

## Treatment of Post-operative Endophthalmitis

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### Abstract

The rates of post-operative endophthalmitis have been low for many years, but recent reports suggest that this type of ocular infection may be on the rise. Fluctuations in the number of cases appear to correlate with the type of intraocular surgery performed. Post-operative endophthalmitis has been reported as a consequence of nearly every type of ocular surgery, but is most common following cataract surgery. Numerous reports have demonstrated that Gram-positive bacteria cause the vast majority of post-operative endophthalmitis cases. Coagulase-negative staphylococcal isolates are the most common. Most intraocular infections resulting from infection with coagulase-negative staphylococci can be treated with antibiotic and anti-inflammatory agents, resulting in restoration of partial or complete vision. However, the more virulent the bacterial strain, the more devastating the visual outcome. Intraocular infections with *Staphylococcus aureus*, enterococci, *Bacillus* or Gram-negative strains are often intractable, and blindness or loss of the eye itself is not uncommon. The therapeutic success of treating post-operative endophthalmitis depends largely on accurate and prompt diagnosis. Antibiotic therapy can be topical, sub-conjunctival, systemic or intravitreal. Vitrectomy must be reserved for patients who present with initial visual acuity of light perception. Only in these cases has vitrectomy been shown to be more advantageous with respect to the intravitreal antibiotic injection.

### Keywords

Endophthalmitis, bacteria, cataract, infections, retina, vitreous, therapy

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Endophthalmitis is a severe inflammation of the interior of the eye caused by the introduction of contaminating micro-organisms following trauma, surgery or haematogenous spread from a distant infection site. Despite appropriate therapeutic intervention, bacterial endophthalmitis frequently results in visual loss, if not loss of the eye itself.

The two types of endophthalmitis are endogenous (metastatic) and exogenous. Endogenous endophthalmitis results from the haematogenous spread of organisms from a distant source of infection (i.e. endocarditis). Endogenous endophthalmitis is rare, occurring in only 2–15% of all cases of endophthalmitis. Average annual incidence is about five per 10,000 hospitalised patients. In unilateral cases, the right eye is twice as likely to become infected as the left eye, probably because of its more proximal location to direct arterial blood flow from the right innominate artery to the right carotid artery.

Since 1980, candidal infections reported in intravenous drug users have increased. The number of people at risk may be increasing because of the spread of AIDS, more frequent use of immunosuppressive agents and more invasive procedures (i.e. bone marrow transplantation).<sup>1</sup>

Exogenous endophthalmitis results from direct inoculation as a complication of ocular surgery, foreign bodies and/or blunt or penetrating ocular trauma. Most cases of exogenous endophthalmitis (about 60%) occur after intraocular surgery. Under normal

circumstances, the blood–ocular barrier provides a natural resistance against invading organisms.<sup>2</sup>

Destruction of intraocular tissues may be due to direct invasion by the organism and/or inflammatory mediators of the immune response. Endophthalmitis may be as subtle as white nodules on the lens capsule, iris, retina or choroid. It can also be as ubiquitous as inflammation of all the ocular tissues, leading to a globe full of purulent exudates. In addition, inflammation can spread to involve the orbital soft tissue.

Any surgical procedure that disrupts the integrity of the globe can lead to exogenous endophthalmitis (cataract, glaucoma, retinal, radial keratotomy, keratoplasty). Although uncommon, endophthalmitis can also result from keratitis, an infection of the cornea that, if left untreated, can result in corneal perforation and intraocular seeding of organisms.

There are many classifications of endophthalmitis, but the most commonly recognised categories are the following: post-surgical: acute, and delayed or chronic; post-traumatic; bleb-related; and endogenous: fungal, bacterial and other. Post-operative infectious endophthalmitis that occurs within six weeks of surgery is classified as acute. The most commonly cultured micro-organism is *Staphylococcus epidermidis*, which is less virulent than the others. *Propionibacterium acnes* and fungi, commonly considered among the causes of more delayed onset

infections, may also cause acute infections. *Bacillus* spp are rarely associated with post-operative endophthalmitis.

Post-operative endophthalmitis that presents more than six weeks after surgery is classified as chronic. This definition is arbitrary because the time of onset can be influenced by the use of anti-inflammatory medications, host characteristics, and in the case of infectious endophthalmitis, the virulence of the offending organism and the inoculum size. The most commonly cultured organisms include *S. epidermidis* (and other coagulase-negative *Staphylococcus* spp), *P. acnes*, fungi (primarily *Candida* spp), anaerobic *Streptococcus* spp, *Actinomyces* spp and *Nocardia asteroides*. *P. acnes* endophthalmitis is usually a delayed-onset infection.

### Epidemiology

Post-operative endophthalmitis has been reported following nearly every type of ocular surgery. It occurs most frequently following cataract surgery, the most commonly performed type of ocular surgery. The overall incidence of post-cataract surgery endophthalmitis in the US, using modern techniques of phacoemulsification and intraocular lens (IOL) implantation, is about 0.1 %.<sup>3-6</sup> In the US, post-cataract endophthalmitis is the most common form, with approximately 0.1–0.3 % of operations having this complication, which has increased over the last three years. Although this is a small percentage, large numbers of cataract operations are performed each year, making the likelihood of physicians encountering this infection higher.

