Endophthalmitis

Endophthalmitis is a severe sight-threatening infection of the eye, specifically involving the vitreous (*Figure 1*). If left untreated endophthalmitis can lead to irreversible blindness in the affected eye within hours to days of the onset of symptoms. Infection may be of bacterial or fungal aetiology; pathogens can be introduced into the eye via exogenous or endogenous routes. Although a rare condition, endophthalmitis is a medical emergency requiring prompt diagnosis and antimicrobial treatment to save vision (Durand, 2017). Therefore, it is crucial for doctors to consider a diagnosis of endophthalmitis in any patient presenting with decreased visual acuity, a painful or red eye, especially in the setting of recent intraocular surgery or injection.

This article summarizes when to suspect a diagnosis of endophthalmitis and what to do subsequently if you identify a patient with endophthalmitis. It focuses particularly on endogenous endophthalmitis because of its systemic involvement while providing an overview of exogenous endophthalmitis.

Endogenous endophthalmitis

Epidemiology

Endogenous endophthalmitis is a rare condition with an annual incidence of 5 in 10 000 hospital inpatients (Fan et al, 2008) and accounts for 2–8% of all cases of endophthalmitis (Jackson et al, 2014). The mean age of diagnosis is 63 years (range 30–85 years), and the condition is extremely rare in children (Binder et al, 2003).

Pathophysiology

Endogenous endophthalmitis occurs from the introduction of pathogens within the eye via haematogenous spread from a primary source of infection. By definition, endophthalmitis refers to such an infection involving the vitreous humour of the eye, rather than being confined to the periocular tissues or conjunctiva, as in orbital cellulitis and conjunctivitis respectively. Around half of cases are caused by bacteria and half by fungi (Binder et al, 2003). Viral and parasitic intraocular infections are considered to be forms of uveitis as they primarily cause chorioretinal disease with varying but generally milder degrees of secondary inflammation in the vitreous. Although the management of viral and parasitic intraocular infections is beyond the scope of this article, they should be included in the differential diagnosis of patients presenting with an acutely red eye with reduced vision, particularly in immunocompromised patients.

The source of infection in endogenous endophthalmitis can be ongoing (e.g. endocarditis, liver abscess, bacteraemia or fungaemia) or may be a transient focus, for example indwelling catheters, intravenous drug use, or following endoscopy or colonoscopy (Durand, 2017). Owing to the highly vascular properties of the choroid it is typically seeded first (*Figure 1*), with subsequent infection spreading to the rest of the posterior segment of the eye (Sadiq et al, 2015). Microbial proliferation results in a progressive inflammatory response within the internal structures of the eye leading to reduced vision. It is important to note that endophthalmitis itself does not serve as a systemic source of infection (Durand, 2017).

The commonest bacterial pathogens associated with endogenous endophthalmitis in European and north American populations are *Staphylococcus aureus* and *Streptococcus pneumoniae*, with *Klebsiella pneumoniae* most frequently seen in east Asia (Jackson et al, 2014). *Candida* is the most common cause of fungal endophthalmitis with moulds (*Aspergillus* and *Fusarium*) the other major fungal pathogens (Durand, 2017). *Table 1* outlines more causative organisms in endogenous endophthalmitis. Fungaemia is associated with higher rates of endophthalmitis (0.4%) than bacteraemia (0.04%) (Vaziri et al, 2015). The most virulent organism associated with endogenous endophthalmitis is *K. pneumoniae* (associated with liver abscess) with as many as 7% of

Figure 1. Anatomy of the eye.

