ESCRS Guidelines on prevention, investigation and management of post-operative endophthalmitis

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Supported by
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1. Introduction

1.1 Endophthalmitis

Endophthalmitis is an inflammatory reaction occurring as a result of intraocular colonisation by bacteria, fungi or rarely parasites. It can be exogenous (post-operative, post-traumatic) due to microbial contamination spreading from the ocular surface or open incision (wound) or contaminated instruments, intraocular lenses (IOLs) or intraocular foreign bodies or endogenous (septicaemia) in origin.

These guidelines on the prophylaxis and treatment of post-operative endophthalmitis are supported in detail with literature references, which were classified according to the criteria of the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) [Association of the Scientific Medical Societies in Germany] and the Ärztliches Zentrum für Qualität [Agency for Quality in Medicine] for evidence-based medicine (EBM) (Table 1.1). This enables the reader to form an accurate opinion of the value of the individual views stated. At the same time, he or she is able to form an opinion him/herself from the extensive literature. Ultimately, it is apparent that there is a lack of well-founded prospective and controlled studies of many procedures - an important task for the future. Results of the recently completed ESCRS Study on the Antibiotic Prophylaxis of Post-operative Endophthalmitis (ESCRS Study) have been included in these Guidelines.

Table 1.1 Classification of evidence type of studies

<table>
<thead>
<tr>
<th>Stage</th>
<th>Evidence based on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>I a</td>
<td>meta-analysis of randomised controlled studies</td>
</tr>
<tr>
<td>I b</td>
<td>at least one randomised controlled study</td>
</tr>
<tr>
<td>II a</td>
<td>at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>II b</td>
<td>at least one well-designed, quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>well-designed, non-experimental descriptive studies (e.g. comparative studies, correlative studies, case-control studies)</td>
</tr>
<tr>
<td>IV</td>
<td>reports/opinions of expert circles, consensus conferences and/or clinical experience of acknowledged authorities</td>
</tr>
</tbody>
</table>

1.2 Pathophysiology

The occurrence, severity and clinical course of endophthalmitis depends on the route of infection, the virulence and number of inoculated pathogens as well as the patient’s immune state and the time of examination [205]. In 29 to 43 per cent of cataract operations, intraocular contamination occurs with facultative pathogenic bacteria from the ocular surface without the development of endophthalmitis [41], [68], [106]. Protective mechanisms, which have been summarised as the “immune privilege of the eye” (anterior or posterior chamber-associated immune deviation, ACAID or POCAID) [205], are particularly effective in the anterior part of the eye, act as a protective barrier and can limit the inflammatory reaction [191], [198]. If this privilege is compromised, e.g. by an intra-operative capsular defect with vitreous loss, the risk of endophthalmitis increases by a factor of 14 [98].

In microbial endophthalmitis, three phases of infection can be observed: an incubation phase, an acceleration phase and a destructive phase [173]. A clinically inapparent incubation phase is observed initially, which lasts at least 16 to 18 hours, even with virulent micro-organisms. Intraocular bacterial inoculation above a critical level then leads to breakdown of the aqueous barrier with fibrin exudation and cellular infiltration by neutrophilic granulocytes [24]. The incubation phase is determined mainly by the generation time of the pathogen (e.g. *Staphylococcus aureus* and *Pseudomonas aeruginosa* up to 10 min, *Propionibacterium sp.* > 5 h) and the specific characteristics of the pathogen such as toxin production. With the commonest pathogens, *Staphylococcus epidermidis* (CNS) and *Staphylococcus aureus*, the greatest infiltration is observed only three days after infection [24], [39].

In the case of primary infection of the posterior part of the eye, inflammation of the anterior chamber occurs initially and this is accompanied within seven days by a specific immune response with macrophages and lymphocytes in the vitreous cavity. Just three days after intraocular infection, pathogen-specific antibodies can be detected, which contribute to pathogen elimination by opsonisation and phagocytosis within about
10 days. This can produce negative laboratory culture results but severe inflammatory disease within the eye [39]. The inflammatory mediators of infiltrating cells, especially cytokines, not only recruit further leukocytes but can directly result in destructive effects, retinal injury and vitreoretinal proliferation (destructive phase) [30], [205].

It has been suggested that the use of phacoemulsification increases pressure within the eye forcing bacteria backwards into the vitreous, where early multiplication gives rise to the anterior vitritis characteristically seen behind the posterior capsule (refer to Investigation Section below).

Intraocular lenses are a potential vector for bacteria. There are differences in adherence to different lens materials. Staphylococcus epidermidis adheres more to polypropylene haptics than to polymethyl methacrylate, (PMMA) [69], [98], [190]. Hydrophilic heparin-coated lenses demonstrate lower adherence for staphylococci [52]. The clinical effects have been variously interpreted [106]. A recent retrospective study has suggested, but not proven, that use of foldable IOLs inserted via a sterile injector lowers the incidence of post-operative endophthalmitis [95].

1.3 Microbial spectrum
This is described in the table of post-operative endophthalmitis below. The spectrum is dependent on various factors including environmental, geographic and climatic conditions and which type of surgery is performed.

Table 1.2: Microbial spectrum of post-operative endophthalmitis
In summary, the most important pathogens causing post-operative phacoemulsification endophthalmitis are:

<table>
<thead>
<tr>
<th>Post-operative (cataract surgery) endophthalmitis [46], [70], [81], [100], [102], [105], [134], [205], [207]</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 - 77 % CNS (coagulase-negative staphylococci)</td>
</tr>
<tr>
<td>10 - 21 % Staphylococcus aureus</td>
</tr>
<tr>
<td>9 - 19 % BHS (β-haemolytic streptococci), S. pneumoniae, α-haemolytic streptococci including S. mitis and S. salivarius</td>
</tr>
<tr>
<td>6 - 22 % Gram-negative bacteria including Ps. aeruginosa (occurs rarely)</td>
</tr>
<tr>
<td>up to 8 % Fungi (Candida sp., Aspergillus sp., Fusarium sp.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delayed post-operative saccular or capsule bag endophthalmitis with IOL implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propionibacterium acnes, corynebacteria including C. macginleyi [164], [175], [205] and fungi [205]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-operative (glaucoma surgery) endophthalmitis [116], [124]</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 67 % CNS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Delayed post-operative (glaucoma surgery) endophthalmitis [78], [142]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococci</td>
</tr>
<tr>
<td>Gram-negative bacteria (especially Haemophilus influenzae)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-traumatic endophthalmitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single pathogen identified in 62–65%, mixed infection in 12–42% [57], [91], [125], [130], [205], [207], [208]</td>
</tr>
<tr>
<td>16 - 44 % CNS</td>
</tr>
<tr>
<td>17 - 32 % Bacillus sp.</td>
</tr>
<tr>
<td>10.5 - 18 % Gram-negative bacteria</td>
</tr>
<tr>
<td>8 - 21 % Streptococci</td>
</tr>
<tr>
<td>4 - 14 % Fungi</td>
</tr>
<tr>
<td>4 - 8 % Corynebacterium sp.</td>
</tr>
<tr>
<td>1 - 2 % Clostridum perfringens and other soil bacteria</td>
</tr>
</tbody>
</table>
In the ESCRS Study, 29 patients presented with presumed post-operative endophthalmitis, of whom 20 were classified as having proven infective endophthalmitis. The causative bacteria were identified by microbiological methods and polymerase chain reaction (PCR) [11]. From 19 cases the following bacteria have been confirmed:

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus epidermidis</td>
<td>6</td>
</tr>
<tr>
<td>CNS</td>
<td>4</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2</td>
</tr>
<tr>
<td>other staphylococci</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>2</td>
</tr>
<tr>
<td>other streptococci</td>
<td>6</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>1</td>
</tr>
<tr>
<td>Gemella haemolysans</td>
<td>1</td>
</tr>
</tbody>
</table>

In summary, the most important pathogens causing post-operative phacoemulsification endophthalmitis are:

**Acute**
- BHS, *S. mitis*, *S. pneumoniae*, *E. faecalis*
- *S. aureus*, CNS, (MRSA, MRSE)
- Gram-negative rods (GNR) including *Haemophilus influenzae* and *Pseudomonas aeruginosa*

**Chronic**
- *P. acnes*
- Diphtheroids
- CNS
- Fungi

### 1.4 Incidence of endophthalmitis after different types of surgery

**Phacoemulsification**
At the start of the 20th century (c1910), the incidence of endophthalmitis after cataract operations was 10 per cent. In the period of ECCE via a scleral or limbal incision and improved hygiene conditions (1970-1990), the infection rate fell to 0.12 per cent in Europe [90] and to 0.072 per cent in the US [88]. However, since the introduction of phacoemulsification and clear cornea incisions, the retrospective data with phacoemulsification are between 0.3 to 0.5 and 0.015 per cent (Table 1.3).

**Table 1.3: Reported incidence for endophthalmitis after cataract surgery**

<table>
<thead>
<tr>
<th>Country</th>
<th>[reference]</th>
<th>Year of Publication</th>
<th>Incidence (%)</th>
<th>No. of Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>[98]</td>
<td>1991</td>
<td>0.22</td>
<td>24105</td>
</tr>
<tr>
<td>USA</td>
<td>[203]</td>
<td>1992</td>
<td>0.015</td>
<td>27181</td>
</tr>
<tr>
<td>France</td>
<td>[40]</td>
<td>1992</td>
<td>0.32</td>
<td>– 34690</td>
</tr>
<tr>
<td>Germany</td>
<td>[126]</td>
<td>1999</td>
<td>0.15</td>
<td>– 103090</td>
</tr>
<tr>
<td>Netherlands</td>
<td>[135]</td>
<td>2000</td>
<td>0.10</td>
<td>– 25330</td>
</tr>
<tr>
<td>Canada</td>
<td>[64]</td>
<td>2000</td>
<td>0.01 to 0.18</td>
<td>13886</td>
</tr>
<tr>
<td>Sweden</td>
<td>[37]</td>
<td>2002</td>
<td>0.10</td>
<td>54666</td>
</tr>
<tr>
<td>Australia</td>
<td>[110]</td>
<td>2003</td>
<td>0.16 to 0.36</td>
<td>83677</td>
</tr>
<tr>
<td>Japan</td>
<td>[8]</td>
<td>2003</td>
<td>0.05 to 0.29</td>
<td>11595</td>
</tr>
<tr>
<td>USA</td>
<td>[86]</td>
<td>2005</td>
<td>0.29</td>
<td>9079</td>
</tr>
<tr>
<td>Ireland</td>
<td>[87]</td>
<td>2005</td>
<td>0.5</td>
<td>8763</td>
</tr>
<tr>
<td>UK</td>
<td>[105]</td>
<td>2007</td>
<td>0.099</td>
<td>101920</td>
</tr>
<tr>
<td>Sweden</td>
<td>[94]</td>
<td>2007</td>
<td>0.048</td>
<td>225471</td>
</tr>
<tr>
<td>Europe</td>
<td>[5]</td>
<td>2007</td>
<td>0.05 to 0.35</td>
<td>16211</td>
</tr>
</tbody>
</table>
While in the majority of studies patients received various additional forms of prophylaxis, the higher incidence rate reported by the ESCRS [5] may be regarded as the true background rate when only povidone-iodine is administered pre-operatively.