The incidence following other types of intraocular surgery has been reported to range between 0.05 % and about 0.5 %<sup>7-10</sup> (see Table 1). In general, those procedures with a higher risk for acute post-operative endophthalmitis (secondary IOL implantation and penetrating keratoplasty) are those with a greater potential for wound leaks with subsequent intraocular bacterial contamination.

Post-operative endophthalmitis can be infective or sterile. The sterile types are post-operative intraocular phlogosis with sterile hypopyon. In the absence of infective factors they can be caused by toxic, irritant and immunological agents (dubious 15 %, bacterial 70 %, negative 15 %). Infective post-operative endophthalmitis can be due to bacteria 90 %, fungi 8–16 %, rarely to helminthes and protozoans.<sup>11-13</sup> Fungal endophthalmitis are more commonly due to *Candida albicans*, and more unusually to *Aspergillus*. Generally, fungal endophthalmitis arises slowly and insidiously during the two to four weeks following the surgical procedure. Post-operative endophthalmitis is the most common cause of the disease. Of these cases, Gram-positive organisms account for almost 90 %, of which the majority are coagulase-negative *Staphylococcus* from the natural conjunctival flora (see Table 2).

The aetiological agents of acute post-operative endophthalmitis are generally micro-organisms of the eyelid margin and preocular tear film. Although preoperative topical antimicrobial agents can decrease colony counts in the tear film, they do not sterilise the area. In one study,<sup>14</sup> culture of aqueous fluid immediately following cataract surgery revealed a 9 % culture-positive rate. Presumably, low inoculum levels and/or low pathogenicity combined with the innate ocular defences against infection explain the low rate of clinical infection despite the relatively high prevalence of micro-organisms in the eye following surgery.

The single most common cause of exogenous endophthalmitis is *S. epidermidis*, which is a normal flora of the skin and conjunctiva.

**Table 1: Incidence of Endophthalmitis after Ocular Surgery**

Cataract		
Ireland (2005)	0.5	8,763
US (2005)	0.29	9,079
Japan (2003)	0.05–0.29	11,595
Australia (2003)	0.16–0.36	83,667
Glaucoma		
Use of antimetabolites	1–11.9	
Use of 5-FU	5.7	
Late infections	0.2–0.7	
Early infections	0.1	
Keratoplasty		
	0.08–0.2	
Vitrectomy		
	0.05–0.14	
Episcleral surgery		
	0.02	
Strabismus		
		one out of 30,000

**Table 2: Aetiological Agents of the Different Types of Endophthalmitis**

Exogenous	
Postsurgical	
Acute	69 % Culture positive
	70 % Coagulase-negative staphylococci
	6 % Gram-negative organisms
	9 % Polymicrobial infections
	15 % Other
	31 % Culture negative
Delayed or Chronic	<i>Propionibacterium acnes</i>
Post-traumatic	20–25 % <i>Bacillus cereus</i> staphylococci
	15 % Fungal
Endogenous	50–62 % Fungal (70 % <i>Candida albicans</i> )
	38–50 % Bacterial
	32–37 % Gram-negative ( <i>Klebsiella</i> spp, <i>Bacillus</i> )
	63–67 % Gram-positive (staphylococci coagulase-negative)

Other common Gram-positive bacteria are *Staphylococcus aureus* and *Streptococcus* spp. The most common Gram-negative organisms associated with post-operative endophthalmitis are *Pseudomonas aeruginosa*, *Proteus* and *Haemophilus* species. Although very rare, many different fungi have caused post-operative endophthalmitis, including *Candida*, *Aspergillus* and *Penicillium* spp.

In most series from the US, coagulase-negative staphylococci are responsible for about 70 % of post-cataract surgery endophthalmitis, followed by *S. aureus* (10–20 %), viridians group streptococci, other Gram-positive micro-organisms and Gram-negative micro-organisms.<sup>13-15</sup> Enterococci (3 %) are notable among the Gram-positive micro-organisms both for prevalence and severity of disease.<sup>16</sup>

When surgery is implicated in the cause, endophthalmitis usually begins within one week of surgery, but may occur months or years later as in the case of *P. acnes*. This delayed infection is likely due either to sequestration of low-virulence organisms introduced at the

