

# Pathogenic Organisms and Prognostic Factors of Visual Outcome in Endogenous Endophthalmitis

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**Objective:** To identify pathogenic organisms and prognostic factors associated with the visual outcome in endogenous endophthalmitis patients.

**Materials and Methods:** A retrospective review of medical record from 65 patients diagnosed with endogenous endophthalmitis at Department of Ophthalmology, Siriraj Hospital, Thailand between January 2003 and December 2014 was done.

**Results:** There were 68 eyes from 65 patients diagnosed with endogenous endophthalmitis. Seventy-six percent of patients had initial visual acuity [VA] ranging between hand motion [HM] and light perception. Diabetes mellitus [DM] was the most common underlying disease. The pathogenic organisms could be identified in 48 cases (70.6%). The identified pathogenic organisms were gram-positive bacteria 39.7%, gram-negative bacteria 23.5%, fungus 1.5%, and mixed organisms 5.9%. Most of the pathogenic organisms were *Streptococcus* spp. (23.5%) and *Klebsiella pneumoniae* (13.2%). Patients who were treated with vitrectomy have 30% lower rate of enucleation compared to patients who were not treated with vitrectomy ( $p = 0.007$ ). Among the prognostic factors, good initial VA (better than HM) was significantly related to a successful VA outcome (VA better than HM,  $p$ -value <0.001). Nevertheless, approximately 70% of the patients had VA outcome worse than counting finger.

**Conclusion:** The trend of pathogenic organisms may be changing from the past, as the authors found the increasing ratio of gram-positive bacteria over 12 years. Although the patients were treated with sufficient anti-infective agents, most of the visual outcome was poor. Good initial VA was a significant prognostic factor for the visual outcome and vitrectomy could reduce rate of enucleation.

**Keywords:** Endogenous endophthalmitis, Pathogenic organisms, Risk factors, Treatment, Vitrectomy, Enucleation

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Endogenous endophthalmitis is an ophthalmic infectious condition of the intraocular cavities. It is caused by hematogenous spreading of pathogens from primary site of infection that cross blood retinal barrier to the affected eye. About two to eight percent of all endophthalmitis cases were caused by endogenous spreading<sup>(1-3)</sup>. Although endogenous endophthalmitis is considered a relatively rare disease, it is severe and may lead to serious results. Most patients lost their vision at the end of the treatment.

Common pathogens in endogenous endophthalmitis are gram-negative bacteria, gram-positive bacteria, and fungus. Common pathogens in Western countries are gram-positive bacteria and fungus such as *Staphylococcus* spp., *Streptococcus* spp., and *Candida*

*albicans*. On the other hand, gram-negative bacteria such as *Klebsiella pneumoniae* are predominated in East Asia<sup>(1-6)</sup>.

In Southeast Asia, there are only a few studies of endogenous endophthalmitis. The data of common pathogen and trend of organisms are insufficiently investigated. The purpose of the present study was to explore the pathogenic organisms, trend of organisms, clinical features, treatment, and outcome of endogenous endophthalmitis patients during 12-year period at Siriraj Hospital, which is one of the tertiary care centers in Thailand. To the best of the authors knowledge, this was the largest epidemiological study of endogenous endophthalmitis in Southeast Asia.

## Materials and Methods

### Study subjects

The authors accessed medical records of 12 years, between 2003 and 2014 at Siriraj Hospital, Thailand. The inclusion criteria were the in-patients diagnosed

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with endogenous endophthalmitis by ophthalmologists and admitted at the Department of Ophthalmology, Siriraj Hospital between January 2003 and December 2014. The exclusion criteria were patients presenting with a history of ocular trauma or that underwent recent intraocular surgery within one year before being diagnosed endogenous endophthalmitis. The authors also excluded patients with evidence of primary external ocular infection such as infectious keratitis or bleb related infection. The present study was approved by the Siriraj Ethics Committee in December 2014 (EC number 818/2557).

### Data collection and statistical analysis

The authors recorded demographic data of the patients, underlying medical conditions, duration of symptoms before diagnosis, presenting symptoms, microbiological profiles, source of infection, initial treatment modality, and initial and final visual acuity [VA]. A best-corrected VA of better than hand motion [HM] was classified as being a good visual outcome.

Data were analyzed using PASW statistics 18.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were described as mean and standard deviation [SD] or median and range, as appropriated. Frequency and percentage were expressed for qualitative data. Mann-Whitney U test was used to compare quantitative data between VA equal or smaller than HM and VA greater than HM. Qualitative data were compared using Chi-square test or Fisher's exact test. Binary logistic regression was used to examine prognosis factors associated with VA outcome. Odds ratio was used to evaluate the strength of association between prognostic factors and VA outcome. All tests of significance were two tailed, and *p*-value smaller than 0.05 was considered as statistically significant.