**Risk factors for endophthalmitis following cataract surgery**

The clear cornea incision is thought to have contributed to the increase in the number of endophthalmitis cases following phacoemulsification surgery [8], [64], [197], [205]. Taban (2005) performed a meta-analysis of 215 studies that addressed post-cataract surgical endophthalmitis which met his selection criteria [129]. A total of 3,140,650 cataract extractions were pooled from ECCE and phacoemulsification surgery giving an overall incidence of 0.128 per cent for post-operative endophthalmitis. He found this incidence varied with time from 0.265 per cent in 2000/2003, 0.087 per cent in the 1990s, 0.158 per cent in the 1980s to 0.327 per cent in the 1970s. He found the clear corneal incision of phacoemulsification to be a risk factor between 1992 and 2003 with an increased rate of 0.189 per cent compared to 0.074 per cent for scleral tunnel incision. However, Taban reviewed the limitations of his meta-analysis study depending mostly on retrospective studies with limited statistical power. He commented on the paucity of prospective randomised case-controlled studies.

Wallin et al. identified potential risk factors in a study of 27 endophthalmitis cases compared with 1525 patients in the cohort control. Main factors found to be statistically associated with endophthalmitis included i) wound leak on the first post-operative day (p<0.001), ii) capsular or zonular surgical complication (p<0.001), and iii) use of topical antibiotic started the day after surgery rather than the day of surgery (p=0.005) [136].

There are only a few data on the incidence of endophthalmitis between inpatient and outpatient surgery respectively. Various studies give no evidence of any difference [56], [84], [118], [143].

There is a range of technical factors relating to the cataract operation that influence the risk of endophthalmitis. With regard to the incision, leak-proof closure plays an important role. When the clear cornea incision (CCI) was first used, the data regarding the incidence of infection tended to be poor; in 1991, Stonecipher et al. published three cases of infectious endophthalmitis after CCI [128] and described how 65 per cent of all CCIs demonstrated wound dehiscence [197]. Williams et al. reported that they found an infection rate of only 0.015 per cent in nearly 30,000 CCIs [203].

The risk of wound dehiscence appears to be greater with CCI [192] than with the corneo-scleral (scleral tunnel) incision (CSI). In Germany, there was an incidence rate of endophthalmitis after CCI of 0.1 per cent versus 0.07 per cent for CSI [126], in Canada the rate was 0.13 per cent for CCI versus 0.05 per cent for CSI [64]. However, in a recent prospective randomised multi-centre study (11,595 eyes), the endophthalmitis risk was reduced fivefold in superior CSI (p = 0.037) compared to temporal CCI [8].

Recently published data from the Swedish National Cataract Register including 225471 cataract extractions between January 2002 and December 2004 showed only a trend for a higher risk of endophthalmitis for CCI. This prospective, non-randomised, observational study indicated that the use of clear corneal and/or temporal approaches would result in one additional post-operative endophthalmitis case in approximately 5500 procedures compared to sclero-corneal or superior incisions [94]. However, not reaching statistical significance may have been a consequence of the widespread use of prophylactic intracameral cefuroxime with its low overall rate of post-operative endophthalmitis in Sweden.

The clear corneal incision as a risk factor has been assessed prospectively in the multi-centre ESCRS study of antibiotic prophylaxis of endophthalmitis with similar results. Patients receiving the clear cornea procedure were found to be 5.88 times more likely to experience endophthalmitis than patients receiving scleral tunnel. While the risk associated with CCIs remains an important finding of the study, the results must be treated with caution. Only two of the participating 24 centres used scleral tunnel incisions routinely, with none of the others using it more than occasionally. It is therefore conceivable that the reduced risk associated with the scleral tunnel technique is due to some other unidentified factors common to both centres, but absent from most of the other centres in the study [5].

An important factor appears to be the construction of the tunnel. In CSI the tunnel is more quadratic, where as in CCI often double wide than radial and thus more prone to gaping. Therefore, the increased risk associated with CCI may be reduced by suturing the corneal incision [183]. Thoms et al. reviewed rates of endophthalmitis among 815 consecutive eyes that received clear corneal cataract surgery over five years. Of these, the incision was sutured in 436 eyes and unsutured in 379 eyes. The researchers found five cases of culture-positive endophthalmitis, all of which occurred in the unsutured group [132].
In a case-control study of post-operative endophthalmitis cases in Sweden between 1994 and 2000, Wejde et al. found that silicone intraocular lenses carried a higher risk than heparin surface modified PMMA implants [138]. Likewise, in the prospective ESCRS study, the type of IOL material was found to be a risk factor which was significantly associated with endophthalmitis. Patients receiving a silicone intraocular lens were 3.13 times more likely to experience endophthalmitis than patients receiving an acrylic (or other material) lens. The hydrophobic nature of silicone may not be the main characteristic explaining the apparent increased risk; the explanation is likely to be more subtle involving an understanding of how differing biofilms are formed based on the surface properties of varying types of IOLs [5].

Finally, the ESCRS study demonstrated that surgical complications contribute to a higher incidence of contracting endophthalmitis following phacoemulsification cataract surgery. Patients experiencing complications at the time of surgery had a 4.95 times higher risk of infection [5].

There are no definite data with regard to other factors such as duration of operation, tissue trauma, and choice of viscoelastic and irrigation solution [127], while there is limited retrospective data for use of injectors for lens (IOL) implantation, suggesting they reduce the infection rate [95], and operative experience, suggesting a higher complication rate by junior staff. All these factors have been assessed prospectively in the multi-centre ESCRS study (Table 1.4).

Because of the low incidence of childhood cataract, an exact estimate of the endophthalmitis risk in this patient population is not possible. In 1990, Good et al. found three cases of endophthalmitis after 671 operations for paediatric or congenital cataract (0.45 per cent). Two of the three cases occurred within the first 24 hours and Gram-positive bacteria were isolated as the cause (S. aureus, S. epidermidis, Strep. pneumoniae) [76]. Wheeler et al. reported 11 cases of endophthalmitis after cataract surgery out of 24,000 cataract or glaucoma operations in children [139].

### Table 1.4: Risk factors for endophthalmitis following phacoemulsification surgery being investigated in the ESCRS multi-centre study

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-cameral injection of cefuroxime – given or not given</td>
<td>4.92</td>
</tr>
<tr>
<td>Clear cornea (and position) versus scleral tunnel incision</td>
<td>5.88</td>
</tr>
<tr>
<td>Type of wound closure – suture or sutureless</td>
<td>no evidence found</td>
</tr>
<tr>
<td>Insertion of IOL – injector or forceps</td>
<td>no evidence found</td>
</tr>
<tr>
<td>Type of IOL material</td>
<td>3.13</td>
</tr>
<tr>
<td>Diabetic or non-diabetic</td>
<td>no evidence found</td>
</tr>
<tr>
<td>Immuno-suppression or not</td>
<td>no evidence found</td>
</tr>
<tr>
<td>Equipment sterilisation – disposable vs reusable</td>
<td>no evidence found</td>
</tr>
<tr>
<td>Complications of surgery</td>
<td>4.95</td>
</tr>
</tbody>
</table>

**Glaucoma surgery**

Early post-operative endophthalmitis following glaucoma surgery has an incidence of about 0.1 per cent [89], [142]. However, the majority of cases of endophthalmitis after glaucoma surgery occur after months or years; the incidence is about 0.2 per cent to 0.7 per cent [89], [142]. The risk of endophthalmitis when using anti-metabolites depends, among other things, on the location of the filter bleb, where the inferior position has a markedly higher risk (Wolner: three per cent with superior vs. 9.4 per cent with inferior position, Greenfield: 1.3 per cent with superior vs. 7.8 per cent with inferior position, Caronia: 11.9 per cent with inferior position, Higginbotham: 1.1 per cent with superior vs. 8 per cent with inferior position) [59], [78], [82], [142]. After 5-FU the incidence of endophthalmitis is 5.7 per cent [142].

In children, six cases of endophthalmitis after glaucoma surgery were reported after 24,000 cataract and glaucoma filtering operations [139]. However, it is not reported how many of the 24,000 operations were glaucoma surgeries alone.

Endophthalmitis after filter bleb operation commences within four weeks in about 19 per cent, so the majority of cases occur later [92], [123]. In about half of the cases, the infection is due to streptococci and Gram-negative bacteria including *Moraxella* sp. [55], [60], [181]. The endophthalmitis is sometimes preceded for days or weeks by eyebrow pain, headache, blepharitis and conjunctivitis [123]. Filter bleb infection can still occur after many years [60], [78], [142].
Penetrating keratoplasty
The incidence of post-operative endophthalmitis after penetrating keratoplasty reported in the literature is between 0.08 per cent and 0.2 per cent (Elfrig: 0.08 per cent, Kattan: 0.11 per cent, Somani: 0.2 per cent) [71], [88], [127]. Contamination of the donor cornea appears to be an important risk factor [152]. Fungal endophthalmitis after keratoplasty tends to be rare [99], [151], [189].

Pars plana vitrectomy
The incidence of post-operative endophthalmitis reported in the literature after pars plana vitrectomy is between 0.05 per cent and 0.14 per cent [83], [88]. A few authors assumed that there was an increased incidence of endophthalmitis after pars plana vitrectomy, as the patient often suffers at the same time from, for example, diabetes mellitus. However, this assumption has not been confirmed.

The largest sample size comes from Cohen et al. in 1995 with 12,216 vitrectomies in eight centres; nine cases of endophthalmitis were reported with an incidence of 0.07 per cent [63]. Since then, Jager et al. have presented a retrospective review for 1972-2002 with 10,563 intravitreal taps in 1326 eyes from 42 published reports [171]; the overall incidence of endophthalmitis was 0.17 per cent (18 cases). For those vitrectomies performed in the operating theatre, the rate was 0.11 per cent (4/3720) while for those performed in out-patients, the rate was 0.17 per cent (5/2965) which was not statistically significant. However, when there was use of topical povidone iodine prior to the tap, the incidence rate was 0.14 per cent (9/6314), which increased to 0.69 per cent (6/869) when iodine was not used - this is statistically significant at p = 0.0009, but relates to multiple taps in non-inflamed eyes.

Post-traumatic endophthalmitis
Post-traumatic endophthalmitis, along with post-operative endophthalmitis, is the second commonest form of endophthalmitis. The incidence of endophthalmitis after perforating injury is between two per cent and 17 per cent [75], [154].

Trauma due to an intraocular foreign body involves a greater risk of endophthalmitis than trauma without a foreign body [131]. The signs of infection usually occur early, but are often masked by the post-traumatic reactions of the injured tissue.

An exact history (e.g. “did the accident happen in the country or in the city?”, type of foreign body, symptoms) enables an early diagnosis to be made. In rural districts, the occurrence of post-traumatic endophthalmitis was reported in 30 per cent of 80 patients after an injury. In contrast, post-traumatic endophthalmitis occurred in 11 per cent of 204 patients in non-rural districts [154].

The start, course and symptoms of endophthalmitis after trauma are very varied, corresponding to the causative organisms. The initial symptoms are usually pain, intraocular inflammation, hypopyon and vitreous clouding. Similar to post-operative endophthalmitis, two thirds of the bacteria in post-traumatic endophthalmitis are Gram-positive and 10 to 15 per cent are Gram-negative [25]. In contrast to post-operative endophthalmitis, virulent Bacillus species are the commonest pathogens in post-traumatic endophthalmitis. They were isolated in 20 per cent of all cases of post-traumatic endophthalmitis. In the rural population, they are found in 42 per cent of cases of post-traumatic endophthalmitis. They are the second commonest cause of all cases of endophthalmitis. Most Bacillus infections are associated with intraocular foreign bodies [154]. Infections that are caused by Bacillus species usually commence with rapid loss of vision together with severe pain.