**Table 3: Differential Diagnoses with Endophthalmitis**

Cavernous sinus thrombosis
Corneal abrasion
Corneal laceration
Corneal ulceration and ulcerative keratitis
Endocarditis
Globe rupture
Herpes zoster ophthalmicus
Iritis and uveitis
Post-operative inflammation
Systemic lupus erythematosus
Vitreous haemorrhage

time of surgery or to delayed inoculation of organisms. In the former case, *P. acnes* is the most common micro-organism encountered, and clinically evident low- to moderate-grade inflammation may occur weeks to months after surgery.<sup>17</sup> In cases with delayed inoculation of micro-organisms, organisms gain access to the eye through wound abnormalities, suture tracks or filtering blebs. The most common clinical situation involves antecedent glaucoma filtering surgery. In addition to reflecting the colonisation of the preocular tear film, delayed infection of this type is associated with a higher prevalence of streptococcal species. Also a penetrating trauma is an evident risk factor for endophthalmitis.<sup>17-19</sup>

Eyes with apparent infection may not grow out bacteria when appropriately subjected to culture. These cases are commonly called sterile endophthalmitis and accounted for 31 % of the post-cataract surgery infected eyes entered into the Endophthalmitis Vitrectomy Study (EVS). Polymerase chain reaction evidence indicates that many of these cases may be the result of bacteria present in the eye that do not grow on culture.<sup>19</sup> Another syndrome, commonly referred to as a toxic anterior segment syndrome, is a reaction to intraocular foreign material, such as IOL or toxic irrigating solutions. The term pseudo-endophthalmitis also has been used, probably incorrectly, to designate accumulation of injected corticosteroid in the anterior chamber producing a white layering called a pseudohypopyon.

## Clinical Diagnosis

Anamnesis should be carried out in the presence of a next of kin in case the patient is scared and does not talk about conditions such as bronchitis, prostatitis, adnexitis, urinary tract inflammation, ulcers of the legs in those with diabetes, tonsillitis, sinusitis or coecistitis. The acute forms of endophthalmitis are due to *Staphylococcus* in 50 %, *Streptococcus* in 10–40 % or *S. aureus*.

Bacterial endophthalmitis usually presents acutely with pain, redness, lid swelling and decreased visual acuity. Also some bacteria (*P. acnes*) may cause chronic inflammation with mild symptoms. *P. acnes* is part of typical skin flora and is usually inoculated against at the time of intraocular surgery.<sup>20</sup>

Fungal endophthalmitis may present with an indolent course over days to weeks. Symptoms are often blurred vision, pain and decreased visual acuity. A history of penetrating injury with a plant substance or soil-contaminated foreign body may often be elicited. People with candidal infection may present with high fever, followed several days later by ocular symptoms. Persistent fever of unknown origin may be associated with an occult retinochoroidal fungal infiltrate.

The symptoms are visual loss, eye pain and irritation, headache, photophobia, ocular discharge, intense ocular and periocular inflammation, red eye. Physical findings correlate with the structures involved and the degree of infection or inflammation. A thorough eye examination should be performed to include acuity, external examination, funduscopic examination and slit-lamp examination. Signs of uveitis and other findings should be looked for, as described below. Emergency referral to an ophthalmologist for further evaluation, including more exhaustive physical examination, is indicated if endophthalmitis is seriously considered. Symptoms include eyelid swelling and erythema, injected conjunctiva and sclera, hypopyon (layering of inflammatory cells and exudates [pus] in the anterior chamber), vitritis, chemosis, reduced or absent red reflex, proptosis (a late finding in panophthalmitis), papillitis, cotton wool spots, corneal oedema and infection, white lesions in the choroid and retina, vitreal mass and debris, purulent discharge, fever, cells and flare in the anterior chamber on slit-lamp examination.

Absence of pain and hypopyon do not rule out endophthalmitis, particularly in the chronic indolent form of *P. acnes* infection. The chronic form usually appears within 15 days to several months of surgery and it is secondary to germs that are not so virulent (*P. acnes*, *S. epidermidis*, *diphtheroids* and fungi). In infections caused by *P. acnes*, 40–89 % of plaques are produced in the capsular bag, 67 % have hypopyon, 48 % have corneal oedema, and in 26 % of fungal endophthalmitis there is associated keratitis. An ocular ultrasonography B-scan may be useful to show the presence of vitritis, retinal detachment, choroidal detachment and vitreous membranes. If fundus examination is not well visualised, ultrasonography may help to determine if a retained intraocular foreign body is present, the density of the vitritis and if the retina is attached or not. The differential diagnoses with endophthalmitis are shown in Table 3.

Patients may require enucleation to eradicate a blind and painful eye. Mortality is related to the patient's comorbidities and the underlying medical problem, especially when considering the aetiology of haematogenous spread in endogenous infections.

An association appears to exist between the development of endophthalmitis in cataract surgery and *P. acnes* in patients aged greater than or equal to 85 years.<sup>21</sup>

## Laboratory Studies

The most important laboratory study for endophthalmitis is Gram stain and culture of the aqueous and vitreous obtained by the ophthalmologist. The possibility of isolating a micro-organism from the vitreal is 56–70 %, whereas it is 36–40 % from the anterior chamber (AC) humour. Routine cultures should include aerobic, anaerobic and fungal cultures. Once the diagnosis has been made, or strongly considered, prompt referral to an ophthalmologist is needed.<sup>22</sup>

The clinician must be alerted to the possibility of a diagnosis of endophthalmitis from the clinical findings. In eyes with greater than expected intraocular inflammation based on the clinical setting, a high degree of suspicion is important. Failure to appreciate the potential severity of the problem may delay diagnosis. If endophthalmitis is suspected, frequent observation versus active intervention must be chosen. In some instances it may be appropriate to initiate anti-inflammatory therapy and monitor the patient two- to three-times daily until the clinical course becomes clear.

