Endogenous Fungal Endophthalmitis: A Single-Center Retrospective Study and Review of the Literature

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• PURPOSE: To evaluate factors that inform systemic antifungal choices in patients with endogenous fungal endophthalmitis (EFE).
• DESIGN: Single-institution retrospective case series.
• METHODS: Charts of EFE patients from 2010 to 2023 were reviewed. Patients treated systemically for EFE with a minimum of 14 days of follow-up were included. Outcome measures included time to improvement in vitritis or chorioretinitis, systemic therapy modification, and need for surgical intervention.
• RESULTS: A total of 20 eyes of 16 patients were included. Candida species were most common (43.8%), followed by culture-negative EFE (37.5%) and Aspergillus species (18.8%). In all, 90% of eyes had vitritis and/or macula-involving chorioretinitis. The majority of Candida infections (60%) or culture-negative EFE (75%) were treated initially with oral antifungals. Patients with a history of immune compromise, positive fungal culture, or positive Fungitell assay were more likely to be treated with early intravenous (IV) antifungal therapy. Two patients required systemic antifungal therapy modification because of worsening chorioretinitis, in 1 case due to voriconazole-resistant Aspergillosis that demonstrated chorioretinal lesion growth despite intravitreal amphotericin B injections and systemic voriconazole, and in the second case due to worsening chorioretinitis from *Candida dubliniensis* infection that regressed upon switch from oral to IV fluconazole.
• CONCLUSIONS: Initial systemic treatment decisions in patients with EFE were driven by systemic culture positivity, systemic symptoms, or comorbidities. Intravitreal antifungal therapy may be insufficient to arrest progression of chorioretinal lesions in some cases. Larger studies are needed to determine whether visible end-organ damage in the form of chorioretinitis may be useful for guiding systemic therapy changes. (Am J Ophthalmol 2024;262: 97–106. © 2024 Elsevier Inc. All rights reserved.)

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Endogenous fungal endophthalmitis (EFE) occurs through hematogenous spread and inoculation of an infectious agent into the choroid, accounting for 5% to 10% of all cases of endophthalmitis.[1-3] Risk factors for the development of endogenous endophthalmitis include urinary tract infection, recent genitourinary instrumentation, sepsis, diabetes mellitus, chronic kidney disease, malignancy, and intravenous drug use (IVDU).[4] EFE caused by yeast (ie, Candida, Cryptococcus) tends to be more indolent, whereas EFE caused by saprophytic molds, such as Aspergillus, is more aggressive and visually damaging.

Only about 25% of intraocular fluid samples yield a positive culture[5]; as such, initial management is often empiric, based on the clinical picture. This presents a challenge in situations in which the patient has minimal or no systemic manifestations of infection, and the primary location of involvement is the eye. In such situations, infectious disease specialists must depend on the ophthalmologist's examination to determine whether the degree of observed end-organ involvement merits modification or escalation of therapy. Because EFE is caused by hematogenous spread of fungal organisms, adequate control of the underlying infection is vital.[6] Systemic antifungals are of paramount importance for source control in all cases, with intravitreal and surgical interventions serving supplementary roles depending primarily upon the degree of vitreous involvement or the location of chorioretinal lesions.

The current Infectious Disease Society of America (IDSA) guidelines for the systemic management of endogenous fungal endophthalmitis recommend treatment with IV or oral fluconazole or voriconazole in susceptible organisms, and IV liposomal amphotericin B for resistant strains.[7] Intravitreal injection of an antifungal agent, most commonly voriconazole or amphotericin B, is indicated in patients with vitritis or in the presence of vision-threatening chorioretinal lesions. Early surgical intervention with pars plana vitrectomy is another treatment that has been found to be effective for vitreous debulking.[7-9] In all cases, treat-

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ment decisions should be made jointly by an ophthalmologist and infectious disease specialist.

The purpose of the current study is to retrospectively review cases of EFE in a single institution over 13 years to evaluate practice patterns, particularly with respect to systemic management.

METHODS

• **PATIENTS AND PROCEDURES:** This is a retrospective chart-review based study performed at a single academic institution in the southeastern United States. This study was considered exempt by the University of Virginia Institutional Review Board, and the methods adhered to the tenets of the Declaration of Helsinki.

The Slicer Dicer tool in Epic was used to identify all patients at a single academic institution from January 1, 2010, through August 5, 2023, who carried a diagnosis of endophthalmitis. Authors E.B. and V.R. reviewed all charts. Patients were considered for inclusion if they were diagnosed with endogenous fungal endophthalmitis based on clinical examination by an ophthalmologist. Patients were excluded if the diagnosis of endogenous fungal endophthalmitis was uncertain, if their treatment and/or clinical course was unable to be deciphered through chart review, or if the patient was lost to follow-up prior to initiating treatment.

The following variables were collected for each patient: demographic data (age, sex, race, and ethnicity); relevant medical history; history of intravenous drug use (IVDU) and timing of last use; systemic symptoms at the time of initial evaluation; the dates of onset of ocular symptoms, evaluation by an outside ophthalmologist or optometrist if applicable, initial and final evaluations at our institution, and improvement; best corrected visual acuity (BCVA), pertinent ophthalmologic examination findings, and notable imaging findings upon initial evaluation; culture data and susceptibilities; medical and surgical management; rationale for initial treatment plan and subsequent changes; BCVA at final evaluation; other ocular pathology that could explain poor visual acuity; and whether the patient was lost to follow-up. The status of the serum Fungitell test, a serum test that is highly sensitive for a constituent of Candida and Aspergillus species' cell walls, was also documented for patients who were culture negative. A patient's EFE was considered to be improving when there was a reduction in the grade of vitreous inflammation and/or chorioretinal lesions that persisted for at least 2 subsequent encounters. The patient's subjective improvement was also documented.

