Understanding and confronting bacterial endophthalmitis

Abdus Samad Ansari highlights the importance of early recognition of this condition using an unusual presentation.

Endophthalmitis is a medical emergency with devastating consequences. Despite adequate treatment, severe cases frequently result in permanent blindness. Endophthalmitis involves inflammation of both the anterior and posterior segments of the eye and is usually secondary to the introduction of an infectious agent; this can be bacterial, fungal or infrequently non-infectious. Aetiological classification separates this into exogenous or endogenous forms with pan-ophthalmitis additionally involving the inflammation of the extraocular structures of the orbit [1]. The blood-ocular barrier functions to avert infiltration from infective organisms. Any disruption in this barrier, whether this be secondary to trauma or the alterations in permeability produced by inflammation poses substantial risk for the development of endophthalmitis. Despite aggressive interventions, both therapeutically and surgically, visual outcomes remain poor. Early detection and postoperative surveillance remain the best options for preventing this destructive condition.

As a clinical diagnosis, endophthalmitis requires empiric treatment once suspected. Intraocular and blood specimens are subsequently used to confirm diagnosis.

Misdiagnosis sadly remains a common occurrence for this visually terminal complication, for seemingly less catastrophic diseases such as uveitis and conjunctivitis [2]. This unfortunate misclassification likely stems from variability in clinical presentation and is reported to be as high as 25% [2]. Despite our efforts, misdiagnosis is an obstacle with severe repercussions to patient recovery. It is vital clinicians and, in particular, trainees establish a clear history and complete a thorough examination to maintain a competent risk stratification approach to endophthalmitis. Patients classically present with symptoms of severe visual disturbance in conjunction with moderate to severe pain. Clinical signs may include that of conjunctival congestion alongside the presence of fibrin deposits, hypopyon and even vitreous opacity. The clinical course is rapid and if the fundus is visualised, it can demonstrate retinal infiltrates and intraretinal haemorrhages.

Don't be caught out! The unusual presentation

A 63-year-old presented to the ophthalmic emergency service with a seven-day history of reduced vision and painless red eye. The patient denied any previous ophthalmic history. Examination revealed the left eye to be markedly injected with anterior chamber inflammation, corneal oedema and vitreous haze. There was normal ocular motility, however, given the marked ocular inflammation the posterior segment could not be visualised. The visual acuity on presentation was noted to be 1.00 logMAR. The patient was systemically well with no history of surgery or trauma. An initial diagnosis of severe panuveitis was made. The patient was started on topical steroids, cycloplegia, and reviewed in 48 hours.

Unfortunately, this misdiagnosis had devastating consequences with severe progression of disease course. On the following clinical review, vision was noted to be counting fingers with periorbital inflammation and restricted ocular movements. Alarmingly,

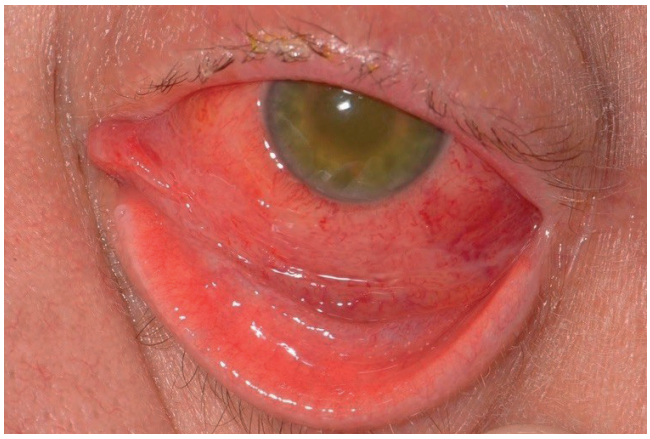

Figure 1: Classical features on endogenous endophthalmitis: conjunctival injection, corneal oedema and trace hypopyon.

the development of a trace hypopyon was also noted (Figure 1). Subsequent investigations and blood tests finally concluded this to be a rare case of iatrogenic endogenous endophthalmitis, caused by biliary sepsis secondary to endoscopic retrograde cholangiopancreatography. The patient in fact had been recently investigated for an episode of painless jaundice by the general surgical team. The causative organism was identified to be *Escherichia coli.*

