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Original Article

Clinical and visual outcomes following endogenous endophthalmitis: 175 consecutive cases from a tertiary referral center in Taiwan

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Vitrectomy

Abstract *Background:* To elucidate the linkage between organisms and visual outcome in cases of endogenous endophthalmitis.
Methods: Patients who presented with signs of endogenous endophthalmitis between January 2008 and December 2015 and underwent a vitreous tapping were enrolled. The patients' demographics and clinical findings were recorded. The outcomes include visual acuity and enucleation.
Results: A total of 175 consecutive patients with endogenous endophthalmitis were enrolled. Forty-four percent of the patients had a known distal focus of infection. The most common focus was liver abscess (24.6%), and the major intravitreal isolate was *Klebsiella pneumoniae* (34.4%). In this series, 51.4% of the intravitreal cultures were positive. The visual acuity of fungal ophthalmitis were better than in bacterial ophthalmitis. Multivariate logistic regression showed that Gram negative vitreous isolates, compared with the negative vitreous culture, were associated with higher risk of enucleation (Odds ratio [OR]: 10.424, 95% confidence interval [95% CI]: 3.019—35.995). The use of intravitreal antibiotics, compared non-users, was associated with a reduced risk of enucleation (OR:0.084, 95% CI: 0.026—0.268). Trans pars plana vitrectomy was not associated with risk of enucleation (OR: 0.307, 95% CI: 0.035—2.693). The post-treatment VA was positively correlated with the presenting VA ($r = 0.718$, $p = 0.0001$).

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Conclusion: Our study demonstrated that liver abscess is the most common source of endogenous endophthalmitis in Taiwan. The visual outcome is good when the presenting visual acuity is relatively well preserved and when the infecting organism is fungus. The use of intra-vitreal antibiotics reduces the risk of enucleation.

Introduction

Endogenous endophthalmitis is a rare form of eye infection, and represents less than 10% of endophthalmitis. The outcome of endogenous endophthalmitis is poor because more than one third of the involved eyes become blinded despite the appropriate treatment.[1—4] The risk factors of endogenous endophthalmitis include comorbidities and an infection focus. The associated comorbidities are closely linked to an immunocompromised status; they include diabetes mellitus (DM), hemodialysis, liver cirrhosis, and the receipt of cytotoxic chemotherapy or immunosuppressants.[5] The dissemination of pathogens from infection foci to the eyes also contribute to endophthalmitis. These infection foci or routes include intravenous drug use, indwelling intravascular catheters, liver abscess, infective endocarditis, osteomyelitis, and urinary tract infection.[1—4,6—12] The treatment of endophthalmitis consists of intravitreal antibiotic treatment and some clinicians also advocate early vitrectomy. Nevertheless, evidence may be inadequate in support of aggressive management of endogenous endophthalmitis because of its low incidence. This study collected and analyzed the largest series of endogenous endophthalmitis in a single tertiary medical center in northern Taiwan. The predictive factors of functional and surgical visual outcomes will be clarified.

Methods

Data source

This retrospective study was conducted at a tertiary referral center with 3700 beds and an annual average of 107,000 inpatient services in northern Taiwan. This study was approved by the Institutional Review Board (IRB) of the study hospital. The need for informed consent was waived because of the study's retrospective, non-interventional design, and the patients' confidentiality was maintained.

The patients were screened by identifying the diagnosis codes for endophthalmitis (ICD9: 36,000, 36,001, 36,002, 36,019) from their discharge summaries from January 01, 2008 to December 31, 2015. The diagnosis of endophthalmitis was made clinically by the ophthalmologists. We reviewed the patients' chart and consultation sheet to make sure the diagnosis of endophthalmitis is correct. The first date of diagnosis was defined as the index date. We excluded patients who were younger than 18 years old, who were solid organ or hematopoietic stem cell recipients, who received any eye surgery or had ocular trauma within 6 weeks prior to the index date.

Covariate and outcomes

The patients' demographics, clinical and laboratory data, prescriptions for immunosuppressants, corticosteroids, or anti-cancer therapies were recorded. We recorded the white blood cell count (WBC) and C-reactive protein (CRP) on index date, and microbiologic cultures from blood, vitreous body and any other foci during hospitalization. The patients were divided into groups based on vitreous culture results, which included culture-negative, Gram-positive bacterium, Gram-negative bacterium, fungi, and polymicrobial. The polymicrobial group was characterized by the presence of more than two groups of pathogens (Gram-positive bacterium, Gram-negative bacterium or fungi).