For unequivocal diagnosis samples of the aqueous and vitreous must be obtained for culture, sensitivity, and stain using the techniques described below. Samples from the vitreous are more often positive than samples from the aqueous.<sup>23,24</sup> Vitreous samples obtained from a tap/biopsy are positive as frequently as those obtained using vitrectomy.<sup>16</sup> Undiluted vitreous and aqueous may be placed on the following media for culture: enriched thioglycolate liquid medium, chocolate agar, Sabouraud's agar. Anaerobic cultures typically use either thioglycolate-enriched broth or blood agar enriched with hemin and vitamin K. In some institutions material from the vitreous cassette after vitrectomy is filtered through a 0.45 µm membrane filter. The filter is subsequently divided into three pieces under sterile conditions and used for culture.<sup>25</sup> Stains are prepared from AC and vitreous specimens. In the EVS, the findings of a positive Gram stain were associated with significantly worse final media clarity and visual acuity. The Gram stain result did not reveal any subgroups in which vitrectomy had a beneficial value and therefore was of little consequence in making initial therapeutic decisions.<sup>26</sup> In the EVS there was no difference in the positive rate for culture between samples obtained by tap and those obtained by vitrectomy. In addition, there was no significant difference in operative complications between the two methods.

### Treatment of Post-operative Endophthalmitis

Treatment depends on the underlying cause of endophthalmitis. Final visual outcome is heavily dependent on timely recognition and treatment. Although multiple different approaches to and advances in treatment have been made, according to recent data, the rate of preservation of visual acuity has not changed significantly since 1995.<sup>26</sup> Emergency consultation is necessary if this diagnosis is suspected. This is an ophthalmological emergency because the patient is in danger of losing vision. Medical therapy, systemic or topical, and pars plana vitrectomy or vitreous aspiration may be performed with administration of intravitreal antibiotics (vancomycin, amikacin, ceftazidime). Consider systemic antibiotic administration as well as intravitreal steroids. Patients with post-operative endophthalmitis are usually not admitted to hospital. However, the decision of whether to admit a patient is made by the ophthalmologist. Successful treatment of microbial endophthalmitis must take into account the unique challenges posed by the delicate anatomy and physiology of ocular tissues. Inflammation-induced opacity of the cornea, AC, lens and/or vitreous impedes formation of a clear image on the retina. Inflammation-mediated damage to the trabecular meshwork and/or ciliary body may produce blinding glaucoma or ocular hypotony. Most critically, damage to the neurosensory retina and retinal pigment epithelium may destroy the basic photochemical process of vision. The centre of the macula (that portion of the retina responsible for central vision) is an area only about 500 µm in diameter. While the retina has a rich blood supply, the vitreous (about 4–5 ml in volume) and the AC (about 2 ml in volume) are avascular and isolated from the systemic circulation by the blood–ocular fluid barrier.<sup>16,27</sup> These unique anatomic features represent a barrier for the delivery of not only cellular and humoral mediators of host immunity, but also antimicrobial or anti-inflammatory agents administered systemically. A second problem lies in the sensitivity of the retinal photoreceptor cells and other retinal cells directly adjacent to the vitreous. Such cells are highly sensitive to the offending pathogen and the resulting inflammatory response, as well as to high doses of antimicrobial agents administered locally to treat the infection.<sup>24</sup>

### Acute Post-operative Endophthalmitis

The intraocular concentration of antibiotics after intravitreal injection is greater than that achieved by any other modality. The infection is

almost always seated in the vitreous cavity and other routes of drug administration, in particular topical and subconjunctival, generally do not achieve satisfactory drug levels. As rapid initiation of therapy is important for successful treatment, antibiotics must be administered before culture reports are available.

Vancomycin is considered the drug of choice for Gram-positive organisms, including methicillin-resistant *Staphylococcus* spp and *Bacillus cereus*. It is not toxic and the recommended intravitreal dose is 1.0 mg/0.1 ml. The EVS has found that 100 % of Gram-positive organisms are sensitive to vancomycin, including methicillin-resistant *S. aureus*. The best choice for antimicrobial treatment of Gram-negative organisms is controversial. In the EVS all patients received intravitreal amikacin (0.4 µg/0.1ml) and vancomycin (1.0 mg/0.1 ml). Out of 420 patients in the EVS, only one case of macular infarction was reported following intravitreal injection of amikacin. Ceftazidime has been recommended as an alternative antibiotic to cover Gram-negative organisms because of its broad therapeutic spectrum, lower risk of retinal toxicity and *in vitro* antimicrobial activity, which is as effective as the aminoglycosides against Gram-negative organisms.

