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Endogenous Endophthalmitis: Recommendation for Empiric Dual Antibacterial and Antifungal Therapy

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Abstract

Purpose: This work compares clinical presentation and course of bacterial and fungal causes of endogenous endophthalmitis (EE). **Methods:** A single-institutional study of consecutive patients diagnosed with EE was conducted at the University of Pittsburgh Medical Center between September 2015 and September 2018. Exclusion criteria included history of ocular trauma, intraocular surgery or injection 6 months before presentation, or primary external ocular infection. Data included demographics, medical and ocular history, clinical examination, culture data, therapeutic interventions, final corrected visual acuity (VA), and mortality. **Results:** Thirty-six eyes of 26 patients were diagnosed with EE during a 3-year period. Median age at diagnosis was 55.5 years (range, 19-86 years). Based on ocular and systemic cultures, 19 patients had bacterial EE and 6 patients had fungal EE; findings from all cultures remained negative in 1 patient. All patients had risk factors for EE. Presenting VA, subjective symptom report, and objective measures of intraocular inflammation were similar between bacterial and fungal causes. Overall, EE presented indolently and was initially misdiagnosed in 19% of cases. Complications including final VA less than 20/200, retinal detachment, enucleation, or death within 6 months of diagnosis were equivalent between bacterial and fungal cases. **Conclusions:** The presentation of EE is remarkably different from that of exogenous endophthalmitis. Without a high index of suspicion, the indolent presentation of EE may lead to misdiagnosis. No clinical features reliably differentiated bacterial and fungal sources. This highlights the importance of considering empiric therapy for antibacterial and antifungal coverage on initial presentation.

Keywords

endogenous endophthalmitis, infectious posterior uveitis, clinical presentation, outcomes

Introduction

Sepsis is an increasing cause of morbidity and mortality, accounting for 1.7 million hospitalizations and 33% of in-hospital deaths in the United States.[1] Early detection of sepsis and its sequelae, including endogenous endophthalmitis (EE), is critical to limiting morbidity and costs to patients and the health care system. EE accounts for 2% to 8% of endophthalmitis cases[2,3] and results from homogeneous dissemination of pathologic bacteria or fungi from a primary source of infection through the blood-ocular barrier. Risk factors include infection in the setting of underlying immune compromise, diabetes, chronic kidney disease, malignancy, indwelling catheters, and intravenous (IV) drug abuse.[3,4]

In general, EE presents more indolently than exogenous endophthalmitis. Prior studies have reported that patients with EE typically present several days after symptoms' onset and have less acute examination findings than those with exogenous endophthalmitis, and as a result, diagnostic errors led to inaccurate or delayed diagnosis in up to 26% of patients.[5]

Overall, the prognosis of both bacterial and fungal endophthalmitis is notably poor. Studies have reported that EE leads to a visual acuity (VA) of 20/200 or less in up to 55% of patients.[5,6] Additionally, EE is a marker of significant morbidity and can be a predictor of mortality in systemically ill patients.[7,8]

Given the rarity and severity of EE, clinicians must maintain a high index of suspicion for it. Few prior studies have compared the clinical presentation of bacterial vs fungal endophthalmitis. In general, bilateral disease is more common in fungal cases,[6] and some studies have reported better visual outcomes in fungal cases of endophthalmitis.[6] However, these studies had a small sample size, and identification of

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Table 1. Clinical Details of Patients With Endogenous Endophthalmitis.

