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**C02**

**Practical Course on Endophthalmitis**

06.06.2015

1430 - 1600 hrs

Hall B

**HAND-OUTS**

Endophthalmitis in cataract surgery. Epidemiology and bacteriology.

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Endophthalmitis remains one of the most feared complications following cataract surgery, although the patient is at greater risk of suffering severe visual damage due to capsule rupture or unplanned aphakia, simply because the latter complications are much more common than postoperative endophthalmitis (PE).

Owing to the generally low rate of PE after cataract extraction, the most reliable frequency figures will be found in large-scale studies counting at least 50 000 operations. Medicare studies from the US (n = 2) and Canada (n = 1) tell of an incidence of 0.1% while a population database study from Denmark showed 0.05%. The Swedish National Cataract Register disposes of an endophthalmitis registry since 1998. There has been a total allegiance of surgical units to report their cases and with increasing data the registry has evolved into an invaluable source of information, unique in its kind. In terms of incidence, there has been a steady decrease down to 0.021% in the 6 most recent years based on more than 540 000 surgeries. Three predisposing factors have been identified consistently: high age, capsule rupture and most importantly the failure to give intracameral antibiotics. This shows that PE does not occur by chance. Interestingly, gender, lens material or incision placement or season of the operation have not proven to be decisive in contrast to what has been found in studies with smaller samples. The lessons to be made based on the Swedish data are that injecting an antibiotic into the anterior chamber, avoiding a capsule breakage by allocating tough cases to experienced surgeons and intervening early in

the course of cataract formation so as to operating at a younger patient age will diminish the risk for PE.

Bacteria-wise, gram-positive organisms dominate, which reflects the bacteriology of the conjunctiva, the usual source of the pathogens. Staphylococci make up for the majority of cases and are generally associated with a favourable outcome, especially coagulase-negative species (CNS), whereas streptococci cause retinal damage and poor vision. From the Swedish data, *enterococci*, a streptococcal species which is resistant to most antibiotics, are slightly more frequent than CNS and together they make up 2/3 of causative organisms. *Enterococci* are aggressive within the eye and their emergence as a dominating but fortunately rare pathogen is likely to be explained by the wide-spread use of prophylactic intracameral cefuroxime which otherwise has an appropriate and broad anti-bacterial spectrum. Strategies to improve the efficacy of intracameral prophylaxis in relation to causative organisms in different risk populations is a priority within the Swedish endophthalmitis surveillance program.

### **Endophthalmitis prophylaxis according to EBM.**

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**Canadian Ophthalmological Society evidence-based clinical practice guidelines for cataract surgery in the adult eye [1]:**

Possible sources of infection include bacterial flora in the conjunctiva and lids, nasolacrimal obstruction or the presence of Jones tube, contaminated instruments or solutions, improper draping at time of surgery, leakage of the wound, rubbing of the eye, immunocompromised host, and bacterial adherence to the IOL. The use of a drop of povidone-iodine 5% solution in the eye 5 minutes preoperatively has produced significant reduction in the rate of endophthalmitis. Factors associated with endophthalmitis after cataract surgery may include wound location, watertightness of the wound, type of cataract operation, concurrent eyelid procedure, and posterior capsule rupture. Additional risk factors include clear corneal incisions, age >80 years, and surgery done in private centres.

### **RECOMMENDATIONS**

55. In order to reduce the risk of endophthalmitis, all patients should have proper draping [*Level 3*], preoperative management of lid margin disease [*Level 3*], and use of 5% povidoneiodine [*Level 2*].

56. Surgeons should be aware of their personal and institutional risk of endophthalmitis. If this rate is comparable to the current best published rates, there is no compelling evidence to warrant changing technique [*Consensus*].

57. If a surgeon's rate of endophthalmitis is higher than published norms, or when a higher risk of postoperative endophthalmitis is anticipated (such as when intraoperative complications occur), consideration should be given to supplemental intracameral or subconjunctival antibiotics [*Consensus*].