• **STATISTICAL ANALYSIS:** Statistical analysis was performed in RStudio Version 4.3.2 using the Wilcoxon rank sum test for continuous variables and the Fisher exact χ^2 test for categorical variables. A P value less than or equal to .05 was considered to represent statistical significance.

RESULTS

• **DEMOGRAPHICS AND MICROBIOLOGY:** A total of 20 eyes of 16 patients met inclusion criteria between 2010 and 2023. Their characteristics are detailed in Table 1. Only 1 eligible patient presented before 2017, whereas 10 (62.5%) patients presented from 2021 to 2023, representing an average increase of about 0.26 cases per year.

Three patients (18.8%) had positive blood cultures for Aspergillus species; of these, none had positive intraocular fluid cultures, but 2 of the 3 patients had been initiated on systemic antifungal therapy prior to vitreous tap. Seven patients (43.8%) tested positive for Candida species. The remaining 6 patients were culture negative, and of these, 2 were Fungitell positive.

A total of 17 eyes (85%) had vitritis, and 2 eyes had chorioretinitis without vitritis or macular involvement.

The most common comorbid conditions were intravenous drug use (IVDU, n = 8), diabetes mellitus (n = 5), and immunocompromised status (n = 5). Half of all patients had a history of IVDU, of whom 3 (42.9%) had Candida endophthalmitis and 5 (83.3%) had culture-negative EFE.

Nearly all patients presented with visual disturbance (n = 15/16, 93.8%), including blurry vision, flashes, and floaters (Table 1). Less than half (n = 6/16, 37.5%) of all patients had systemic symptoms at the time of evaluation; systemic illness was defined as the presence of fevers, chills, night sweats, cough, or other constitutional symptoms. Of these patients, 4 patients were initiated on IV antifungal therapy at presentation. One of 2 patients with systemic symptoms who was not treated with IV antifungals had fever, nausea, and vomiting related to bacteremia from a concurrent intra-abdominal Pseudomonas infection.

• **TREATMENT STRATEGIES AND CLINICAL OUTCOMES:** Table 2 compares patient characteristics and clinical courses based on initial treatment with IV or oral systemic antifungal therapy. Of the 7 patients (43.8%) managed initially with IV antifungals, 5 were treated with IV voriconazole and 2 with IV amphotericin B. Agent choice was based on culture sensitivities when available, or Infectious Diseases service preference in the absence of culture data.

Of the 6 patients initially treated with IV antifungal therapy, the rationale for initial IV treatment was immunocompromise in 3 patients, presence of a prosthetic valve in 1 patient, and intraocular fluid culture positivity in patient 10 for *Candida dubliniensis*, a hardy organism that the consulting Infectious Diseases service deemed was more appropriate to manage with IV antifungal therapy. This decision conflicted with the initial management of patient 4 with

TABLE 1. Individual Patient Characteristics, Clinical Courses, Treatment Strategies, and Outcomes