Fungi are the causative organisms in 10 to 15 per cent of cases of endophthalmitis after trauma. Fungal endophthalmitis usually commences only weeks to months after the injury. While mixed infections tend to be rarer in post-operative endophthalmitis, they were isolated in 42 per cent of the trauma-associated cases of endophthalmitis [154].

Compared to post-operative endophthalmitis, the prognosis of post-traumatic endophthalmitis is usually poor. This is due to a spectrum of more virulent pathogens, to mixed infections, to the degree of tissue injury caused by the preceding trauma and to the failure to instil prophylactic intravitreal antibiotics at the time of surgery. While final vision of 20/400 or better occurs in 85 per cent of cases of post-operative endophthalmitis, patients with post-traumatic endophthalmitis achieve a final vision of 20/400 or better in only 26 to 54 per cent with the remaining losing all vision [49], [57], [114], [131].
Medical conditions

Diabetes mellitus
About 14 to 21 per cent of all patients who develop post-operative endophthalmitis after cataract operations are diabetic [67], [122]. However, pre-existing diabetes mellitus has not been confirmed as an isolated risk factor for post-operative endophthalmitis after cataract extraction [4], [5]. If endophthalmitis occurs in diabetics after cataract extraction, however, the functional prognosis must be regarded as poorer especially if diabetic retinopathy is present pre-operatively [67]. Endophthalmitis in diabetics is caused more often by Gram-negative bacteria than in non-diabetics [122]. In the EVS, endophthalmitis patients with diabetes mellitus benefited particularly from vitrectomy even when their initial vision was better than light perception [4].

Immune-suppression
Patients on topically or systemically administered immuno-suppressant therapy (corticosteroids, anti-metabolites) at the time of intraoperative procedures have a significantly higher risk of endophthalmitis [106]. A change in the local pre-operative flora was not confirmed in patients on immuno-suppressant therapy, nor was there an alteration in the spectrum of the organisms causing the endophthalmitis [185].

Altered bacterial flora
Atopic patients and those with rosacea have altered conjunctival and lid bacterial flora with a preponderance of Staphylococcus aureus [12]; in addition rosacea patients have enhanced systemic cell-mediated immunity to S. aureus which is thought to contribute to their blepharitis and keratitis [12]. While no trial data exists for an increased incidence of endophthalmitis after cataract surgery in these patients, anecdotal evidence does exist and it is prudent to give them anti-staphylococcal prophylaxis prior to and after surgery [207].
2. Prophylaxis

2.1 Operating theatre

Air flow design
There are no current guidelines or data for the type of airflow best required to prevent post-operative endophthalmitis after phacoemulsification. For ECCE operations, it has been shown in the past that 85 per cent of endophthalmitis cases could be traced to the patient by comparing DNA profiles of vitreous isolates of bacteria with those collected from the lid and skin flora of the patient [42]. Nevertheless, a risk remains of infecting the eye with bacterial flora from the surgical team by the airborne route.

Old data on aerobiology has suggested that a hospital operating theatre should have a minimum of 20 air changes per hour to reduce the airborne bacterial count, but this is arbitrary as all the airborne bacteria, attached to skin scales, will settle to the floor in still air after 30 minutes. Research on ultra-clean air for hip surgery has shown that a fast laminar flow of air in an operating theatre can remove airborne bacteria within seconds, rather than minutes with traditional airflow systems at 20 air changes per hour, but is this required for phacoemulsification surgery through a very small incision? This question has been investigated by the ESCR multi-centre study of endophthalmitis after phacoemulsification surgery, as some clinical partners operate with minimal airflow, others 20 air changes per hour and others have ultraclean air systems with either horizontal or vertical laminar flow. However, the result of this investigation was inconclusive, a relationship between air changes per hour and incidence of endophthalmitis has not been established [5].

Equipment – sterilisation and single-use
All instruments for surgery should be sterile. Single-use is even more robust, as there have been occasions recently when instruments have not been washed properly prior to sterilising which itself may have been faulty. Care is required with both washing the instruments and autoclaving them, as the latter is never absolute nor an exact science! Both matters should be investigated if there is an ongoing ‘epidemic’ of post-operative endophthalmitis with different types of skin bacteria viz. coagulase-negative staphylococci within a surgical unit for no obvious reason.

Single-use of tubing and other equipment that becomes wet within the operative procedure is always preferable, if cost allows. Tubing is not easy to effectively sterilise unless an ethylene oxide gas steriliser is available. Bottles of solution containing BSS (balanced salt solution) etc. should never be kept or used for more than one operating session. Any air vent applied to these bottles should be protected by a bacterial filter. Wet areas are easily contaminated with Pseudomonas aeruginosa, which can then cause devastating endophthalmitis.

2.2 Antisepsis

The goal of pre-operative antisepsis is to reduce the likelihood of a wound infection by reducing the total bacterial count in the wound area and immediate wound environment. In view of the low incidence of endophthalmitis, controlled studies comparing the effectiveness of different antiseptics are hardly feasible because of the random sample sizes required.

For peri-orbital skin antisepsis, a five to 10 per cent povidone-iodine solution is recommended which should be allowed to act for a minimum of 3 min, as the skin contains many sebaceous glands. If this is contraindicated (allergy or hyperthyroidism), an aqueous solution of chlorhexidine (0.05 per cent) should be used instead [212]. Single use of chlorhexidine is non-toxic at this concentration.

For antisepsis of the conjunctiva and cornea, povidone-iodine is the chemical preparation of choice. The numbers of bacteria on the conjunctiva and cornea can be reduced by 1 log10 count (10 fold) to a maximum of 2 log10 count (100 fold) in the pre-operative phase by a five per cent povidone-iodine solution left in place for a minimum of three minutes [22], [23], [27], [28], [85]; a 10 per cent solution of povidone-iodine can be diluted 1:1 with BSS or isotonic saline. Post-operatively, a significant reduction in bacterial count in the conjunctival sac can also be achieved by antisepsis with a 1.25 per cent povidone-iodine solution [28].

Schmitz et al. in their questionnaire survey of 469 ophthalmic surgical institutions in Germany, came to the conclusion that the pre-operative use of povidone-iodine on the conjunctiva significantly reduced the risk of endophthalmitis [126]. However, the survey gave no indication of the method of application, contact time, or concentration of the povidone-iodine solution employed, so the conclusion remains unproven. In an analysis of the literature from 1966 to 2000 listed in Medline, the benefit of povidone-iodine antisepsis is also confirmed, even if only with category EbM III (= moderately important to clinical outcome) [61].
In 1991, Bohigian was able to show in a retrospective analysis of a total of 19,269 cataract extractions that the incidence of endophthalmitis fell from 0.08 per cent to 0.03 per cent following the introduction of antisepsis with five per cent povidone-iodine. This difference indicates a benefit but was not statistically significant and it is doubtful whether it can be attributed exclusively to povidone-iodine antisepsis [56]. In the same year, Speaker and Menikoff in their study of 8,083 patients showed a significant difference, at the 0.05 level, between the incidence of endophthalmitis with antisepsis using five per cent povidone-iodine (0.06 per cent) and the control group in which silver-protein solution was used (0.24 per cent) [18].

The optimum concentration of povidone-iodine for use in pre-operative eye antisepsis has not been established at present. From the aspect of tolerability, there is evidence that even a 10 per cent povidone-iodine solution (without the addition of detergent) is associated with low external corneal toxicity [177]. On the other hand, considerable side effects can be expected if even a five per cent povidone-iodine solution gets into the anterior chamber [145]. In animal experiments, the healing of skin wounds is significantly delayed even by two per cent povidone-iodine [211], while it is tolerated by the sensitive nasociliary epithelium in a concentration of 1.25 per cent [17] and by adult cartilage at one per cent [16] without the efficacy in vitro being restricted at these dilutions even with a large protein and blood load [38].

Studies of the use of chlorhexidine digluconate on the conjunctiva or cornea give conflicting results. A four per cent chlorhexidine solution induces corneal damage and should NOT be used [177], [200]. Complications have also been described for the 0.02 per cent chlorhexidine solution [188], but when used as long-term therapy (four times daily for eight weeks in the presence of a corneal ulcer presumed due to Acanthamoeba) rather than as single-use prophylaxis on an intact epithelium prior to surgery. On the other hand, pre-operative conjunctival irrigation with 0.05 per cent chlorhexidine diacetate solution [107], as used by Per Montan and all colleagues in Sweden, is found satisfactory.

Application of 10ml of five per cent povidone-iodine onto a sponge pad one hour prior to surgery clamped against the closed lids was associated with significantly fewer positive conjunctival cultures immediately prior to surgery (p = 0.02) and at the conclusion of the surgery (p = 0.05) compared with the application of two drops of five per cent povidone-iodine [35].

Clinicians should avoid use of large bottles of readily diluted povidone-iodine or chlorhexidine whenever possible, and use single-use sachets or vials instead, as both antiseptics can become contaminated with Ps. aeruginosa.

In conclusion, it can be stated on the basis of the available clinical studies that only povidone-iodine in a concentration of five per cent in BSS or isotonic saline can be recommended at present as the pre-operative antiseptic of choice. It has not been established whether similar results can be obtained with a lower concentration, such as 2.5 or 1.25 per cent. However, a significant effect for a reduction in the conjunctival bacterial count after surgery has been confirmed when 1.25 per cent povidone-iodine was used [28]. Povidone iodine solution containing a detergent must NOT be used as it coagulates the cornea irreversibly.

2.3 Antibiotics

Pre-operative prophylaxis

Pre-operative topical antibiotic prophylaxis appears rational to reduce the number of bacteria in the conjunctival sac. Various antibiotics have been used in the past including fluoroquinolones, chloramphenicol, aminoglycosides, fusidic acid and combination products of polymyxin / bacitracin / neomycin, but their use, including current use of topical fluoroquinolones, is not yet scientifically proven to reduce the rate of post-operative endophthalmitis [53], [61], [77], [146], [178]. However, a recent retrospective analysis has suggested a lower endophthalmitis rate following use of topical ofloxacin compared to topical ciprofloxacin [86].

The randomised, placebo-controlled prospective multi-centre ECRS study has investigated if use of peri-operative topical levofloxacin, which reaches significantly higher concentrations in the anterior chamber than ofloxacin and ciprofloxacin [2], [3], [7], can prevent post-operative endophthalmitis. Patients were administered one drop of levofloxacin 0.5 per cent solution one hour before surgery, one drop 30 minutes before surgery and three drops at five-minute intervals immediately following surgery. Dosing was interrupted until the following day to study the effect of peri-operative prophylaxis only. Although there appeared to be some benefit from the use of peri-operative levofloxacin, the effect was smaller than for intracameral injection of cefuroxime (see below) and did not reach statistical significance [5]. To maintain an adequate level of levofloxacin in the anterior chamber it may be considered continuing to dose every two hours post-operatively on the day of surgery [43].
In a retrospective analysis of 20,013 cataract surgeries, the effect of gatifloxacin 0.3 per cent and moxifloxacin 0.5 per cent given three times within one hour before surgery and four times daily for one week after surgery was shown to be comparable with other prophylactic measures. Estimated endophthalmitis rates of 0.06 per cent for gatifloxacin and 0.1 per cent for moxifloxacin, respectively, were reported. The authors concluded that older fluoroquinolones may be used instead and these newer ones be reserved for frank infections [112].

