Role of topical, subconjunctival, intracameral, and irrigative antibiotics in cataract surgery

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Purpose of review
To summarize current understanding of antibiotic prophylaxis in cataract surgery, with particular emphasis on available evidence and change in practice patterns over the past decade.

Recent findings
Povidone–iodine application prior to cataract surgery remains a universal practice, and is backed by good quality evidence. Subsequent to the results of the European multicenter trial documenting decreased risk of endophthalmitis with intracameral cefuroxime injection at the end of surgery, similar benefit with intracameral antibiotic use has been reported in studies with large sample sizes from multiple centers around the world. There has been a distinct change in practice patterns in many countries, with intracameral antibiotic use becoming part of routine protocol. In the USA, topical fluoroquinolone application remains the most popular mode of antibiotic prophylaxis. A promising approach is the development of novel drug delivery methods like polymeric devices designed for sustained antibiotic release.

Summary
Based on current evidence, the recommended measures for endophthalmitis prophylaxis are preoperative topical instillation of povidone–iodine and intracameral antibiotic injection at the end of cataract surgery.

Keywords
antibiotic prophylaxis, cataract surgery, endophthalmitis, intracameral, topical

INTRODUCTION

Cataract surgery is one of the most commonly performed surgical procedures across the world. Despite the advances in technology and technique that have transformed cataract surgery outcomes over the past few decades, postoperative endophthalmitis remains a significant concern. A meta-analysis of published literature estimated the worldwide incidence of endophthalmitis following cataract surgery to be 0.265% from 2000 to 2003 [1]. Alarmingly, this percentage was higher than reported rates in the 1980s (0.158%) and 1990s (0.087%) [1].

A variety of antiseptic and antibiotic agents have been tried in an effort to prevent postoperative endophthalmitis. Until recently, topical povidone–iodine was the only agent demonstrated in a prospective study to be effective in reducing the risk of endophthalmitis [2]. In the last decade, the European Society of Cataract and Refractive Surgeons (ESCRS) study provided high quality evidence for the utility of intracameral cefuroxime in reducing endophthalmitis rates [3]. Excellent review articles summarizing the factors implicated in causation of endophthalmitis postcataract surgery and the roles of antibiotic prophylaxis using different routes are available [4–7]. Here, we attempt to review recent literature on the topic, in particular the change in practice patterns around the world based on the ESCRS study results, and the subsequent impact on endophthalmitis rates.

POVIDONE–IODINE

Povidone–iodine is a nonselective antiseptic agent, with broad-spectrum microbicidal activity. In a nonrandomized prospective study, application of a 5% solution on the conjunctiva prior to surgery was found to reduce the rate of endophthalmitis by

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KEY POINTS

- Povidone–iodine application prior to cataract surgery is universally accepted as a standard of care practice.
- Perioperative use of topical fluoroquinolones remains extremely popular.
- Intracameral antibiotic instillation at the end of cataract surgery has proven value in reducing endophthalmitis rates, and is being increasingly adopted as routine practice in many countries.

four-fold [2]. Other studies have also shown a reduction in concentration of conjunctival bacteria with povidone–iodine application [8–10]. A recent study determined that the preoperative use of topical fluoroquinolone antibiotics was more effective than povidone–iodine in conjunctival sterilization [11]. These conclusions need to be viewed in light of the small sample size in each of the groups and the difference in pretreatment cultures between groups. Preoperative use of topical povidone–iodine has become standard of care practice in cataract surgery, and has been mandated in the guidelines for infection prophylaxis from the American Academy of Ophthalmology [12]. No consensus exists regarding the concentration of povidone–iodine to be used, although a randomized prospective study demonstrated no difference in conjunctival cultures with use of either 5% or 10% solutions [13].

TOPICAL ANTIBIOTICS

Topical antibiotics are commonly used preoperatively, with the aim of sterilizing the ocular surface and achieving therapeutic concentrations in the anterior chamber of the eye. The most common strains from conjunctival isolates are found to be coagulase-negative staphylococci [14], which correlates well with the most commonly implicated organisms in endophthalmitis [15]. The antibiotic sensitivity profile of these organisms [14], coupled with the proven penetration into the anterior chamber [16] of topically administered fluoroquinolones, probably contributes to their popularity amongst surgeons. An overwhelming 91% of surgeons surveyed in the 2007 American Society of Cataract and Refractive Surgery (ASCRS) survey used topical antibiotic prophylaxis at the time of cataract surgery [17]. Of these, 81% preferred fourth generation fluoroquinolones (gatifloxacin or moxifloxacin). The preference for topical antibiotics continued in the 2011 ASCRS survey, wherein only 1% of surgeons reported not using them, and 77% preferred fourth generation fluoroquinolones [18]. This factor serves to highlight the chasm between evidence-based medicine and practice patterns, as the efficacy of topical antibiotics in preventing endophthalmitis has never been validated in a prospective trial. An argument advanced in favor of continuing prophylactic use of fluoroquinolones, rather than intracameral antibiotics as suggested by the strong evidence provided by the ESCRS study, is that the results of this trial are outdated [19]. Fourth generation fluoroquinolones such as moxifloxacin were not part of the ESCRS trial, and are now commercially available. It has been hypothesized that the results of the study might be different if the trial were to be repeated, substituting moxifloxacin for levofloxacin.