Patient No.	Organism	Vitreous/ Aqueous Cultures	Systemic Cultures	Other Cultures	Comorbidities	IVDU History (Last Use)	Presenting Systemic Symptoms	Laterality	Presenting BCVA	Vitreous and Fundus Exam	Systemic Therapy	Intravitreal Antifungal Injections (No., Agent)	Surgical Intervention (Weeks After Presentation)	Final BCVA	Time to Improvement (Days)	Follow-up Duration (Weeks)	LTFU or Transfer of Care
Patients Treated Initially With Intravenous Therapy																	
1a	*Aspergillus fumigatus*	Negative	Negative	BAL: (+); Bone Bx: (+)	Erdheim Chester, immune compromised, urosepsis	None	Tachycardia, fever, chest pain, cough, blurred vision, floaters	OD	20/50 (near)	+Vitreous opacities, +CR lesions in macula, +CR lesions in periphery	IV vori x 3 wk -> IV ampho x 7 mo -> PO posa ongoing	8 (vori x 3, ampho x 5)	None	NLP	32	37.9	No
1b	*Aspergillus fumigatus*	NA	Negative	BAL: (+); Bone Bx: (+)	Erdheim Chester, immune compromised, urosepsis	None	Tachycardia, fever, chest pain, cough, blurred vision, floaters	OS	20/20 (near)	+CR lesions in periphery	IV vori x 3 wk-> IV ampho x 7 mo -> PO posa ongoing	None	None	20/20	32	37.9	No
2	*Aspergillus flavus*	Negative	Negative	Arm thrombus Cx: (+)	Prosthetic mitral valve, septic thrombophlebitis	None	Fever, focal weakness, headache, jaw pain, blurry vision	OD	HM	1+ Vitreous cell, +CR lesions in periphery	IV vori x 9 days -> PO vori x 8 mo	None	Enucleation (13)	NA	100	21.1	No
3	*Aspergillus fumigatus*	Negative	Negative	Heart tissue Bx: (+)	CLL, osteomyelitis, endocarditis, cardioembolic ischemic stroke	None	Fever, tachycardia, focal weakness, sensory changes, eye pain, and vision loss	OS	HM @4′	No view	IV vori x 2 wk -> PO vori ongoing	2 (vori)	None	LP	8	8.9	Ongoing
6	*Candida albicans*	Positive	Negative	NA	Tobacco use, IVDU	Yes (5 y)	Vision loss, blurry vision, red swollen eye	OS	20/100	+Vitreous opacities, no view of retina	IV vori x 4 days -> oral vori x 3.5 wk	1 (ampho)	None	20/100	11	4.6	LTFU
10	*Candida dubliniensis*	Positive	Negative	NA	T2DM, IVDU, stroke	Yes(1 mo)	Floaters, blurry vision	OS	HM @4′	No view	IV fluc x 3 days -> PO fluc x 2 weeks	5 (vori)	None	HM@1'	5	1.7	Transfer of care
11a	None	Negative	Negative	Fungitell (+)	Mixed lymphoid leukemia, immune compromised, bacteremia, hepatosplenic candidiasis	None	Fever, chest pain	OD	20/100 (near)	+CR lesions in macula	IV ampho x 3 weeks -> PO vori x 17 wk[a]	1 (vori)	None	20/20 (near)	5	14.3	LTFU
11b	None	Negative	Negative	Fungitell (+)	Mixed lymphoid leukemia, immune compromised, bacteremia, hepatosplenic candidiasis	None	Fever, chest pain	OS	20/100 (near)	+CR lesions in periphery	IV ampho x 3 wk -> PO vori x 17 wk[a]	None	None	20/20 (near)	Unclear	15.3	LTFU
12	None	Negative	Negative	Fungitell (+)	IVDU	Yes (2 wk)	Blurry vision, painful red eye	OD	20/400 (near)	4+ Vitreous cell, +CR lesions in macula	IV vori x 1 wk -> PO vori x 5 mo	1 (vori)	None	20/50	5	26.3	No
Patients Treated Initially With Oral Therapy																	
4a	*Candida dubliniensis*	Positive	Negative	Urine Cx: (–)	T2DM, severe NPDR	None	Eye pain, light sensitivity, headache	OD	4/200E	4+ Vitreous haze, +CR lesions in macula, +CR lesions in periphery	PO fluc x 11 days -> IV fluc x 1 mo -> PO fluc x 1 wk	17 (vori)	None	20/70	15	21	No
4b	*Candida dubliniensis*	Negative (contralateral eye positive)	Negative	Urine Cx: (–)	T2DM, PDR	None	Eye pain, light sensitivity, headache	OS	20/60	Clear[b]	PO fluc x 11 days -> IV fluc x 1 mo -> PO fluc x 1 wk	13 (vori)	None	20/20	15	21	No
5	*Candida albicans and Candida dubliniensis*	Positive	Negative	Chest tube fluid Cx: (+)	T1DM, COP, immune compromised, NPDR	None	Scotoma, blurry vision	OD	20/60	+CR lesions in macula	PO Bactrim[c] -> PO vori x 4 days -> PO fluc x 4.5 mo	None	PPV (9)	20/20	25	147	No
7	*Candida albicans*	Negative	Negative	Urine Cx: (+)	Ureteral stricture with implant, UTI	None	Dysuria, blurry vision	OD	5/200E	4+ Vitreous cell, + vitreous opacities, no view of retina	PO fluc x 6.5 wk	None	None	20/40	4	9.9	No

(*continued on next page*)

TABLE 1. (*continued*)

Patient No.	Organism	Vitreous/ Aqueous Cultures	Systemic Cultures	Other Cultures	Comorbidities	IVDU History (Last Use)	Presenting Systemic Symptoms	Laterality	Presenting BCVA	Vitreous and Fundus Exam	Systemic Therapy	Intravitreal Antifungal Injections (No., Agent)	Surgical Intervention (Weeks After Presentation)	Final BCVA	Time to Improvement (Days)	Follow-up Duration (Weeks)	LTFU or Transfer of Care
8	*Candida albicans*	Positive	Negative	NA	T1DM, IVDU	Yes (2 wk)	Blurry vision, painful red eye, floaters	OS	20/40	3+ Vitreous cell, + vitreous opacities	PO fluc x 3.5 wk -> PO vori x 2 wk	None	PPV w/ air (3.5)	20/30	14	48.7	Transfer of care and LTFU
9a	*Candida albicans*	NA	Positive	Urine Cx: (–)	T2DM, UCC s/p nephroureterectomy and nephrostomy tube, SBO	None	Fever, malaise, nausea, vomiting, blurry vision, floaters	OD	20/40 (near)	+Vitreous debris, +CR lesions in macula, +CR lesion in periphery	PO fluc x 2 wk -> PO vori x 3 wk[d]	None	None	20/20	14	4.9	Transfer of care
9b	*Candida albicans*	NA	Positive	Urine Cx: (–)	T2DM, UCC s/p nephroureterectomy and nephrostomy tube, SBO	None	Fever, malaise, nausea, vomiting, blurry vision, floaters	OS	20/40 (near)	+Vitreous debris, +CR lesion in macula, +CR lesion in periphery	PO fluc x 2 wk -> PO vori x 3 wk[d]	None	None	20/20	14	4.9	Transfer of care
13	None	Negative	Negative	Fungitell Negative	IVDU	Yes (1 y)	Blurry vision, flashes, floaters	OS	20/400	3+ Vitreous cell, + vitreous opacities	PO fluc x 3 wk	1 (ampho)	PPV w/ oil and lensectomy (11)	HM@1'	2	14.9	N
14	None	Negative	Negative	NA	IVDU	Yes (1 y)	Blurry vision, floaters, painful red eye	OD	20/80	+Vitreous debris, +CR lesion in periphery	PO vori x 2 mo	1 (ampho)	PPV (2.5)	20/25	2	124	N
15	None	Negative	Negative	NA	IVDU	Yes (<1 mo)	Chest pain, arthralgias, vision loss, floaters, photophobia	OS	20/80	1+ Vitreous cell, 3+ vitreous haze	PO vori x 2.5 wk	1 (ampho)	PPV w/ air (3)	20/70	2	2.1	LTFU
16	None	Negative	Negative	NA	IVDU, spinal abscess	Yes (6 wk)	Scotoma, floaters, photophobia, painful red eye	OD	20/200	1+ Vitreous cell, +vitreous opacities	PO vori ongoing	5 (vori)	None	20/100	2	3.3	LTFU

