2 cases (15%) had final vision worse than 20/400 (no light perception in one and 5/200 in the other). In contrast, no open-globe patient achieved a final vision better than 20/400, with the final vision measuring 20/400 in one patient and 3/200 in another. There was no significant difference in final mean logarithm of the minimum angle of resolution visual acuity related to the 4 most common fungal genera ($P = 0.78$, analysis of variance). Additionally, there were no statistically significant differences in final mean logarithm of the minimum angle of resolution visual acuity regardless of whether corticosteroids were used before a diagnosis of endophthalmitis ($P = 0.38$, **t** test); regardless of whether corticosteroids were used as part of initial management after a diagnosis of endophthalmitis ($P = 0.13$, *t* test); or regardless of whether corticosteroids were used in subsequent management ($P = 0.43$, *t* test).

Although no primary enucleation was performed, 10 eyes (10 of 41; 24%) underwent enucleation as a later procedure. Eight of the enucleations (8/10; 80%) were performed within 2 months of initiation of treatment for endophthalmitis except cases 25 and 28,

Table 3. Comparison of Other Exogenous Fungal Endophthalmitis Series

Clinical Category	Keratitis	Postoperative				Penetrating Trauma			
First author	*Current study*	*Current study*	*Narang et al*[15]	*Kunimoto et al*[19]	*Maji et al*[6]	*Current study*	*Kunimoto et al*[10]	*Maji et al*[6]	*Gupta et al*[11]
Study dates	1990–2006	1990–2006	1995–1999	1991–1997	1991–1996	1990–2006	1991–1997	1991–1996	2003–2005
Geographic location	Florida	Florida	India	India	India	Florida	India	India	India
No. of patients	18	13	27	21	11	10	20	9	8
Microbiologic results									
Yeast	6%	23%	19%	0%	0%	20%	0%	0%	12.50%
Molds	94%	77%	81%	100%	100%	80%	100%	100%	87.50%
Fusarium species	76%	0%	0%	0%	0%	0%	10%	0%	29%
Aspergillus species	6%	50%	91%	81%	82%	25%	45%	44%	43%
Acremonium species	6%	10%	5%	0%	0%	12.50%	5%	11%	14.00%
Paecilomyces species	0%	20%	0%	0%	0%	12.50%	0%	0%	14.00%
Other molds	12%	20%	5%	19%	18%	50%	40%	44%	0%
Treatment strategies									
Pars plana vitrectomy	39%	69%	67%	NR	100%	90%	NR	100%	25%
Amphotericin B	83%	100%	100%	NR	100%	80%	NR	100%	75%
> 2 Antifungals used	72%	54%	at least 7%	NR	NR	40%	NR	NR	75%
Visual outcome									
≥20/80	61%	54%	19%	NR	18%	0%	NR	44%	0%
≥20/400	67%	77%	30%	NR	27%	0%	NR	56%	37.50%
NLP or phthisical	11%	8%	15%	NR	73%	70%	NR	33%	50%

NLP = no light perception; NR = not reported.

which were enucleated at 32 and 11 months after their open-globe injuries, respectively. The differences in enucleation rates among the groups was statistically significant, with 7 (70%) of 10 of the open-globe–associated cases undergoing enucleation in comparison with approximately 10% of the other 2 clinical categories (1 of 13 of the postoperative cases and 2 of 18 of the keratitis associated cases; $P = 0.009$).

Discussion

Rychener[26] first described the 3 principal causes of exogenous fungal endophthalmitis in 1933: contiguous spread from an external ocular infection, penetrating trauma, and intraocular surgery. The current study is a large consecutive case series reporting all categories of exogenous fungal endophthalmitis. Among the 3 clinical categories, visual outcomes were highly variable, with the open-globe–associated patients having the poorest outcomes. Other large series of exogenous fungal endophthalmitis have revealed similar spectrums of visual outcomes compared with the current report (Table 3), although few studies have examined all 3 clinical categories. Specifically, there have been 3 comprehensive reports of intraocular fungal infections,[20–22] the first by Jones et al[20] in 1970, who summarized the clinical experience in Britain: of 25 cases, 9 (36%) were cases of exogenous fungal endophthalmitis. Visual acuity outcomes were poor in these 9 eyes, with 7 being enucleated or eviscerated (7 of 9; 78%).