Case	Age, y, sex	Eye	Infectious source	Organism	Initial VA	Final VA
1	58, F	Left	IVDU	MSSA	CF	20/30
2	28, F	Left × 2	IVDU with secondary arm abscess and ICD lead infection	*Candida albicans*, MSSA	First: 20/800 Second: HM	First: 20/30 Second: 20/60
3	42, M	Left	Skin lesion	*Staphylococcus aureus*	HM	20/60
4	34, M	Right and left	IVDU	*Staphylococcus aureus*	CF	20/30
5	64, F	Right and left	MVP	MSSA	20/200 OD, HM OS	20/20 OU
6	86, F	Right and left	Venous stasis ulcers	Group C beta hemolytic *Streptococcus*	Unable to obtain	Unable to obtain
7	55, F	Right and left	Liver abscess	*Klebsiella pneumonia*	OD: LP OS: 20/50	OD: LP OS: 20/600
8	26, M	Right	IVDU	*Candida albicans*	20/250	20/600
9	45, M	Right	Unknown	Gram-positive cocci in pairs	LP	20/70
10	19, M	Left	IVDU	Coagulase-negative *Staphylococcus*	20/800	20/400
11	61, M	Right	Arm cellulitis	MRSA	20/800	20/50
12	79, M	Right and left, left × 2	Chemotherapy port	*Candida albicans*	OD: 20/25 OS 20/25	OD: 20/25 OS:20/25
13	61, F	Right and left	Infectious endocarditis	*Escherichia coli*	OD: CF OS: HM	OD: 20/80 OS: NLP
14	71, F	Right and left	TPN port	*Candida* (species unknown)	OD: 20/250 OS: 20/250	OD: 20/50 OS: 20/80
15	64, M	Right	Skin lesion	MSSA	20/200	20/30
16	56, M	Left	ICD lead	MRSA	20/800	20/30
17	38, F	Right	Abdominal abscess	MRSA	20/400	20/80
18	55, M	Left	Osteomyelitis	MSSA	LP	NLP
19	59, M	Right and left	Splenectomy	*Streptococcus pneumonia*	Unable to assess	OU: NLP
20	33, F	Right	IVDU	Unknown	CF	CF
21	57, M	Left	Skin lesion	MSSA	CF	NLP
22	59, F	Left	Invasive aspergillosis	*Aspergillus fumigatus*	LP	Enucleated
23	45, F	Right	Infectious endocarditis	MRSA	CF	20/40
24	23, M	Right	IVDU	*Candida dubliniensis*	HM	20/80
25	73, M	Right	Unknown	MRSA	LP	NLP
26	51, M	Left	Skin lesion	MSSA	20/200	20/200

Abbreviations: CF, counting fingers; F, female; HM, hand motion; ICD, implantable cardioverter-defibrillator; IVDU, intravenous drug use; LP, light perception; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MVP, mitral valve prolapse; NLP, no light perception; OD, right eye; OS, left eye; OU, both eyes; TPN, total parenteral nutrition; VA, visual acuity.

distinguishing features between different causes of EE was not a primary aim.

We present a series of consecutive cases of EE managed at a tertiary care center over a 3-year period. This study sought to compare the clinical features and course between bacterial and fungal cases of EE. The specific aim was to identify features that may allow ophthalmologists to accurately diagnose EE and institute timely, targeted medical and surgical intervention.

Methods

This study was conducted according to the Declaration of Helsinki code of ethics and was exempt from review by the institutional review board of the University of Pittsburgh. We reviewed the records of all patients diagnosed with EE at the University of Pittsburgh Medical Center from September 2015 to September 2018. Exclusion criteria included history of ocular trauma, intraocular surgery or intraocular injection within 6 months of presentation, or a primary external ocular infection. Data collected included demographics, medical and ocular history, clinical examination, culture data, treatment modalities and timing, final corrected VA, and mortality. All ophthalmic samples were analyzed by the Charles T. Campbell Ophthalmic Microbiology Laboratory at the University of Pittsburgh Medical Center. Statistics were performed using SPSS, version 24.0 (IBM Corp), and a P value of less than .05 was regarded as statistically significant.

Results

Thirty-six eyes of 26 patients were diagnosed with EE during a 3-year period (Table 1). Sixteen patients (62%) were men and 10 (38%) were women. Median age at diagnosis was 55.5 years (range, 19-86 years). Sixteen patients (62%) had no significant ocular history. Four patients had a remote history of cataract surgery, and 1 patient had a prior penetrating keratoplasty for

Table 2. Baseline Demographics of Patients With Endogenous Endophthalmitis.[a]

Feature	All patients (N = 26)	Bacterial (n = 19)	Fungal (n = 6)	*P*
Median age (range), y	55.5 (19-86)	56.0 (19-86)	43.5 (23-79)	.70
Proportion male, %	62 (n = 16)	68 (n = 13)	50 (n = 3)	.74
Proportion with history of diabetes, %	58 (n = 15)	68 (n = 13)	33 (n = 2)	.29
Proportion with history of intravenous drug abuse, %	39 (n = 10)	32 (n = 6)	50 (n = 3)	.74

[a]Medians compared using Mann-Whitney U test, proportions compared using chi-square test. Patient with unknown etiology excluded from subgroup analysis.