ampho = Amphotericin B; BAL = bronchoalveolar lavage; BCVA = best corrected visual acuity; Bx = biopsy; CLL = chronic lymphocytic leukemia; COP = cryptogenic organizing pneumonia; CR = chorioretinal; Cx = culture; fluc = fluconazole; IVDU = intravenous drug use; LTFU = lost to follow-up; NPDR = non-proliferative diabetic retinopathy; PO = oral; posa = posaconazole; PPV = pars plana vitrectomy; SBO = small bowel obstruction; T1/T2DM = type 1/type 2 diabetes mellitus; UCC = invasive ureteral and urothelial cell carcinoma; UTI = urinary tract infection; vori = voriconazole.

[a] 2 Weeks at time of last ophthalmology evaluation, but completed at least 17 weeks per last documentation.

[b] Developed 4+ vitritis.

[c] Bactrim given for presumed toxoplasmosis.

[d] Change because of intolerance to fluconazole.

TABLE 2. Correlation of Variables with Initial Oral or Intravenous Systemic Antifungal Therapy

Variable	Oral n = 11	Intravenous n = 9	*P* Value[a]
Age, y, median (IQR)	47 (36, 64)	41 (30, 58)	.3
Sex, n (%)			>.9
Female	4 (36%)	3 (33%)	
Male	7 (64%)	6 (67%)	
Race, n (%)			.074
African American	0 (0%)	1 (11%)	
Other	0 (0%)	2 (22%)	
White or Caucasian	11 (100%)	6 (67%)	
Ethnicity n (%)			.2
Hispanic	0 (0%)	2 (22%)	
Non-Hispanic	11 (100%)	7 (78%)	
Other Serious Systemic Comorbidity, n (%)[b]	4 (36%)	6 (67%)	.4
Diabetes, n (%)	6 (55%)	1 (11%)	.07
IVDU history, n (%)	5 (45%)	3 (33%)	.7
Systemic symptoms, n (%)	4 (36%)	6 (67%)	.4
Vitritis, n (%)	9 (82%)	6 (67%)	.6
Location of Chorioretinal Lesion, n (%)			.12
Macula	1 (9.1%)	2 (22%)	
Macula + periphery	5 (45%)	1 (11%)	
Periphery	1 (9.1%)	3 (33%)	
No view	1 (9.1%)	3 (33%)	
None	3 (27%)	0 (0%)	
Surgical Intervention, n (%)			.074
Enucleation	0 (0%)	1 (11%)	
PPV	4 (36%)	0 (0%)	
PPV and lensectomy	1 (9.1%)	0 (0%)	
None	6 (55%)	8 (89%)	
Organism, n (%)			.2
Aspergillus flavus	0 (0%)	1 (11%)	
Aspergillus fumigatus	0 (0%)	3 (33%)	
Candida albicans	4 (36%)	1 (11%)	
Candida albicans and Candida dubliniensis	1 (9.1%)	0 (0%)	
Candida dubliniensis	2 (18%)	1 (11%)	
None	4 (36%)	3 (33%)	
Intraocular Fluid Culture, n (%)			>.9
Positive	3 (27%)	2 (22%)	
Negative	6 (55%)	6 (67%)	
NA	2 (18%)	1 (11%)	
Systemic Culture, n (%)			**.029**
Positive	3 (27%)	4 (44%)	
Fungitell positive	0 (0%)	3 (33%)	
Negative	8 (73%)	2 (22%)	
No. intravitreal injections, median (IQR)	1 (0, 5)	1 (0, 3.5)	>.9
Initial BCVA, n (%)			.3
<20/200	3 (27%)	4 (44%)	
>20/50	3 (27%)	0 (0%)	
20/50 to 20/200	5 (45%)	5 (56%)	
Final BCVA, n (%)			.3
<20/200	1 (9.1%)	4 (44%)	
>20/50	7 (64%)	3 (33%)	
20/50 to 20/200	3 (27%)	2 (22%)	
Time, days, to improvement, median (IQR)	14 (2, 15)	10 (5, 32)[c]	.3

BCVA = best corrected visual acuity; IV = intravenous; PO = oral/by mouth.

[a]Wilcoxon rank sum test; Fisher exact test.

