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Paediatric endophthalmitis: a 10-year retrospective study at Hospital Kuala Lumpur for incidence, risk factors, and outcomes

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Abstract

Purpose: Paediatric infectious endophthalmitis is a serious sightthreatening disease for children. The purpose of this study was to investigate the incidence, aetiology, microbiological spectrum, management, and visual outcomes of infectious endophthalmitis in children referred to the Department of Ophthalmology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia.
Study design: Retrospective study.
Methods: The medical records of all patients under 18 years of age with histories of endophthalmitis treated at Hospital Kuala Lumpur from January 2009 to December 2018 were reviewed. The clinical characteristics, aetiology, microbiological spectrum, management, as well as the visual outcomes were analysed.
Results: A total of 23 children were identified, with a mean age of 3.15 (ranging from 20 days to 8 years of age). Previous ocular surgery (47.8%) and ocular trauma (30.4%) were the most common causes of endophthalmitis. Overall, eight (38.1%) cases with positive cultures were identified. The most commonly identified organism was *Staphylococcus* sp. comprising 50% of the isolates. Moreover, five isolates (62.5%) were grampositive organisms and three isolates (37.5%) were gramnegative organisms. The final visual outcome was 20/200 or better in one eye (4.3 %), hand movement in two eyes (8.7%), light perception in five eyes (21.7%), and no

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light perception in 13 eyes (56.5%). The visual outcome was not available for two patients (8.7%).
Conclusions: Previous ocular surgery and penetrating ocular trauma are the most frequent causes of paediatric endophthalmitis in our centre. *Staphylococcus* sp. was the most commonly identified organism in paediatric endophthalmitis. In this study, despite aggressive management with intravitreal antibiotics and vitrectomy, the visual prognosis was found to be generally poor.

Keywords: intravitreal antibiotics, Malaysia, paediatric endophthalmitis, visual acuity, vitrectomy

Endoftalmitis dikalangan kanak-kanak: kajian retrospektif selama 10 tahun di Hospital Kuala Lumpur

Abstrak

Tujuan: Endoftalmitis akibat jangkitan kuman dikalangan kanak-kanak merupakan penyakit serius yang mengancam penglihatan mereka. Tujuan kajian ini adalah untuk menyelidik kejadian, etiologi, spektrum mikrobiologi, rawatan dan penglihatan akhir jangkitan endoftalmitis di antara kanak-kanak yang dirujuk ke Jabatan Oftalmologi, Hospital Kuala Lumpur.
Kaedah kajian: Retrospektif.
Metodologi: Kajian ini berdasarkan rekod perubatan ke atas semua pesakit di bawah 18 tahun yang mempunyai sejarah endoftalmitis akibat jangkitan kuman, yang menjalani rawatan di Hospital Kuala Lumpur dari Januari 2009 sehingga Disember 2018. Manifestasi klinikal, etiologi, spektrum mikrobiologi, rawatan, dan juga ketajaman penglihatan terakhir telah dianalisakan.
Keputusan: Sejumlah 23 orang kanak-kanak telah dikenal pasti dengan purata usia 3.15 tahun (lingkungan antara 20 hari hingga 8 tahun). Endoftalmitis paling kerap terjadi selepas pembedahan okular (47.8%) dan trauma melibatkan tisu okular (30.4%). Kultur positif telah dikenalpasti dari lapan (38.1%) kes. Bakteria yang paling kerap dikenal pasti ialah *Staphylococcus* sp. (50%). Dari 8 kes berkultur positif, 5 (62.5%) adalah gram-positif dan 3 (37.5%) adalah gram-negatif. Ketajaman penglihatan terakhir adalah seperti berikut: 1 (4.3%) mata ≥ 20/200, 2 (8.7%) mata hanya dalam melihat pergerakan tangan, 5 (21.7%) mata hanya dapat mengamat cahaya dan 13 (56.5%) mata hilang penglihatan. Terdapat 2 pesakit yang ketajaman penglihatan terakhir tiada dalam rekod.
Kesimpulan: Kanak-kanak yang mempunyai sejarah pembedahan dan trauma

menglibatkan tisu okular adalah lebih kerap mendapat endoftalmitis akibat jangkitan. *Staphylococcus sp* adalah organisma yang paling kerap dikenal pasti. Dalam kajian ini, walaupun rawatan agresif dengan pemberian antibiotik secara intravitreal dan pembedahan vitrektomi, prognosis penglihatan secara keseluruhannya didapati kurang memuaskan.