### **ESCRS Guidelines for Prevention and Treatment of Endophthalmitis Following Cataract Surgery [2]:**

#### **REDUCED ENDOPHTHALMITIS RATES AFTER INITIATION OF INTRACAMERAL ANTIBIOTIC PROPHYLAXIS**

More important, is the now universal finding that when prophylaxis with intracameral injection of 1 mg cefuroxime at the close of cataract surgery is initiated, a clinical benefit ensues in the reduction of postoperative endophthalmitis rates by several-fold. (...) The recent report by Rodríguez-Caravaca and associates<sup>9</sup> from Spain, which expands on the 2010 report by Garcia- Saenz, shows that endophthalmitis rates dropped from 0.59% to 0.039% (5/12 868 cases), after addition of intracameral

cefuroxime. In 6595 cases during the period 1999 - October 2005, the endophthalmitis rate was 0.59% (39/6595 cases), where the prophylactic regimen included PVI (or chlorhexidine), postoperative ofloxacin 0.3% and dexamethasone 0.1% drops, and gentamicin 20mg subconjunctivally in cases of retrobulbar anesthesia. During the period October 2005 to December 2012, intracameral cefuroxime 1mg (or vancomycin in allergic patients) was added to the regimen, with a subsequent drop in endophthalmitis rates of approximately 15-fold. The overall reduction in endophthalmitis rates - from the pre-IC injection period, to the time when all patients received the IC injections - was from 0.31% to 0.014%, an overall 22-fold reduction! (This report also underscores the efficacy of intracameral cefuroxime in cases of posterior capsular rupture.) These findings lend tremendous support to findings of the ESCRS study regarding the intracameral injection, particularly since the use of topical antibiotic drops was not restricted in that U.S. study.

A recent study from Singapore also lends support to the intracameral injection where cefazolin was used, rather than cefuroxime. Tan and associates (2012) (Table 8) evaluated postoperative endophthalmitis rates prior to, and after, the initiation of intracameral cefazolin at the close of surgery. Prophylaxis in prior time periods included subconjunctival cefazolin, gentamicin, dexamethasone; subconjunctival cefazolin was then changed to intracameral cefazolin injection, with other interventions remaining similar. Endophthalmitis rates prior to IC cefazolin were 0.064% (29 539 patients), but reduced to 0.01% (20 638 patients) when intracameral cefazolin was added to prophylactic regimens - a reduction in endophthalmitis rates of approximately 6-fold.

Romero-Aroca also describes results before and after an intracameral cefazolin injection was routinely administered at the close of cataract surgery. After initiation of the intracameral injection (pre-dating the ESCRS study), postoperative endophthalmitis rates were reduced approximately 12-fold (Table 8). Garat (2009) reported an almost 9-fold reduction in postoperative endophthalmitis rates when intracameral cefazolin was initiated after phacoemulsification procedures.

These most recent additions to the literature, originating worldwide (Figure 2) continue to support fundamental findings of the ESCRS study on prophylaxis of endophthalmitis and the clinical benefit of the intracameral cefuroxime injection.

Preferred practice guidelines issued by the American Academy of Ophthalmology in 2011 state “only intracameral antibiotics at the end of the case guarantees suprathreshold antibiotic levels for an extended period of time.” (AAO).

### **PREOPERATIVE ANTISEPSIS POVIDONE-IODINE (PVI)**

More than any other form of preoperative antisepsis, the literature supports the essential role of PVI for ocular surface preparation prior to cataract surgery. Topical PVI as a form of prophylaxis for cataract surgery has become a standard of care (Table 15).

A mandatory step to reduce bacteria in the wound area is to apply povidone iodine 5-10% to the cornea, conjunctival sac and periocular skin for a minimum of three minutes prior to surgery. Where povidone iodine is contraindicated (true allergy is rare and hyperthyroidism only a relative contraindication to this singular use), aqueous chlorhexidine 0.05% may be used.

Early data showed that near 90% of ocular surface flora were reduced with use of PVI [Apt 1984] and the literature continues to support PVI as the primary evidence-based preoperative intervention to reduce postoperative endophthalmitis rates [Speaker 1991, Cuilla 2002, Wu 2006, Carrim 2009, Quiroga 2010, Ferguson 2013].

Investigators have examined the use of different PVI concentrations with varying results. There may be increasing interest in the time/kill profile of PVI against microbial strains currently isolated from endophthalmitis cases, but this type of data remains sparse [Hosseini 2012]. Because of current interest in variations in PVI use, the bibliography in these Guidelines includes a number of literature references on this topic.