Table 3. Clinical Presentation of Endogenous Endophthalmitis by Eye.[a]

Clinical feature		Total (N = 33)	Bacterial (n = 25)	Fungal (n = 10)	*P*
Presentation	Median number of days from symptom onset to presentation	4.00 (range: 0-28)	4.0 (range: 0-28)	5.0 (range: 0-28)	.70
	Proportion with ocular findings as presenting feature of sepsis	36 (n = 13)	32 (n = 8)	50 (n = 5)	.55
Symptoms	Proportion with no symptoms, %	8 (n = 3)	4 (n = 1)	20 (n = 2)	.16
	Proportion presenting with pain, %	25 (n = 9)	24 (n = 6)	30 (n = 3)	.71
	Proportion presenting with decreased vision, %	81 (n = 29)	84 (n = 21)	70 (n = 7)	.35
	Proportion presenting with new or worsened floaters, %	22 (n = 8)	20 (n = 5)	30 (n = 3)	.52
Signs	Mean (SD) grade of conjunctival injection	1.37 (1.29)	1.42 (1.22)	1.42 (1.44)	.95
	Mean (SD) grade of anterior chamber cell	2.00 (1.77)	1.75 (1.92)	1.85 (1.42)	.61
	Presence of hypopyon, %	28 (n = 10)	32 (n = 8)	20 (n = 2)	.48
	View to posterior pole on initial examination, %	58 (n = 21)	42 (n = 15)	50 (n = 5)	.59
Visual acuity	Median initial logMAR acuity	1.90 (range, 0.1-2.7)	1.90 (range, 0.4-2.7)	1.10 (range, 0.1-2.7)	.06

Abbreviation: logMAR, logarithm of the minimum angle of resolution.
[a]Patient with unknown etiology included in overall analysis but excluded from subgroup analysis.

keratoconus. Two patients (8%) had medically managed glaucoma, 3 (12%) had diabetic retinopathy, and 1 (4%) had macular degeneration. Three patients (12%) had EE previously; 2 had EE in the affected eye previously, and 1 patient had EE in the fellow eye previously. Further, 2 patients developed 2 separate episodes of EE during the study period.

There were several noteworthy features of patients' systemic health (Table 2). All patients were immunocompromised. Two patients were on chronic oral steroids or oral chemotherapy. The remaining patients were functionally immunocompromised because of their medical comorbidities. Ten patients (39%) had a history of IV drug use, and 2 patients additionally had hepatitis C. Fifteen patients (58%) were diabetic, with 8 patients noted to have hemoglobin A_{1c} greater than 10%, and 1 patient presented in diabetic ketoacidosis. Six patients (23%) had a current or prior malignancy. One patient had a history of a chronic indwelling line for short gut syndrome; one line had a chemotherapy port, and the other had a radiotherapy port.

In 33 eyes (92%), ocular symptoms prompted an ophthalmology evaluation (Table 3). Symptomatic patients were evaluated at a median of 4.0 days (range, 0-28 days) after symptom onset. The most common presenting symptom was a subjective reduction in VA, reported in 29 eyes (81%). Additionally, 9 eyes (25%) presented with pain, and 8 (22%) presented with new or worsening floaters. Sixteen patients (62%) were diagnosed with EE on an inpatient basis. Thirteen patients (54%) were admitted for sepsis and subsequently developed ocular

Table 4. Clinical Course of Endogenous Endophthalmitis.[a]