Visual acuity (VA) was recorded from the consultation sheet during hospitalization and the outpatient record during follow-up. It was obtained in a Snellen test with a measurement distance of 6 m (6/6 vision). VAs below 6/60 were grouped into four categories in descending order - count fingers (CF), hand movement (HM), perception of light (PL) and no perception of light (NPL). Four functional outcome groups were defined based on the VA before and after treatment; they were improvement, stationary, worsening, or enucleation/evisceration. Improvement in VA was defined as a gain of more than two lines of Snellen VA or a one-step improvement on the "below Snellen" scale (such as from PL to HM or from CF to 6/60). Worsening was defined as a loss of more than two lines of Snellen VA or a one-step worsening on the "below Snellen" scale (such as from 6/60 to CF, from PL to NPL, or from CF to HM). The Snellen scale was transformed into a logarithm of the minimum angle of resolution (logMAR) and the "below Snellen" scale was transformed as CF: 1.85, HM: 2.30, PL: 2.70 and NPL: 3.00, as in previous studies.[13,14]

Statistical analysis

Categorical variables are presented as numbers and proportions, and they are compared by performing Chi-square test or Fisher exact test. Continuous variables are presented as mean with standard deviation, and they are tested by ANOVA. Bonferroni adjustment was conducted for multiple pairwise comparisons. The correlation between the presenting and post-treatment VA on the logMAR scales was analyzed by linear regression. The odds ratio of different factors on the risk of enucleation was analyzed

with logistic regression (The *glm* function). All statistical analysis was performed using R 4.0.2.

Results

During the study period, 1145 consecutive hospitalized patients with endophthalmitis were identified. After excluding patients who were younger than 18 years old, solid organ or hematopoietic stem cell recipients, and patients who had exogenous endophthalmitis, 190 patients with endogenous endophthalmitis remained. A vitreous culture had not been obtained from 15 patients because of thrombocytopenia, refusal, or an extremely critical condition. The final analyses therefore involved a total of 175 patients.

Table 1 presents the patients' demographics among different intravitreal pathogen groups. Age did not change significantly as a result of Bonferroni adjustment for multiple pairwise comparisons. The sex distribution and comorbidities did not vary significantly across groups. More patients with Gram-negative bacterial infection had DM, but this difference did not reach statistical significance.

Table 2 presents clinical features of endogenous endophthalmitis. The group-average number of days from the onset of symptoms to ophthalmologists' visit was 4—15, but large variations existed within groups. The presenting symptoms were blurred vision (74.3%), eye pain (50.9%), fever (49.1%) and periocular swelling (29.7%). As many as 56.5% of patients did not have a definite extra-ocular infection focus despite extensive septic work-ups. Forty-four patients were diagnosed with liver abscesses, and these represented 57.8% of extra-ocular infection foci; they were concentrated in the culture-negative and Gram-negative groups. The rates of concurrent bacteremia were higher in the culture-negative and Gram-negative group than in other groups, but this difference did not reach statistical significance. In the culture-negative group, up to 44 patients had no identifiable extraocular infection foci, this "double negative" condition represented 25.1% of the overall cohort.

The visual outcomes differed significantly among the groups. The patients who were infected with bacteria (Gram-negative or Gram-positive group) had the worst outcomes with respect to final VA and functional outcomes (Table 3). These patients were more likely to undergo enucleation or evisceration (Gram-negative: 37.5% and Gram-positive: 21.7%, versus culture-negative: 8.2% and fungi: 6.7%). With respect to specific pathogens, a positive vitreous culture of *Klebsiella pneumonia* was associated with the worst outcome: 90.3% of these patients had a final VA worse than 6/60 on Snellen scale and 45.2% of them required enucleation. Multivariate logistic regression showed that Gram negative vitreous isolates, compared with the negative vitreous culture, were associated with higher risk of enucleation (Odds ratio [OR]: 10.424, 95% confidence interval [95% CI]: 3.019—35.995). The use of intravitreal antibiotics, compared non-users, was associated with a reduced risk of enucleation (OR:0.084, 95% CI: 0.026—0.268). Trans pars plana vitrectomy was not associated with risk of enucleation (OR: 0.307, 95% CI: 0.035—2.693) (Table 4). The final VA (in logMAR scale) following treatment was positively correlated with the presenting VA ($r = 0.718$, $p = 0.0001$, Fig. 1).