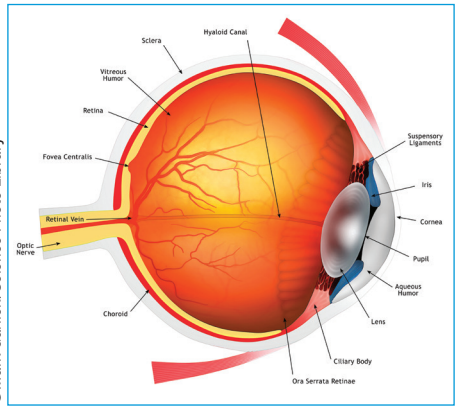

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Table 1. Causative organisms in endogenous endophthalmitis

Bacterial	Gram positive	*Staphylococcus aureus*
		Streptococcus pneumoniae
		Streptococcus viridians
		Group A + B streptococci
		Bacillus cereus
	Gram negative	*Pseudomonas aeruginosa*
		Klebsiella pneumoniae
		Escherichia coli
Fungal	Yeasts	*Candida* spp.
		Cryptococcus neoformans
	Moulds	*Aspergillus* spp.
		Fusarium spp.

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systemically infected patients developing the condition (Durand, 2017).

Risk factors

Patients who develop endogenous endophthalmitis often have underlying systemic risk factors (*Table 2*). Immunosuppressed individuals, intensive care patients, diabetics, patients with malignancy and intravenous drug users are among those at highest risk of developing endogenous endophthalmitis (Jackson et al, 2014; Sadiq et al, 2015). However, it is important to recognize that endogenous endophthalmitis can manifest in immunocompetent individuals without underlying conditions or risk factors in the presence of a systemic focus of infection (ongoing or transient) (Sadiq et al, 2015). Therefore patients with liver abscess, infective endocarditis, meningitis, bacterial or fungal sepsis merit consideration of endophthalmitis in the presence of any clinical features of endogenous endophthalmitis.

Clinical features

Most cases of endogenous endophthalmitis present acutely or subacutely with decreased vision (Durand, 2017). Red eye, ocular pain and floaters are other common presenting features (*Table 3*). Ocular involvement is generally unilateral but around 30% of cases are bilateral (Vaziri et al, 2015). Bilateral endophthalmitis is more likely to develop in the setting of *Mycobacterium tuberculosis* and *Candida* infections (Sadiq et al, 2015). Systemic features such as fever and symptoms relating to a specific source of infection elsewhere in the body are seen in around half of patients presenting with endogenous endophthalmitis (Okada et al, 1994; Jackson et al, 2014).

The presence of a hypopyon in the eye (*Figure 2*) is highly suggestive of endophthalmitis – this can often be seen with careful inspection even without access to a slit lamp. However, the key feature to look for in the diagnosis of endophthalmitis is the presence of vitritis (inflammatory cells in the vitreous cavity), which requires slit lamp examination for identification. In many cases the vitritis is severe enough to preclude meaningful examination of the fundus – in these cases, patients will have an absent red reflex when examined with a funduscope. Other clinical signs are outlined in *Table 3*.

The time course of these presenting features often depends on the infective pathogen. Bacterial cases of endophthalmitis typically present acutely with symptoms progressing over hours to days. Fungal endophthalmitis is associated with less inflammation, milder pain and generally presents sub-acutely with the development of symptoms over a course of days to weeks (Durand, 2017). The pattern of vitritis also varies between bacterial and fungal endophthalmitis – it is typically diffuse in bacterial endophthalmitis and appears in 'clumps' in fungal endophthalmitis (Durand, 2017). Fungal endophthalmitis as a result of *Candida* usually manifests initially as chorioretinitis (white fluffy retinal lesions) before the development of vitritis (Oude Lashof et al, 2011) (*Figure 3*). The current recommendation is that all patients with candidaemia need baseline dilated fundal exam within the first week of diagnosis. Furthermore, if the patient is neutropaenic, he/she may lack clinical findings of chorioretinitis and vitritis, therefore it is recommended that the patient has a repeat eye exam within a week after recovering from neutropaenia (Pappas et al, 2016).

Many of these clinical features are non-specific for endogenous endophthalmitis and as a result diagnosis can be particularly challenging. Therefore, diagnosis requires a high index of clinical suspicion in the presence of any clinical features of endophthalmitis, especially in the setting of an acutely unwell patient or a patient with risk factors for developing the condition.