Clinical feature		Total (36 eyes)	Bacterial (25 eyes)	Fungal (10 eyes)	P^b
Systemic culture results	Blood cultures obtained	34/36	24/25	9/10	
	Blood cultures positive	20/36	13/25	7/10	.33
Ocular culture results	Ocular cultures obtained	36/36	25/25	10/10	
	Ocular cultures positive	18/36	13/25	5/10	.62
Misdiagnosis	Misdiagnosed on initial presentation	7/36	4/25	2/10	.78
Empiric intravitreal therapy	Empiric intravitreal antibacterial only	19/36	18/25	1/10	**.003**
	Empiric intravitreal antifungal only	7/36	2/25	4/10	.08
	Empiric dual intravitreal antibacterial and antifungal	5/36	2/25	3/10	.25
	No empiric antimicrobial therapy on initial presentation	5/36	3/25	2/10	.67
	Inadequate empiric therapy on initial presentation	8/36	5/25	3/10	.86
Surgical intervention	Diagnostic vitrectomy	7/36	6/25	1/10	.35
	Therapeutic vitrectomy	7/36	5/25	2/10	.64
Outcomes	Median final logMAR acuity	0.54 (range, 0-3.0)	0.57 (range, 0-3.0)	0.44 (range, 0.1-3.0)	.21
	Final vision worse than 20/200	13/36	10/25	2/10	.37
	Retinal detachment	11/36	9/25	2/10	.60
	Median duration of hospitalization, d	13.00 (range, 0-82)	13.00 (range, 0-66)	12.50 (range, 4-82)	.70
	Death within 1 y of diagnosis	4/26	3/19	1/6	.56

Abbreviation: logMAR, logarithm of the minimum angle of resolution.
[a]Patient with unknown etiology of endogenous endophthalmitis included in overall analysis but excluded from subgroup analysis by pathogen type. Vision unable to be assessed in 2 eyes because of altered mental status.
[b]Bold indicates statistically significant result.

symptoms during hospitalization prompting an ophthalmology evaluation, and 2 cases were detected as part of a baseline screening examination after returning blood culture results that were positive for EE. The remaining 10 patients were initially evaluated in the ophthalmic outpatient setting. In these cases, the clinical diagnosis of EE was the presenting feature that prompted referral to the emergency department for workup of sepsis.

The clinical signs of EE were notably subtle. On average, patients had only mild to moderate conjunctival injections, with 8 eyes (22%) presenting without any conjunctival injection and 9 eyes (25%) having only trace injection. Eyes had on average 2+ grade cells, with 12 eyes (33%) without any anterior chamber cells on initial examination. Only 10 eyes (28%) presented with hypopyon. Posterior pole details were readily visible in 21 eyes (58%). Initial VA on presentation ranged from 20/25 to light perception. The median logarithm of the minimum angle of resolution (logMAR) vision on presentation was 1.76 (SD 0.70), corresponding to a vision of approximately 20/1000. The VA of 2 patients was unable to be assessed secondary to altered mental status. There were no reliable differences in the symptoms or severity of presentation between bacterial and fungal causes of EE.

Clinical evaluation of suspected EE varied greatly between patients (Table 4). Blood cultures were obtained in 24 of 26 patients, whereas ocular cultures were obtained in all patients. Blood cultures were not obtained in 2 patients managed on an outpatient basis who each had a history of EE in the same or fellow eye. The rate of culture positivity was approximately equal between blood and ocular cultures, with no difference in culture positivity between bacterial and fungal causes of endophthalmitis. Samples yielding cultures positive for ocular EE included 3 aqueous samples, 2 vitreous samples, 5 vitrectomy specimens, and 3 enucleation specimens. One patient with clinical features consistent with endophthalmitis had both ocular systemic cultures that were negative for EE. Of note, 7 eyes (19%) were misdiagnosed as noninfectious anterior uveitis on initial presentation, either by the referring physician or by our institution.

Of 36 eyes with EE, 25 cases (69%) were attributed to a bacterial pathogen and 10 cases (27%) were attributed to a fungal pathogen. Of the 25 eyes that had bacterial endophthalmitis, 21 cases (88%) were due to gram-positive species, whereas 3 eyes were revealed to have gram-negative bacteria. The most common bacterial cause of EE in our study was *Staphylococcus aureus* (16 eyes), with other causative organisms including *Streptococcus* (5 eyes). Both eyes affected by gram-negative species (*Escherichia coli* and *Klebsiella pneumonia*) were notable for bilateral involvement on presentation. The most common fungal cause was *Candida* (9 eyes), whereas 1 case was due to *Aspergillus*.

Common sources of primary infection included 8 patients (30%) with skin, soft-tissue, or bone infections, 2 patients with solid organ infections, and 3 patients were immunocompromised because of chemotherapy, splenectomy, or malignancy. Eleven patients (42%) had complications of infectious endocarditis, most commonly in the setting of IV drug use. The infectious source was not identified in 2 patients.