Nevertheless, complete sterilization of the ocular surface should not be expected, with PVI alone, or with addition of topical antibiotic drops (discussed below), and bacterial contamination of the aqueous humor in the range of 2 to >40% is reported in the literature in large series of patients, despite preoperative measures.

It is important to note that PVI should not be used or injected inside the eye due to corneal endothelial cell toxicity.

### **The Royal College of Ophthalmologists Cataract Surgery Guidelines [3]:**

Routine pre-operative antibiotics have not been shown to be effective but surgery should be delayed if there is concurrent infection.

**Prophylaxis against infection:**

A simple effective prophylactic measure in infection prevention has been Povidone iodine 5% aqueous solution irrigated into the conjunctival sac immediately pre-operatively. A prospective study by the ESCRS Endophthalmitis Study Group showed a significant decreased risk of endophthalmitis with intracameral cefuroxime compared with topical levofloxacin. The study was criticised on two counts, firstly that the endophthalmitis rate in the patients not receiving the intracameral antibiotic was higher than in previous reports, and secondly that it did not compare the intracameral route to the more conventional subconjunctival route of antibiotic administration in cataract surgery. A subsequent paper has shown superiority of intracameral cefuroxime over subconjunctival administration. However, this latter paper was retrospective and may have had a number of confounding factors affecting the results. An additional report found lower baseline rates of endophthalmitis without the use of intracameral cefuroxime. The national rate reported in the 2000 BOSU study was 0.14%; that in the Bolton study above was 0.055% which is itself a little lower than reported case series in similar settings.

The current advice is therefore that:

- If local rates of endophthalmitis over a properly audited time frame are similar to those reported in the Bolton study, then continuing with whatever preventative/prophylactic measures are in place would seem reasonable.
- If local rates are higher than those reported in the Bolton study then intracameral cefuroxime may be added as part of a package of measures to lower endophthalmitis rates after a suitable analysis of processes has taken place.

If the use of intracameral cefuroxime is considered there are potential problems that must be

addressed:

- The drug is heat labile, it cannot be heat sterilised and must be produced aseptically.
- Commercial preparations of the drug for intracameral use are available, and their use will prevent the possibly significant risks associated with the preparation of a suitable intracameral dose of the drug in the operating theatre.

- The possibility of an adverse reaction to the drug given intracamerally (toxic anterior segment syndrome) remains.

In summary, reaching a decision on whether or not to give the drug intra-camerally, may involve a comparison of the local rate of endophthalmitis with that in the studies mentioned. Additionally the exact dose and best antibiotic prophylaxis (for example the possible use of two different antibiotics) has not yet been determined.

American Academy of Ophthalmology guidelines are available at:

<http://www.aao.org/preferred-practice-pattern/cataract-in-adult-eye-ppp--october-2011>

The use of topical antibiotics in endophthalmitis prophylaxis, which is practiced all over the world is controversial and based mainly on historical and individual approach. ESCRS Endophthalmitis Study did not show any benefit of peri-operative levofloxacin use. [4] The review of the literature between 2008 and 2012 showed the addition of antibiotics preoperatively has not resulted in any effective conjunctival sac bacterial flora reduction. [5] Moreover, the recent retrospective study [6] shown that the topical antibiotics use did not offer any extra protection against endophthalmitis.[7]

The 2013 update of **ESCRS Guidelines for Prevention and Treatment of Endophthalmitis Following Cataract Surgery** gives a review of major studies evaluating the value of topical antibiotic in endophthalmitis prophylaxis. It concludes that “these reports underscore that not only has no clear benefit been established for the administration of antibiotic drops preoperatively, but that bacterial resistance may be induced, and complete bacterial eradication on the ocular surface is not achieved”.