Bacterial endophthalmitis

Endophthalmitis is classified into two main forms of disease, exogenous and endogenous. The exogenous form of disease is a consequence of direct inoculation of bacterium as a complication of surgery or secondary to trauma (postoperative and post-traumatic endophthalmitis). Rarely, exogenous endophthalmitis can occur secondary to a perforation stemming from untreated keratitis [3]. The progression of disease course results in the destruction of intraocular structures. This occurs alongside a cascade of severe inflammatory and immune responses. Conversely, endogenous endophthalmitis occurs secondary to the haematogenous spread of organisms located elsewhere in the body. Literature would suggest incidence rates of exogenous endophthalmitis to be much higher than its endogenous counterpart, with it being described to account for as high as 92.6% of all cases of endophthalmitis [4].

Endogenous endophthalmitis

Incidence rates have been estimated to be around five per 10,000 hospitalised patients for this form of endophthalmitis. At highest risk are those in an immuno-compromised state. Risk factors reported in 60% of cases include malignancy, immunosuppressive therapy, the presence of indwelling devices, intravenous drug use and diabetes [1]. Literature reports a differential risk profile based on sex, whereby males with right-sided involvement account for the majority of reported events. Surprisingly, in close to 40% of

cases the primary source of infection is not identified [1,2]. Despite early aggressive intervention, there remains a significant incidence of consequent evisceration. Worldwide prevalence rates implicate gram-negative infections as the more common source of disease in cases of evisceration. This is likely explained by the predominance of gram-negative cases seen in Asia [2]. Common pathogens for bacterial endogenous disease include *Staphylococcus aureus*, *Baccilus cereus* and *Escherichia coli*.

Exogenous endophthalmitis

Postoperative endophthalmitis is the most frequently encountered exogenous form of disease. In the United Kingdom, this is most commonly seen post cataract surgery [5]. It may be argued that this is simply selection bias, accounted for by the sheer volume of cataract operations completed in comparison to other forms ocular surgery. Nonetheless, it remains a potential complication in all forms of intra and extraocular surgery.

Table 1: Common causative agents in endophthalmitis [2,11,13,14].

Form of infection	Endophthalmitis sub-type	Pathogen involved	
Endogenous		Fungi • *Candida* species • *Aspergillus* spp. • *Fusarium* spp.	Most common
		Gram positive bacteria • *S. aureus* • *B. Cereus*	
		Gram negative bacteria • *Escherichia coli* • *Neisseria meningitides* • *Klebsiella*	
		Rarely protozoa and amoeba	
Exogenous			
Postoperative:	***Acute <6 weeks after surgery***	Coagulase-negative *staphylococci*	Most common
		Staphylococcus aureus	
		Viridans group *Streptococci*	
		Enterococci	
		Gram negative organisms	
		Fungi: *Candida* • *Parasilosis* • *Aspergillus* • *Fusarium*	
Delayed postoperative	**Delayed >6 weeks after surgery**	*Propionibacterium acnes*	Most common
		Streptococcus	
		Coagulase-negative *Staphylococci:* • *Epidermidis*	
		Filamentous bacteria • *Actinomyces* • *Nocardia*	
		Hemophilus influenzae	
		Non-tuberculous mycobacteria • *Abscesses* • *Chelonae*	
		Candida parapsilosis	
Post-traumatic		*Staphylococci*	Most common
		Bacillus cereus	
		Streptococci	
		Pseudomonas aeruginosa	
		Polymicrobial infections	
		Filamentous Fungi • *Aspergillus* • *Fusarium*	

Bacteria usually arise from the eyelid margin or ocular tear film [6,7]. Risk factors include corneal perforation, systemic autoimmune dysfunction, pre-existing infection (i.e. blepharitis, conjunctivitis), the use of topical or oral corticosteroids, and chronic use of topical antibiotics. Instances of clustered endophthalmitis presentations would suggest tainted materials / solutions or fundamental issues with apparatus sterilisation [8].