Patients were followed for a median of 79 days (range, 0-930 days). Empiric ophthalmic intervention included medical and surgical therapy. On initial evaluation, 29 of 36 eyes were treated empirically for EE. All of these patients were offered intraocular antimicrobial therapy, including combinations of vancomycin (1.0 mg/0.1 mL), ceftazidime (2.25 mg/0.1 mL), and amphotericin B (5 μg /0.1 mL) at the discretion of the providing physician. The 7 eyes that were not initially suspected to be due to EE were not treated with antimicrobial agents on first presentation. In 3 cases, the empiric antimicrobial agent choice failed to cover the organism that ultimately grew from blood or ocular cultures. Only 5 eyes received dual antibacterial and antifungal coverage on initial presentation. One patient refused intravitreal therapy and was successfully treated with systemic antimicrobial therapy alone. As described earlier, a causative organism was not identified in 1 eye, and the patient was treated with empiric antifungal therapy, given a history of both malignancy and IV drug use.

Surgical intervention was undertaken in 16 eyes. Diagnostic vitrectomy was performed in 7 eyes within 1 week of initial presentation. In recalcitrant cases, 7 eyes underwent therapeutic vitrectomy to help reduce the inflammatory burden of EE. Two painful eyes with poor visual potential were enucleated.

Complications of EE were not uncommon. The retinal detachment rate was 31%. There was no reliable difference in retinal detachment rate between those who did and did not undergo vitrectomy. Other complications included choroidal detachment on initial evaluation and a retinal abscess. Of patients cognitively intact to measure vision, the median final logMAR VA was 0.54 (range, 0-3.0), corresponding to a vision of 20/80. However, the final VA was less than 20/200 in 36% of eyes. Seven eyes progressed to no light perception level of vision despite interventions. Four eyes developed phthisis bulbi, and 1 blind, painful eye was enucleated.

EE additionally represented a marker of systemic morbidity and mortality. The median length of hospitalization for these patients was 13.0 days, and 15% of patients in this cohort died within 1 year of diagnosis. Ultimately, there were no statistically significant differences in visual or systemic outcomes between bacterial and fungal causes of endophthalmitis.

Conclusions

Over 3 years, there were 36 cases of EE diagnosed at this institution. To our knowledge, this series from a tertiary referral center represents one of the largest case series of EE in the United States.

Our results reinforce several important principles in the management of suspected EE. Of importance, the presentation of EE differs greatly from exogenous endophthalmitis. As characterized by the Endophthalmitis Vitrectomy Study (EVS), exogenous endophthalmitis presents with sudden-onset pain, often associated with an inflamed eye, classically 3 to 5 days after inoculation. In contrast, EE tends to have an indolent presentation. Whereas 98.8% of patients in the EVS were symptomatic, 3 patients (8%) in our study were asymptomatic. On examination, EE presented with only mild injection, anterior chamber cell, or vitritis, and only 10% presented with hypopyon, compared with 86% of EVS patients. Perhaps most important, whereas the morbidity associated with exogenous endophthalmitis is typically limited to the eye, EE is associated with substantial systemic morbidity, and 15% of patients in this study died within 12 months of diagnosis. The subacute presentation of EE may lead to diagnostic errors. Prior reports in the literature have demonstrated a 26% rate of delayed or inaccurate diagnosis. Similarly, in this study, 7 of 36 eyes with EE (19%) were initially misdiagnosed. As a result, patients were either observed without intervention or treated with steroids that potentially unmasked and worsened the underlying disease process.

Ocular cultures were obtained in all 26 patients and systemic cultures were obtained in 24 of 26 patients in this study. A similar proportion of blood (57%) and ocular (50%) cultures yielded growth. These results are similar to prior studies that have reported culture-positive rates for intraocular specimens ranging from 24%[9] to 64%.[10] Consistent with prior studies,[11,12] the diagnostic yield of vitrectomy concentrate was the highest, whereas the yield of aqueous samples was notably poor. Patients were treated according to the results of their systemic cultures. If findings from systemic cultures were negative but those from ocular cultures were positive, then patients were treated based on the results of the ocular culture. These findings emphasize the need to obtain both ocular and systemic blood cultures in suspected cases of EE to increase the likelihood of identifying the causative organism and guide antimicrobial therapy. Ultimately, the organism responsible for the EE was identified in 25 of 26 patients. Consistent with prior studies undertaken in North America, the most common bacterial causes were gram-positive organisms (specifically *S aureus*), whereas the most common fungal cause was *Candida albicans*.