More recently, Pflugfelder et al[22] described 19 cases over a 17-year period (1969–1986) associated with keratitis (n = 7), trauma (n = 6), or surgery (n = 6; Table 4). In comparison with the current report, a similar proportion of fungal isolates were molds and similar proportions of patients were treated with amphotericin B. Of note, however, the percentage of patients receiving at least 3 different antifungal agents and the percentage of patients with a final visual acuity of 20/80 or better were both higher in the current report. Additionally, the percentage of patients with a final visual acuity of no light perception was 32% in the previous study and 24% in the current study (Table 4).

Table 4. Comparison of Prior Study[22] versus Current Study of Exogenous Fungal Endophthalmitis

Reported Data	Pflugfelder et al[22]	Current Study
Study dates	1969–1986	1990–2006
Patient population	19	41
Keratitis associated	7 (37%)	18 (44%)
Postoperative	6 (32%)	13 (32%)
Penetrating trauma	6 (32%)	10 (24%)
Microbiology		
Yeast	2 (11%)	6 (15%)
Molds	17 (90%)	35 (85%)
Fusarium species	5 (26%)	13 (32%)
Aspergillus species	2 (11%)	6 (15%)
Acremonium species	3 (16%)	2 (5%)
Paecilomyces species	2 (11%)	3 (7%)
Treatment strategies		
Pars plana vitrectomy	16 (84%)	25 (61%)
Intraocular amphotericin B	17 (90%)	36 (88%)
> 2 Antifungals used	4 (21%)	24 (59%)
Visual acuity outcome		
≥20/80	6 (32%)	18 (44%)
≥20/400	8 (42%)	22 (54%)
NLP	6 (32%)	10 (24%)

NLP = no light perception.

The reasons for this apparent improvement in visual outcomes since the first summary report of exogenous fungal endophthalmitis in 1970 are uncertain. One factor may be an increased recognition of the variable antimicrobial susceptibility of different fungal isolates and of the need to use alternative antifungal agents earlier in the clinical course, when resistance is suspected.

Historically, amphotericin B has been the preferred antifungal agent in the setting of fungal endophthalmitis. Systemically delivered amphotericin B does not achieve therapeutic concentrations in the eye, even in the presence of intraocular inflammation.[27] In comparison, intravitreal injection of amphotericin B achieves therapeutic concentrations and limits systemic toxicity. In the current report, amphotericin B was the most commonly used antifungal agent, used intraocularly in 36 (88%) of 41 cases. However, intravitreal amphotericin B can cause retinal necrosis,[28] and the number of necessary injections is not standardized, but rather dependent on the clinical response and whether the vitreous has been removed.[29] The devastating nature of fungal endophthalmitis coupled with a growing concern for resistance to antifungal agents[30] has led to the simultaneous use of multiple antifungal agents. In support of this, Lalitha et al[31] recently reported the antifungal profiles of 90 fungal isolates in which voriconazole and other triazoles demonstrated the broadest spectrum of activity, but no single agent was universally effective. In the current report, more than 1 antifungal agent was used in 38 (93%) of 41 cases, and 24 (59%) of 41 cases were treated with at least 3 different antifungal agents.

Newer antifungal agents have expanded the treatment armamentarium. Voriconazole, a triazole available since 2002, has excellent oral bioavailability and intraocular penetration.[32–34] The most common side effect is reversible disturbance of vision (photopsia or blurring of vision) seen in approximately one third of patients.[35] Recent reports have suggested that voriconazole may have a broader spectrum of antifungal activity compared with amphotericin B.[30,31] Additionally, various authors have reported intravitreal voriconazole to be safe both in vitro and in vivo.[36–38] Since 2003, 10 (71%) of the 14 exogenous fungal endophthalmitis patients reported here were treated with voriconazole, and now the authors use voriconazole routinely as a first-line antifungal therapy.[34]

Even newer antifungal agents, such as posaconazole, a triazole with excellent oral bioavailability and intraocular penetration,[39] and caspofungin, an echinocandin administered parenterally, have been used successfully in managing intraocular fungal infections.[37] Further studies are required to determine the optimal antifungal regimen for the various forms of ocular fungal infection.