The EVS has also found that Gram-negative isolates were equally sensitive to amikacin and ceftazidime. Ceftazidime has been reported to be physically incompatible with vancomycin, causing the drugs to precipitate out of solution when combined. This can be avoided by injecting in separate syringes. Subconjunctival and topical antibiotics are often used with intravitreal antibiotics. The rationale underlying this approach is to increase the number of routes of antibiotic delivery to increase the likelihood of achieving a high concentration of antibiotics within the eye and also in the anterior segment. The EVS has shown that intravenous systemic antibiotics (ceftazidime and amikacin) are the most used adjuncts to intravitreal antibiotics in the setting of acute and subacute operative endophthalmitis, but there was no difference in final visual acuity or media clarity with or without the use of systemic antibiotics.

Systemic, topical, subconjunctival and intravitreal corticosteroids are often used in combination with antibiotics to reduce the destructive effect of significant inflammation that coexists with endophthalmitis. There are several clinical and experimental reports that intravitreal corticosteroid therapy in conjunction with antibiotics with or without vitrectomy reduces the inflammatory process and secondary complications associated with microbial endophthalmitis. Due to a lack of randomised clinical trials or evaluation, the use of intravitreal corticosteroids remains controversial.

Despite these uncertainties, systemic and intravitreal corticosteroids may be beneficial and are unlikely to be harmful.

### Chronic Post-operative Endophthalmitis

If inflammation is not severe, therapy can be delayed until smear, culture and sensitivity data are available from aqueous samples. If inflammation is severe, management should proceed according to the protocol for acute endophthalmitis. If *P. acnes* or fungal endophthalmitis is suspected (clinical findings/smear/culture) then all areas of the involved lens capsule and retained lens cortex should be excised. This is done along with pars plana vitrectomy. It is reasonable to preserve the areas of lens capsule that stabilise the IOL. Antibiotics can be injected into the capsular bag at the time of vitrectomy. Removal of the IOL and capsular bag should be considered in patients who do not

respond adequately to limited capsulectomy, removal of sequestrum and injection of antibiotics into the capsular bag.

Vancomycin is a better choice of antibiotic as it is effective against *P. acnes* and also has a better coverage for other causes of delayed onset endophthalmitis. Therapy should be guided by culture and sensitivity when available. Intravitreal amphotericin B (5–10 µg/0.1 ml) is usually effective against fungi. Intravitreal therapy may be repeated because single dose administration may be insufficient.<sup>26</sup>

## Choice of Antimicrobial Agent

Since endophthalmitis therapy must be initiated urgently, the identity of the organism is unlikely to be known at the time the antimicrobial agents must be chosen. The vast majority of endophthalmitis infections are Gram positive in origin.<sup>26,28</sup> As already noted, the clinical setting often determines which organisms are more likely to be present. As it is almost impossible initially to rule out Gram-negative organisms as the cause of most infections on clinical examination, broad-spectrum antibiotic coverage is usually chosen.<sup>29</sup> In practice, this usually means empirical treatment with two separate antimicrobial agents as the initial choice. Unfortunately, clinical features of infection and culture results often do not correlate adequately to guide the choice of antibiotics upon presentation.<sup>30</sup> Furthermore, despite coverage with broad-spectrum antibiotics, visual loss remains a common result.<sup>26,31</sup> An outcome of endophthalmitis management is likely due to several factors, including the responsible pathogen, the patient's age, the duration between injury and treatment, the therapy chosen and the condition of the eye upon presentation. Clinical and experimental studies have firmly established that delay in therapy will result in poor visual outcome, especially in severe cases of endophthalmitis.<sup>32,33</sup>

The recommended management of bacterial endophthalmitis includes direct injection of antibiotics into the vitreous.<sup>34,35</sup> Systemic antibiotics have also been used concurrently for bacterial endophthalmitis, although some potentially effective antibiotics (vancomycin and aminoglycosides) do not penetrate readily into the vitreous, due in part to the protective effect of the blood–ocular fluid barrier. Intraocular inflammation increases the permeability of the blood–ocular fluid barrier, enhancing penetration of systemic antibiotics into the vitreous cavity.<sup>26</sup> However, intravitreal levels achieved vary substantially, frequently falling below the minimum inhibitory concentrations (MICs) for many ocular pathogens.

Due to variable penetration into the vitreous cavity of aminoglycosides, vancomycin and cephalosporins (the traditional mainstays of antimicrobial therapy in bacterial endophthalmitis), the EVS evaluated their clinical efficacy in a post-cataract surgery endophthalmitis controlled trial. Systemic antibiotics, as used in the study, did not enhance visual outcomes when used in combination with intravitreal administration.<sup>36</sup> Based on the EVS, parenteral antimicrobial agents are not recommended for eyes that would have satisfied criteria for EVS eligibility.