### Results

There were 485 endophthalmitis patients over the 12-year study period. The present study included 65 patients with 68 eyes that passed the inclusion criteria for analysis. The median age of the 65 patients was 52 years (range 4 to 89 years old). Sixty percent of the patients were male and 40% were female. The right and left eye were involved in 34 cases (52%) and 28 cases (43%), respectively. There was bilateral involvement in three patients (5%). Of the 65 patients, 22 patients (34%) came directly to Siriraj Hospital and 43 patients (66%) were referred from other hospitals.

Seventy percent of patients had one or more underlying medical conditions. The most common

underlying disease of patients was diabetes mellitus [DM] (39%), followed by liver disease (17%). Valvular heart disease and patients on immunosuppressive drug were found 5% equally. Thirty percent of patients had no underlying disease.

Presenting symptoms were blurred vision (82%), eye pain (65%), and eye redness (52%). About 40% of patients had fever. The median duration from the onset of ocular signs or symptoms to the diagnosis of endogenous endophthalmitis was 6.5 days (range 1 to 60 days).

The initial VA of the 68 eyes was mostly between HM and light perception (51 eyes, 75%), better than HM was 10 eyes (15%) and no light perception at initial visit was six eyes (9%). One patient could not evaluate initial VA due to severe mental retardation (Table 1).

The initial diagnosis of patients was done by ophthalmologist at Siriraj Hospital or ophthalmologist at primary care unit who referred patients to Siriraj Hospital. Majority of the patients were diagnosed with endogenous endophthalmitis at first visit (44 eyes, 65%), however 24 eyes (35%) were misdiagnosed. The most common misdiagnosis was uveitis (22 eyes, 32%). Two eyes were diagnosed with cataract and neovascular glaucoma with hyphemia.

The immediate treatment at Siriraj Hospital after diagnosed were intravitreal [IVT] anti-infectious agents combined with systemic anti-infectious agents

**Table 1.** Characteristics of patients

Characteristics	65 cases (68 eyes)
Age (year), median (min-max)	52 (4 to 89)
Gender, n (%)	
Male	39 (60.0)
Female	26 (40.0)
Eye involvement, n (%)	
Right	34 (52.3)
Left	28 (43.1)
Both	3 (4.6)
Initial VA, n (%)	
6/60 or better	(67 eyes)
6/240 to 6/76	3 (4.5)
CF	2 (3.0)
PL to HM	5 (7.5)
No PL	51 (76.1)
	6 (9.0)
Final VA, n (%)	
6/60 or better	12 (17.6)
6/240 to 6/76	3 (4.4)
CF	5 (7.4)
PL to HM	14 (20.6)
No PL	34 (50.0)

n = number; CF = counting fingers; HM = hand motion; PL = light perception; No PL = no light perception

**Table 2.** Pathogenic organisms

Organism	No. of eye (%)
Unidentified	20 (29.4)
Gram-positive	27 (39.7)
<i>Streptococcus agalactiae</i>	7 (10.3)
<i>Staphylococcus aureus</i>	5 (7.4)
<i>Streptococcus pneumoniae</i>	4 (5.9)
<i>Streptococcus</i> spp.	2 (2.9)
<i>Streptococcus mitis</i>	2 (2.9)
<i>Streptococcus epidermidis</i>	1 (1.5)
<i>Staphylococcus</i> spp.	1 (1.5)
<i>Bacillus cereus</i>	1 (1.5)
<i>Enterococcus</i> spp.	4 (5.9)
Gram-negative	16 (23.5)
<i>Klebsiella pneumoniae</i>	9 (13.2)
<i>Escherichia coli</i>	2 (2.9)
<i>Haemophilus influenzae</i>	2 (2.9)
<i>Pseudomonas aeruginosa</i>	1 (1.5)
<i>Brucella</i> spp.	1 (1.5)
<i>Aeromonas hydrophilla</i>	1 (1.5)
Fungus	1 (1.5)
<i>Candida albicans</i>	1 (1.5)
Mixed organisms	4 (5.9)
<i>Acinetobacter baumannii</i> + <i>Corynebacterium</i> spp.	1 (1.5)
<i>Staphylococcus aureus</i> + <i>Escherichia coli</i>	1 (1.5)
<i>Prevotella</i> spp. + <i>Penicillium</i> spp.	1 (1.5)
<i>Staphylococcus aureus</i> + <i>Enterococcus faecalis</i>	1 (1.5)