Combining prophylaxis for three days by the oral route with short-term prophylaxis by the topical route (1 h) provides higher antibiotic levels in the anterior chamber than either alone [44]. However, a reduction in intraocular bacterial contamination using this approach has not been proven [74], [157]. From considerations of principle (development of resistance, allergies) and because of the higher efficacy of antiseptics in vitro, equivalent results can be expected with antiseptics (e.g. povidone-iodine) on the ocular surface, but with the major disadvantage of a lack of an antibiotic effect within the anterior chamber.

The effect of a combined antiseptic and antibiotic approach with ciprofloxacin, ofloxacin and povidone-iodine has been investigated in vitro [174], but large numbers of patients are needed for a prospective clinical trial. Ofloxacin and levofloxacin are absorbed through the cornea into the anterior chamber to give an antibiotic effect which does not happen with povidone iodine. Topical levofloxacin four times on the day prior to surgery and three drops within one hour before surgery in combination with povidone-iodine irrigation was shown to be highly effective in reducing the bacterial conjunctival flora compared to the use of povidone-iodine prophylaxis alone. This schedule may be prudent in reducing bacteria from the surgical field in order to minimise the risk of endophthalmitis [36].

Vancomycin and other reserve antibiotics should not be used for prophylaxis [156].

Systemic antibiotic prophylaxis

Intravenous antibiotic prophylaxis is not used for conventional intra- and extra-ocular procedures and is not proven to be of benefit against post-operative endophthalmitis. As low levels of antibiotic penetrate the globe in the non-inflamed eye, this route is NOT recommended. Oral quinolones, however, penetrate the globe to give concentration levels (up to 1.3 µg/ml after three doses of 200mg levofloxacin), which increase up to 1.86 µg/ml with topical therapy pre-operatively [6]. However, routine cataract surgery does not require oral prophylaxis unless the patient has severe atopic disease when the lid margins are more frequently colonised with S. aureus [133].

After a penetrating injury, a prophylactic antibiotic is given systemically, as well as by the intravitreal route, and the same drug should be used. This has been reviewed recently [150], [205]. Antibiotic cover must include Bacillus sp., with vancomycin, gentamicin or clindamycin, as well as CNS, S. aureus and Clostridium sp. The importance of intravitreal antibiotic was shown in two recent studies. In the first study, at the end of wound repair, vancomycin (1mg) plus ceftazidime (2.25mg) were injected intravitreally in 32 eyes, whereas 38 eyes remained without this prophylaxis. Seven of the latter 38 eyes (18.42 per cent) developed endophthalmitis compared to only two of the prophylaxis group (6.25 per cent), which had an initially undetected intraocular foreign body (cilia) in the vitreous cavity [9]. In the second study, 179 eyes were randomly assigned to either intracameral injections of 40µg of gentamicin and 45µg of clindamycin or to injection of balanced salt solution. Endophthalmitis developed within two weeks postop in eight eyes (2.3 per cent) in the control group, compared to one eye (0.3 per cent) in the study group. [13]. A significant association was also noted between endophthalmitis and the presence of an intraocular foreign body (IOFB). Endophthalmitis developed in seven of 25 control eyes with an IOFB, but in none of the 27 antibiotic-treated eyes with an IOFB.

Irrigation of the lacrimal passages

Pre-operative irrigation of the lacrimal passages has no significant effect on the contamination of investigated aqueous aspirates. However, it should not be performed immediately before the operation, as then even more bacteria are washed from the lacrimal sac into the conjunctival sac [51].

Covering the periorbital area

With regard to the endophthalmitis risk, there has been no randomised controlled study of pre-operative cutting of the eyelashes.

The information available in the literature suggests that cutting the lashes is not associated with a reduction of risk [126], and demonstrates that the periocular flora is not influenced on the day of the operation or in the immediately succeeding days [194].

Taping back the lashes with adhesive tape nevertheless appears recommendable after PVP treatment of the skin [53], as in this way a conceivable additional risk is eliminated without side effects, all the more so as the annoying presence of lashes in the operating area can be avoided.
Intra-operative prophylaxis

Addition of antibiotic to irrigating solutions

According to Questionnaire Reporting Surveys in various countries, antibiotics are used in the irrigating solution by approximately 60 per cent of responding cataract surgeons in Germany [126], 35 per cent in the US [182], 16 per cent in New Zealand [163], 8.5 per cent in England [161] and 8 per cent in Australia [186]. However, while these surveys can be used for crude comparative rates, they are not accurate because of a limited response rate around the 65 per cent limit [205]. Antibiotics added to the irrigating solution include vancomycin and gentamicin.

While it is suggested in various surveys that the addition of antibiotics to the irrigating solution has a protective effect, it has not been possible to reduce the incidence of endophthalmitis in any prospective scientific study. All information on the incidence of endophthalmitis comes either from retrospective studies or from studies of antibiotic use where there was no control group [108], [167], [169].

Anterior chamber contamination at the end of a cataract operation varies between 0 per cent (0 of 98 eyes) and an extreme figure of 43 per cent (13 of 30 eyes) [68], [93], but even with a greater number of investigated eyes it is between 0.18 per cent (1/552) and 13.7 per cent (98/700) [104], [187]. Whether the reduction in the contamination rate from 12/100 to 5/100 when vancomycin is used in the irrigation solution [97] and from 22/110 to 3/110 with vancomycin/gentamicin [54] is meaningful remains doubtful, especially as no difference was found in another corresponding study (8/190 control, 9/182 vancomycin) [72].

In any case, the onset of action of various antibiotics, but in particular vancomycin, in vitro is observed only after three to four hours and full activity only occurs after about one day [31], [58], [79], [174]. This contrasts with the half-life of the drug in the anterior chamber of three hours. In animal studies of pars plana vitrectomy, antibiotic prophylaxis can be established only for low but not for moderate numbers of bacteria [33].

There is also the risk of overdose (aminoglycoside retinal toxicity) and the danger of developing resistance, which is disturbing particularly with the reserve antibiotic vancomycin. Relevant scientific organisations and authors therefore advise against giving prophylactic antibiotics in the irrigating solutions or call this in question, especially as a benefit has not so far been proven (Center for Disease Control in 1995 regarding vancomycin [156], American Academy of Ophthalmology in 1999 regarding vancomycin [144] and May et al. in 2000 regarding aminoglycosides [184]).

Addition of antibiotic as an intra-cameral injection in 0.1ml at the end of surgery

All Swedish cataract surgeons now routinely give an intra-cameral injection of 1mg cefuroxime in 0.1ml at the end of phacoemulsification surgery before closing the wound [108], [109]. This technique has been developed in Sweden and data from over 400,000 Swedish patients both retrospective and prospective demonstrate the efficacy of intracameral cefuroxime [94][137]. The technique has now been proven by the results of the prospective, randomised and controlled multi-centre ESCRs study [1], [5], [10]. Cefuroxime is very active against staphylococci and streptococci (except MRSA, MRSE and Enterococcus faecalis), Gram-negative bacteria (except Pseudomonas aeruginosa) and P. acnes.

The study found that the risk for contracting endophthalmitis following phacoemulsification cataract surgery was significantly reduced (five fold) by an intracameral injection of cefuroxime at the end of surgery, $p=0.001$ for presumed endophthalmitis and $p=0.005$ for proven endophthalmitis [1], [5], [10]. The lowest observed incidence rates were in Group D of this four-arm study [10], which received both intracameral cefuroxime and peri-operative topical levofloxacin. These rates were 0.049 per cent for presumed endophthalmitis and 0.025 per cent for proven endophthalmitis.

It must be remembered that some patients still developed post-operative endophthalmitis even after they received intracameral cefuroxime in both Sweden and the ESCRs study. There were three isolates of coagulase-negative staphylococci in the ESCRs study that were shown to be resistant to cefuroxime. On sub-analysis, the evidence for benefit of cefuroxime against CNS endophthalmitis appears to be weaker than against streptococcal endophthalmitis, while intensive peri-operative antibiotic eye drops are likely to work synergistically with cefuroxime.

The risk of an allergic reaction to cefuroxime in patients with a known allergy to penicillin is present but small [195] and must be weighed up against the increased risk of endophthalmitis if the cefuroxime injection is withheld. In these patients, an antihistamine tablet 15 minutes before surgery may be considered. There has been a case report of severe anaphylactic reaction attributed to intracameral injection of cefuroxime [199]. In patients with a known allergy to cephalosporins, cefuroxime should not be used and...
as an exception an intracameral injection of vancomycin should be considered instead. Intensive topical quinolones, e.g. levofloxacin, may be a useful adjunct for coverage of Gram-negative bacteria.

Besides cefuroxime, other antibiotics that have been given intracameral include vancomycin (effective against all Gram-positive bacteria only) [168], gentamicin (effective against staphylococci, but not streptococci and P. acnes; and effective against Gram-negative bacteria including Ps. aeruginosa) and clindamycin in combination with gentamicin [13], [14]. Anecdotal evidence from those who use antibiotics in this way suggests that they prevent post-operative or post-traumatic endophthalmitis but no scientific study has been mounted in their support.

The intracameral application of antibiotics, including cefuroxime, vancomycin and aminoglycosides, is not licensed by regulatory authority and it is given at the surgeon’s discretion. Clinicians should be aware of country specific implications as regards liability, medical insurance and reimbursement.

Subconjunctival antibiotic injection prophylaxis
This technique has been much used over the last 30 years, especially in the UK, but probably has little prophylactic effect on the prevention of endophthalmitis [61], [205]. While there has been no formal study to establish the technique, there have been plenty of studies, including the EVS, in which patients who develop endophthalmitis have received a prophylactic subconjunctival injection. One of the reasons why this might have occurred is that many surgeons used gentamicin which has no antibiotic effect on streptococci and Propionibacterium acnes. Researchers have investigated the pharmacokinetics of cefuroxime when 125mg given by the subconjunctival route gave levels of 20 µg/ml in the anterior chamber [29], which is far lower than that (3,000 µg/ml) which occurs when injected by the intracameral route. However, one recent retrospective uncontrolled study from Canada found one case of endophthalmitis in 8856 surgeries using subconjunctival antibiotics and nine cases of endophthalmitis out of 5030 surgeries not using them [64]. While this was statistically significant (p < 0.009), the study was open to bias as regards surgeon, incision and type of patient; such data needs to be repeated in a controlled prospective study.

Post-operative prophylaxis
In order to minimise the risk of infection, particularly after clear cornea incisions (see above) until wound healing is secure, use of the pre-operatively applied topical antibiotic (a quinolone or other drug - see below) is recommended for up to two weeks but is not proven. Longer application (more than two weeks) is discouraged unless there are other medical reasons for it. Post-operative quinolone drops should be applied every one to two hours after surgery to sleeping and from the next day on four times daily, from first waking in the morning to just before sleeping, with one drop well placed in the conjunctival sac [193]. Alternatively, topical chloramphenicol has been demonstrated to be safe for use for one week, without the risk of causing aplastic anaemia [45], or a combination product such as polymyxin/bacitracin/neomycin may be used, which has broad spectrum, low resistance and is not used systemically.