Our results highlight several new conclusions. A holistic approach to the patient's systemic health may reduce diagnostic error. In retrospect, the majority of patients in this study had known risk factors for EE or other underlying medical comorbidities. Additionally, most patients (92%) were symptomatic and either concurrently or recently hospitalized. Moreover, 62% of patients were septic at the time of initial examination, including every case of bacterial EE. These aspects of clinical history, coupled with signs of anterior and posterior segment inflammation, support an infectious source for panuveitis.

Furthermore, this analysis highlights the similarities in presentation of bacterial and fungal EE. Specifically, there were no statistically significant differences in demographics, ocular history, or medical history between patients who had bacterial or fungal endophthalmitis. The primary infectious source did not differ between bacterial and fungal disease, with the complications of IV drug use representing the most common cause of EE overall. There were no differences in symptoms or examination findings that reliably distinguished between bacterial and fungal causes of endophthalmitis. This is in contrast to prior smaller studies that have suggested that bacterial EE presents with more rapid onset than fungal endophthalmiitis.[6]

Therefore, one cannot rely on features of the ophthalmic examination alone to guide empiric treatment of suspected EE.

Finally, this study provides new insights into the complexities of medical and surgical management of EE. In our study, the medical management of EE was determined by the providing physician. In select cases, the indolent clinical presentation did not raise suspicion for EE, and thus, 7 eyes did not receive empiric antimicrobials on initial presentation. All eyes suspected to have EE received both systemic and local antimicrobials. Intravitreal antimicrobials were administered on initial presentation based on the treating ophthalmologist's suspicion for the causative organism. The practice pattern at our institution for fungal coverage is to use 5 μg of amphotericin B to minimize the risk of retinal toxicity while providing broad coverage of yeast species. Only 5 eyes were treated with dual antibacterial and antifungal therapy on initial presentation. In 22% of eyes, initial therapy was based on clinical suspicion alone and failed to treat the ultimate causative organism.

Empiric systemic treatment was determined by the consulting medical teams based on medical history and known risk factors and was later altered based on culture results. The treatment duration for systemic therapy at our institution is 42 days. We prefer empiric treatment of fungal endophthalmitis with amphotericin 5 μg/0.1 mL given its low risk for retinal toxicity in our experience. Unlike amphotericin B, there is known voriconazole resistance among some *Candida* species.[13]

The surgical management of EE remains less established. Given their systemic comorbidities, patients with EE are often not surgical candidates. However, diagnostic pars plana vitrectomy (PPV) can provide a specimen for intraocular culture, whereas therapeutic PPV can help reduce the inflammatory burden associated with endophthalmitis or treat complications such as nonclearing vitritis or retinal detachment.[14] Some studies have suggested that early vitrectomy may be beneficial in cases due to aggressive microbes such as *Klebsiella*, mold, or fungi, whereas others have found no statistically significant benefit.[15] The overall rate of PPV in our study was 42%, of which half were diagnostic and half were therapeutic. This rate was lower than prior reports of a 60% PPV rate for the diagnosis and management of endophthalmitis.[3] In this study, there was no difference in the rate of diagnostic or therapeutic PPV between bacterial and fungal causes of endophthalmitis. Further, there was no difference in visual outcomes between eyes that underwent vitrectomy and those that did not. It is possible that these results were confounded by anesthesia risks that may have precluded some patients who may have benefited from vitrectomy from undergoing surgery.

Ultimately, visual outcomes did not differ significantly between bacterial and fungal causes of endophthalmitis. This is consistent with the body of literature on this topic. Overall, our visual outcomes were more favorable than those reported previously in the literature.[5,16,17]

Importantly, this study included 3 patients who were previously treated for EE and 2 patients who developed multiple episodes of EE in the same eye during the study period. This highlights the need for continued surveillance of patients diagnosed with EE. Furthermore, the 12-month mortality rate in this cohort was 15%, emphasizing the need for a comprehensive approach to patients with EE to reduce morbidity, mortality, and costs to the health care system.