**Table 3.** Pathogenic organisms in diabetes mellitus patients

Organism	No. of eye
Unidentified	10
Gram-positive	10
<i>Staphylococcus aureus</i>	3
<i>Staphylococcus</i> spp.	1
<i>Streptococcus agalactiae</i>	1
<i>Streptococcus</i> spp.	1
<i>Enterococcus</i> spp.	2
<i>Bacillus cereus</i>	1
<i>Haemophilus influenzae</i>	1
Gram-negative	5
<i>Klebsiella pneumoniae</i>	4
<i>Escherichia coli</i>	1
Fungus	1
<i>Candida albicans</i>	1
Mixed organisms	1
<i>Acinetobacter baumannii</i> + <i>Corynebacterium</i> spp.	1

in 36 cases. Twenty-one cases received only systemic anti-infectious agents. Eight cases were treated only IVT anti-infectious agents. Only one case was treated with IVT anti-infectious agents combined with pars plana vitrectomy [PPV], and two cases received combination of IVT anti-infectious agents, systemic anti-infectious agents, and PPV.

To identify pathogenic organism, all 68 cases from 65 patients underwent microbiological culture or

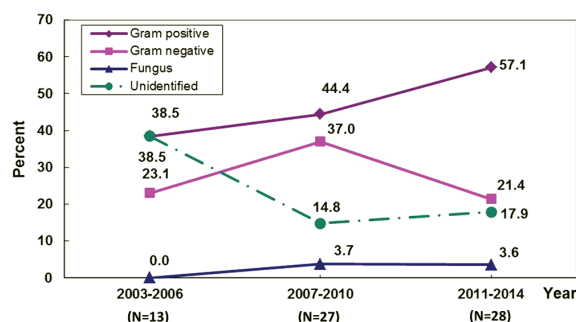
primer specific polymerase chain reaction [PCR] from various specimens depending on suspicious primary site of infection. The organisms were identified in 41 eyes (60%). Of these, identification of organisms was found in vitreous, aqueous and eye globe in 31 eyes, 9 eyes and one eye, respectively. The organisms were identified from blood culture in 14 cases and from others specimen in 10 cases, such as pus from liver abscess 3 cases, synovial fluid culture 1 case, urine culture 2 cases, pus from soft tissue infection 3 cases, and from tooth swab 1 case. However, there were 20 cases (29.4%) that all microbiologic culture or microbial DNA detection from PCR were negative.

The most common pathogenic organism was gram-positive bacteria (27 cases, 39.7%), predominated with *Streptococcus* spp. followed by *Staphylococcus aureus*. Gram-negative bacteria were identified in 16 cases (23.5%). The most common was *K. pneumoniae*. Only one case was infected with *C. albicans* (1.5%). However, there were four patients with mixed organism infection (Table 2).

In DM patients, the gram-positive bacteria were predominately found resembling the other patients, although the most common pathogenic organism was *K. pneumoniae* (Table 3).

In the present study, the authors divided the time of the study into 3 periods (2003 to 2006, 2007 to 2010, and 2011 to 2014) to show the trend of pathogenic organism. The incidence of endogenous endophthalmitis caused by gram-positive bacteria was increasing over the 12-year period of the study as shown in Figure 1.

Urinary tract infection was the most common source of infection (6 patients), follow by gastrointestinal tract infection (4 patients), whereas liver abscess was found in 3 patients. One of the patients had catheter related infection. However, the source of infection could not be identified in 37 cases (56.9%) (Table 4).

**Figure 1.** Trend of pathogenic organisms.

The visual outcome of patients was better than HM in 20 cases (29%), between HM and light perception in 14 cases (21%), no light perception in 34 cases (50%).

**Table 4.** Source of infection

Source of infection	No. of patient (%)
UTI	6 (9.2)
GI tract infection	4 (6.2)
Liver abscess	3 (4.6)
Skin and soft tissue infection	3 (4.6)
Dental caries	3 (4.6)
Septic arthritis	3 (4.6)
Osteomyelitis	1 (1.5)
Meningitis	1 (1.5)
Sinusitis	1 (1.5)
Otitis media	1 (1.5)
Infectious endocarditis	1 (1.5)
Catheter related infection	1 (1.5)
Unknown	37 (56.9)

UTI = urinary tract infection; GI = gastrointestinal

Compared with the initial VA of each patient, 19 cases (28%) had improved VA, 10 cases (15%) had the same VA, 23 cases (34%) had worse VA without enucleation, 15 cases (22%) were end up with enucleation and no death in the present study.