2.4 Limitations of the ESCRS Study
One of the objectives of the study was to assess the true background rate of post-operative endophthalmitis in Europe when no antibiotics were given on the days before or at the time of surgery. Patients in Group A, the control group, received instead peri-operative placebo eye drops without the cefuroxime injection [10]. However, it was considered unethical to withhold povidone iodine at the time of study design as it was the only prophylaxis for which there was a true evidence base [18]. Hence, all patients received povidone-iodine antisepsis following a standard protocol, which the background rate was established with. Topical levofloxacin was given as standardised medication for six days beginning on the first post-operative day, to prevent wound infection [149], but this was considered irrelevant for testing, whether or not an antibiotic administered at the time of surgery was effective.

The study did not evaluate the role of pre-operative antibiotics, which are normally administered anywhere between one hour to three days before surgery. Instead, it tested intensive peri-operative antibiotic drops versus intensive peri-operative placebo drops, commencing one hour before and concluding 15 minutes after the surgery.

Cefuroxime was chosen for the study, because its benefit had been demonstrated in more than 32,000 procedures in Sweden by the time of study design [109], [149], and it is effective against the majority of organisms that cause post-operative endophthalmitis [10]. The objective of the study was to prove the efficacy of the technique of intracameral cefuroxime in a prospective, randomised controlled trial. Although other intracameral agents or alternative systems of drug delivery might be superior to cefuroxime, they would have required additional safety studies prior to their use in this trial.
Levofloxacin was chosen as a topical antibiotic for similar reasons. It is well absorbed into the anterior chamber and has enhanced antibacterial activity compared to older fluoroquinolones [10]. Whilst newer fluoroquinolones, such as moxifloxacin and gatifloxacin may have a higher potency against Gram-positive bacteria and are widely used pre-operatively in the US, their use, like that of intracameral vancomycin, raises ethical questions about the utilisation of reserve antibiotics for prophylaxis as opposed to treatment [149]. Furthermore, both antibiotics are not yet available for topical ophthalmic use in Europe.

The applied dosing regimen of topical levofloxacin was based upon studies investigating its ocular penetration with four or five drops pre-operatively [2], [3], [7]. There has been a lack of specific pharmacokinetic data of fluoroquinolones in the anterior chamber and the PK study by Sundelin et al. [43] was conducted only after completion of the ESCRS study. The results of this latter study suggest a continued dosing on the day of surgery to maintain adequate drug levels in the aqueous humour. This is endorsed by Wallin et al., who showed that commencing post-operative topical antibiotics as late as one day after surgery is associated with a higher risk of contracting endophthalmitis [136].

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**Preparation of cefuroxime solution for intra-cameral injection**

The use of cefuroxime should be discussed with the hospital pharmacist and, in particular, the method agreed about how to make the dilution to 10 mg/ml.

It is recommended to use ZINACEF (GlaxoSmithKline) or an equivalent preparation containing cefuroxime as cefuroxime sodium in powder form, without any excipients. It MUST be diluted in sterile 0.9 per cent sodium chloride solution (saline) and NOT sterile water for injection as stated in the product data sheet, to achieve the correct pH of approx. 7.4 and osmolality of approx. 310 mOsm/kg for ocular injection [109]. 250mg cefuroxime are dissolved in 2.5ml of 0.9 per cent saline. 1ml of this solution is mixed with 9ml of 0.9 per cent saline to obtain a cefuroxime concentration of 10 mg/ml. 0.4ml of this solution are drawn up in a 1ml syringe and a fine metal cannula is attached to it. The first 0.1ml is displaced through the cannula for disposal. The cannula is inserted through the clear corneal wound or the corneo-scleral tunnel to the location of the intra-ocular lens and 0.1ml is injected intra-camerally.
2.5 FLOW CHART – PROPHYLAXIS GUIDELINES

(Based on the results of ESCRs multi-centre study [1], [5], [10] as well as Healy et al. 2004 [26], Jensen et al. 2005 [86] and Peyman, Lee & Seal 2004 [205]

Consider use of topical quinolone (levofloxacin* or ofloxacin one drop four times daily) or a topical combination of polymyxin B/bacitarcin/neomycin for 24 or 48 hours prior to surgery

and/or Apply topical quinolone (same type) to cornea and conjunctiva with one drop one hour prior to surgery and one drop one half-hour prior to surgery

It is mandatory to apply one drop povidone iodine five per cent [61], or 10ml povidone iodine five per cent on a sponge pad [35], or aq. chlorhexidine 0.05 per cent [107], to the cornea and conjunctival sac for a minimum of three minutes prior to surgery – preferably this is done in the preparation room prior to taking the patient into the operating theatre (OT)

Apply 10 per cent povidone iodine or 0.05 per cent chlorhexidine to the peri-orbital area in the OT as skin antisepsis, and allow to spill over into the conjunctival sac

Surgeon washes hands with antiseptic soap solution (povidone iodine or chlorhexidine), gowns up and wears sterile gloves and a mask. Check that theatre airflow is running and that doors are closed

Apply surgical drapes and taping of eyelids to remove eye lashes from the surgical field (do not cut eyelashes)

Perform phacoemulsification surgery. Consider using foldable IOLs that can be inserted through a sterile injector

Apply 1mg cefuroxime in 0.1ml saline (0.9 per cent) by intra-cameral injection [108], [109] at the end of surgery. This is an unlicensed use of cefuroxime given at the surgeon's discretion.

Use of vancomycin (or gentamicin) in the irrigation fluid or by intra-cameral injection is not proven and is not encouraged (refer to text)

Re-apply topical quinolone (same type) at the end of surgery as one drop stat, one drop five minutes later and one drop five minutes later again, or reapply polymyxin B/bacitarcin/neomycin or apply topical chloramphenicol (1 drop stat)

Use of subconjunctival antibiotic (gentamicin, cefuroxime) is not thought to offer effective prophylaxis (refer to text)

Give post-operative topical prophylaxis with the same quinolone as one drop every one to two hours on the day of surgery. From the next day, give four times daily (six hourly) for one week if scleral tunnel or sutured clear cornea incision was used, and for two weeks if an unsutured clear cornea incision was used. If not using quinolones, give topical chloramphenicol or polymyxin B/bacitarcin/neomycin using the same regimen as with quinolones.

* gives three to four times higher levels of the active isomer in the anterior chamber than ofloxacin [7], [26], [205]
3. Diagnosis

3.1 Commencement and symptoms

Acute early endophthalmitis after cataract operations commences between the first post-operative day and approximately two weeks after the operation. It is associated in 74 to 85 per cent with ocular pain and in > 90 per cent with reduced vision [15], [122]. It is characterised in 75 to 86 per cent by hypopyon, in > 80 per cent by a red eye and in 35 per cent by lid swelling [141]. Additionally, there can be corneal oedema and involvement of the posterior segment (refer to chart below) [205].

Chronic late endophthalmitis after cataract operations commences only after two weeks but may also take many months to appear [50], [96], [113], [117]. It is usually caused by Propionibacterium acnes, S. epidermidis (CNS), diphtheroids and fungi [15], [122]. In P. acnes endophthalmitis, whitish plaques are found in the capsular sac in 40 to 89 per cent [50], [62], [205]. Hypopyon is found in 67 per cent, corneal oedema in 48 per cent and keratitis in 26 per cent of cases of fungal endophthalmitis [113], [124]; pyramid-shaped hypopyon is typical of a mycotic cause [204], [210]. Refer to chart below.

The course and final outcome depend on the type and number of pathogens. In 44 to 53 per cent there is an achievement of only one metre vision with bacterial infection [15], [122], and similar for fungal infection in 41 to 70 per cent of patients [113], [151]. Endophthalmitis after pars plana vitrectomy has a poorer prognosis than after cataract or glaucoma surgery [46], [63].

The diagnosis of acute bacterial endophthalmitis is a medical emergency requiring an immediate vitreal tap and instillation of intravitreal antibiotics and corticosteroid.

Figure 3.1 Early presentation of acute endophthalmitis due to Streptococcus mitis

(Courtesy of Suleyman Kaynak)

Figure 3.2 Presentation of acute endophthalmitis due to Staphylococcus aureus

(Courtesy of Uwe Pleyer)
3.2 FLOW CHART – DIAGNOSTIC GUIDELINES FOR ACUTE VIRULENT ENDOPHTHALMITIS [205]

Observe the patient for:

- pain
- blurring or loss of vision, which may appear as a darkened image due to developing vitritis, down to perception of light
- swollen lids
- inflamed or oedematous conjunctiva
- discharge into conjunctiva
- cloudy anterior chamber with cells, hypopyon or fibrin clot
- afferent pupillary defect
- vitreous clouding (vitritis) from inflammation precluding a view of the retinal vessels
- involvement of posterior segment with retinitis, and/or retinal periphlebitis, retinal oedema and papillary oedema
- absent red reflex when the vitreous is viewed through the pupil may be a poor guide to the state of the vitreous, which may be most opaque anteriorly where the inflammatory process has begun. If the pupil is observed while transilluminating the sclera, the red reflex may become apparent and can then form a better guide to control of the disease.

Check B-scan ultrasonography for vitritis and retinal detachment – this is a useful adjunct for the clinical evaluation of infectious endophthalmitis especially in an eye with opaque media.

MAKE A CLINICAL DIAGNOSIS OF ENDOPHTHALMITIS (with photography if possible)

BEWARE OF DELAYING THE DIAGNOSIS WITH A TRIAL OF CORTICOSTEROID DROPS
(refer to Section 5.3)

THIS IS A MEDICAL EMERGENCY!

PERFORM AN INTRAVITREAL TAP WITHIN ONE HOUR!

- Perform a vitreous tap in the OT using a vitrector or phaco/vitrector or use a portable vitrector (BD Visitec 5100) in the outpatient clinic (refer to text)
- Also, perform an anterior chamber tap for microbiology
- Collect samples of vitreous and aqueous for microbiology (Gram stain, culture & PCR*)
- Inject empirical choice of antibiotics** (refer to text and flow diagram below) AND dexamethasone (400 µg unpreserved drug in 0.1ml) into vitreous with separate syringes and needles

* Expert PCR (polymerase chain reaction) for bacteria and fungi causing acute and chronic endophthalmitis is available from Dr Udo Reischl, Institute for Medical Microbiology and Hygiene, University Hospital, 93053 Regensburg, Germany (udo.reischl@klinik.uni-regensburg.de; Tel: +49-941-944-6450, Fax: -6402) or from Prof Jorge Aloe & Dr Consuelo Ferrer, VISSUM-Instituto Oftalmologico de Alicante, 03016 Alicante, Spain (cferrer@vissum.com; Tel: 34-9651-50025, Fax: -60468) at a cost of 250 EUR per sample. Collect samples of one drop of aqueous and one drop of vitreous, each placed in a separate sterile Eppendorf plastic tube or other sealable tube. Specimens should be stored at + 4°C for up to 24 hours and sent by next-day courier service to the laboratory or stored at -20°C for longer periods. Do not send by courier over a weekend. It is advisable to contact the units by telephone, email or fax before sending any samples.