This recommendation against systemic antimicrobial therapy does not apply to eyes following other types of ocular surgery, trauma or suspected endogenous endophthalmitis. Clinicians are also always at liberty to modify EVS recommendations based on modifying clinical signs or new therapeutic information. Although new data suggest that fluoroquinolones penetrate into the inflamed and non-inflamed

vitreous better than other classes of antibiotics, they have not been subjected to rigorous, blinded clinical trials.<sup>26,37</sup> Despite this, fluoroquinolones in particular are currently used by many clinicians in combination with intravitreal antibiotics in the management of some severe endophthalmitis cases. Systemic antibiotics remain an integral part of the therapeutic approach to endogenous endophthalmitis where there is concomitant bacteraemia.

Intravitreal administration of antibiotics is a key component of the clinical management of exogenous bacterial endophthalmitis. Known intravitreal levels of antibiotics can be directly and immediately achieved and remain above the MICs for most pathogens for protracted periods of time. The three most commonly used antibiotics for intravitreal administration include 1.0 mg of vancomycin, 0.4 mg of amikacin and 2.2 mg of ceftazidime. Vancomycin and amikacin were included in the EVS protocol. Virtually all post-cataract surgery endophthalmitis isolates are sensitive to one or both agents.<sup>38</sup> Many clinicians prefer to substitute ceftazidime for amikacin because of the well recognised destructive retinal microvasculitis that may occur as a dose-dependent toxicity of aminoglycosides.<sup>38–40</sup> The spectra and sensitivities of ceftazidime and amikacin are similar for most ocular isolates. Therefore, the two most commonly used combinations are vancomycin and amikacin or vancomycin and ceftazidime.

In post-operative endophthalmitis, parenteral therapy is not necessary unless evidence of infection exists outside the globe. The use of systemic antibiotics does not represent an advantage for final visual recovery.

In other forms of endophthalmitis, broad-spectrum antibiotics should be administered once cultures have been obtained. An ophthalmologist usually administers intravitreal and subconjunctival injections. The systemic antibiotics given below can be administered in conjunction with injections.

Despite broad-spectrum antibacterial activity, fluoroquinolones are not widely used for direct intraocular administration, due in part to concerns about possible toxicity.<sup>41,42</sup> The emergence of antibiotic-resistant organisms, particularly vancomycin-resistant Gram-positive pathogens, such as *Enterococcus faecalis* and potentially *S. aureus*, may affect future therapeutic design.

## Anti-inflammatory Agents

Although an ocular inflammatory response is vital for the clearance of organisms during infection, this response can induce bystander damage to sensitive neurologic tissues. The ocular inflammatory response to intravitreal Gram-positive organisms is induced by growing organisms as well as metabolically inactive organisms, whole cell walls, and cell wall components.<sup>43,44</sup> Intravitreal injection of Gram-negative lipopolysaccharide induces inflammatory-cell infiltration and protein leakage into the aqueous humour.<sup>45,46</sup> Antibiotic-induced release of cell walls or their components may therefore exacerbate intraocular inflammation during endophthalmitis treatment. The phenomenon of antibiotic-induced inflammation is similarly well established in animal models of otitis media and meningitis. For meningitis, adjunctive use of corticosteroids has been shown to effectively suppress inflammation.<sup>47</sup> However, for the treatment of endophthalmitis, reports on the benefits of corticosteroid administration have been contradictory, and as a result, the use of intravitreal steroids to treat bacterial endophthalmitis remains controversial. In experimental

models of bacterial endophthalmitis, concomitant administration of dexamethasone was reported to be beneficial,<sup>48,49</sup> had no effect<sup>50,51</sup> or was detrimental to infection outcome.<sup>52</sup> Despite these conflicting results, dexamethasone is frequently used as an adjunct to antibiotic therapy in endophthalmitis.

Empirical antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting.

### Vancomycin

Vancomycin (Vancocin®) provides empirical coverage for Gram-positive organisms, including *B. cereus*. It is effective for both intravitreal and systemic administration. Vancomycin has the added advantage of providing better coverage against resistant organisms, is bactericidal against most organisms and is bacteriostatic for enterococci. It inhibits cell wall biosynthesis, interfering with cell-membrane permeability and RNA synthesis. The spectrum of coverage is entirely Gram positive but it includes all the staphylococcal species, streptococci, *P. acnes* and *Bacillus* organisms. Although some vitreous sampling after intraocular injections in human infected eyes has demonstrated persistent therapeutic levels for three to four days after initial injection,<sup>53,54</sup> in animal studies the half-life suggests that therapeutic concentrations should be maintained for only about 48 hours after intravitreal injection.<sup>55,56</sup> Creatine clearance should be used to adjust dose in patients with renal impairment.

### Gentamicin

Gentamicin (Gentacidin®, Garamycin®) provides empirical coverage for Gram-negative organisms, including *P. aeruginosa*.<sup>57</sup> It is the first choice aminoglycoside for systemic Gram-negative coverage and is a bactericidal inhibitor of protein synthesis (30S ribosomal subunit).