The authors also analyzed factors that could be associated with enucleation. The patients underwent Par plana vitrectomy had rate of enucleation less than patients who did not undergo par plana vitrectomy with statistical significance (0% vs. 30%,  $p = 0.007$ ).

The prognostic factor that could predict the good visual outcome (VA better than HM) with statistical significant ( $p < 0.001$ ) was good initial VA (VA better than HM). Fungal infection showed slightly better visual outcome than other organisms, although, there was no statistical significant (10% vs. 0%,  $p = 0.083$ ). Other prognostic factors, for example, diabetic status, others underlying medical condition, HbA1C level, gram-positive or gram-negative bacterial infection, or initial treatment modality were not associated with visual outcome (Table 5).

**Table 5.** Prognostic factors associated with good visual outcome

Factors	Final visual outcome		<i>p</i> -value	Odds ratio (95% CI)	<i>p</i> -value
	VA > HM (n = 20)	VA ≤ HM (n = 48)			
Liver disease, n (%)			0.737		
No	16 (80.0)	40 (83.3)		1.00	
Yes	4 (20.0)	8 (16.7)		1.25 (0.33 to 4.74)	0.743
Valvular heart disease, n (%)			0.205		
No	18 (90.0)	47 (97.9)		1.00	
Yes	2 (10.0)	1 (2.1)		5.22 (0.45 to 61.20)	0.188
On immunosuppressive Rx, n (%)			0.205		
No	18 (90.0)	47 (97.9)		1.00	
Yes	2 (10.0)	1 (2.1)		5.22 (0.45 to 61.20)	0.188
Diabetes mellitus, n (%)			0.786		
No	13 (65.0)	28 (58.3)		1.00	
Yes	7 (35.0)	20 (41.7)		0.75 (0.26 to 2.23)	0.609
HbA1C (%)	(n = 7)	(n = 16)			
Median (min, max)	6.8 (6.2, 14.1)	7.4 (5.5, 15.1)	0.763	0.99 (0.70 to 1.40)	0.943
Initial visual acuity, n (%)			<0.001		
≤ HM	11 (55.0)	46 (97.9)		1.00	
> HM	9 (45.0)	1 (2.1)		37.64 (4.31 to 329.03)	0.001
Gram positive, n (%)			1.000		
No	10 (50.0)	25 (52.1)		1.00	
Yes	10 (50.0)	23 (47.9)		1.09 (0.38 to 3.09)	0.876
Gram-negative, n (%)			1.000		
No	14 (70.0)	35 (72.9)		1.00	
Yes	6 (30.0)	13 (27.1)		1.15 (0.37 to 3.64)	0.807
Fungus, n (%)			0.083		
No	18 (90.0)	48 (100)		N/A	N/A
Yes	2 (10.0)	0 (0.0)			

HM = hand motion; VA = visual acuity; Rx = treatment; N/A = not applicable

## Discussion

Endogenous endophthalmitis is an ocular infection. Hosts with underlying medical condition causing a relative immunocompromised state are a common association such as DM, liver disease, and autoimmune disease reported in many previous studies<sup>(3-5,7-9)</sup>. In the present study, DM is the most common underlying medical condition. The authors tried to find out the association of blood sugar control by using HbA1C level in diabetes patients and visual outcome but there was no significant association.

Endogenous endophthalmitis is infectious condition of the intraocular cavities induces inflammatory process, so the symptoms of patients were eye pain, eye redness and blurred vision from cells in anterior chamber or vitreous. In current study, the mean duration of symptom and the diagnosis of endogenous endophthalmitis was 6.5 days, but the range was relatively wide (1 to 60 days). Most of the patients who had delayed diagnosis had been misdiagnosed as uveitis. Moreover, in the present study, 22 cases (32%) were misdiagnosed as uveitis similar to the previous studies<sup>(3,10,11)</sup>. Because the inflammation in the eye can be found in both uveitis and endogenous endophthalmitis, it is difficult to make a correct diagnosis at the initial visit in patients who look healthy and have few systemic symptoms.

In the 68 eyes of 65 patients, extraocular infectious foci were identified in 43%. Urinary tract infection was the most common infection follow by gastrointestinal infection and liver abscess. Okada et al<sup>(5)</sup> reported that the most common site of endogenous endophthalmitis was infective endocarditis but in the current study, the authors found only one case of infective endocarditis. Many studies in Asia<sup>(4,6,7,12)</sup> reported endogenous endophthalmitis caused by *K. pneumoniae* from liver abscess were the most common pathogenic organism and source of infection. In the present study, all patients with liver abscess were caused by *K. pneumoniae*. However, there were only three patients with liver abscess.