** ALWAYS have a chosen empirical regime of antibiotics ready in advance for intravitreal use in a clinic or OT setting. Have instructions prepared for making-up correct dilutions and have necessary sterile equipment (bottles and syringes) available in an ‘endophthalmitis pack’ within the operating theatre.
3.3 FLOW CHART – DIAGNOSTIC GUIDELINES FOR CHRONIC ENDOPHTHALMITIS [205]

Observe the patient for:

- pain
- blurring or loss of vision
- cloudy anterior chamber with cells
- recurrent hypopyon uveitis that fails to respond to corticosteroids
- plaque in the capsular bag (= saccular or granulomatous endophthalmitis)
- vitreous clouding (viritis) from chronic inflammation reducing a view of the retinal vessels

Check B-scan ultrasonography for vitritis and retinal detachment

MAKE A CLINICAL DIAGNOSIS OF CHRONIC ENDOPHTHALMITIS

INVESTIGATE FOR A MICROBIAL SOURCE

- perform an anterior chamber tap for microbiology (Gram stain, culture & PCR) (refer above for details) – PCR is often positive here when culture is negative as bacteria are intra-cellular
- perform a vitreous tap, if vitritis is present, for microbiology (Gram stain, culture & PCR)
- if a decision is made to remove the IOL, then collect and send the capsule fragments to the microbiologist and to the histopathologist for paraffin-section based Gram stained films which will reveal the presence of intra-cellular Gram-positive bacteria within macrophages lining the capsule [47], [205]. Also collect a sample into glutaraldehyde to perform election microscopy, which can identify the intra-cellular bacteria [205].

Figure 3.3 Gram stain of vitreous tap from acute endophthalmitis due to Streptococcus salivarius

(Courtesy of Roland Koerner)
3.4 Differential diagnosis – the toxic anterior segment syndrome

The toxic anterior segment syndrome (TASS) is an acute inflammation of the anterior chamber of the eye. TASS may be related to any of the irrigating solutions, medications, or materials that gain access to the eye during anterior segment surgery. In addition, factors related to the cleaning and sterilisation of instruments may be a major problem causing TASS. Some cases have been related to heat stable endotoxins from overgrowth of Gram-negative bacilli in water baths of ultrasonic cleaners.

TASS rarely occurs in one patient only, but usually in three or more, because most or all the patients have been exposed to the incriminating toxin during one or two operating sessions. If an outbreak occurs, then the surgeon must stop operating and investigate for the source of the problem.

The common signs noted in the patients in a recent outbreak of TASS in the US included blurred vision, marked increase in anterior segment inflammation, including hypopyon formation as well as fibrin in the anterior chamber of the eye. It is always Gram stain and culture negative. There may be diffuse corneal oedema, classically from limbus to limbus, with endothelial cell damage. Patients present within 12 to 48 hours of cataract surgery and seem to respond well to intense topical corticosteroid treatment [147], [148], [179].
4. Investigation

4.1 AC tap, vitreous tap, vitrectomy for Gram stain, culture and PCR tests

The previous section describes diagnostic guidelines. A medical emergency exists as soon as the clinical diagnosis is made of acute bacterial endophthalmitis. There is a need to perform an anterior chamber tap and a vitreous tap within ONE hour of clinical diagnosis and to instil intravitreal antibiotics. The acute bacterial process is very ‘unforgiving’, giving rise to massive inflammation within the posterior segment with a breakdown of the blood-ocular barrier. Hence, to save vision there is need to stop the acute bacterial process but also to minimise the acute inflammation that it has caused, hence the current opinion that unpreserved dexamethasone 400 µg in 0.1ml should be injected intravitreally at the same time as the antibiotics. The full arguments for and against this approach, based on a scientific review, are considered by Peyman, Lee & Seal [205].

The question arises how to carry out the urgent taps and antibiotic instillation. In some hospitals it is not possible to take the patient to the operating theatre (OT) at any given time because of use of the OT by others. It is not advisable to keep the patient waiting for more than three hours, because the chances of retaining reasonable vision are diminishing fast. For this reason, a portable vitrector has been developed by Peyman and Visitec (Figure 5.1) to make an intravitreal tap within the outpatient clinic and to instil intravitreal antibiotics and dexamethasone at the same time in the clinic (refer to surgical section below). Jager et al. [171] have found that it is safe to perform vitrectomy in the outpatient (OP) clinic providing that antiseptic prophylaxis is used with povidone iodine; they found no statistical difference in acquired endophthalmitis rates after vitrectomy between the two sites – OT and OP (refer to incidence section above).

Use of the phaco/vitrector equipment, for a partial or full vitrectomy, is considered below in the treatment (surgical) section. It can be used for both sample collection and a full vitrectomy.

Antibiotics (refer below) are instilled with separate syringes and 25 or 30 G needles for each drug, either injecting directly through the pars plana or by injecting through the sclerotomy wound if present. The scleral wound is usually self-sealing and does not need to be sutured.

Identification of the pathogen in infectious endophthalmitis is rational as this allows targeted antibiotic therapy. The sampling should be done as soon as possible, and within ONE hour, after the diagnosis is made. Enlist the help of the microbiologist.

Microscopy and Gram stain results are available after one hour, pathogen culture results after 24 h, and antibiotic sensitivity testing results after six to 10 hours when the RAST method is used, or after 24 to 48 h with conventional methods [103].

The highest rate of pathogen identification is obtained with microscopic and microbiological processing of vitreous material, obtained either using the vitrectomy cutter before switching on the irrigation or as an aspirate, or using the portable vitrector. Use of a syringe and needle gives an unreliable sample that is often dry and culture-negative.

Pathogen identification from the anterior chamber is less successful and also potentially contaminated by the vitrectomy cassette [20], [101]. Conjunctival and corneal swabs are pointless, as the correlation with the micro-organisms isolated is too low [42]. The culture media should be inoculated directly in the operating theatre [189]. Transportation of material on cotton buds produces a high loss of pathogens and reduces the detection rate, which ideally is about 90 per cent [102].

The polymerase chain reaction (PCR) method offers much improved pathogen detection especially in the case of chronic endophthalmitis with low pathogen counts [34], [205]. However, the increased risk of contamination because of the high sensitivity of the method, the lack of antibiotic sensitivity testing and the partial lack of quality control standards in routine diagnostic laboratories have limited its routine use so far. PCR has been evaluated in depth in the multi-centre ECRS study by the two expert laboratories mentioned above. Results of this cross-validation study are not yet published [11].

4.2 Epidemiology

For detailed discussion on how to investigate an outbreak of cataract-surgery-associated post-operative endophthalmitis, the reader is referred to Chapter 4 of Peyman, Lee & Seal’s book [205]. This chapter considers the epidemiology of post-operative endophthalmitis in detail and has tables from which actual numbers of cases of endophthalmitis can be compared with predicted numbers for different incidence rates of infection, and thus determine whether the number of cases is greater-than-expected statistically, requiring the unit to close for detailed investigations. One of the most important aspects to then determine is whether there is a common source outbreak or whether it is due to a selection of different types of bacteria out of those normally found on the lid margin or in the conjunctival sac [214]. The former is often associated with a staff carrier for Staphylococcus aureus or Pseudomonas aeruginosa if contaminated solutions are involved, while the latter is more often associated with failures of either washing the instruments or with their sterilisation or with a failure of the air conditioning system in summer, causing the surgeons to shed excessive numbers of bacteria. It may be necessary to introduce an intra-cameral injection of antibiotic when the unit reopens if the source cannot be found.
5. Treatment

5.1 Surgical management of endophthalmitis. Diagnostic and therapeutic vitrectomy

The GOLD STANDARD of treatment of acute post-operative endophthalmitis is immediate (within a few hours) “complete” three port pars plana vitrectomy by a vitreoretinal surgeon. First, the infusion port is inserted through the pars plana, 3.5mm from the limbus, but is NOT TURNED ON. The vitreous cutter is inserted through a separate 3.5mm sclerotomy and directly visualised through the pupil. A hand-held syringe is attached to the aspirating line and the surgical assistant aspirates whilst the surgeon activates the cutter until the eye visibly softens and the cutter is disappearing from view. The infusion is turned on to reform the globe and the cutter removed. The syringe and the tubing now contain 1-2ml of infected but undiluted vitreous and the two together are promptly sent to the laboratory for immediate Gram stain, culture and PCR analysis.

The microbiologist has previously been informed the sample is en route.

The vitreous cutter is now connected to the machine for aspiration control and a light pipe is inserted through the pars plana. A standard three-port vitrectomy is performed within the limits of visualisation. It is useful to perform a posterior capsulotomy with the cutter and aspirate the fibrin and pus from the anterior chamber and intraocular lens surface. This procedure not only improves visualisation but permits flow through the entire eye and facilitates recovery.

Caution must be exercised against too aggressive surgery. These eyes have concomitant retinal vasculitis and retinal oedema and the inadvertent creation of a retinal break can be catastrophic. Iatrogenic retinal detachment in eyes with acute endophthalmitis is comparable to that of AIDS.

Once the vitrectomy is as complete as possible, the intravitreal antibiotics (see text) are injected. Note that the dose is reduced by 50 per cent if a full vitrectomy has been performed. This injection should be given SLOWLY, over minutes, and the needle pointed away from the macula. Separate syringes and separate needles are used through an existing entry site. Intravitreal dexamethasone (preservative free) is then injected.

The procedure is performed under general, peribulbar or retrobulbar anaesthesia but not topical.

The authors favour general anaesthesia as the patients are usually old, frail, sick, and in pain. Furthermore, the eyes are inflamed, hyperaemic and bleed.

While the above GOLD STANDARD achieves immediate diagnostic and therapeutic vitrectomy and reduces the need for re-operation, it is often not possible due to the lack of a vitreoretinal surgeon and a vitreoretinal operating room. The duty surgeon frequently does not have the required skill.

As TIME is of the essence, a SILVER STANDARD may be the practical option. The basic fundamental requirement is the intravitreal injection of the antibiotics. This should be preceded by vitreous biopsy. Simple aspiration with a needle is frequently unsuccessful unless the needle fortuitously enters the syneretic vitreous cavity; infected vitreous cannot be aspirated with a syringe and needle. Every duty surgeon must be taught to perform a vitreous biopsy with a vitreous cutter. The simplest technique is with the portable vitrector with a microvitreoretinal (MVR) blade at its tip as marketed by Visitec (Becton Dickinson Visitec Vitrectomy System 5100 Visitrec™ Surgical Vitrectomy Unit) and Insight Instruments, Inc. (The Intrjector® Portable Office-based Drug Injection/Vitrectomy System). Following the sampling, antibiotics and corticosteroids are injected through the sclerotomy as above. The incision does not require suture closure and no conjunctival incision is necessary.

This SILVER STANDARD has the advantage of time over completeness. While it ignores the fundamental surgical principle of 'ubi pus, ibi evacuat' (where there is pus, let it out) and it provides a smaller sample, it permits the earlier injection of intravitreal antibiotics and earlier microbiology. It also buys time pending the availability of a vitreoretinal surgeon and vitreoretinal operating room and the technique should be mandatory for all cataract surgeons.