[b]Includes immune compromise, sepsis, malignancy, endocarditis, and osteomyelitis.

[c]Excluding the left eye from patient 11, for which it was unclear.

P values in boldface type indicate statistical significance.

C *dubliniensis*, whose clinical course is outlined in Clinical Vignette 2 below.

The organism type also affected initial systemic management choice of IV vs oral antifungal therapy; all patients with endogenous Aspergillus endophthalmitis were initiated on IV antifungal therapy. However, all patients with Aspergillus EFE were also systemically ill, which likely also affected initial management choice.

Although immune status and organism type were considerations for initiation of IV management in the cases described above, they were not universal or consistent factors in EFE management. One immune compromised patient (patient 5) was not initiated on IV therapy because of a lack of significant vitritis and good visual acuity. Two patients with Candida species infection (patients 6 and 10) were started on IV antifungal therapy and did not have any history of immune compromise or systemic symptoms on presentation.

The only factor that showed a statistically significant correlation with initial treatment with IV vs oral antifungal agent choice was systemic culture. Patients with systemic culture or Fungitell positivity were significantly more likely than non–culture positive patients to be treated initially with IV antifungals ($P = .029$). The culture-negative patients who were initiated on IV antifungals were Fungitell positive. Of the 9 patients initially treated with oral antifungal therapy, all culture-positive cases were due to Candida species; 4 of 7 eyes were positive for C *albicans*, 2 for C *dubliniensis*, and 1 for both. Culture-negative patients with normal Fungitell assay results were clinically diagnosed with fungal endophthalmitis and treated with oral antifungal therapy.

Other factors such as history of diabetes, IVDU, or other serious systemic comorbidities did not meet statistical significance with respect to initial systemic antifungal therapy choice. There was also no statistically significant correlation between vitritis or chorioretinal lesion location and systemic treatment choice.

Eyes with Aspergillus endophthalmitis took longer to demonstrate clinical improvement (mean 43 days) than did eyes with Candida endophthalmitis (mean 13 days) or culture-negative EFE (mean 3 days, $P = .009$). Of the eyes with Candida endophthalmitis, those in patients who were treated with IV antifungals improved more rapidly (n = 2, mean 7.4 days) than eyes in patients treated initially with oral antifungals (n = 7, mean 13.0 days), with the exception of 1 eye from patient 7 that demonstrated improvement on oral fluconazole within 4 days.

On average, eyes treated with intravitreal antifungals showed improvement in vitritis sooner (mean 8.7 days) than eyes that were not treated with intravitreal therapy (mean 29 days, $P = .053$). All eyes that received a single injection (6/12) were culture negative and demonstrated improvement within 2 to 5 days. All eyes that received serial injections were culture positive (2 *Aspergillus fumigatus*, 2 C *dubliniensis*, and 1 C *albicans*). Eyes that received serial injections were also evaluated by an ophthalmologist sooner (mean 4.7 days) than eyes that required only a single injection (mean 10.7 days). There was no statistically significant correlation between intravitreal antifungal therapy and systemic oral versus IV antifungal treatment ($P > .9$).

More eyes in patients treated initially with oral antifungals (n = 5, 45.5%), of which 2 were culture positive for Candida and 3 were culture negative, ultimately underwent surgical intervention as compared with eyes treated initially with IV therapy (n = 1, 11.1%). The eye treated initially with IV antifungals that ultimately required surgical intervention was culture positive for Aspergillus and was ultimately enucleated. Of the remaining eyes that underwent surgical intervention, 2 grew Candida from the vitreous, and the 3 that were systemically culture negative also had negative vitreous fluid cultures despite systemic antifungal therapy being initiated following the vitreous tap. These eyes underwent pars plana vitrectomy at an average of 4.5 weeks from the initiation of antimicrobial therapy. Visual outcomes were good in eyes that were vitrectomized, except for 1 eye with worse than 20/200 vision; of note, vision in this eye was limited by silicone oil fill.

Of the 2 eyes with chorioretinitis without macular involvement or vitritis, 1 was culture positive for Aspergillus and the other was culture negative and Fungitell positive. Both eyes were treated with IV antifungal therapy initially and had 20/20 vision at final follow-up. In both cases, the fellow eye had macular involvement; in the Fungitell-positive, culture-negative patient, the fellow eye also regained 20/20 vision. The course of the Aspergillus-positive patient is outlined below in Clinical Vignette 1; the fellow eye of this patient was positive for both macular involvement and vitritis.

Based on chorioretinitis, 2 patients required a change in systemic therapy as dictated by the ophthalmologist and are detailed in the clinical vignettes below.

• **CLINICAL VIGNETTE 1:** A 28-year-old woman with a history of immune compromise secondary to suppressive therapy following a renal transplant presented with systemic illness secondary to fungemia. Blood cultures were positive for *Aspergillus fumigatus* on initial presentation, and the patient was started on IV voriconazole therapy. Ophthalmology was consulted because of patient complaints of blurred vision and floaters, and she was found to have a macula-involving chorioretinal lesion in the right eye and peripheral chorioretinal lesions in both eyes. At the time of initial Ophthalmology consultation, all immunosuppressive therapy had been held, with the exception of prednisone 5 mg.