Although pathogenic organism in North American and European were predominantly gram-positive, and predominantly gram-negative in Asia. The present study was different, gram-positive bacteria were the predominant organism in patients with endogenous endophthalmitis. In previous study from Thailand, Somsiri et al<sup>(9)</sup> reported gram-positive bacteria were the predominant infection. Thus, it could be said that in Thailand, gram-positive bacterial infection in endogenous endophthalmitis had higher incidence than

gram-negative bacterial infection. The most common organism was group B streptococci (seven eyes). In contrast to Lee and Chee<sup>(13)</sup> study that found that group B streptococci infection was rare. The second common pathogenic organism was *S. aureus*. Fortunately, all cases were methicillin-susceptible *S. aureus* [MSSA] strain. Moreover, the trend of pathogenic organisms in the past 12 years of our study, the incidence of endogenous endophthalmitis caused by gram-positive bacteria, especially gram-positive cocci, was increasing over the 12-year period of the study.

And unidentified organism was decreased due to improvement in collecting specimen, laboratory culture process, and the PCR technology.

Most patients were treated with systemic anti-infectious agents combined with IVT anti-infectious agents. Drugs of choice at initial treatment were broad spectrum antibiotic such as vancomycin combined with ceftazidime. After bacterial sensitivity was reported, antibiotics were changed as appropriate. In Zhang and Wang<sup>(14)</sup> study, patients who underwent PPV had better visual outcome as vitrectomy can reduce the burden of microorganisms and inflammatory mediators present in the vitreous cavity. Eighty percent of patient in Zhang and Wang study had visual outcome better than HM and the rate of enucleation was reduced<sup>(14)</sup>. Eighteen patients in the present study underwent PPV, only 39% of patients had visual outcome better than HM. Nevertheless, in our study patients who underwent PPV had a reduced rate of enucleation to 30% compared with patients who did not received PPV treatment.

In the present study, a final VA of better than HM was achieved in 29% of the cases thus, endogenous endophthalmitis had a poor visual outcome. Our results revealed that initial VA is a strong prognosis of final visual outcome consistent with previous studies<sup>(1,6-8,11,12,15)</sup>. It maybe implied that decreased VA in endogenous endophthalmitis is mainly caused by direct injury to retinal tissue, which cannot be regenerated. Therefore, early diagnosis and early treatment may help patients save their remaining vision.

The present study had several limitations, including being retrospective, non-randomized and the wide inclusion criteria that enrolled patients with culture negative. In addition, the present study included only patients who were admitted at the ophthalmology department, so the patients with critical illness admitted to other departments were not included in the study. Consequently, randomized prospective studies are needed to define prognostic factors and the efficacy of therapeutic interventions in patients with endogenous



endophthalmitis.

## Conclusion

The trend of pathogenic organisms may be changing from the past as the authors found the increasing ratio of gram-positive bacteria in endogenous endophthalmitis. Although the patients were treated with sufficient anti-infectious agents, most of the visual outcomes were poor. PPV may reduce rate of enucleation. Good initial VA was a significant prognostic factor for the visual outcome. Early diagnosis and early treatment of endogenous endophthalmitis prior to deterioration of vision is recommended.

## What is already known on this topic?

Endogenous endophthalmitis is an ophthalmic infectious disease. Although endogenous endophthalmitis is considered a relatively rare disease, it is severe and may lead to serious results. Most patients with the disease lost their vision at the end of the treatment.

Common pathogens in endogenous endophthalmitis are gram-negative bacteria, gram-positive bacteria, and fungus. In many previous studies showed common pathogens in Western countries are gram-positive bacteria and fungus such as *Staphylococcus* spp., *Streptococcus* spp., and *C. albicans*. On the other hand, gram-negative bacteria such as *K. pneumoniae* are predominated in East Asian country.

## What this study adds?

The authors found that the common pathogenic organisms were gram-positive bacteria, which is different from previous papers that reported in Asian countries that the common organisms were gram-negative bacteria. This result is important in selecting the empirical antibiotic.

Patients who underwent vitrectomy in the course of treatment could reduce the rate of enucleation significantly. The result of the reduction rate of enucleation in patients that underwent vitrectomy changed the trend of treatment modality in this disease. Previously, anti-infectious agents were the leading role of treatment.

Nevertheless, this study will provide additional important information of endogenous endophthalmitis to other population, especially, in South East Asian countries that have only a few studies of endogenous endophthalmitis.

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## Potential conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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