In the current series, selection of antifungal agents was made by the individual treating physician, and no prospective protocol was used. Despite this, amphotericin B or voriconazole was the first-line antifungal agent used in 95% of cases after a diagnosis of fungal endophthalmitis was made. All of the keratitis-associated patients were using topical and systemic antifungal agents at the time of diagnosis of endophthalmitis, given the progression of their disease. When the intraocular infection primarily involved the anterior chamber with minimal involvement of the vitreous, as assessed by ultrasound, treatment was tailored accordingly, often using intracameral injection of the antifungal agent (Table 2; available at http://aaojournal.org). In comparison, when the infection was more diffuse clinically, involving the vitreous, intravitreal injection was used primarily. For example, although 50% of the keratitis-associated cases and 38% of the postoperative cases were given intracameral antifungal injections, only one open-globe patient (10%) was treated with intracameral injection. Instead, the open-globe–associated patients were treated primarily with intravitreal antifungal injections. Systemic antifungal agents were used in most patients (83%), including all of the keratitis-associated cases, 85% of the postoperative patients, and 50% of the open-globe patients. The reasons why a smaller percentage of open-globe–associated patients were given systemic antifungal agents is unknown, but may have contributed to their poorer outcomes. Although there have been no randomized trials examining the duration of antifungal therapy for fungal endophthalmitis, 88% of the patients in the current study were treated for longer than 1 month, and generally 6 to 12 weeks of treatment is recommended.

The large incidence of fungal ocular infections over the last 80 years may be attributed, at least in part, to the introduction of widespread steroid use in the 1950s.[21,40] Corticosteroids used in the absence of an efficacious antifungal agent have been proposed to potentiate ocular fungal infections by suppressing the immune response, permitting more aggressive fungal behavior and permitting fungi to penetrate deeper into ocular tissue.[2,3,40,41] In comparison, some authors have postulated that the concurrent use of corticosteroids and antifungals may allow more rapid clearance of inflammation.[6] In the current series, 85% of patients received topical corticosteroids before a diagnosis of fungal endophthalmitis was made and there was no significant difference in visual outcomes or enucleation rates related to corticosteroid usage. Generally, the authors recommend that steroids be used with caution in patients with possible ocular fungal infection.

The incidence of fungal endophthalmitis versus bacterial endophthalmitis in postoperative and open-globe–related patients is highly variable, and in some reports, fungi represents more than 20% of isolates.[5,7–9] It has been proposed that the rates of fungal endophthalmitis are driven primarily by climate and not by the mechanism of injury, such that warmer, more tropical locations have a higher incidence of fungal organisms.[10] Therefore, in the appropriate setting, antifungal agents should be considered as part of the initial management of suspected postoperative or open-globe–associated endophthalmitis.

In comparison with bacterial endophthalmitis, exogenous fungal endophthalmitis often presents with a latency period of weeks to months after intraocular inoculation.[12,13] In the current study, despite a mean latency period of 1.7 months (SD, 1.7 months), 1.8 months (SD, 2.0 months), and 5.6 months (SD, 8.2 months) in the keratitis, traumatic, and postoperative cases, respectively, exogenous fungal endophthalmitis developed in 3 cases within 4 days of inoculation. Similarly, many reports have noted a highly variable latency period in the setting of exogenous fungal

endophthalmitis from 1 day to many months.[6,11,15,22] Therefore, in suspected exogenous endophthalmitis, intraocular specimens should be analyzed for both bacteria and fungus.

Traditionally, a vitreous aspirate has been believed to be more sensitive than an anterior chamber aspirate for diagnosing bacterial endophthalmitis.[42] In accord with this, aqueous aspirates demonstrated negative results in 4 cases, despite positive vitreous culture results in the current study. Importantly, however, 6 cases with positive anterior chamber aspirate results had negative vitreous culture results, a situation reported by others.[11,43] This may be related to the primary location of the infection; if the infection starts in the front of the eye, an aqueous aspirate may be more sensitive than a vitreous aspirate for diagnosing endophthalmitis. In support of this, 4 of 6 such cases were keratitis-associated patients in the current study. Additionally, some fungi may be less capable of penetrating the vitreous cavity than bacteria.[18] Therefore whenever possible, both anterior chamber and vitreous aspirates should be performed for a complete endophthalmitis evaluation. Of note, the use of polymerase chain reaction for diagnosis of fungal endophthalmitis may be more sensitive than the conventional methods used in this study and may expedite correct diagnosis[44]; this needs further clinical study.