Gram-positive isolates are the most commonly seen postoperative bacterial endophthalmitis. These cases frequently report coagulase negative *Staphylococcus, Streptococci* and *Enterococci.* Among gram-negative cases the most common isolate is that of *Pseudomonas Aeruginosa* [9,10]. Fungal infection in comparison is considerably less common and usually occurs secondary to contaminated ocular irrigation fluids [11].

Delayed bacterial exogenous endophthalmitis occurs up to six weeks after initial surgery. Commonly identified bacteria include *Staphylococcal Epidermidis, Propionibacterium Acnes* and *Hemophilus Influenza.* Organisms are often introduced at time of surgery or achieve entry via wound irregularities, suture tracks and even filtering blebs [11,12].

Post-traumatic endophthalmitis frequently occurs after penetrating injuries to the eye. Infection rates are documented to be between 1-17% of all cases [15]. Variability in the estimated prevalence is likely explained by a number of influencing factors which include the presence of intraocular foreign body, delayed operative repair, virulence of organism and autoimmune dysfunction of patient. As expected, the isolates involved include species colonising the injury setting, commonly *Staphylococcus* and *Streptococcus* spp. An important pathogen requiring urgent intervention includes *Bacillus* spp. It exhibits a rapid course with severe destruction often leading to irreversible visual loss within 24-48 hours post infection. It demonstrates poor response to both medical and surgical intervention [16].

Pathogenesis

In healthy eyes, the blood-ocular barrier creates a physiological protective wall against invading organisms. It safeguards the efficient performance of the structures of the eye and is vital for immune privilege [14]. In cases of exogenous endophthalmitis, organisms causing disease are usually found within the conjunctival flora. Organisms enter the anterior chamber and adhere to the intraocular lens, creating micro-colonies through the formation of bio-film. This provides protection against the host's inflammatory response, not only physically but also through the alteration of antigenicity secondary to genetic changes. These organisms are particularly hard to eradicate and organisms within this bio-film may persist despite aggressive management [11].

A number of toxins and enzymes are created and released by assaulting organisms during bacterial cell growth. This leads to the impairment and destruction of retinal function. Peptidoglycan fragments, cell envelopes and lipopolysaccharides are liberated into the ocular compartments during this period. Once in contact with occupant immune cells, they cause the production of pro-inflammatory cytokines and supplementary immune mediators. A cascade of inflammatory events ensues, leading to an amplified permeability of the blood-ocular fluid barrier; this in turn causes the recruitment of phagocytic inflammatory cytokines, toxic enzymes and reactive oxygen species [11]. Through advanced phases of disease, there is lymphocyte migration into the inflamed structures of the eye and an immunoglobulin response. Ultimately, this causes the destruction and death of the retina and retinal photoreceptors that cannot regenerate.

Confirming your suspicions

The diagnosis of endophthalmitis can only be confirmed by obtaining intraocular vitreous or aqueous specimens. Studies have suggested that, despite adequate sampling, the possibility of confirming diagnosis ranges between 36 and 70% [11,17]. Vitreous sampling has been shown to be more reliable, however, sensitivity of this technique is suboptimal. Ultimately, the specimens are used to guide treatment by determining the type of organism and antibiotic sensitivity. In cases of endogenous disease, it is essential that a complete systemic work up, including a full septic screen, especially when the source of infection is unknown.

Anterior chamber sampling can be completed under topical anaesthesia. This involves the introduction of a 30-guage needle through the limbus into the anterior chamber. It is important to avoid the surrounding lens, iris and endothelium. The aim is to obtain a 0.1ml sample of aqueous.

A vitreous sample, however, requires a tap to be completed or a biopsy via an automated vitrectomy set. Sampling usually requires sub-tenons anaesthesia. For a vitreous tap to be completed, a 21-guage needle is inserted to obtain 0.1-0.2mls of specimen. Conversely, for a biopsy to be completed, a vitrectomy cutter is inserted via the pars plana.