Table 5 presents the positive vitreous culture results from the current study and related data from the literatures. In our study, there were 23 Gram-positive bacterial isolates, and the Coagulase-negative *Staphylococcus* (CoNS) was the majority (6/23, 26.1%). Within the 48 Gram-negative bacterial isolates, *Klebsiella pneumoniae* was the major species (31/48, 64.6%), and was followed by *Pseudomonas aeruginosa* (11/48, 22.9%). *Candida albicans* was the main fungus that was isolated from the vitreous samples (6/15, 40.0%); however, the pathogenic fungal species varied substantially. Table 5 summarizes the pathogens of four polymicrobial isolates in our study.

Table 1 Patient demographic of endogenous endophthalmitis among different intravitreal pathogen groups.

	Total N = 175	Negative culture N = 85	Gram positive N = 24	Gram negative N = 48	Fungi N = 14	Polymicrobial N = 4	P value
N	175	85	23	48	15	4	
Male sex (n, %)	108 (61.7%)	59 (69.4%)	14 (58.3%)	26 (54.2%)	8 (57.1%)	1 (25.0%)	0.214
age (mean ± SD)	61 ± 14	60 ± 14	69 ± 10	64 ± 14	54 ± 14	50 ± 11	0.002
Comorbidities (n, %)							
Diabetes Mellitus	102 (58.3%)	49 (57.6%)	10 (41.7%)	32 (66.7%)	9 (64.3%)	2 (50%)	0.349
End Stage Renal Disease	27 (15.4%)	12 (14.1%)	5 (20.8%)	7 (14.6%)	1 (7.1%)	2 (50%)	0.280
Hypertension	65 (37.1%)	26 (30.6%)	15 (62.5%)	21 (43.8%)	2 (14.3%)	1 (25.0%)	0.014
Cirrhosis	21 (12.0%)	9 (10.6%)	4 (16.7%)	6 (12.5%)	1 (7.1%)	1 (25.0%)	0.805
Old stroke	13 (7.4%)	3 (3.5%)	2 (8.3%)	8 (16.7%)	0 (0%)	0 (0%)	0.054
Heart failure	9 (5.1%)	4 (4.7%)	3 (12.5%)	1 (2.1%)	1 (7.1%)	0 (0%)	0.413
Coronary artery disease	9 (5.1%)	4 (4.7%)	1 (4.2%)	3 (6.2%)	1 (7.1%)	0 (0%)	0.970
Human immunodeficiency virus infection	4 (2.3%)	1 (1.2%)	0 (0%)	2 (4.2%)	1 (7.1%)	0 (0%)	0.499
Cancer	12 (6.9%)	5 (5.9%)	4 (16.7%)	1 (2.1%)	2 (14.3%)	0 (0%)	0.144
Immunosuppressive drugs	2 (1.1%)	2 (2.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.710

Table 2 Clinical manifestations of endogenous endophthalmitis in different intravitreal pathogen groups.