Kata kunci: antibiotik intravitreal, endoftalmitis pada kanak-kanak, ketajaman penglihatan, Malaysia, vitrektomi

Introduction

Paediatric endophthalmitis is a devastating condition and a serious complication that may follow intraocular surgery, systemic infection, or penetrating ocular trauma. Open-globe injuries and glaucoma surgery are among the most common causes of paediatric endophthalmitis, whereas endogenous infection is the least common cause.[1-3] Unlike adults, who might complain of pain or blurred vision, children might not be able to either recognize or explain their symptoms, so it is more difficult to provide prompt diagnosis and treatment in the paediatric age group.

The reported incidence of paediatric endophthalmitis following cataract surgery ranges from 0.38% to 0.45%.[4] The incidence of paediatric post-traumatic endophthalmitis is estimated at 2.8–54.2%, which varies by country,[5,6] whereas, paediatric endogenous endophthalmitis is rare and constitutes only 0.1–4% of all endophthalmitis cases.[7]

Worldwide, infectious endophthalmitis is a rare but serious disease that frequently has a poor visual prognosis.[2,3] However, it is not as common in the paediatric age group as in adults, and less research has been devoted to this group. Available literature on paediatric endophthalmitis is limited and, to date, no studies on paediatric endophthalmitis have been conducted in Malaysia.

The aim of this study was to provide data on the incidence, aetiology, microbiological spectrum, management, and visual outcomes of infectious endophthalmitis in children referred to the Department of Ophthalmology of Hospital Kuala Lumpur, (HKL) Kuala Lumpur, Malaysia.

Methods

This was a retrospective observational study performed at the Department of Ophthalmology of HKL, which is the main tertiary referral centre for paediatric ophthalmology in Malaysia. We reviewed the medical records of patients 18 years and below with diagnosis of endophthalmitis who were seen and referred to the centre from

January 2009 to December 2018. Ethical approval for this study was obtained from Clinical Research Centre, HKL and Medical Research and Ethics Committee, Ministry of Health, Malaysia.

We retrieved records of 23 patients. All names and identification number of these patients were traced from the operation theatre and ward admission census and the medical records were retrieved from the record office. Information from both inpatient and outpatient records, including demographics, aetiology, underlying systemic and ocular comorbidities, time interval from the onset of ocular symptoms to presentation, clinical symptoms and signs, B scan findings, surgical procedures, vitreous and aqueous culture results, follow up treatment, complications, and final visual acuity were collected and recorded into the data collection sheet.

Statistical analysis

Data was analysed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive data was expressed as mean ± standard deviation (SD) for numerical data, and categorical variables were presented in frequencies and percentages. Statistical analysis was performed using Fischer's exact test for potential factors associated with phthisical eyes. $P < 0.05$ was considered significant.

Table 1. Demographic data of children with endophthalmitis

Parameter	***N* (%)**
Ethnicity	
Malay	15 (65.2)
Indian	4 (17.4)
Chinese	2 (8.8)
Orang asli	1 (4.3)
Others	1 (4.3)
Gender	
Female	8 (34.8)
Male	15 (65.2)
Age (years)	Mean: 3.15 (SD: 2.536)
Less than 1	6 (26.1)
1–5	11 (47.8)
6–8	6 (26.1)
9–18	0 (0)

Results

Demographic data

From this study, a total of 23 eyes of 23 children were identified. There were eight females (34.8%) and 15 males (65.2%) identified with a mean age of 3.15 years old (range, 20 days old to 8 years old). The racial distribution reflected the multiracial population in our country, with 15 Malay children (65.2%), four Indians (17.4%), two Chinese (8.8%) and one Vietnamese child. The demographic data are illustrated in Table 1. From these data, we noted that the peak age of incidence was 1–5 years of age and more specifically 2–3 years of age.