Table 2. Risk factors for endogenous endophthalmitis

Recent hospital admission
Diabetes mellitus
Immunosuppression (malignancy, neutropenia, HIV, chemotherapy, organ transplant)
Infection (liver abscess, meningitis, endocarditis, bacteraemia, fungaemia)
Intravenous drug use
Indwelling catheters
Recent colonoscopy or endoscopy
Intensive care admission

Table 3. Clinical features of endogenous endophthalmitis

Symptoms	Decreased or blurred vision
	Eye pain
	Red eye
	Floaters
	Photophobia
	Fevers
Signs	Reduced visual acuity
	Conjunctival injection or lid oedema
	Corneal oedema
	Anterior chamber cells
	Hypopyon
	Vitritis
	Absent red reflex
	Relative afferent pupillary defect (if optic nerve involvement or very extensive retinal involvement)

Figure 2. Hypopyon. This image of a patient's right eye shows a diffusely injected conjunctiva, a hazy cornea stained with fluorescein and a hypopyon in the anterior chamber (arrow).

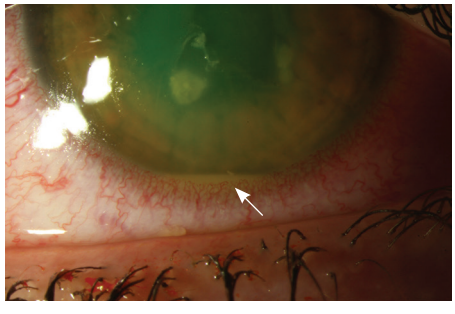
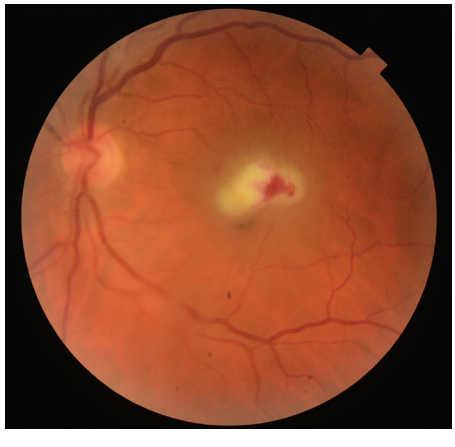


Figure 3. Candida chorioretinitis lesion. Dilated fundal examination of a patient's left eye showing chorioretinitis at the macula, characterized by deep focal creamy white yellow lesion with central haemorrhage. Vitreous haze is also noted around this central lesion.



Diagnosis

Endogenous endophthalmitis is a clinical diagnosis with confirmation via microbiological specimens. Wherever a diagnosis of endophthalmitis is suspected, urgent same day ophthalmology input should be sought for thorough slit lamp and dilated fundal examination. A B-scan ultrasound may be used to confirm the extent of vitritis and assess for any associated retinal detachment if the retina cannot be visualized (*Figure 4*). Aqueous and/or vitreous samples will be taken by an ophthalmologist either by needle aspiration or surgically by vitrectomy (this can be both diagnostic and therapeutic). These samples are subsequently sent for Gram stain, microbiological culture and if indicated polymerase chain reaction. In cases of endophthalmitis, positive cultures are obtained from 90% of vitrectomy samples, 50–70% of vitreous aspirates and 40% of aqueous aspirates (Durand, 2017). Negative cultures do not exclude a diagnosis of endogenous endophthalmitis. Polymerase chain reaction is of value in culture-negative endophthalmitis, with identification of a pathogen achieved in most cases (Zhang and Wang, 2005). Positive blood cultures are obtained in 33% of cases (Vaziri et al, 2015).

Systemic workup for a source of infection (if not already identified) should be carried out and *Table 4* outlines suggested investigations; these should be guided by patient history and presentation. *Table 5* lists other conditions that should be considered when making a diagnosis of endogenous endophthalmitis.