In the current series, 35 (85%) of 41 fungal isolates were molds. Most keratitis cases were caused by Fusarium species (13 of 18; 72%), and a significant proportion of the postoperative cases were caused by Aspergillus (5 of 13; 38%). In comparison, the open-globe cases were caused by a broader spectrum of organisms. The specific organisms associated with each clinical category in the current series are remarkably similar to those reported in other series of exogenous fungal endophthalmitis (Tables 3 and 4). For example, Pflugfelder et al[22] reported that 90% of all clinical categories were caused by molds (17 of 19), Kunimoto et al,[6] Maji et al,[15] and Narang et al[19] all reported that 81% to 100% of postoperative cases were caused by molds, with the large majority of each series attributable to Aspergillus. Finally, 3 reports of trauma-associated fungal endophthalmitis found a broader spectrum of causative organisms, with Aspergillus being the most frequent organism in each series.[6,10,11]

The main limitation of this study is its retrospective design. A prospective study would allow a consistent management protocol and would provide more accurate outcome data. This is challenging, however, given the rarity of the disease and the unique clinical situation of each patient with exogenous fungal endophthalmitis. This study is also limited by the long period over which patients were treated (17 years), because medical options for treating fungal infections have expanded and management strategies may have changed.

In conclusion, this report highlights the differences among the 3 clinical categories of exogenous fungal endophthalmitis, each with its own unique causative organisms and prognoses. Although 85% of all cases were caused by molds, Fusarium and Aspergillus represented 72% and 38% of the keratitis and postoperative isolates, respectively, and a broader range of fungi were responsible for the trauma-associated cases. The open-globe–associated patients had the worst visual outcomes, with 70% of eyes being enucleated. Conversely, keratitis and postoperative patients had much better outcomes, with 61% and 54%, respectively, achieving vision of 20/80 or better with aggressive medical and surgical management. Overall, 44% of eyes achieved a final vision of 20/80 or better.

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Table 1. Demographics, Clinical Features, and Culture Data from Patients with Exogenous Fungal Endophthalmitis

Patient No.	Gender	Year of Diagnosis	Age (yrs)	Time from Event to Endophthalmitis Diagnosis	Organism(s)	Culture Results	
						Vitreous	*Aqueous*
Keratitis-associated cases				Time from diagnosis of keratitis			
1	F	2001	81	6 mos (23 days after therapeutic PK)	*Candida albicans*	+	NP
2	F	1999	38	25 days (SCL)	*Fusarium oxysporum*	NP	+
3	M	2005	40	4 days (SCL)	*Fusarium oxysporum*	Negative	+
4	M	1999	41	16 days (LASIK)	*Fusarium oxysporum*	NP	+
5	M	1999	49	49 days (10 days after therapeutic PK)	*Fusarium oxysporum*	+	NP
6	M	1995	51	5 wks (organic)	*Fusarium oxysporum*	NP	+
7	M	2000	51	33 days (organic)	*Fusarium oxysporum*	+	NP
8	F	2001	53	6 wks	*Fusarium oxysporum*	Negative	+
9	M	2004	59	14 days	*Fusarium oxysporum*	NP	+
10	M	1990	64	27 days (organic)	*Fusarium oxysporum*	Negative	+
11	F	2002	22	20 days (SCL)	*Fusarium solani*	NP	+
12	M	1996	61	93 days	*Fusarium species*	Negative	+
13	F	2006	54	22 days (SCL, 10 days after therapeutic PK)	*Fusarium species*	NP	+
14	F	2006	72	1 mo (SCL)	*Fusarium species*	+	NP
15	M	1996	55	5 wks (organic)	*Aspergillus glaucus & niger*	+	NP
16	F	2006	52	31 days (LASIK)	*Acremonium species*	NP	+
17	M	2002	51	47 days (organic)	*Colletotrichum species*	+	Negative
18	M	1995	58	6 mos	*Fonsecaea pedrosi*	NP	+
Penetrating trauma cases				Time from penetrating trauma			
19	M	2005	60	1 days (organic)	*Candida albicans*	+	+
20	M	2003	80	1 days (metal)	*Candida tropicalis*	+	NP
21	M	2001	48	2 mos (metal)	*Aspergillus niger*	+	Negative
22	M	2004	19	1 mos (metal)	*Aspergillus terreus*	+	NP
23	M	2001	39	3 mos (metal)	*Paecilomyces species*	Negative	+
24	M	2005	75	4 mos (unknown)	*Acremonium species*	+	Negative
25	M	1990	23	1 mos (organic)	*Helicomyces species*	+	NP
26	M	1993	67	14 days (metal)	*Diplodia species*	+	NP
27	F	1995	81	3 w (organic)	*Dematiaceous mold*	+	+
28	M	2001	36	6 mos (metal)	*Phialophora richardsiae*	+	NP
Postoperative cases				Time from intraocular surgery			
29	F	1992	90	3 mos after PK/IOL exchange	*Candida albicans*	+	+
30	M	1991	73	5 wks after PK/IOL exchange	*Candida glabrata*	Negative	+
31	F	2003	74	4 mos after CE/IOL	*Candida parapsilosis*	+	NP
32	M	1994	74	3 mos after CE/IOL	*Aspergillus fumigatus*	+	NP
33	F	1995	74	10 days after CE/IOL	*Aspergillus fumigatus*	+	NP
34	F	2002	79	24 days after CE/IOL	*Aspergillus fumigatus*	+	NP
35	F	1992	73	11 days after CE/IOL	*Aspergillus niger*	+	+
36	F	2004	70	2 mos after CE/IOL	*Aspergillus terreus*	+	NP
37	F	2005	67	23 mos after CE/IOL	*Paecilomyces variotti*	+	NP
38	F	1994	68	18 days after PK	*Paecilomyces species*	NP	+
39	F	2000	65	8 mos after CE/IOL	*Penicillium citrinum*	+	NP
40	M	2003	80	3 mos after CE/IOL	*Acremonium strictum*	+	Negative
41	F	2003	40	24 mos after trabeculectomy	*Lecythophoria mutabilis*	+	+