	Total N = 175	Negative culture N = 85	Gram positive N = 24	Gram negative N = 48	Fungi N = 15	Polymicrobial N = 4	P value
Duration from symptoms to ophthalmologists' visit (days, mean ± SD)	7 ± 10	7 ± 11	8 ± 9	6 ± 6	16 ± 15	4 ± 3	0.016
Clinical manifestation (n, %)							
Fever	86 (49.4%)	49 (57.6%)	8 (33.3%)	24 (50.0%)	3 (21.4%)	2 (66.7%)	0.049
Blurred vision	130 (74.7%)	66 (77.6%)	17 (70.8%)	34 (70.8%)	13 (92.9%)	0 (0%)	0.015
Eye pain	89 (51.1%)	49 (57.6%)	13 (54.2%)	21 (43.8%)	5 (35.7%)	1 (33.3%)	0.368
Periocular swelling	52 (29.9%)	22 (25.9%)	11 (45.8%)	15 (31.2%)	2 (14.3%)	2 (66.7%)	0.127
Bacteremia	59 (33.9%)	34 (40.0%)	6 (25.0%)	17 (35.4%)	1 (7.1%)	1 (33.3%)	0.148
Fungemia	2 (1.1%)	2 (2.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.714
Shock	7 (4.0%)	5 (5.9%)	0 (0%)	2 (4.2%)	0 (0%)	0 (0%)	0.648
Respiratory Failure	13 (7.5%)	9 (10.6%)	2 (8.3%)	2 (4.2%)	0 (0%)	0 (0%)	0.501
Extraocular infection focus (n, %)							0.508
No identifiable focus	99 (56.6%)	44 (51.8%)	17 (70.6%)	24 (50.0%)	11 (78.6%)	3 (75.0%)	
Liver abscess	43 (24.6%)	24 (28.2%)	2 (8.4%)	14 (29.2%)	2 (13.3%)	1 (25.0%)	
Renal abscess	4 (2.3%%)	0 (0%)	0 (0%)	4 (8.3%)	0 (0%)	0 (0%)	
Pneumonia	6 (3.4%)	4 (4.7%)	0 (0%)	2 (4.2%)	0 (0%)	0 (0%)	
Biliary tract infection	1 (0.6%)	1 (1.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Bloodstream	3 (1.7%)	2 (2.4%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	
Infective endocarditis	4 (2.3%)	3 (3.5%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	
Splenic abscess	1 (0.6%)	0 (0%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	
Soft tissue	3 (1.7%)	1 (1.2%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	
Urinary tract	6 (3.4%)	3 (3.5%)	0 (0%)	2 (4.2%)	1 (6.7%)	0 (0%)	
Spine	4 (2.3%)	1 (1.2%)	2 (8.4%)	1 (2.1%)	0 (0%)	0 (0%)	
Dialysis vascular access	2 (1.1%)	2 (2.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Laboratory exam (mean ± SD)							
White blood cell count (/μL)	10.7 ± 4.5	10.3 ± 4.3	12.5 ± 5.7	11.5 ± 4.8	9.6 ± 0.4	6.6 ± 1.6	0.528
C-reactive protein (U/L)	116.7 ± 109.9	124.9 ± 115.9	122.7 ± 118.4	127.7 ± 101.7	34.6 ± 50.0	38.4 ± 24.4	0.147
Eye involved (n, %)							0.398
Bilateral eyes	19 (10.9%)	8 (9.4%)	1 (4.2%)	8 (16.7%)	2 (14.3%)	0 (0%)	
Left eye	80 (46.0%)	42 (49.4%)	14 (58.3%)	20 (41.7%)	3 (21.4%)	1 (33.3%)	
Right eye	75 (43.1%)	35 (41.2%)	9 (37.5%)	20 (41.7%)	9 (64.3%)	2 (66.7%)	
Therapy (n, %)							
Systemic antimicrobials	161 (92.0%)	77 (90.6%)	22 (91.7%)	44 (91.7%)	14 (100.0%)	4 (100.0%)	0.862
IVI	137 (82.0%)	68 (81.0%)	16 (72.7%)	37 (84.1%)	13 (92.9%)	3 (100.0%)	0.516
TPPV	29 (17.3%)	11 (13.1%)	5 (22.7%)	6 (13.3%)	7 (50.0%)	0 (0%)	0.011
Enucleation or evisceration	31 (18.3%)	7 (8.3%)	5 (22.7%)	17 (37.0%)	1 (7.1%)	1 (33.3%)	0.001

Discussion

Endogenous endophthalmitis is a rare but devastating eye infection that typically occurs in patients with risk factors, including DM, the taking of immunosuppressants, intravenous drug use, and an ongoing infection, such as bacteremia, fungemia, infective endocarditis, or a liver abscess. The causative pathogens circulate from extra-ocular foci or translocate from the colonization site into the bloodstream.[1—4,6—10,12] Varizi et al. reported incidence rates of 0.4% for endogenous bacterial endophthalmitis and 0.04% for endogenous fungal endophthalmitis in hospitalized patients with documented bloodstream infection.[15] Although smaller studies have reported high rates of concurrent bacteremia and endogenous endophthalmitis (55—100%),[2,4,9] Jackson et al. and this work have separately reported a lower rate of bacteremia (33—56%).[3] This difference implies that hematogenous pathogen spread may be transient, contributing to the large variation among studies. Unlike post-operative endophthalmitis, endogenous endophthalmitis cannot unfeasibly be treated with prophylactic antibiotics because a clear assaulting event is lacking. Accordingly, prompt recognition and treatment remain the cornerstone of management.