Aetiology

The aetiologies of paediatric endophthalmitis in this study are illustrated in Table 2, with the most common being previous ocular surgery, accounting for 11 (47.8%) of the 23 cases. Six out of 11 (26.1%) patients had a history of previous cataract surgery. Of these, four patients developed endophthalmitis within a month after surgery and two cases developed endophthalmitis at 5 weeks and 6 months post-

Table 2. Aetiologies of paediatric endophthalmitis

Aetiology	Number of patients, *N* = 23	Percentage (%)
Ocular trauma		
Toy gun pellets	1	4.3
Hair clip	1	4.3
Yoyo	1	4.3
Porcupine quill	1	4.3
Metal wire	1	4.3
Pencil	1	4.3
Others	1	4.3
Previous ocular surgery		
Cataract	6	26.1
Glaucoma	5	21.7
Endogenous		
Infected leg wound from scratch by cat	1	4.3
Thrombophlebitis	1	4.3
Haemophilus influenza meningitis	1	4.3
Respiratory tract infection	1	4.3
Urinary tract infection	1	4.3

operatively. Five out of 11 (21.7%) patients had glaucoma-related procedures, which included trabeculectomy with mitomycin C, Baerveldt tube repositioning, Baerveldt tube removal and reimplantation, and pupilloplasty for pupillary-block glaucoma. Of these five cases associated with glaucoma surgery, four patients developed delayed onset endophthalmitis, ranging from 2 months to 3 years. Risk factors identified in our patients were repeated and prolonged duration of surgery, bathing in well water, swimming at the beach, history of conjunctivitis, lack of proper postoperative care due to the patient being in an orphanage, and use of mitomycin C in filtering surgery.

Ocular trauma was the second leading cause of endophthalmitis in our study, which accounted for seven cases (30.4%). Of these, none had intraocular foreign body. The sources included hair clip, toy gun pellet, yoyo, metal wire, porcupine quill, pencil, and one unknown injury. In this group, the time from onset of ocular trauma to presentation to hospital was within 24 hours in six cases and 24 to 48 hours in one case.

Endogenous causes were the least common in children with five (21.7%) cases, two of which occurred in preterm babies. The primary sources in these cases are shown in Table 2.

A total of 753 paediatric cataract cases and 385 glaucoma-related procedures were performed at HKL from 2009 to 2018. Of the 11 postoperative endophthalmitis cases, ten were operated at HKL, whereas one was operated elsewhere and subsequently referred to HKL for endophthalmitis. The incidence of postoperative endophthalmitis in HKL for cataract cases was 0.6% and for glaucoma-related procedures was 1.3% over 10 years.

Comorbidities, risk factors, and ocular features

Eleven children had no ocular comorbidities, eight (34.8%) had glaucoma, four (17.4%) had congenital cataract, and one had retinopathy of prematurity. Two premature babies had developed endogenous endophthalmitis; the risk factors for these babies were urinary tract infection and *Haemophilus influenza* meningitis.

Most of the children presented with complaints of pain, redness, and eyelid swelling; however, two children were asymptomatic and noted to have low-grade endophthalmitis during their follow-up at the eye clinic. B scans performed in these children showed thickened sclera, loculation, and vitritis. Intraoperatively, these children were mostly found to have hypopyon and vitritis similarly as adults.

The patients' visual acuities (VA) at the time of the initial presentation and final follow-up are illustrated in Table 3. The initial VA could not be obtained because of non-cooperation in ten (43.5%) patients, nine had light perception, and four had hand movement vision. The final VA was recorded at 3 months, 1 year, and at last follow-up at the eye clinic. The final VA was not documented in two (8.7%) patients because these children were referred back to their original hospital for follow up at 1-month postoperative for continuation of care. Of the 23 eyes, only one patient

Table 3. Relationship between initial and final visual acuity

Final VA	Initial VA					
	Not available	**NLP**	**LP**	**HM**	**20/200 or better**	**Total**
20/200 or better	0	0	0	1	0	1
HM	0	0	1	1	0	2
LP	3	0	2	0	0	5
NLP	7	0	4	2	0	13
Not available	0	0	2	0	0	2
Total	10	0	9	4	0	23

VA: visual acuity; NLP: no light perception; LP: light perception; HM: hand movement

who had post-traumatic endophthalmitis achieved final VA of 20/200 or better and 20 patients had a final VA of hand movement or worse. Of the 20 eyes that had an unfavourable functional outcome, 13 (61.9%) eyes had phthisis bulbi. Overall, two patients had improved vision post-treatment and three maintained preoperative vision. Causes of poor vision included corneal scar, band keratopathy post-retinal detachment repair, advanced glaucoma, and macular scar.