Figure 4. B-scan ultrasound of the eye. Display screen for an ophthalmic ultrasound scan. The lens and front of the eye can be seen at the far left of the image. This technique uses high-frequency sound waves, reflected from inside the body, to visualize the internal structures of the eye. This B-scan is used to demonstrate the investigation and does not show the presence of vitritis or retinal detachment.

Treatment

As soon as a diagnosis of endophthalmitis is suspected treatment should be initiated promptly, as delays are associated with poorer visual outcomes (Sadiq et al, 2015). Do not wait for culture results before starting treatment. Treatment should start with timely broad spectrum intravenous antimicrobial agents for systemic infection, intravitreal antimicrobials, infectious disease input and hospital admission. Culture results and sensitivities, along with disease severity, should be used to guide further ongoing treatment.

Surgical management of endophthalmitis is with pars plana vitrectomy in selected cases, a procedure that debrides the vitreous humour. It can be a very challenging procedure to perform in the setting of a systemically unwell patient and the mainstay of treatment is with intravitreal therapy for the eye in addition to systemic therapy for the systemic source of infection. Vitrectomy can be performed in select cases of bacterial endophthalmitis, specifically in patients with very poor vision and a dense vitritis that either deteriorates or does not improve after 48 hours of intravitreal and intravenous treatment (Jackson et al, 2014). More commonly vitrectomy is performed early in fungal endophthalmitis as it is associated with better visual outcomes in these patients (Chee and Eliott, 2016).

In the UK, vancomycin and amikacin are generally the intravitreal antibiotics of choice in cases of bacterial endophthalmitis with an amikacin and clindamycin combination for patients who are allergic to penicillin (Sadiq et al, 2015). Ceftazidime with vancomycin is another common alternative. For cases with fungal infection amphotericin B or voriconazole are the intravitreal antifungal agents most commonly used (Sadiq et al, 2015). Systemic antibiotics and antifungals should be targeted at the underlying infection along with culture results and sensitivities. The choice and duration of systemic and intravitreal antimicrobial agents should be in accordance with local guidelines and be guided by an infectious disease physician.

Table 4. Investigations for suspected endogenous endophthalmitis

Ocular fluid (vitreous or aqueous)	Gram stain and culture
	Fungal stain and culture
	Polymerase chain reaction
Blood tests	Full blood count, renal profile, C-reactive protein, erythrocyte sedimentation rate, liver function tests
	Blood-borne viruses (HIV, hepatitis B, hepatitis C)
	Aspergillus antigen
	Toxoplasma serology
	Quantiferon-tuberculosis gold
	Angiotensin-converting enzyme (for sarcoidosis)
	Syphilis serology
Fluid cultures	Blood cultures (bacterial and fungal)
	Urine culture
	CSF culture (if signs of intracranial infection)
Imaging	Echocardiogram (for endocarditis)
	Chest X-ray (for tuberculosis, sarcoidosis)
	Ultrasound liver (for liver abscess)
	Magnetic resonance imaging of the brain and orbits

Prognosis

Endogenous endophthalmitis very commonly results in some degree of long-term vision loss (Wu et al, 2012). Prognosis is variable and is influenced by a number of factors with the causative pathogen and visual acuity at the time of diagnosis the major predictors of outcome (Durand, 2017). Other predictors of poorer outcomes include older age, diabetes and absence of red reflex at the time of diagnosis (Schwartz et al, 2016). Studies have shown *Candida* infection to be

Table 5. Differential diagnosis of endogenous endophthalmitis

Non-infectious uveitis (e.g. sarcoidosis, Behçet's syndrome, birdshot chorioretinopathy)
Viral chorioretinitis (herpes simplex virus, varicella zoster virus, Epstein–Barr virus, cytomegalovirus)
Intraocular lymphoma
Exogenous endophthalmitis, e.g. recent trauma, intraocular foreign body, recent intraocular surgery
Vitreous haemorrhage
Corneal ulcer with associated hypopyon

associated with the best outcomes followed by bacterial and then mould organisms. Endogenous endophthalmitis caused by *Candida* resulted in visual acuity of greater than 6/60 in 56% of patients, compared to 41% in bacterial and 33% in mould-related endophthalmitis (Lingappan et al, 2012).