This study found that the visual outcome of endogenous fungal endophthalmitis is better than those that of endogenous bacterial endophthalmitis: higher proportion of VAs is better than 6/60 on the Snellen chart; improvement upon

Table 3 Outcomes of endogenous endophthalmitis in different intravitreal pathogen groups.

Outcome	Total N = 175	Negative culture N = 85	Gram positive N = 24	Gram negative N = 48	Fungi N = 14	Polymicrobial N = 4	P value
Duration of hospitalization (days, mean ± SD)	23 ± 15	23 ± 15	22 ± 18	26 ± 14	18 ± 9	22 ± 13	0.497
Visual outcomes at presentation and after treatment							
Initial VA better than 6/60	13 (7.4%)	8 (9.4%)	0 (0%)	2 (4.2%)	1 (6.7%)	2 (50.0%)	0.004
Follow up VA better than 6/60	29 (16.6%)	24 (8.2%)	0 (0%)	2 (4.2%)	2 (13.3%)	1 (25.0%)	0.005
Visual outcome categories							0.007
Worsening	27 (15.4%)	13 (15.3%)	6 (25.0%)	6 (12.5%)	0 (0%)	1 (25.0%)	
Improvement	49 (28.0%)	31 (36.5%)	2 (8.3%)	8 (16.7%)	7 (50.0%)	1 (25.0%)	
Stationary	36 (20.6%)	20 (23.5%)	8 (33.3%)	6 (12.5%)	2 (14.3%)	0 (0%)	
Enucleation or evisceration	32 (18.3%)	7 (8.2%)	5 (20.8%)	18 (37.5%)	1 (7.1%)	1 (25.0%)	
Missing data	19 (10.9%)	8 (9.4%)	3 (12.5%)	7 (14.6%)	4 (28.6%)	0 (0%)	

Abbreviations: SD, standard deviation; VA, visual acuity.

therapy is greater and fewer patients need enucleation or evisceration for infection control. This finding is consistent with previous studies that have found that fungal endogenous endophthalmitis, and especially that caused by *C. albicans*, is associated with better visual outcome.[1,4,12] Studies have reported final VAs of 6/60 or better in 14–56% of treated eyes, and the final VA is generally better than that at presentation.[12,16–18] Similar to previous studies, our study found a higher proportion of DM among patients with fungal endophthalmitis than infection caused by other pathogens, and the majority of fungal isolates are *C. albicans*. Contrary to some studies, none of the patients with fungal endophthalmitis in this work was an intravenous drug user, possibly reflecting the geographical variation in the prevalence of intravenous drug users.[1,12,19]

The major causative pathogens in this study were bacteria. Unlike acute post-operative endophthalmitis, which is predominantly (90–95%) caused by Gram-positive bacteria, endogenous bacterial endophthalmitis is mostly caused by Gram-negative bacteria.[20] In this study, 56.4% of culture positive cases were caused by Gram-negative bacteria. This result is consistent with several previous studies. Jackson et al. systematically reviewed the literature from 1986 to 2012 and found that Gram-negative bacteria account for 50% of recorded cases. *K. pneumoniae*, responsible for 27–36% of total reported cases, is the most important Gram-negative bacterium in endogenous endophthalmitis.[2–4] *K. pneumoniae* is the pathogen that is most frequently associated with liver abscesses.[9,10,21,22] Among the 44 patients with ultrasound-proven liver abscesses, 20 liver abscesses and 16 vitreous aspirates are positive for *K. pneumoniae*. The prevalence of DM is higher in this group (n = 31, 70.5%) than in the overall study population (58.3%). This finding further supports the claim that DM is the strongest risk factor for *K. pneumoniae*-associated disseminated infection.[10] The outcomes of endogenous *K. pneumoniae* endophthalmitis are generally poor. The patients in this study with *K. pneumoniae* endophthalmitis also had the poorest visual outcomes; this result is similar to that of Ang et al., who reported that

Table 4 Multivariate logistic regression analysis of risk factors associated with enucleation/evisceration in endogenous endophthalmitis patients.