The portable vitrector consists of a battery box, with 'off/on' and cutting speed switches, and a handheld vitrector (Figure 5.1). The vitrector has a 23 G guillotine probe, for use through a sclerotomy puncture site. In addition, a 20 G bevel needle can be placed on it, to allow direct puncture and use at the pars plana. The micro-guillotine cutter is controlled with a switch on the hand-piece. There is also an irrigating and aspiration module, to allow collection of the vitreous sample (Figure 5.1). The portable vitrector is designed for sample collection only and not for use for a therapeutic vitrectomy. These techniques are also described by Peyman et al. [206].
Figure 5.1  Portable Vitrector* – Becton Dickinson Visitec Vitrectomy System 5100 Visitec™

* PORTABLE VITRECTOR – Becton Dickinson Visitec Vitrectomy System 5100 Visitec™ Surgical Vitrectomy Unit marketed by Visitec, Waterloo Industrial Estate, Bidford-on-Avon, Warwickshire B50 4JH, UK. Tel: +44-1789-490909 Fax: +44-1789-490511

Figure 5.2  Site of insertion of vitreector guillotine
The patient is supine (lying flat). The eye is prepared with povidone iodine and then anaesthetised by topical, peri- or retro-bulbar anaesthetic. A lid speculum is inserted and an anterior chamber tap is made for Gram stain, culture and PCR.

For the portable vitrector, the biopsy probe is inserted through the pars plana transconjunctivally. The probe has a MVR blade at its tip so no incision is necessary. The single instrument provides one-step sclerotomy, cutting and aspiration. A mini-core vitrectomy can also be performed with slow manual aspiration of up to 1ml vitreous for microbiology and PCR.

The cutting probe is removed from the eye. Antibiotics and corticosteroids are injected with a 30mm (30 G) needle through the same incision site with separate syringes and needles. The incision is small enough not to need suture closure.

### 5.2 Anti-microbial therapy

An antibiotic combination is injected intravitreally and repeated as necessary according to the clinical response at intervals of 48 to 72 hours, depending on the persistence of the drugs selected within the eye. Intravitreal antibiotic doses are scaled down to avoid retinal toxicity but the margin for error between chemotherapy and toxicity is narrow for the aminoglycosides (for gentamicin, 200 µg is effective but 400 µg can be toxic, causing macular infarction); thus, the total dose injected must be highly accurate.

A combination of intravitreal antibiotics should be instilled as vancomycin (1mg) plus ceftazidime (2mg) (first choice) [32] (cave: physical incompatibility of vancomycin and ceftazidime [165], [176]) or amikacin (0.4mg) plus vancomycin (2mg) (second choice); 0.1ml of each of the two chosen antibiotics should be injected separately intravitreally after the tap or vitrectomy has been performed. An intravitreal injection of dexamethasone 0.4mg in 0.1ml should be given at the same time in most circumstances, again by a separate syringe and needle.

Antibiotics that have been used relatively safely for intravitreal use are shown in Table 5.1 below. The table lists the non-toxic doses of antibiotics, but the dose should be reduced by at least 50 per cent if given with a full vitrectomy, since the vitreous prevents rapid diffusion of antibiotics towards the retina [205]; some clinicians reduce the dose even by 90 per cent.

### Table 5.1 - Doses of antibiotics for intra-vitreal treatment of acute post-operative endophthalmitis

<table>
<thead>
<tr>
<th>Antibiotic injection</th>
<th>Intravitreal dose* (micrograms)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>400</td>
<td>24-48</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2000</td>
<td>24</td>
</tr>
<tr>
<td>Ampotericin</td>
<td>5 or 10</td>
<td>24-48</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2000</td>
<td>16</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2000</td>
<td>16-24</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2000</td>
<td>16-24</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1000</td>
<td>16-24</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>500</td>
<td>24</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>200</td>
<td>48</td>
</tr>
<tr>
<td>Methicillin</td>
<td>2000</td>
<td>16-24</td>
</tr>
<tr>
<td>Miconazole</td>
<td>5 or 10</td>
<td>24-48</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>500</td>
<td>24</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1000</td>
<td>48-72</td>
</tr>
</tbody>
</table>

*maximum intravitreal injection volume is usually 0.3ml but give each drug separately in 0.1ml amounts (use the intrathecal preparation when available because they are preservative free); intravitreal ciprofloxacin has been used [205], while the use of intravitreal levofloxacin is still experimental [19]. Intravitreal concentrations of 625µg or less of levofloxacin and 400µg or less of gatifloxacin appeared to be non-toxic in rabbit eyes [172].
How To Make Up The Antibiotics

The antibiotics should be supplied freshly diluted by the hospital pharmacy department. However, for emergency cases, a method for diluting the drugs in the operating theatre is given below. The procedure must use sterile equipment and be undertaken on a sterile surface; ideally, the hospital makes up sterile packs with drugs, bottles for dilution and instructions in advance for this purpose. All drugs should be mixed by inverting or rolling the bottle 25 times, avoiding frothing.

Some important “dos” and “don’ts” are:

- Never return diluted drugs to the same or original vial for further dilution
- Never dilute at greater than 1 in 10
- Do not use syringes more than once
- Do not reuse bottles
- Avoid use of drugs with preservatives if possible
- Do inject the drugs slowly over 1 to 2 minutes

Prior to preparing the dilutions it is mandatory to check the amount of the antibiotic in the vial as the same antibiotic may be sold in different strengths in each EU country.

**Vancomycin**  
*Dose for use* = 1000µg. Reconstitute one vial of 250mg and make up to 10ml with sterile normal (0.9 per cent) saline (SNS) in a sterile bottle with lid. Mix well. Withdraw 2ml accurately and add to 3ml of SNS in a sterile bottle with lid. Mix well (= 10mg/ml). Use 0.1ml = 1000µg.

**Ceftazidime** (or other cephalosporin)  
*Dose for use* = 2000µg. Reconstitute one vial of 500mg and make up to 10ml with SNS in a sterile bottle with lid. Mix well. Withdraw 2ml accurately and add to 3ml of SNS in a sterile bottle with lid. Mix well (= 20mg/ml). Use 0.1ml = 2000µg.  
Note: the percentage of drug precipitation is less when using SNS instead of BSS [32].

**Amikacin**  
*Dose for use* = 400µg. Reconstitute one vial of 500mg and make up to 10ml with SNS or balanced salt solution (BSS) in a sterile bottle with lid. Mix well. Withdraw 0.8ml, using a 1ml syringe, and add to 9.2ml of SNS or BSS in a sterile bottle with lid. Mix well (= 4.0mg/ml). Use 0.1ml = 400µg.

**Gentamicin**  
*Dose for use* = 200µg. Method 1: Use a ‘Minim’ which contains 3000µg/ml. Dilute to 2000µg/ml by adding 2ml of the Minim formulation to 1ml SNS in a sterile bottle with lid. Mix well. Use 0.1ml = 200µg for injection. Method 2: Remove 0.5ml, using a 1ml syringe, from a vial containing 40mg/ml unpreserved gentamicin and place in a sterile bottle with lid. Add 9.5ml of SNS or BSS and mix well (= 2.0mg/ml). Use 0.1ml = 200µg.

**Clindamycin**  
*Dose for use* = 1000µg. Transfer the contents of a 2ml ampule containing 300mg to a sterile bottle and add 1ml SNS or BSS, replace lid, and mix well. Withdraw 1ml, using a 1ml syringe, and add to 9ml of SNS or BSS in a sterile bottle with lid. Mix well (=10mg/ml). Use 0.1ml = 1000µg.

**Amphotericin**  
*Dose for use* = 5µg. Reconstitute a 50mg vial with 10ml water for injection. Withdraw 1ml, using a 1ml syringe, and add to 9ml of water in a sterile bottle with lid for injection. Mix well. Withdraw 1ml of this dilution, using a 1ml syringe, and add to 9ml of dextrose five per cent in a sterile bottle with lid, to complete a dilution of 1/100. Mix well (= 50µg/ml). Use 0.1ml = 5µg. (A dose of 10µg has been used by some clinicians.)

**Miconazole**  
*Dose for use* = 10µg. Withdraw 1ml, using a 1ml syringe, from an ampule of intravenous miconazole containing 10mg/ml and add to 9ml SNS or BSS in a sterile bottle with lid. Mix well. Withdraw 1ml, using a 1ml syringe, and add to 9ml SNS or BSS in a sterile bottle with lid. Mix well (= 100µg/ml). Use 0.1ml = 10µg.

Within Europe, various manufacturers produce sterile bottles of saline of different volumes for injection with side-ports, but many are not sold universally. For example in Spain and Portugal, the following method can be used with Braun’s 50ml bottles of saline, suitable for drug dilution with two rubber injection ports [159]:

**Vancomycin** - mix vial of 500mg with 5ml saline withdrawn from Braun 50ml bottle, shake well and then return to Braun bottle. Dilution gives 10mg/ml (dose of 0.1ml contains 1mg).

**Ceftazidime** - mix vial of 1g (1000mg) with 5ml saline withdrawn from Braun 50ml bottle, shake well and then return to Braun bottle. Dilution gives 20mg/ml (dose of 0.1ml contains 2mg).

**Amikacin** - add 2ml saline to vial of 500mg. Shake well and remove 0.8ml (= 200mg) to Braun 50ml bottle and shake well. Dilution gives 4 mg/ml (dose of 0.1ml contains 400µg).
Acute purulent endophthalmitis should be treated with additional systemic antibiotic therapy with the same drugs as used for intravitreal therapy. This adjunctive regimen will maintain effective intravitreal levels of the drug for a longer period by reducing the diffusion gradient out of the eye as well as its penetration into the inflamed eye [205]. High doses are required and there is a need to be aware of the risks of systemic toxicity. Vancomycin levels should be assayed. Use of oral probenecid (dose 500mg every 12 hours) retards outward transport of penicillins, cephalosporins and fluoroquinolones across the retinal capillary endothelial cells, thus extending the half-life of the drug within the vitreous. Probenecid also raises the plasma level by blocking secretion of these drugs by the proximal renal tubule.

Vancomycin levels should be assayed. Use of oral probenecid (dose 500mg every 12 hours) retards outward transport of penicillins, cephalosporins and fluoroquinolones across the retinal capillary endothelial cells, thus extending the half-life of the drug within the vitreous. Probenecid also raises the plasma level by blocking secretion of these drugs by the proximal renal tubule.

Dexamethasone (preservative-free) is often given by intravitreal injection (dose = 400 µg in 0.1ml [use the commercial preparation containing 4 mg/ml]) but should NOT be mixed with antibiotics in the same syringe. Refer to section 5.3. Prednisolone can be added to the systemic regimen to reduce the vitreous inflammatory response and subsequent vitreous organisation (oral prednisolone e.g. 200mg (see p. 21) daily on a reducing scale).

Antibiotic therapy may be modified after 24 to 48 hours according to the clinical response and the antibiotic sensitivity profile of the cultured organism. However, the inflammation usually becomes worse before becoming better, even with the correct antibiotic regime, hence the need to give a broad-spectrum antibiotic combination empirically by the intravitreal route that will be effective against most Gram-positive and negative bacteria causing post-operative endophthalmitis.

Intravitreal administration of the antibiotic gives the highest drug concentration “at the target site” but only lasts for a limited time period. Injection alone can be successful [119], but is usually combined with pars plana vitrectomy (PPV). Vancomycin (1mg/ 0.1ml) is suitable for Gram-positive bacteria [15], [180] and is above the MIC90 of Staphylococcus epidermidis (CNS) for > 48 h [80]; even 0.2mg/ 0.1ml vancomycin can remain at a therapeutic level for three days [73]. For treating Gram-negative bacteria, many surgeons are abandoning the use of aminoglycosides because of retinal toxicity and low therapeutic spectrum and are instead giving ceftazidime 2mg/ 0.1ml [155], [166], [170]. Vancomycin is used for Propionibacterium acnes [50], [62], but P. acnes is also very sensitive to cefuroxime.