Serial intravitreal voriconazole therapy was initiated 2 to 3 times weekly. The chorioretinal lesions continued to grow and expand into the vitreous, prompting a switch to intravitreal amphotericin B. Despite injection of intravitreal amphotericin B, the chorioretinal lesions continued to en-

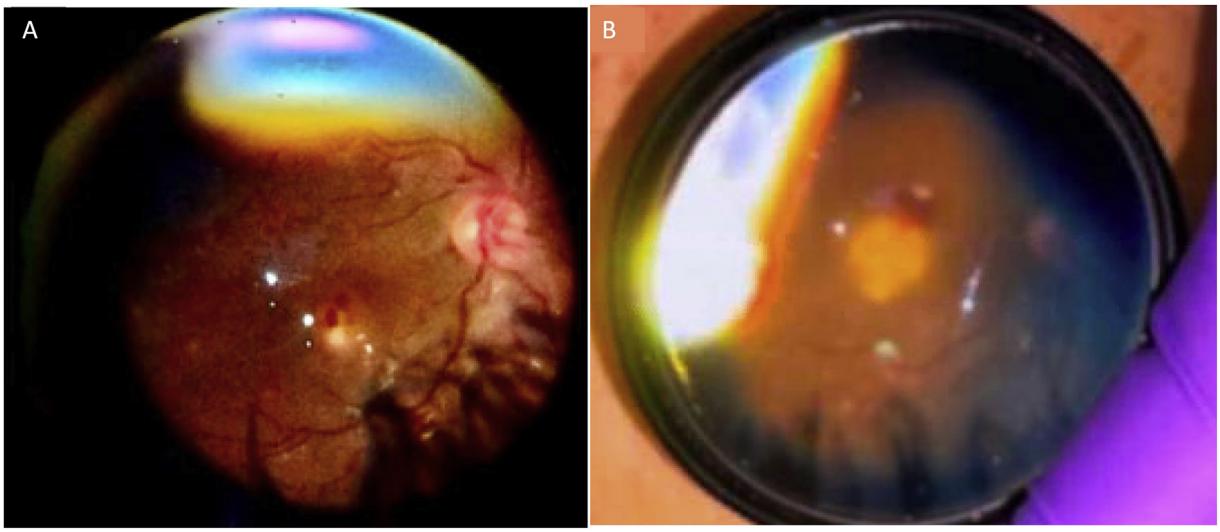

FIGURE 1. Color fundus photographs of the right eye from patient 1, demonstrating growth of the macular chorioretinal lesion from day of presentation (a) to 20 days later (b).

large, and the patient continued to spike fevers (Figure 1). Ultimately, there was concern that the organism was resistant to voriconazole, and lobectomy of the lung was performed for source control. The organism was indeed found to be resistant based on cultures from the resected lung tissue, and the patient was switched from IV voriconazole to IV amphotericin B. Ten days after this change of therapy, the chorioretinal lesions began to regress.

• **CLINICAL VIGNETTE 2:** A 56-year-old man with a history of poorly controlled diabetes and recent history of protracted urinary tract infection/pyelonephritis treated with 1 month of antibacterial therapy presented to the outpatient Ophthalmology clinic with decreased vision. He was found to have 4+ vitreous haze and multiple chorioretinal lesions in the macula and the periphery of the right eye; his left eye had no vitritis at presentation and a single flat chorioretinal macular lesion as well as 2 peripheral lesions. He was admitted because of concern for fungal endophthalmitis, and tap and inject of the right eye revealed culture positive *Candida dubliniensis*. He was treated initially with 4 days of oral fluconazole 400 mg followed by 8 days of oral fluconazole 800 mg daily, in addition to serial intravitreal voriconazole injections twice weekly. On day 8, repeat vitreous tap was performed on both eyes, which did not yield any organisms. However, despite this, his vitritis worsened, and his chorioretinal lesions continued to enlarge and burgeon into the vitreous (Figures 2 and 3). At this point, the ophthalmology team recommended switching systemic therapy from oral to IV fluconazole. Initially, therapy was not changed, as the Infectious Diseases team deemed that oral and IV fluconazole were bioequivalent and that vitrectomy should be considered for source control. Because of the involvement of the fellow eye with enlarging chorioretinal lesions without vitritis, the patient was eventually switched to IV fluconazole on the day 11 following initial presentation. Four days after this switch, the chorioretinal lesions showed involution on optical coherence tomography (Figure 3). Following control of his active infection, the patient underwent cataract extraction with intraocular lens implant and achieved 20/70 and 20/20 vision in the right and left eyes, respectively.

DISCUSSION

In this single-center retrospective study of 20 eyes with endogenous fungal endophthalmitis, systemic treatment strategies are reviewed. Because of the very small sample size and lack of a defined protocol for treatment, the following statements are intended as discussion points with the understanding that a larger, more systemic study is needed to verify or to refute these claims. Although in many cases, the initiation of systemic therapy in line with IDSA guidelines and based on culture sensitivity is appropriate, in cases where cultures are unavailable or the ophthalmic clinical course worsens despite appropriate antifungal coverage, reconsideration of systemic coverage may be prudent.

The management of endogenous fungal endophthalmitis presents multiple challenges, including a lack of clear guidelines for the use of specific IV or oral agents, and protocols for when there should be a transition of systemic treatment based on the ophthalmic examination. Although current IDSA guidelines recommend the use of fluconazole or voriconazole for sensitive organisms and amphotericin B for resistant organisms, there is no robust evidence to support the use of IV vs oral antifungal therapy.