### Ceftazidime

Ceftazidime (Fortaz®, Ceptaz®) is a third-generation cephalosporin with broad Gram-negative coverage but decreased efficacy for Gram-positive organisms. Gram-negative coverage includes *Enterobacter*, *Citrobacter*, *Serratia*, *Neisseria*, *Providencia* and *Haemophilus* spp. Cephalosporins bind to one or more of the penicillin-binding proteins and prevent cell wall synthesis, inhibiting bacterial growth. Ceftazidime has an even greater penetration, particularly into inflamed eyes.<sup>57,58</sup> It has better *Pseudomonas* coverage than cefazolin, but it is not as effective against some Gram-positive organisms.

### Ceftriaxone

Ceftriaxone (Rocefin®) is a third-generation cephalosporin that crosses the blood–brain barrier. It is active against resistant bacteria, including gonococci, *Haemophilus influenzae* and other Gram-negative organisms. It is used in suspected haematogenous spread of endophthalmitis in combination with vancomycin while cultures are pending. Cephalosporins bind to the penicillin-binding protein and prevent cell wall synthesis, which inhibits bacterial growth.<sup>58</sup>

### Cefotaxime

Cefotaxime (Claforan®) is a third-generation cephalosporin that has broad Gram-negative coverage but lower efficacy for Gram-positive organisms. Cephalosporins bind to one or more of the penicillin-binding proteins and prevent cell wall synthesis, inhibiting bacterial growth.<sup>59</sup>

### Antifungal

An antifungal is used for suspected candidal or *Aspergillus* infection. It is indicated in patients who are immunosuppressed,

**Table 4: Medical Therapy**

Topical
Vancomycin 50 mg/ml every hour
Ceftazidime 50 mg/ml every hour
(EVS: vancomycin + amikacin)
Subconjunctival
Vancomycin 25 mg in 0.5 ml
Ceftazidime 100 mg in 0.5 ml
Dexamethasone 6 mg
Systemic
Vancomycin 1 g every 12 hours
Ceftazidime 2 g every eight hours
(EVS: ceftazidime + amikacin + prednisone)
Intravitreal
Vancomycin 1 mg in 0.1 ml
Amikacin 0.4 mg in 0.1 ml
Dexamethasone 0.4 mg in 0.1 ml
(EVS: no steroid)

EVS = Endophthalmitis Vitrectomy Study.

**Table 5: Antifungal Medical Therapy**

The available drugs are amphotericin B, ketoconazole, fluconazole
Systemic: 400 mg on the first day, then 200 mg/day
Intravitreal: 5 µg in 0.1 ml of H <sub>2</sub> O
Topical: in 0.2–2 % H <sub>2</sub> O solution
At the moment voriconazole is also in use

who have indwelling venous catheters or who are currently taking broad-spectrum antibiotics.

### Amphotericin B

Amphotericin B (AmBisome®) is a fungistatic or fungicidal depending on the concentration attained in body fluids; polyene antibiotic produced by a strain of *Streptomyces nodosus*. Amphotericin B changes the permeability of the fungal cell membrane by binding to sterols, which causes fungal cell death as intracellular components leak out.

In the treatment of candidal endophthalmitis oral fluconazole is indicated. Amphotericin B intravenously or intravitreally may be considered, in association with cycloplegic drops (i.e. atropine).

The limitations of intravenous amphotericin B include required hospitalisation, severe ocular inflammation and numerous systemic adverse effects such as nephrotoxicity, fever, rigors and hypotension.<sup>60</sup>

### Triazole Agents

Fluconazole is an older-generation triazole that has been used systemically as a supplement or alternative to amphotericin B, but it lacks the broad spectrum of coverage necessary for the most commonly encountered fungal species in eye disease. Furthermore, intraocular penetration is marginal.<sup>61</sup> Itraconazole is rarely used in the treatment of ocular fungal eye infections as it lacks a broad spectrum of coverage, specifically against *Fusarium* spp.<sup>4,62</sup> The newest triazole agents, including ravuconazole, posaconazole and voriconazole, are synthetic derivatives of fluconazole but have a significantly broader spectrum of activity. At present, only voriconazole (Vfend®) is commercially available. It has been approved by the US Food and Drug Administration for the treatment of invasive aspergillosis, oesophageal candidiasis and other systemic indications, and is available in oral and intravenous formulations. Voriconazole has been shown to have a broad spectrum

of activity against non-ocular isolates of *Aspergillus* spp, *Candida* spp, *Paecilomyces lilacinus*, *Cryptococcus neoformans*, *Scedosporium* spp, *Curvularia* spp and others.<sup>12-15</sup> It has excellent *in vitro* activity with low MICs against *Candida* and *Aspergillus* spp, known to be resistant to amphotericin B, fluconazole and itraconazole. Activity against *Fusarium* spp has been variable. Adverse effects, including visual disturbances and skin rashes, have been mild and transient. Visual disturbances, including abnormal vision, colour vision change and/or photophobia, typically resolve within one month, even with continued therapy. Elevations in hepatic enzyme levels can occur. The medical therapy is showed in Tables 4 and 5.