The problem of antibiotic resistance (AR) is of rising importance in general medicine and ophthalmology. The use of topical antibiotics peri-operatively in intravitreal injections led to increase of AR of ocular surface flora, and numerous multicenter clinical trials have failed to show evidence that topical antibiotics reduce the rate of endophthalmitis following intravitreal injections. [8] Thus, this practice has been unrecommended, and this did not lead to increase in post-injection endophthalmitis rate. [9]

References

1. Canadian Ophthalmological Society Cataract Surgery Clinical Practice Guideline Expert Committee. Canadian Ophthalmological Society evidence-based clinical practice guidelines for cataract surgery in the adult eye. *Can J Ophthalmol*. 2008 Oct;43 Suppl 1:S7-57.
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4. Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg*. 2007;33(6):978-88.
5. Grzybowski A., Pucilowska P, Pieczynski J., Beiko G. Effectiveness of Preoperative Antibiotic Use ASCRS 2014, Boston, 25-29.04, 2014.
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7. Bhavsar AR, Googe JM Jr, Stockdale CR, et al. The Risk of Endophthalmitis Following Intravitreal Injection in the DRCR.net Laser-Ranibizumab-Triamcinolone Clinical Trials. *Arch Ophthalmol*. 2009; 127(12):1581–1583.
8. Grzybowski A. The role of antibiotics in the prevention of post-intravitreal anti-VEGF endophthalmitis: primum non nocere! *Eye (Lond)*. 2014; 28(4):500.

## **Endophthalmitis in Intravitreal Injections: Epidemiology and Prophylaxis**

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1. Disclosure
  - a. Advisory boards: Alimera, Bausch + Lomb
  - b. Honorarium: Vindico
2. Incidence rates
  - a. Rates may be reported per injection or per patient
  - b. Per-patient rates are cumulative and typically higher
3. Representative rates
  - a. Gregori et al. 2015 (OSLI Retina in press):
    - i. 20/121,285 injections (0.016%) at BPEI
    - ii. 391/740,757 injections (0.053%) in MarketScan
  - b. CATT 2-year per-patient cumulative rates:
    - i. 0.7% ranibizumab
    - ii. 1.2% bevacizumab
    - iii. (not statistically significant)
4. Risk reduction, not prevention
  - a. No RCTs on technique
  - b. Expert committee consensus guidelines updated 2014
5. "Areas of general agreement"
  - a. Povidone-iodine 5%-10% as the last agent applied to the injection site
  - b. Topical antibiotics are unnecessary
  - c. Sterile drape is unnecessary
  - d. Avoid contamination of needle and injection site by eyelid margin or eyelashes
  - e. Avoid extensive eyelid massage
  - f. "Adequate" anesthesia
  - g. Sterile or non-sterile gloves
  - h. Surgical masks or minimize speaking
  - i. Monitor IOP
  - j. Routine AC paracentesis not necessary
6. Eyelid speculum?
  - a. Fineman et al. Retina 2013
    - i. 3/10,164 (0.03%) using bimanual lid retraction and no speculum
  - b. ASRS 2014 PAT survey
    - i. Only 13.0% of US members and 15.8% of international members use speculum for "all" injections
7. Topical antibiotics
  - a. No RCTs address this question
  - b. Their use is declining, especially in US
  - c. ASRS 2013 PAT survey:
    - i. 21.8% US members use
    - ii. 70.9% international members use
  - d. "Bottom line"

- i. Routine topical antibiotics do not appear to significantly decrease the rates of endophthalmitis following intravitreal injections

- 8. My technique
  - a. Clinic room
  - b. RN preps patient
  - c. Face masks
  - d. Povidone-iodine
  - e. No topical antibiotics
  - f. Prep kits

Study	Injections	Rate With Antibiotics	Rate Without Antibiotics	Statistical Significance
Bhavsar et al. <i>Arch Oph</i> 2012	8,027	0.13%	0.03%	Not significant
Cheung et al. <i>Ophth</i> 2012	15,895	0.06%-0.08%	0.04%	Not significant
Falavarjani et al. <i>Retina</i> 2013	5,901	0.10%	0%	Not significant
Park et al. <i>JOPT</i> 2013	17,332	0%	0.04%	Not significant
Ramel et al. <i>JFO</i> 2014	11,450	0.04%	0.23%	p = 0.024
Storey et al. <i>Ophth</i> 2014	117,171	0.05%	0.03%	Not significant
Meredith et al. <i>Ophth</i> 2015	18,509	0.04%-0.08%	0.15%	Not significant
Falavarjani et al. <i>CJO</i> 2015	8,037	0.01%	0%	Not significant