Microbiology data

In all, there were eight positive cultures identified from 21 patients during this study. In two patients, the culture findings were not documented. Gram-positive organisms were isolated in five patients (62.5%). The most common organism isolated was coagulase-negative staphylococci, seen in two (8.7%) patients. In the postoperative group, coagulase-negative staphylococci and *Streptococcus pneumoniae* were the most common isolates. In the post-traumatic group, two (28.6%) of seven patients had positive culture results, and the isolated organisms were *Staphylococcus aureus and Enterobacter* sp. In the endogenous group, three of five patients had positive cultures identified, with *S. aureus* as the most common isolate. One patient with endogenous endophthalmitis secondary to urinary tract infection had *Pseudomonas aeruginosa* in urine sample and coagulase-negative staphylococci isolated from vitreous culture. Blood and urine cultures were sent for all patients with endogenous endophthalmitis. The microbiology of causative organisms is summarized in Table 4.

Table 4. Organisms isolated in paediatric endophthalmitis

Organism	Number, *n* = 23	Percentage %
Vitreous culture		
Coagulase-negative staphylococci	2	8.7
Staphylococcus aureus	1	4.3
Streptococcus pneumoniae	1	4.3
Enterobacter sp.	1	4.3
Blood sample		
Staphylococcus aureus	1	4.3
Urine sample		
Pseudomonas aeruginosa	1	4.3
Cerebrospinal fluid		
Haemophilus influenza	1	4.3
No growth	13	56.5
Not documented	2	8.7

Treatment

All patients received intravenous and topical antibiotics as soon as they were treated in HKL, although the antibiotic regime varied as there was no standard paediatric protocol available at the time. Of 23 children, 17 of them received intravenous cephalosporins (ceftazidime/ cephalexin/ ceftriaxone) and 6/23 received intravenous fluoroquinolones (ciprofloxacin).

Vancomycin and ceftazidime were used as intravitreal (IVT) antibiotics. IVT amphotericin B was given to one patient along with vancomycin and ceftazidime as fungal endophthalmitis was suspected. IVT dexamethasone was given to four patients. Primary pars plana vitrectomy (PPV) with IVT injection of antibiotics was directly performed in 19 patients (82.6%) due to severe vitreous inflammation. Four 4 (17.4%) patients were treated with vitreous sampling and IVT antibiotics alone. Of these, three patients presented with low-grade endophthalmitis that responded to IVT antibiotics and one patient had no fundus view due to opaque cornea, thus PPV could not be performed. None of the eyes were eviscerated/ enucleated. The number of IVT injections ranged from one to four.

As for topical antibiotic drops, 16 of the 23 were given topical moxifloxacin 0.5% and dexamethasone 0.1% drops and seven of 23 received topical moxifloxacin 0.5%, gentamicin, and dexamethasone 0.1 % drops.

Of the 19 patients who underwent PPV, nine (47.3%) cases were performed within 24 hours, seven were done within 1–7 days. and three were done after 7 days. Of the

Table 5. Analysis of possible factors associated with phthisical eyes

Variables (n)		**Non-phthisical eye, (*n* = 8)**	**Phthisical eye, (*n* = 13)**	***P****
Culture (21)	Positive (7)	2 (71.4%)	5 (28.6%)	0.656
	Negative (12)	5 (58.3%)	7 (41.7%)	
Time to hospitalization (21)	< 24 hours (12)	6 (50.0%)	6 (50.0 %)	0.274
	1–7 days (2)	1 (50%)	1 (50%)	
	> 7 days (7)	1 (14.3%)	6 (85.7%)	
Time of diagnosis to vitrectomy (18)	< 24 hours (8)	3 (37.5%)	5 (62.5%)	0.999
	> 24 hours (10)	4 (40%)	6 (60.0%)	
Vitrectomy (18)	Vitrectomy (18)	7 (38.9%)	11 (61.1%)	0.999
	No vitrectomy (3)	1 (33.3%)	2 (66.7%)	
Ocular comorbidity (21)	Yes (11)	8 (72.7%)	3 (27.3%)	0.438
	No (10)	6 (60%)	4 (40%)	

* Fischer's exact test

ten patients who had PPV after 24 hours, eight were referred from other hospitals and received multiple IVT injections prior to admission.