Amphotericin B (5-7.5 µg) is the only fungicidal antibiotic available for intravitreal injection but its spectrum does not cover all fungi; in particular, Scedosporium apiospermum (Pseudallescheria boydii) is resistant to it but sensitive to miconazole which can be used instead [120], [121], [205], [210]. Miconazole is fungistatic but can be given intravitreally (Table 5.1). Systemic anti-fungal therapy is also required and the source of the infection needs to be identified.

**How To Give The Antibiotics**

**UP TO 0.1ML CAN BE LOST IN THE HUB OF THE SYRINGE AND THE NEEDLE** when drugs are diluted or made up for injection into the eye. Always draw up sufficient drug to fill a 1ml syringe to at least the halfway mark (0.5ml) and expel 0.1ml accurately from the syringe. Never expel the drug from the 0.1ml mark, because of errors with the hub.

**Adjunctive Routes**

**Systemic administration**

According to the randomised, multi-centre “Endophthalmitis Vitrectomy Study” (EVS), systemic antibiotics do not appear to have any effect on the course and outcome of endophthalmitis after cataract operations [15]. However, the study design used different drugs systemically (amikacin and ceftazidime) to those used intravitreally (vancomycin and ceftazidime [162], [196]), which does not contribute towards maintaining effective antibiotic levels within the eye. Thirty-eight per cent of the endophthalmitic eyes demonstrated Gram-positive cocci, against which ceftazidime has limited activity, whereas vancomycin would have been much more effective. Thus, adjunctive systemic antibiotic therapy with the same antibiotics as those given intravitreally is recommended for management of acute virulent bacterial endophthalmitis [162], [196], [209] when the patient should be closely observed in hospital. This may not be needed for less severe cases such as those caused by CNS.

Vancomycin provides good cover for Gram-positive bacteria including methicillin-resistant staphylococci (MRSA, MRSE). Ceftazidime is used to cover the Gram-negative spectrum incl. Ps. aeruginosa [153], [158]. Imipenem, which is also suitable for Gram-positive bacteria, and fluoroquinolones for Gram-negative bacteria, have not yet been fully evaluated for intravitreal use and should only be administered if there are contraindications against vancomycin and ceftazidime [21], [48], [153]. Experimental studies have been performed to show that levofloxacin can be used to kill bacteria causing experimental endophthalmitis in
rabbits but the final dose to use, that is also non-toxic, has not yet been established [19], [205].

Clindamycin, vancomycin or cefuroxime are effective for *Propionibacterium acnes* endophthalmitis [47], [140]. However, this must often be preceded by surgery [66], combined with intravitreal antibiotic injection [50], [62].

For fungal infection, amphotericin should be used systemically if it has been given by the intravitreal route. It is relatively toxic, but quite safe with experience, and the help of an infectious disease specialist should be found. In addition, systemic imidazoles are often given but are more likely to be effective for systemic infection than for the endophthalmitis. Voriconazole or fluconazole (for *Candida albicans*) or itraconazole (for other *Candida* species, *Aspergillus* or *Cryptococcus*) can be given but are not usually as effective as amphotericin [113], [205], [210]. 5-fluorocytosine can be used in combination therapy for *Candida albicans*. Fusarium endophthalmitis is particularly difficult to treat requiring both surgical removal where possible and chemotherapy (intravitreal, AC instillation or wash-outs, topical and systemic routes); Fusarium is usually but not always sensitive to amphotericin and combination therapy is often given with imidazoles [205].

5.3 Anti-inflammatory therapy

Effective anti-inflammatory therapy, e.g. with corticosteroids, is rational in order a) to limit tissue destruction by infiltrating leukocytes, b) to stem the effect of antigens and highly inflammatory cell walls released by bacterial disintegration after administration of antibiotics and c) to diminish the toxic effects of intraocular cytokines. Intravitreal dexamethasone injection (400 µg in 0.1ml) at the end of the vitrectomy leads under antimicrobial therapy to a more rapid subsidence of the intraocular inflammation [65], but without improving the long-term functional outcome although this finding may reflect studies in which dexamethasone or corticosteroid has been given later rather than initially with the first injection of antibiotics.

Oral administration of prednisolone (1mg/kg body weight) one day after intravitreal antibiotic therapy with or without vitrectomy has not shown any negative effect on the course of infection in bacterial endophthalmitis [15]. Steroidal steroid administration with mycotic infections, likewise without adverse effects [173]. 200mg prednisolone is often rationally given systemically in parallel with intra-venous antibiotics; however, there are no published studies on this subject.

From reports of recent experience from others, there seems to be quite a widespread use of a trial of corticosteroid drops in post-operative inflammation. Our view is that in uncomplicated phacoemulsification surgery with significant post-operative inflammation the patients should have an immediate vitreous biopsy and intravitreal antibiotics with no delay, and a trial of corticosteroid drops should not be performed.

To summarise, not only the microbes but also their interplay with the immune mechanisms, are important in the outcome of endophthalmitis. Cell walls of dead bacteria, especially those of streptococci, and including those recently killed by antibiotics, are highly inflammatory. As a direct consequence, anti-inflammatory treatment with intravitreal dexamethasone (400 µg in 0.1ml) should be given along with specific intravitreal anti-microbial therapy. In addition, surgical removal of a high bacterial load in the vitreous can also be important to save vision, by removing the main source of the acute inflammatory effect.

5.4 Other types of post-operative endophthalmitis

Late cases of endophthalmitis after cataract operation are the second commonest form of endophthalmitis accounting for 20 to 30 per cent in past studies following ECCE surgery; the symptoms are milder and *Propionibacterium acnes* has been identified as the principal pathogen. There is difficulty in culturing it as the bacterium is often enclosed in the synechised capsular sac. The high rate of recurrence is problematic, which can only be reduced by vitrectomy, possibly combined with posterior capsulectomy [160]. A further advantage of vitrectomy is that adequate material for culturing the causative organism can be obtained but capsular bag material is needed as well (refer to Flow Chart 3.3). Early vitrectomy is advisable [111]. A trial of therapy should be given with clarithromycin 250mg twice daily (refer to Flow Chart 5.7, [115]) which can be effective without surgery because the drug is well absorbed and concentrated 200 times into macrophages and other cells.
5.5 Limitations of EVS study

The Endophthalmitis Vitrectomy Study (EVS) [15] conclusions refer mostly to sub-acute post-operative endophthalmitis due to coagulase negative staphylococci (CNS) (80 per cent of cases) and the advice and conclusions overall do not relate to acute pyogenic pathogens such as *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus pneumoniae*. The conclusions also do not apply to late post-operative (saccular), bleb-induced, post-traumatic or endogenous endophthalmitis. These forms of endophthalmitis have a more aggressive bacterial spectrum and therefore require different operative techniques (vitrectomy), and both intravitreal and systemic antibiotics [205], [206]. The principles of management are the same for post-traumatic and endogenous endophthalmitis, as for acute post-operative endophthalmitis, but the visual outcome is poorer [205].

According to the EVS, conducted in the US [15], patients with acute endophthalmitis after a cataract operation with an initial vision of hand movements or better should be treated by vitreous biopsy and intravitreal antibiotics. In patients whose vision consists only of light perception, immediate vitrectomy is recommended. This advice however was based on the selection of patients admitted to the study and does not reflect the management of acute streptococcal endophthalmitis, where there is good reason to proceed with an immediate vitrectomy in order to remove the highly inflammatory bacterial cell walls from within the vitreous milieu. Retrospective studies have shown that affected patients can profit from early vitrectomy [192].

In the EVS, ceftazidime and amikacin were used systemically, while vancomycin and amikacin were used intravitreally, which does not contribute towards maintaining effective drug levels within the eye. However, 38 per cent of the eyes with < 5/200 outcome were infected by gram-positive strains. Ceftazidime is not the drug of choice for these bacteria. Therefore, the design of the EVS can not answer the question of intravenous use of antibiotics [162], [196]. In fact, this was not the primary objective of this study.

Follow-up EVS analyses showed differences between diabetics and non-diabetics. Diabetics with a visual acuity of hand movements or better obtained vision of 20/40 more often (57 per cent) by vitrectomy than after biopsy (40 per cent) but the results ultimately were not statistically significant because of the low number of diabetic participants in the study [4].
5.6 FLOW CHART - TREATMENT GUIDELINES FOR ACUTE VIRULENT ENDOPHTHALMITIS
(presumed and not proven) [205]

Make clinical diagnosis of endophthalmitis

Perform ultrasonography of vitreous and retina

Perform aqueous and vitreous tap and/or vitrectomy, through the pars plana, collecting samples for microbiology investigation (Gram stain, culture & PCR)

Inject antibiotics empirically into the vitreous using a combination of either vancomycin 1mg in 0.1ml and ceftazidime 2mg in 0.1ml (first choice) or amikacin 400 µg in 0.1ml and vancomycin 2mg in 0.1ml (second choice).

USE A SEPARATE SYRINGE AND 30 G NEEDLE FOR EACH DRUG AND DO NOT MIX DRUGS TOGETHER IN THE SAME SYRINGE. Do NOT point the needle towards the retina but forwards instead and inject very slowly into the mid-vitreous

Inject dexamethasone 400 µg (preservative-free) in 0.1ml into the vitreous at the same time by a separate syringe and needle

For acute virulent endophthalmitis begin adjunctive systemic therapy with the same antibiotics as those used intravitreally for 48 hours to maintain higher levels within the posterior segment of the eye (measure serum levels for intravenous vancomycin therapy); this may not be needed for less severe cases due to CNS

Consider beginning systemic therapy with corticosteroids (prednisolone 1 or even 2 mg/kg/day)

Consider referral to a vitreoretinal surgeon for an opinion on a full vitrectomy (refer to text) and repeated intravitreal antibiotics

OBSERVE PATIENT (inflammation becomes worse before better again, hence need for a defined initial empirical approach)
5.7 FLOW CHART – TREATMENT GUIDELINES FOR CHRONIC ENDOPTHALMITIS (presumed and not proven) [205]

Make a clinical diagnosis

Conduct a trial of therapy with clarithromycin 250mg twice daily for two weeks (this derivative of erythromycin is well absorbed orally, penetrates well into the eye and is concentrated 200 times into PMNs and macrophages, to kill intra-cellular Gram-positive bacteria and Haemophilus sp., but not other Gram-negative rods; clarithromycin is also effective against many atypical bacteria) [115], [201], [205]

If successful, retain IOL but if therapy fails, make a decision on whether to retain or remove the IOL and consider performing a vitrectomy possibly combined with a posterior capsulectomy [160]

If IOL is retained, give trial of therapy with intravitreal vancomycin and cefazolin or cefuroxime, together with intravenous therapy for one week

If combination anti-microbial therapy fails as well, remove the IOL – collect samples of capsule fragment for histology, electron microscopy and microbiology investigation (Gram stain, culture & PCR) [47], [202], [205]

Inflammation usually subsides after the IOL has been removed with the capsule but further antibiotic therapy can be given, such as an oral quinolone, but may not be needed
6. References

References categorised as EbM IIB


References categorised as EbM IIA


References categorised as EbM IIB


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References categorised as EbM III


References categorised as EbM IV


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References to books


References to book chapters


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