CE/IOL = cataract extraction with intraocular lens; F = female; IOL = intraocular lens; M = male; metal = a metal object caused the trauma; NP = not performed; organic = organic matter was the source of initial infection; PK = penetrating keratoplasty; SCL = soft contact lens; + = positive. Cases 2, 6, and 10, were reported previously.[3] Case 14 was reported previously.[16] Case 33 was reported previously.[17] Case 40 was reported previously.[2]

Table 2. Treatments and Visual Outcomes in Patients with Exogenous Funal Endophthalmitis

Patient No.	Presenting Visual Acuity	Initial Management	Total Number of Intraocular Procedures	Antifungals	Final Vision (Follow-up)
Keratitis-associated cases					
1	CF	PPV	1	Ampho (IV, TOP, venous)	20/60 (15 mos)
2	HM	PK	1	Fluc (PO, TOP), Nata (TOP)	20/60 (9 mos)
3	HM	PK	1	Ampho (AC, SC), Vori (PO,TOP), Nata(TOP)	20/20 (13 mos)
4	HM	PK	4	Ampho (IV), Itra (PO), Fluc (PO), Keto (TOP), Nata (TOP)	NLP (E<2 mos)
5	HM	PPV	3	Ampho (IV, SC), Nata (TOP), Keto (PO)	LP (8 mos)
6	LP	PK	3	Ampho (AC), Fluc (PO), Keto (PO), Nata (TOP)	NLP (E<2 mos)
7	LP	PPV	8	Ampho (IV, AC), Fluc (PO), Nata (TOP)	20/80 (14 mos)
8	LP	PK	3	Ampho (IV), Keto (PO), Nata (TOP)	20/60 (3 mos)
9	LP	PK	4	Ampho (IV), Vori (IV), Fluc (PO), Nata (TOP)	LP (7 mos)
10	HM	PK	4	Ampho (AC), Keto (PO, TOP), Nata (TOP)	2/200 (1 mos)
11	20/300	PK	4	Ampho (AC), Fluc (PO), Nata (TOP), Keto (PO, TOP)	20/20 (12 mos)
12	HM	AC & Vit tap/inject	3	Ampho (IV, AC, venous), Fluc (PO, TOP)	HM (12 mos)
13	LP	PPV	1	Vori (IV, AC, PO, TOP), Nata (TOP)	20/50 (4 mos)
14	HM	PK	4	Vori (SC, PO), Nata (TOP)	20/60 (11 mos)
15	HM	PK, AV	7	Ampho (IV), Fluc (PO), Itra (PO), Nata (TOP)	20/40 (4 mos)
16	1/200	AC tap/inject	5	Ampho (AC), Vori (AC, PO, TOP), Keto (TOP), Nata (TOP)	20/30 (11 mos)
17	HM	PK and PPV	7	Ampho (IV), Keto (PO), Nata (TOP)	HM (7 mos)
18	20/40	PK	8	Ampho (IV, AC), Nata (Top), Fluc (PO, TOP), Itra (PO)	20/40 (6 mos)
Penetrating trauma cases					
19	HM	PPV	6	Ampho (IV), Vori (IV), Fluc (PO)	NLP (E<2 mos)
20	LP	PPV	2	Ampho (IV), Fluc (PO)	3/200 (1 mos)