Table 5 summarizes the analysis of possible factors associated with phthisical eye using Fischer's exact test. There was no significant association found between culture, time to hospitalization, time from diagnosis to vitrectomy, whether vitrectomy was performed or not, and ocular comorbidities with phthisical eye in our study.

Discussion

In this retrospective study done at the HKL Department of Ophthalmology, 23 cases of endophthalmitis were identified in children under 18 years over a period of 10 years. This relatively low number of cases is consistent with the low rate of this complication. Previous ocular surgery (47.8%) consisting of cataract and glaucoma procedures was the most common causes of endophthalmitis. This is because they are the most common paediatric cases seen and managed at Hospital Kula Lumpur over the past 10 years. This differs from previously published papers by Zhang *et al.*[8] and Thordsen *et al.*,[9] where trauma accounted for a greater proportion of cases of endophthalmitis. The incidence of postoperative endophthalmitis in the study by Thordsen *et al.* was 38%,[9] while it was 3% in Zhang *et al.*[8]

Glaucoma surgery is a well-recognized risk factor for endophthalmitis. Previous studies have shown that endophthalmitis following glaucoma drainage device surgery usually occurs late, months to years after surgery, and is associated with tube repositioning, needling, and implant exposure, which was also seen in four of our patients.[3,9] In a series of 60 paediatric eyes with Ahmed implants, Parvizi *et al.* found that the rates of tube exposure and endophthalmitis were high, at 12% and 3%, respectively.[3] This emphasizes the importance of inspecting the overlying conjunctiva for tube exposure whenever the child is examined and parents being warned should there be only a thin layer of conjunctiva over the tube. The use of a 5% povidoneiodine solution has been proven effective in decreasing the incidence of infectious endophthalmitis.

Ocular trauma was the second leading cause of endophthalmitis, seen in 30.4% of our patients of which most were males (85.7 %). Rishi *et al.* reported almost similar rates (72%) in their series.[6] The higher incidence of traumatic ocular injuries in boys compared with girls puts them at a higher risk of developing endophthalmitis. Delayed repair of penetrating ocular trauma is among the major risk factors for development of infective endophthalmitis. Other risk factors are posterior location of the wound, lens disruption, vitreous prolapse, and eyes with retained intraocular foreign body.[5,10] Among our patients with ocular trauma, 71.4% had traumatic lenticular changes, which is one of the risk factors for developing endophthalmitis. Urgent referral of these cases to vitreoretinal surgeons is mandatory when penetrating eye injury is associated with signs of endophthalmitis. Aggressive management in the form of vitrectomy along with IVT antibiotics in paediatric post-traumatic endophthalmitis cases is associated with better clinical outcomes.[6,10,11]

Endogenous endophthalmitis is a rare but highly destructive infection of the eye, in which the pathogenic organisms reach the eye through the systemic circulation. Studies have shown that endogenous endophthalmitis accounts for 0.1% to 4% of all endophthalmitis cases.[7,12,13] Our study had five (21.7%) patients with endogenous endophthalmitis. It has been reported that the severity and rapidity of the progression of endophthalmitis are associated with the virulence of the infecting organism, and that more virulent organisms such as streptococci and gram-negative species usually lead to worse visual outcomes. However, in children it is not only the microbial virulence and exaggerated inflammatory response, but the inevitable delay in diagnosis and definitive treatment requiring general anaesthetic which are also likely to contribute to the poor outcome.[3,13]

The earliest symptoms of adult endogenous endophthalmitis include pain and decreased visual acuity. In adults, early symptoms may prompt patients to seek medical attention, allowing earlier diagnosis and a good outcome with appropriate management. However, because of poor communication in paediatric patients, it is difficult to diagnose endogenous endophthalmitis at an early stage and it may be misdiagnosed as uveitis, persistent foetal vasculature, cataract, retinopathy of

prematurity, toxocariasis, Coat's disease, retinal detachment, and retinoblastoma.[13] In a study by Basu *et al.*, six premature infants with extremely low birth weight developed endogenous endophthalmitis. They reported *Klebsiella pneumoniae* and *P. aeruginosa* in two cases each and *Candida albicans* and methicillin-resistant *S. aureus* in one case each.[14] Our study had two premature infants, of which one was secondary to urinary tract infection with coagulase-negative staphylococci and the other one was due to *H. influenza* meningitis. Since there is a usually a septic focus, systemic antibiotics seem to play a much definitive role in treatment in endogenous cases.