Several clinically relevant practice points can be made by looking at specific subgroups of patients included in this study. Three patients were initially misdiagnosed at our institution after presenting to the emergency department for new visual symptoms. On review of these cases, posterior segment examinations on initial presentation noted vitreous hemorrhage (1 case), a cotton-wool spot (1 case), and a chorioretinal lesion (1 case) in absence of frank anterior or posterior segment inflammation. These were nonspecific examination findings that may be seen in patients with systemic comorbidities in the absence of active intraocular infection and therefore did not raise clinical suspicion for EE. However, these diagnostic errors suggest EE should remain on the differential diagnosis for medically complex patients presenting with new visual symptoms, and any abnormalities on examination should be closely followed for resolution.

Seven patients received empiric therapy that did not cover the causative organism. In most cases the treating physicians chose empiric therapy based on their subjective interpretation of examination findings as being consistent with either bacterial or fungal disease. However, our study underscores that there are no reliable differences in presentation between bacterial and fungal disease based on examination. In 2 cases, there was a history of bacteremia, either at the time of examination, or in the past. However, ocular cultures demonstrated fungal endophthalmitis. Physicians must be aware that patients with risk factors for EE are at risk for polymicrobial disease, again supporting consideration of empiric dual antibacterial and antifungal coverage.

Both patients who had recurrent EE in the same eye may have had continued inoculation with *Candida* owing to continued IV drug use or a compromised chemotherapy port. Both received 6 weeks of outpatient fluconazole therapy per recommendations from infectious disease colleagues but still had recurrent disease. As a result, clinicians should consider close, long-term monitoring of patients with *Candida* endophthalmitis and review return precautions with such patients.

There were several limitations to our study. First, this was a nonrandomized, retrospective study of only 36 cases. As a result, this study may have been underpowered to detect true differences in the presentation and course between bacterial and fungal causes. The majority of statistical analyses in this paper used the χ^2 test to compare the proportion of bacterial vs fungal cases of EE demonstrating particular clinical features. However, using the sample size from this study, an α of .05, and a κ of 0.8, a 45% difference in proportion of a feature of the presentation or course of bacterial or fungal EE would be needed to generate a statistically significant result. Therefore, a future study using a larger sample size might be better powered to detect more subtle differences in clinical features of EE. Second, these cases were managed at a tertiary care referral

center with a high case-mix index, indicating that these patients may not be representative of all patients with EE. Lastly, universal polymerase chain reaction (PCR) studies were not performed on intraocular specimens. Prior studies have demonstrated that the high sensitivity and specificity of PCR may be beneficial in detecting the causative organism in culture-negative specimens while reducing the risk of false-positive results due to accidental contamination.[18] As a result, one could consider use of PCR for diagnostic testing if logistically and financially feasible.

In summary, this study provides new insights into the management of EE in the United States. EE presents with clinical features that can differ vastly from exogenous endophthalmitis, highlighting the need for a comprehensive approach to our patients' overall health. Given similar rates of culture positivity, we recommend obtaining both ocular and blood culture specimens on initial presentation to guide therapy. Because there were no reliable differences in the presentation of bacterial and fungal causes of endophthalmitis, it would be prudent to consider empiric broad-spectrum, dual antibacterial and antifungal therapy while awaiting culture data results.

Finally, EE is associated with significant morbidity and mortality, particularly in the setting of sepsis. As a result, we recommend that patients presenting in the outpatient setting be referred to the emergency department for further evaluation and systemic therapy. The role of surgical intervention in these patients, however, still requires further study; these patients tended to have poor postoperative outcomes, and vitrectomy was fraught with potential complications. Patients with EE have complex medical histories with multiple comorbidities, representing a vulnerable population. Ultimately, a multidisciplinary approach with close, long-term follow-up is necessary to help adequately treat EE and detect possible recurrences.

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected health information was performed in a Health Insurance Portability and Accountability Act (HIPAA)—compliant manner.

Statement of Informed Consent

Informed consent was not sought for this study because it was a retrospective review of medical records.

Declaration of Conflicting Interests

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