These samples can be handled by a number of techniques. One method involves the sample being passed through 0.45mm filter paper, which allows for the concentration of microorganisms and particulate matter. This is subsequently divided and dispersed on the appropriate media. Five percent sheep blood agar allows

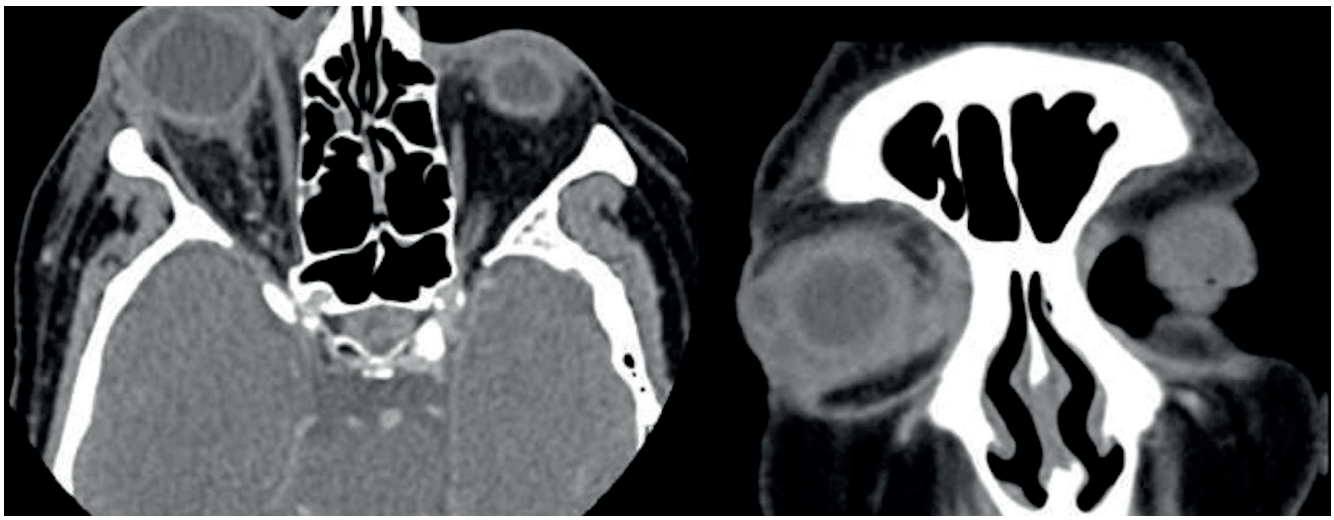

Figure 2: This patient presented with severe exogenous endophthalmitis. The CT images show significant proptosis on the right side with some diffuse swelling of the periorbital soft tissues. Additionally, there is diffuse thickening of the globe of the right eye.

the recovery of most bacterial and fungal pathogens. Sabouraud agar is used for fungal isolates, whereas chocolate agar is used to isolate organisms such as *Neisseria gonorrhoeae* and *Hemophilus influenzae*. Additionally, the use of Thioglycollate broth and anaerobic blood agar can be used to isolate a number of rare aerobic and anaerobic organisms [11]. Immunological and genetics-based testing allows for prompt and precise identification of the causative agent. The current evidence advocates for the use of polymerase chain reaction in cases of culture negative biopsy. In the Endophthalmitis Vitrectomy Study (EVS) there was no variation in sampling accuracy or complications when evaluating vitreous tap vs. biopsy [18]. Thus, clinical management should be based on resource availability and clinician skill set.

Imaging modalities can assist in confirming diagnosis. B-scan ultrasound may reveal choroidal thickening, associated vitreous haemorrhage, retinal detachment and echoes within the vitreous. In cases of traumatic injury, computerised topography (CT) can help identify the presence of a retained foreign body as well as elucidate orbital infiltration, inflammation and thickening of the uveal and scleral tissues [19] (Figure 2).