## Vitreotomy

Vitreotomy applies to the eye the classical principals of incision and drainage with consequent reduction of micro-organisms and their toxins. Although intravitreal antibiotic therapy can provide effective killing of bacteria during endophthalmitis, vitrectomy is an appealing adjunct to management. Vitrectomy (surgical cutting and aspiration of vitreous contents and replacement with balanced salt solution) debrides the vitreous cavity of bacteria, inflammatory cells and other toxic debris; promotes better diffusion of antibiotics; removes inflammatory membranes; permits earlier visualisation of the retina; and may speed recovery of vision. Vitrectomy has been shown to improve visual outcome in severe post-operative EVS-eligible cases.<sup>26</sup> An ongoing debate exists concerning the appropriate timing for vitrectomy in traumatised eyes. However, most reports agree that vitrectomy should be performed without delay in severe cases of endophthalmitis, especially in those involving intraocular foreign bodies. Vitrectomy must be reserved for patients who present with initial visual acuity of light perception. In fact, only in these cases has it been demonstrated to be more advantageous compared with intravitreal antibiotic injection.

Our approach is removal of the IOL and the bag, scleral buckling, total vitrectomy with injection of polydimethylsiloxane that has antimicrobial activity *in vitro* against *S. aureus*, *S. epidermidis*, *P. Aeruginosa*, *C. Albicans* and *Aspergillus*. Micro-organisms may be recovered from extracted vitreous, but the microbiological yield does not appear to be enhanced over that recovered from a needle tap.

No study to date has effectively looked at the question of antibiotic prophylaxis. Proper pre-assessment of the patient, identifying and treating risk factors such as blepharitis, mucocoele of the lacrimal sac or conjunctivitis is probably more useful than blunderbuss prophylaxis.

Outcomes following appropriate surgical management are related to a number of factors, most importantly, the level of visual function at the time of clinical presentation. In the EVS, a National Institutes of Health-funded multicentre prospective study, eyes presenting with a visual acuity of only light perception achieved a final vision of 20/40 in 33 % of cases, even though the most efficacious management protocol was used. If the presenting vision was better than light

perception, over 60 % of eyes achieved 20/40 or better vision using the same treatment protocol.

In the prevention of postsurgical infections it is fundamental that skin and conjunctival sac preparation takes place with 5 % aqueous povidone iodine, at least five minutes before surgery; this is safe and effective in significantly reducing ocular surface flora. Instillation of this material into the sac at the end of the procedure may be additionally effective. The use of antibiotics in irrigating solutions has been widely condemned and the choice of vancomycin can be especially criticised from a public health stance for the following reasons: resistance to vancomycin has been encountered, it has a low therapeutic index, there are possible dosage errors and retinal toxicity. However, in the US 80 % of eye surgeons use vancomycin 5 mg in 500 ml balanced salt solution (BSS) in liquid infusion, while gentamicin 4 mg in 500 ml BSS is used by 40 % of surgeons. Vancomycin added to the irrigating solution used during cataract surgery has been found in effective concentrations in the AC at the end of surgery.<sup>63</sup>

The addition of gentamicin and vancomycin to the irrigating fluid during phacoemulsification results in a highly significant reduction in the microbial contamination of AC aspirates.<sup>64</sup>

Also, many studies have proven the efficacy of intracameral antibiotics in the prevention of post-operative endophthalmitis. Intracameral bolus injection of cefazolin (1 mg in 0.1 ml solution) and also intracameral cefuroxime 1 mg at the end of cataract surgery have been shown to reduce the rate of post-operative endophthalmitis without toxic effects on the cornea or retina.<sup>65</sup> The type of IOL material, and whether it is foldable or not, has significant influence on the incidence of endophthalmitis. Injectable IOLs are associated with the lowest risk of post-operative endophthalmitis (0.028 %). This lower rate of endophthalmitis with injectable IOLs is due to the ease of insertion and non-contact with the ocular surface.<sup>66</sup>

It has been shown that implanting a heparinised IOL may also reduce the chances of endophthalmitis.<sup>67</sup> Hydrophilic polymer surfaces (hydrogel and probably hydrophilic acrylic) are useful in avoiding the development of bacterial colonies (*S. epidermidis* strains). These lenses either inhibit or delay bacterial colonisation.<sup>68</sup> Prophylactic subconjunctival antibiotic injections at the conclusion of cataract surgery decrease the incidence of post-operative endophthalmitis. This is because the very high concentrations of antibiotics achieved in the AC from such injections destroy any bacteria that may have been introduced during surgery. Wallin et al. recommend that the topical antibiotic should be started from the day of the operation and not from the next day.<sup>69</sup>

It has been recommended that placing a patch after the surgery is protective and should be kept for approximately four hours. This helps to keep the wound sealed and hence reduce the chance of endophthalmitis.<sup>68</sup> ■

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