Few studies have described treatment strategies for endogenous fungal endophthalmitis.[8,10-12] A retrospective

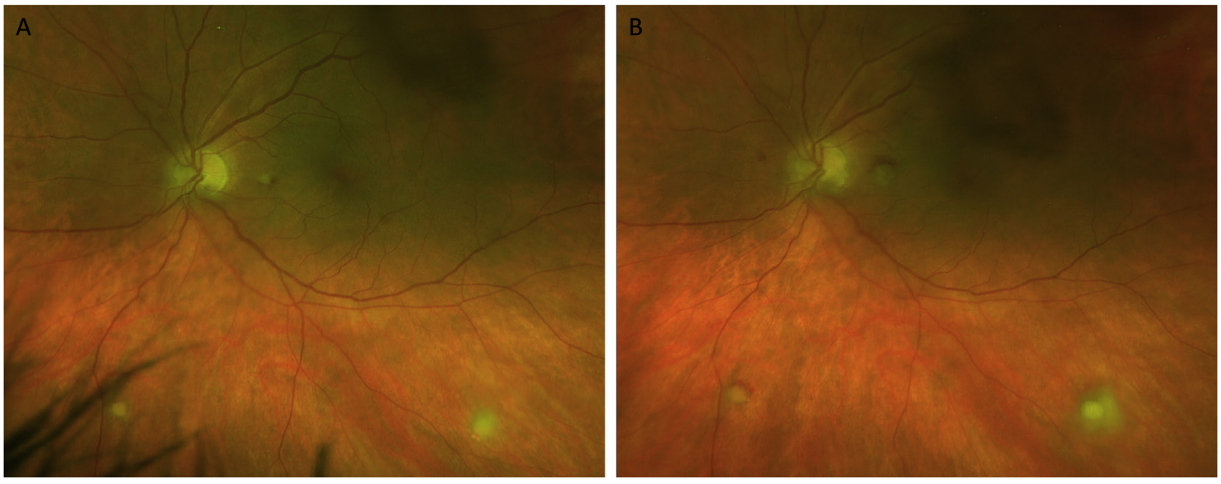

FIGURE 2. Pseudo-color fundus photographs of the left eye from patient 4, demonstrating growth of macular and inferotemporal chorioretinal lesions from day of presentation (a) to 9 days later (b).

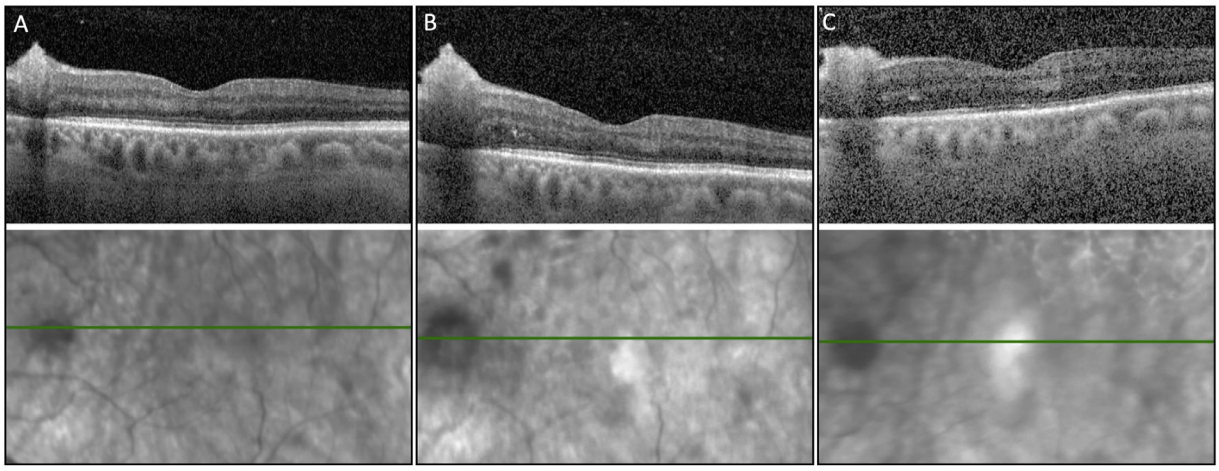

FIGURE 3. Optical coherence tomography of the left eye from patient 4, demonstrating growth of a macular chorioretinal lesion from day of presentation (a) to 9 days later (b), followed by involution on day 15 (4 days after switching from oral to intravenous antifungals (c).

study of 65 eyes of 51 patients with culture-positive EFE found that 65% were treated initially with oral antifungals, 29% with intravenous antifungals, and 43% with a combination of systemic and intravitreal treatment.[6] Of note, in this study, systemic voriconazole was used for only 1 patient, whereas the majority were treated with fluconazole (n = 28) or amphotericin B (n = 12), and nearly all eyes (91%) underwent vitrectomy. In comparison, in the present study, 55% were treated initially with oral antifungals (3 with voriconazole, 7 with fluconazole), 45% with IV (5 voriconazole, 1 amphotericin B, and 1 fluconazole), and only 25% underwent pars plana vitrectomy (PPV).