The most commonly identified organisms in our study were coagulase-negative staphylococci and *S. aureus*, comprising 50% of the isolates, as seen in other studies.[3,8,15] Culture-positive rates have been reported to range from 44% to 75% in Western studies.[11] Narang *et al.* reported 27% culture positivity from ocular specimens in India. In our study, culture positivity rate was 21.7%. The lower culture-positivity rates in our study may be due to the fact that most of the patients had received prior intravenous and IVT antibiotic treatment elsewhere before they were referred to our HKL.[5]

Therapeutic PPV was performed in 82.6% of cases in our study. Eyes with severe forms of endophthalmitis in the paediatric population benefit from PPV. Early PPV drastically decreases the microbiological load and aids the diffusion of IVT and systemic antibiotics within the eye. Patients undergoing PPV were more likely to have good anatomical outcome than those treated with antibiotics alone on presentation.[9,16] However, 13 (61.9%) of our patients had phthisis bulbi as a final outcome despite PPV being performed within 24 hours from diagnosis. The reason for this may be due to unfavourable presentation with corneal abscess, extensive retinal necrosis, subretinal abscess, and retinal detachment, which was noted intraoperatively in these patients. In addition, two of our patients developed retinal detachment post-PPV. It has been reported that corneal abscess and retinal detachment were associated with poor outcomes in children with endophthalmitis.[6] This may explain the poor outcomes in our cohort, where despite early and aggressive treatment, many did not have a favourable outcome.

The visual prognosis in paediatric endophthalmitis is generally poor, with most eyes having no residual functional vision. In our series, 13 (56.5%) cases were left with phthisical eye. Trauma portends a poor prognosis in children due to their greater risk of retinal detachment and subsequent development of proliferative vitreoretinopathy and amblyopia.[17] In contrast to previous reports, our study found that more children in the postoperative group ended resulted in phthisical eye compared to the post-traumatic and endogenous groups.

Study limitations

This study is limited by a retrospective study design of a rare condition. As the data was collected retrospectively, some data was unavailable. Lack of uniform guidelines

and treatment protocols were also limitations. While the study population is diverse, the numbers are small and do not allow for definitive comparison between groups.

Conclusion

This study provides information on a rare but sight-threatening complication in children. Paediatric endophthalmitis differs from adult endophthalmitis in many respects. First, the visual outcomes are generally poor. For some severe cases, even if visual acuity cannot be preserved, efforts should be made to retain the eyeball because eyeball contour is crucial for the development of the orbit and the children's psychological health. Second, diagnosis and treatment are likely to be delayed, as children are usually poor providers of case history, so they might not complain of symptoms promptly. Furthermore, treatment might be delayed by parents or by primary care doctors if the presenting signs are not obvious. Third, the paediatric vitreous cavity is filled with gel, which hinders the dispersion of drugs in the vitreous cavity, and children are more prone to retinal detachment complicated by proliferative vitreoretinopathy.

Treatment of paediatric endophthalmitis remains challenging and the visual prognosis is generally poor. Therefore, prevention of postoperative endophthalmitis is crucial and steps should be taken to reduce its occurrence. Regular maintenance of the air conditioning filters, use of povidone iodine 5% solution in the conjunctival sac a few minutes prior to surgery, proper construction of wound, use of prophylactic intracameral antibiotics or prophylactic subconjunctival antibiotic injection at the conclusion of surgery, and early initiation of topical antibiotics all help lower the frequency of postoperative endophthalmitis. Educating parents about the signs of endophthalmitis, especially lethargy, asymmetrical eye redness, eyelid swelling, and fever as well as proper postoperative care are also important. In the unfortunate event of endophthalmitis in children, prompt administration of systemic antibiotics with good intraocular penetration is more important due to the inevitable delay in arranging for intraocular injections in these group.

It is clear from our study that paediatric endophthalmitis is a serious condition that requires a high index of suspicion in children and aggressive management. We hope that this study will help to diagnose promptly, guide treatment, and improve the prognosis in this unique set of patients in future.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from Clinical Research Centre, HKL and Medical Research and Ethics Committee, Ministry of Health, Malaysia. As this was a

non-interventional, retrospective study, informed consent was not required from subjects and/or their guardians.

Competing interests
None to declare

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None to declare.

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