Keeping it at bay

Prevention is essential to effectively reduce endophthalmitis rates. Aseptic, sterile techniques should be employed during any intraocular surgery or manipulation. The use of 5% pov-iodine instilled for three minutes on the peri-ocular and ocular surface has been shown to be the most effective method for reducing the occurrence of endophthalmitis. This should be completed alongside aseptic preparation for surgery and draping of surgical field. All surgical instruments require optimal sterilisation with autoclaving, as well as tubing sterilisation with ethylene oxide gas. Simple measures, including single use instrumentation, as well as preventing re-use and timely disposal of balance salt solution, dramatically reduce infection rates. Postoperatively patients should be given topical antibiotics for two weeks and in cases of penetrating injury, patients should be treated with broad-spectrum intravenous antibiotics.

How to treat

As one of the few ophthalmic emergencies it is paramount that treatment be administered as soon as possible to limit the potential complications. This is often considered a therapeutic challenge in light of the delicate anatomy and physiology involved. Although the retina has a rich blood supply, the vitreous and anterior chamber are avascular and independent of systemic circulation. This feature creates a barrier for both the delivery of antibiotics and access to damaged structures by the essential cellular and humoral mediators of our host immune system. This anatomical challenge limits the delivery methods of effective therapies. The most common approach to circumventing this challenge includes direct intravitreal administration of treatment. Unfortunately, this approach poses its own risks, including retinal toxicity, artery occlusion, lens damage and vitreous / retinal haemorrhage [14]. The retinal photoreceptor cells are at risk of damage, not simply by the invading pathogens, but also by the inflammatory response caused by antimicrobial agents injected.

Long-term outcomes resulting from endophthalmitis are dependent on a number of factors. These include the causative pathogen, the stage of presentation, age and the interval between injury and treatment [11,14]. Any delay in treatment leads to worse visual outcomes. The bacterial form of disease is treated with intravitreal antibiotics. Due to the increased permeability of the blood-retinal barrier in times of acute inflammation, the effects of aminoglycosides and vancomycin that usually would not penetrate the vitreous cavity becomes amplified. Although clinicians advocate for the use of systemic antibiotics, there is often poor penetration due to inflammation and necrosis of the blood vessels that create this barrier. The EVS study evaluated the efficacy of systemic antibiotics in post-surgery endophthalmitis, which demonstrated they did not improve visual outcomes [18]. Nonetheless, this does not hold true for cases of post-traumatic and endogenous endophthalmitis. In such cases, systemic antibiotics play an integral role in the treatment of endophthalmitis, which can be life-threatening.

The most commonly used drug regimes include the use of third generation cephalosporin such as Ceftazidime or alternatively Amikacin for gram-negative bacteria, alongside Vancomycin for gram-positive bacteria [20]. Patients often require multiple injections with treatment guided by microbiology sensitivities. Equally, the use of corticosteroids plays an important adjunct to therapy, which can be delivered both orally or by intravitreal delivery systems. However, this can only be initiated once the infection is controlled.

Conclusion

Bacterial endophthalmitis is a devastating disease that can cause catastrophic visual compromise. The timely recognition of disease and implementation of appropriate investigations in conjunction with immediate treatment plays a critical role in preserving patients' vision. Although it is fortunate this disease is rare, given the paucity of prospective clinical trial data establishing optimal management techniques, clinicians must implement best available data and their own clinical judgement whilst maintaining a low threshold to initiate treatment.