	Odds ratio	95% Confidence interval	p value
Vitreous culture (ref: culture-negative group)			
Gram positive bacterium	2.715	0.621–11.87	0.1810
Gram negative bacterium	10.424	3.019–35.995	0.0002
Fungus	1.802	0.153–21.182	0.6370
Treatment modalities			
Trans pars plana vitrectomy	0.307	0.035–2.693	0.2826
Intravitreal anti-microbial injection	0.084	0.026–0.268	<0.0001
Systemic antimicrobials	2.156	0.237–19.611	0.4919

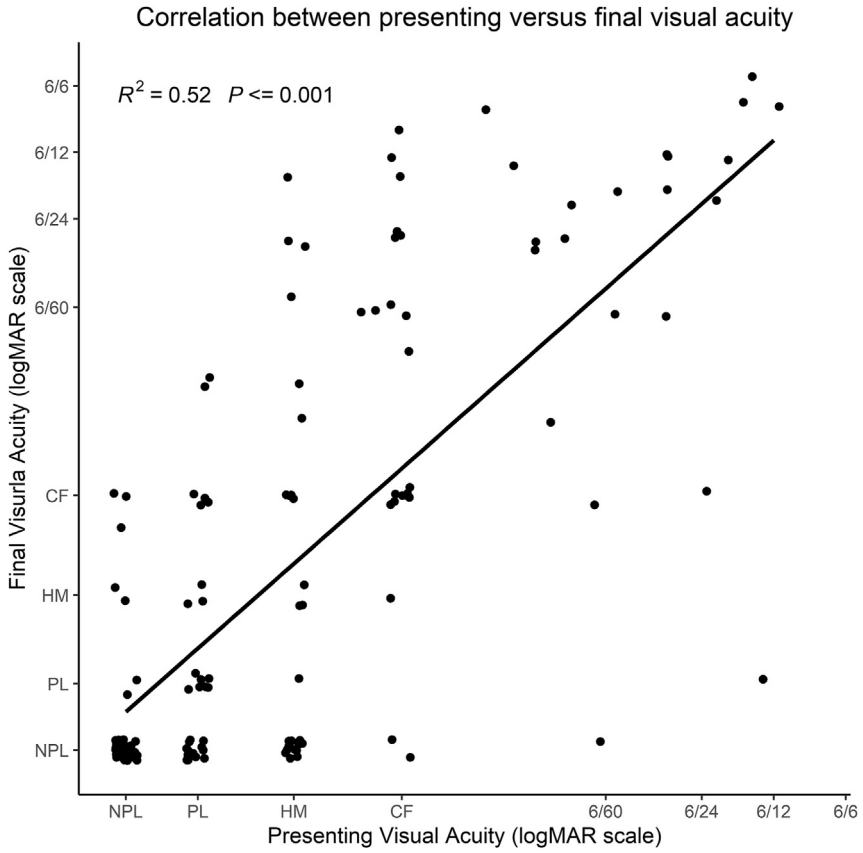

Figure. 1. Correlation between visual acuity of endogenous endophthalmitis patients at presentation and final visual acuity.

57.8% of involved eyes finally had no perception of light and 26.8% of eyes needed enucleation to eradicate infection.[23]

In the series herein, a total of 85 patients had negative vitreous culture despite repeated vitreous taps. These patients had better visual outcomes than the others and the least consideration of enucleation. However, a higher proportion of them had fever (57.6%) and bacteremia (40%). This phenomenon may be explained by the following. First, their pathogen burden may be lower but more persistent, activating immunological bacterial clearance and resulting in a milder disease and consequently, a better VA outcome. A polymerase chain reaction (PCR)-based examination in vitreous aspirate can be used to detect the resulting pathogen in this group. Second, these patients are more likely to present with fever and bacteremia, and so were treated with systemic antibiotics. Systemic antibiotic treatment prior to vitreous sampling may reduce the likelihood of a positive yield.[24]