In contrast to the aforementioned reference and this single-center series, a recent review article that summarized data from a number of case series and retrospective review studies based largely out of Asia suggested using IV voriconazole as first-line initial treatment for patients with suspected EFE.[12] However, it is unclear where this recommendation derives from, as the associated citation suggests either IV or oral fluconazole or voriconazole as initial treatment, and references an earlier version of this same review article as a source.[11] Anecdotally, the authors of the present study have found that many other institutions almost uniformly favor initiation of IV antifungals in the setting of EFE. Combined, this information reinforces the absence of clear and specific guidelines to support the use of oral vs IV antifungal therapy, and that the decision is based on factors outside the presence of EFE.

Existing literature regarding antifungal pharmacodynamics suggest that both oral fluconazole and voriconazole have at least 90% bioavailability.[13-15] Human studies regarding the intraocular penetration of oral antifungals is limited, but 1 study of 20 cataract patients demonstrated that 200 mg of oral fluconazole achieved aqueous levels 80% that

of serum levels at 2 hours following administration.[16] Another study of 14 patients undergoing PPV demonstrated that two 400 mg doses of oral voriconazole administered 12 hours apart resulted in vitreous and aqueous concentrations 38% and 53% those of serum concentrations, respectively.[17] Even at these reduced levels, adequate therapeutic levels were reached in both compartments, based on in vitro studies of the minimal inhibitory concentration of voriconazole for various yeasts, molds, and fungi.[17]

Although the available literature suggests that oral fluconazole achieves adequate therapeutic levels in the vitreous cavity,[13] Clinical Vignette 2 highlights a scenario in which IV fluconazole appeared to control chorioretinal involvement more robustly as compared to oral fluconazole. In this case, although the vitritis was being managed with the use of oral fluconazole in combination with serial intravitreal voriconazole, chorioretinal lesions did not regress until therapy was switched from oral to IV fluconazole.

Although the aforementioned data reference drug levels in the aqueous and vitreous, they do not address the level of drug in the choroid. Choroidal circulation differs from systemic circulation because of significant permeability that allows medications to extravasate rapidly into the extravascular choroid. Data that support oral fluconazole or voriconazole as sufficient coverage for EFE do not take the pharmacokinetics of the choroid into account.[18] This may account for cases in which vitritis is improved by intravitreal and oral systemic antifungal therapy but chorioretinal lesions continue to grow and expand, as shown in the 2 Clinical Vignettes described above.

In addition, although current IDSA guidelines state that decision making regarding EFE treatment should occur with Ophthalmology guidance, the inclusion of more specific parameters with respect to the ophthalmic examination can better guide management. This is evidenced in Clinical Vignette 1, in which progressive eye involvement suggested voriconazole resistance but the decision to change systemic therapy was not enacted until later in the course, when repeat cultures demonstrated resistance. Serious consideration of the ophthalmic examination, which demonstrated enlarging chorioretinal lesions, could have led to an earlier transition to IV amphotericin B and, potentially, a better ophthalmic outcome.

Visual acuity has often been used in studies as the primary outcome measure to determine response to therapy.[19,20] However, as seen in the present study, visual acuity may be of limited utility in determining treatment response in eyes that have experienced significant inflammation, have comorbid conditions, or have undergone PPV with silicone oil. Serial examination and multimodal imaging are often more telling than visual acuity alone.[2,21,22] In patients with fungal endophthalmitis, close serial follow-up is crucial. The ability to determine whether chorioretinitis is worsening, or whether vitritis is developing, can markedly change the recommendations made by the ophthalmologist. Increasing size or number of chorioretinal lesions is more suggestive of increasing organism burden in the choroid, as opposed to vitritis, which indicates organism burden in the vitreous. Vitreous involvement of fungal endophthalmitis can persist even once chorioretinal lesions begin to regress, and can often endure long after the active infection is controlled. In such patients, vitrectomy is an appropriate consideration.

For patients with macular chorioretinal involvement and/or vitritis, the IDSA recommends combination therapy with systemic antifungals as above in addition to intravitreal therapy and, for severe cases, consideration of PPV. The presence of ocular fluid culture positivity and more rapid time to ophthalmologic evaluation in eyes requiring serial injections may be indicative of a more aggressive disease process. In such cases, the need for serial intravitreal injections may signal that the patient would benefit from a change in systemic therapy.

The decision to use oral antimicrobial agents over IV agents when appropriate stems largely from the tenets of good antimicrobial stewardship and efforts to reduce healthcare costs and length of hospital stay.[23] The existing infectious disease literature suggests that the bioavailability of IV and oral formulations of multiple antifungal drugs is equivalent. Despite this assertion, this series demonstrates that preference may be given to the initial use of IV antifungals in the setting of systemic culture positivity. Although oral antifungals are likely adequate in most situations, the input of the ophthalmologist and careful attention to the growth of chorioretinal lesions can identify situations in which initial IV therapy for induction followed by oral outpatient therapy could be more appropriate.

As a pilot study, this series cannot and should not be used to draw conclusions regarding the potential superiority of certain systemic antifungal treatments over others. This study is limited by its small sample size, homogeneity with respect to racial or ethnic background, its retrospective nature, lack of uniform management strategies, and limited follow-up for many patients. However, larger multi-center studies are merited to better elucidate specifically the need for guidelines for systemic therapy modification in patients with clinical evidence of worsening fungal chorioretinitis. Survey studies to determine current practice patterns of Infectious Diseases specialists and ophthalmologists would also further elucidate variability in the treatment of EFE patients and assist in the determination of more standardized guidance for management of these patients.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Eleanor Burton: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Vishal Reddy:** Writing – review & editing, Writing – original draft, Data curation.

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