Visual acuity at the time of diagnosis showed poorest outcomes in those presenting with light perception or worse (Schwartz et al, 2016). In one study of 324 patients with endogenous endophthalmitis, 24% required evisceration or enucleation, and there was a 4% mortality rate (Jackson et al, 2014). Prompt initiation of treatment is the most important action that can be taken to improve visual outcomes in endogenous endophthalmitis.

Exogenous endophthalmitis

Exogenous endophthalmitis occurs when microbes present on the ocular surface or from an external source are introduced into the eye, commonly in the setting of cataract surgery, intravitreal injection or penetrating ocular trauma. Exogenous endophthalmitis accounts for the vast majority of cases of endophthalmitis and occurs in 0.1% of cases post-cataract surgery, 0.09% of cases post-intravitreal injection and 3–10% of penetrating eye injuries (Durand, 2013). Coagulase-negative staphylococci are the most common pathogens resulting in endophthalmitis following cataract surgery and intravitreal injection (Schwartz et al, 2016). Contamination of the aqueous humour occurs from ocular surface or lid flora during ocular surgery or injection into the eye. *Bacillus cereus* is the major cause of post-traumatic endophthalmitis and is associated with poor visual outcomes (Durand, 2017). Nearly all cases of exogenous endophthalmitis are the result of bacteria rather than fungi in Europe and North America (Durand, 2013).

Risk factors in exogenous endophthalmitis include inadequate cleaning of the lid and ocular surface with povidone iodine before starting intraocular surgery. Individuals with immune compromise are at further increased risk (Schwartz et al, 2016). Clinical features are the same as for endogenous endophthalmitis with most patients presenting with decreased vision and eye pain, but patients remain systemically well (Durand, 2017). Intraocular inflammation and hypopyon are typical examination findings and patients often develop symptoms at day 2 with a peak incidence at days 7–10 following ocular surgery (Durand, 2013).

Exogenous endophthalmitis is a clinical diagnosis with confirmation via cultures. Sterile endophthalmitis (non-infectious inflammatory reaction commonly following intravitreal injection) is the main differential diagnosis which improves without any specific treatment, but must be treated as an infective endophthalmitis if there is any clinical uncertainty (Schwartz et al, 2016). Timely initiation of intravitreal antibiotics with or without vitrectomy are key to treatment. The benefit of adjunctive systemic antibiotics in exogenous endophthalmitis is not known but they are administered at some units. An oral fluoroquinolone is often the drug of choice. Prognosis is generally better in exogenous than endogenous endophthalmitis with most cases caused by coagulase-negative staphylococci recovering good vision (Durand, 2017).

Conclusions

Endogenous endophthalmitis is a severe infection of the eye and is a medical and ophthalmological emergency which can result in irreversible blindness. Presentation is commonly with reduced vision in a patient with a systemic focus of infection. The diagnosis of endogenous endophthalmitis is clinical with confirmation by vitreous and/or aqueous cultures. Treatment is with systemic and intravitreal antimicrobial agents in addition to surgical intervention by pars plana vitrectomy in severe cases. A high index of clinical suspicion is critical to diagnose and promptly treat cases of endogenous endophthalmitis in order to save vision. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Endogenous endophthalmitis is a medical and ophthalmic emergency.
- Clinical presentation is often acute with reduced vision and a systemic focus of infection.
- Diagnosis is clinical and requires a high index of clinical suspicion.
- Suspected endogenous endophthalmitis requires urgent ophthalmology input, hospital admission, intravenous and intravitreal antimicrobials.
- Delays in treatment can result in permanent vision loss, and in some cases death.

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