Despite the various outcomes among pathogen categories, the overall positive rate of vitreous culture was only 51.4% (85 of the 175 patients from whom vitreous culture was obtained). Previous series have also revealed considerable negative culture rates from 30 to 50%, indicating the difficulty of making a microbiological diagnosis and determination of antibiotic susceptibility.[1,3,4,7] PCR for detecting bacterial genetic sequences may be used in conjunction with the traditional plate-culture method to facilitate the microbiologic diagnosis of endophthalmitis.[25,26] Owing to the unsatisfactory positive culture rate, the use of appropriate empiric antimicrobial agents will be very important. Several reports have indicated that the most common Gram-positive bacterium is coagulase-negative Staphylococcus (CoNS) and frequently detected Gram-negative bacteria include *K. pneumoniae*, *Escherichia coli*, *Enterobacter cloacae*, and *P. aeruginosa*. Antibiotic susceptibility studies using ocular isolates from post-operative, post-traumatic and endogenous endophthalmitis indicate that most Gram-positive isolates are susceptible to vancomycin, whereas Gram-negative bacteria are most susceptible to ceftazidime, gentamicin and amikacin.[27—29] A susceptibility study of anti-fungal agents revealed that *C. albicans* that was isolated from infected eyes is susceptible to amphotericin B, fluconazole and voriconazole. Since the positive rate from current sampling and culture methods is unsatisfactory, a broad coverage of empiric antibiotics against common pathogens will be very important in controlling endogenous endophthalmitis infection. At the authors' hospital, patients who were diagnosed with bacterial endophthalmitis are treated empirically with intravitreal vancomycin and ceftazidime, whereas those diagnosed with fungal endophthalmitis are treated with intravitreal amphotericin B or systemic fluconazole. Hence, our initial management of endophthalmitis is consistent with the current evidence provided herein.

A total of 85 (56.5%) of the patients in our study did not exhibit any extra-ocular infection focus, in spite of extensive septic surveys, including blood culture, chest plain

Table 5 Summary of endogenous endophthalmitis pathogen distribution of vitreous cultures in different studies.

Pathogens	Current study (n = 90)	Benz[29] (n = 24)	Schiedler[20] (n = 21)	Jackson[3] (n = 342)	Wu[4] (n = 22)	Nishida[2] (n = 6)[a]	Connell[1] (n = 41)	Zhang[9] (n = 15)[b]
Gram positive								
MSSA	1 (1.1%)	4 (16.6%)	3 (14.3%)	33 (10%)	1 (4.5%)	1 (16.7%)	3 (7.3%)	2 (13.3%)
MRSA	3 (3.3%)		2 (9.5%)					
Enterococcus faecalis or faecium	3 (3.3%)							
CoNS	6 (6.7%)	4 (16.6%)				1 (16.7%)	1 (2.4%)	1 (6.7%)
Streptoccous pneumoniae	4 (4.4%)	1 (4.1%)		17 (5%)	1 (4.5%)			1 (6.7%)
Group B Streptoccous	4 (4.4%)	2 (8.3%)			1 (4.5%)	1 (16.7%)		1 (6.7%)
Unspecified streptococcus		1 (4.1%)	2 (9.5%)	44 (13%)	1 (4.5%)			
MSSA + Group B Streptoccous	1 (1.1%)				1 (4.5%)			
MRSA + Group B Streptoccous	1 (1.1%)							
Others		2 (8.3%)		32 (9%)			2 (4.9%)	
Gram negative								
Klebsiella pneumonia	31 (34.4%)		1 (4.7%)	93 (27%)	8 (36.4%)	2 (33.3%)	4 (9.8%)	
Escherichia coli	2 (2.2%)			23 (7%)	2 (9.1%)	1 (16.7%)		
Pseudomonas aeruginosa	11 (12.2%)			20 (6%)			1 (2.4%)	
NFGNB	3 (3.3%)							
Stenotrophomonas maltopilia	1 (1.1%)							
Others				28 (8%)	1 (4.5%)		3 (7.3%)	
Fungus								
Candida albicans	6 (6.7%)	3 (12.5%)	7 (33.3%)		5 (22.7%)		15 (36.6%)	7 (46.7%)
Candida parasilosis	1 (1.1%)							1 (6.7%)
Unspecified Candida sp	1 (1.1%)						6 (14.6%)	
Acremonium	1 (1.1%)							
Cladosporium	1 (1.1%)							
Penicillium	1 (1.1%)							
Pseudoallescheria boydii	1 (1.1%)		1 (4.7%)					
Chrysonilia	1 (1.1%)							
Aspergillus		5 (20.8%)	4 (19.0%)		1 (4.5%)		1 (2.4%)	2 (13.3%)
Others	1 (1.1%)	1 (4.1%)	1 (4.7%)				5 (12.2%)	
Polymicrobial								
K. pneumonia, CoNS	1 (1.1%)							
CoNS, *Pseudomonas fluorescens*	1 (1.1%)							
Aerococcus, GPB, *C. parasilosis*	1 (1.1%)							
P. aeruginosa, Rhizopus	1 (1.1%)							