References

1. Ansari AS, Lai K, Tejwani D. An unexpected case of iatrogenic Escherichia coli endogenous pan-endopthalmitis after ERCP-associated biliary sepsis: A case report. *Eur J Ophthalmol* 2019;**29(1 sSuppl)**:4-9.
2. Jackson TL, Paraskevopoulos T, Georgalas I. Systematic review of 342 cases of endogenous bacterial endophthalmitis. *Surv Ophthalmol* 2014;**59(6)**:627-35.
3. Dursun D, Fernandez V, Miller D, Alfonso EC. Advanced Fusarium keratitis progressing to endophthalmitis. *Cornea* 2003;**22(4)**:300-3.
4. Ramakrishnan R, Bharathi M, Shivkumar C, et al. Microbiological profile of culture-proven cases of exogenous and endogenous endophthalmitis: a 10-year retrospective study. *Eye* 2009;**23(4)**:945.
5. Kamalarajah S, Silvestri G, Sharma N, et al. Surveillance of endophthalmitis following cataract surgery in the UK. *Eye* 2004;**18(6)**:580.
6. Kresloff MS, Castellarin AA, Zarbin MA. Endophthalmitis. *Surv Ophthalmol* 1998;**43(3)**:193-224.
7. Kernt M, Kampik A. Endophthalmitis: pathogenesis, clinical presentation, management, and perspectives. *Clin Ophthalmol* (Auckland, NZ) 2010;**4**:121.
8. Korah S, Braganza A, Jacob P, Balaji V. An 'epidemic' of post cataract surgery endophthalmitis by a new organism. *Indian J Ophthalmol* 2007;**55(6)**:464.
9. Jambulingam M, Parameswaran SK, Lysa S, et al. A study on the incidence, microbiological analysis and investigations on the source of infection of postoperative infectious endophthalmitis in a tertiary care ophthalmic hospital: an 8-year study. *Indian J Ophthalmol* 2010;**58(4)**:297.
10. Anand N, Brogden P, Menage MJ. E. coli endophthalmitis. *Eye* 1996;**10**:142.
11. Malhotra S, Sharma S, Bhatia N, et al. Bacterial endophthalmitis. *Advances in Common Eye Infections* 2016;**21**.
12. Gedde SJ, Scott IU, Tabandeh H, et al. Late endophthalmitis associated with glaucoma drainage implants. *Ophthalmology* 2001;**108(7)**:1323-7.
13. Durand ML. Endophthalmitis. *Clin Microbiol Infect* 2013;**19(3)**:227-34.
14. Callegan MC, Engelbert M, Parke DW, et al. Bacterial endophthalmitis: epidemiology, therapeutics, and bacterium-host interactions. *Clin Microbiol Rev* 2002;**15(1)**:111.
15. Bhagat N, Nagori S, Zarbin M. Post-traumatic infectious endophthalmitis. *Surv Ophthalmol* 2011;**56(3)**:214-51.
16. Ramadan RT, Ramirez R, Novosad BD, Callegan MC. Acute inflammation and loss of retinal architecture and function during experimental Bacillus endophthalmitis. *Curr Eye Res* 2006;**31(11)**:955-65.
17. Stepien KE, Eaton AM, Jaffe GJ, et al. Increased incidence of sterile endophthalmitis after intravitreal triamcinolone acetonide in spring 2006. *Retina* 2009;**29(2)**:207-13.
18. Johnson MW, Doft BH, Kelsey SF, et al. The endophthalmitis vitrectomy study: relationship between clinical presentation and microbioloaic spectrum. *Ophthalmology* 1997;**104(2)**:261-72.
19. Lee C-C, Chen C-Y, Chen F-H, et al. Septic metastatic endophthalmitis from Klebsiella pneumoniae liver abscess: CT and MR imaging characteristics - report of three cases. *Radiology* 1998;**207(2)**:411-6.
20. Relhan N, Albini TA, Pathengay A, et al. Endophthalmitis caused by Gram-positive organisms with reduced vancomycin susceptibility: literature review and options for treatment. *Brit J Ophthalmol* 2016;**100(4)**:446-52.

TAKE HOME MESSAGE

- Misdiagnosis sadly remains a common occurrence; early recognition and surveillance in postoperative period are critical in optimising final visual outcomes.
- Preventative measures are based on preoperative planning, surgical technique, sterility and prophylactic antibiotics.
- Education remains the optimal screening method by other subspecialities. It is important ophthalmologists highlight the key clinical features to look out for in a patient's history and examination if endophthalmitis is suspected.
- There must be no delay in the initiation of treatment and gathering of samples.
- The need for better risk stratification for further research in the development of a risk score, which could highlight those at greatest risk.

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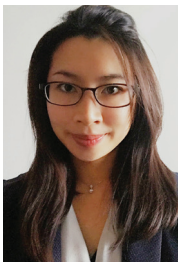

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