21	3/200	PPV	2	Ampho (IV)	20/400 (4 mos)
22	CF	PPV	5	Ampho (IV), Vori (IV)	NLP (E<2 mos)
23	LP	AC & Vit tap/inject	3	Ampho (IV)	NLP (E<2 mos)
24	LP	PPV	2	Vori (IV, AC), Keto (PO), Nata (TOP)	LP (1 mos)
25	LP	AC & Vit tap/inject	5	Ampho (IV), Nata (TOP)	NLP (E at 32 mos)
26	HM	PPV, AV	3	Ampho (IV), Nata (TOP)	NLP (E<2 mos)
27	HM	PPV	6	Ampho (IV, TOP), Fluc (PO), Keto (PO), Mic (SC, TOP)	NLP (E<2 mos)
28	LP	PPV	3	Mic (IV), Keto (PO), Fluc (PO)	NLP (E at 11 mos)
Postoperative cases					
29	CF	AC tap	5	Ampho (AC, TOP), Fluc (PO), Mic (TOP)	3/200 (1 mos)
30	CF	AC & Vit tap/inject	1	Ampho (IV)	20/30 (18 mos)
31	20/200	PPV	6	Ampho (IV), Vori (IV), Fluc (TOP)	20/30 (5 mos)
32	20/40	PPV, IOL removal	2	Ampho (IV), Fluc (PO)	20/25 (12 mos)
33	3/200	PPV	4	Ampho (IV, AC), Fluc (PO)	20/200 (9 mos)
34	20/400	Vit tap/inject	6	Ampho (IV), Vori (PO), Itra (PO)	NLP (E<2 mos)
35	20/100	AC & Vit tap/inject	4	Ampho (IV, AC), Fluc (PO)	20/200 (17 mos)
36	20/400	PPV	2	Ampho (IV), Itra (PO)	20/50 (13 mos)
37	CF	PPV	5	Ampho (IV), Keto (PO)	5/200 (8 mos)
38	LP	AC & Vit tap/inject	3	Ampho (IV, AC, TOP), Keto (PO), Mic (IV, venous, SC), Fluc (PO, TOP)	20/400 (6 mos)
39	20/60	PPV	2	Ampho (IV), Itra (PO), Fluc (PO)	20/30 (2 mos)
40	20/200	PPV	2	Ampho (IV), Vori (PO), Fluc (PO)	20/30 (15 mos)
41	20/400	AC & Vit tap/inject	5	Ampho (IV, TOP), Vori (AC, SC, PO), Nata (TOP), Fluc (PO)	20/40 (16 mos)

AC = anterior chamber; Ampho = amphotericin; AV = anterior vitrectomy; CF = counting fingers; E = enucleation; E<2 mos = enucleated within 2 months of initiation of treatment for exogenous fungal endophthalmitis; Fluc = fluconazole; f/u = month at which the final vision was measured; HM = hand movements; Itra = itraconazole; IV = intravitreal; Keto = ketoconazole; LP = light perception; MIC = miconazole; Nata = natamycin; NLP = no light perception; PPV = pars plana vitrectomy; PK = penetrating keratoplasty; PO = by mouth; SC = subconjunctival; TOP = topical; venous = intravenous; Vit inject = intravitreal injection; Vit tap = vitreous tap; Vori = voriconazole.