[a] Total 21 patients, with 6 positive vitreous/aqueous cultures.
[b] Total 19 patients, with 15 positive vitreous/aqueous cultures.
Abbreviations.
MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; CoNS, Coagulase negative Staphylococcus; NFGNB, Glucose non-fermenting Gram negative bacilli; GPB, Gram positive bacilli.

film, urinalysis, echocardiography and if indicated, whole body imaging. Among the remaining patients with an extra-ocular focus, liver abscess was the most common associated infection (25.1% of the total study population). The rate of concurrent liver abscess and endogenous endophthalmitis was similar to that in previous studies from China, Hong Kong, Korea, but much higher than those observed in Japan and Australia.[1,2,4,8,9] Other infection foci include respiratory, biliary, genitourinary, bloodstream and infective endocarditis; all of them account for a minority of extra-ocular foci. Forty-four patients in the vitreous culture negative group also had no identifiable extraocular infection foci. These "double negative" patients accounted for 25.1% of the total cohort. The "double negative" rates were seldom reported even in the large report by Jackson et al., In 2011, Cornell et al. reported a series with 64 cases, in which 6 patients had no extraocular foci as well as negative vitreous culture (9.3%). The differences between these "double negative" rates were not clear; however, how to infer an "extraocular focus" in the absence of positive vitreous culture may matter.

The presenting VA is positively correlated with post-treatment VA, especially when the logMAR scale is used for VA assessment. Nishida et al. and Sheu identified the same correlation in smaller studies.[2,10] This correlation has two possible explanations. First, patients who present at an earlier stage of infection may have better initial VA, and therefore a better post-treatment VA because of early intervention and control of infection. Second, patients may have worse VA at baseline because of comorbidities such as DM or hypertension and they therefore cannot achieve a visual outcome that is better than their baseline, even with early and aggressive treatment. The accuracy of both hypotheses to the correlation between presenting and post-treatment VA could not be fully confirmed by our data, because most patients did not have a baseline VA record before hospitalization, making difficult analysis of the extent of eye structure destruction and the effectiveness of treatment. This fact represents a limitation of our study.

This study supports the finding that early, aggressive treatment with IVI may reduce the risk of enucleation or evisceration, but no association between TPPV and visual outcome was identified. Jackson et al. reviewed 342 historically reported cases and concluded that early treatment with an intravitreal antibiotic may reduce the risk of enucleation.[3] Although vitrectomy is frequently used in post-operative bacterial endophthalmitis or fungal endophthalmitis, its usefulness in endogenous bacterial endophthalmitis remains unclear and typically depends on the clinician's judgment.[17,18,27] A small series (ten eyes) that was reported by Yoon et al. revealed that early vitrectomy with intravitreal antibiotic may improve the visual outcome in endogenous Klebsiella endophthalmitis.[21] Romero et al. suggested vitrectomy in cases of severe vitreous involvement, infection with a virulent organism, or presentation with a VA of worse than 20/400 (equivalent to 6/120 or logMAR 1.30).[30]

This work has limitations. First, its retrospective design did not permit the direct inference of the causal relationship between clinically important factors and the final outcome. Second, this study was performed in a single, tertiary medical center, leading to possible bias because patients who suffer less severe infection were therefore not included. However, this study, involving many consecutive cases, still provides important therapeutic information about the outcome of endogenous endophthalmitis.

In conclusion, this study revealed that endogenous fungal endophthalmitis has better post-treatment visual outcomes than bacterial endophthalmitis. The visual outcome of endogenous endophthalmitis is better in patients with more preserved VA at presentation. DM is the most common associated comorbidity, and *K. pneumoniae* endogenous endophthalmitis is most frequently associated with liver abscess as the extra-ocular infection focus. Early intravitreal antibiotic treatment may reduce the risk of enucleation/evisceration. Since endogenous endophthalmitis has devastating consequences, clinicians should promptly refer patients to an ophthalmologist when they have any suspicion thereof.

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Ethic statement

This study was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital, approval number: 201600974B0.

Declaration of competing interest

The authors declared no conflict of interests.

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