Studies have demonstrated a reduction in bacterial load of the conjunctival sac with preoperative application of topical fluoroquinolones [20–23]. A 3-day application of topical ofloxacin prior to surgery was found to be more effective than a 1-day or 1-h application [20,24]. With moxifloxacin, there appeared to be no difference between 3-day and 1-day applications [23]. The clinical relevance of these findings is open to debate, as the effect of reduced conjunctival bacterial load on endophthalmitis rates has not been explored. A randomized study found that topical application of moxifloxacin 1 day prior to surgery resulted in significant increase in fluoroquinolone-resistant bacteria [25]. The authors recommended that moxifloxacin, when used prophylactically, should be started 3 days prior to surgery, as such a regimen was not found to select for resistant organisms. This factor is particularly important in view of the increasing resistance of bacteria causing endophthalmitis to fluoroquinolones [26–28].

The newest fluoroquinolone developed solely for ophthalmic use is besifloxacin, with the objective of eliminating the contribution to resistance development due to systemic use [29–31]. Another purported advantage of this formulation is the use of DuraSite, a mucoadhesive polymer designed to prolong the adherence of the drug to the ocular surface [32]. Interestingly, though having broad spectrum antimicrobial activity, the aqueous humor concentrations achieved after topical application are less than that for moxifloxacin, and are deemed unlikely to be effective against drug-resistant bacteria frequently responsible for endophthalmitis [33]. Besifloxacin has been found to be well tolerated when used topically for infection prophylaxis prior to cataract surgery [34], though its efficacy has not been tested. As is usually the case with new drugs, the might of substantial marketing budgets is likely to ensure widespread adoption of this molecule by

clinicians and relegation of 'older generation' antibiotics to the archives.

In summary, the preoperative use of topical antibiotics is widespread, particularly in the USA. A well entrenched practice pattern, it is unlikely to change in the near future, with newer fluoroquinolones being increasingly used. Postoperative topical antibiotic use is also near universal. Retrospective studies suggest that endophthalmitis rates are lower with the postoperative use of topical fourth generation fluoroquinolone use than those from historical controls [35,36]. The efficacy of this modality is unproven in a placebo-controlled prospective study.

SUBCONJUNCTIVAL AND IRRIGATIVE ANTIBIOTICS

Adequate aqueous humor concentrations of antibiotics have been demonstrated after subconjunctival injections [37,38]. Two large, retrospective studies have identified subconjunctival antibiotic use as highly effective in lowering the incidence of postoperative endophthalmitis [39,40]. A population-based study from Australia [39] found preoperative antiseptic preparation and use of subconjunctival antibiotics to be the only two factors independently associated with a decreased risk of endophthalmitis. Subconjunctival antibiotics were found to decrease the risk of endophthalmitis by half. Likewise, a hospital-based study [40] found a significant decrease in endophthalmitis rates with the use of subconjunctival antibiotics. With the increasing adoption of topical anesthesia for cataract surgery, the use of subconjunctival antibiotics is bound to wane.

Vancomycin added to the irrigating fluid during phacoemulsification has been found to achieve adequate concentrations in the aqueous humor [41]. A study found use of vancomycin in irrigating fluid to be more effective than preoperative topical antibiotic use in reducing anterior chamber microbial contamination [42]. Close to 15% of surgeons in the 2007 ASCRS survey and 21% in the 2011 survey reported use of irrigative antibiotics during cataract surgery [17,18]. High-quality evidence either supporting or refuting this practice is lacking.

INTRACAMERAL ANTIBIOTICS

The efficacy of prophylactic intracameral cefuroxime in preventing endophthalmitis after cataract surgery was suggested by retrospective data from Sweden [43], which showed a markedly lower rate of endophthalmitis with routine use of this modality. This finding was further substantiated by the ESCRS multicentre study of postoperative endophthalmitis. The ESCRS study remains, to date, the only prospective, randomized, placebo-controlled trial of prophylactic antibiotic use in cataract surgery [3]. The study initially aimed to enrol 35 000 patients across 24 ophthalmology units in Europe. A preliminary report [44] showed that incident rate of endophthalmitis in groups not receiving cefuroxime prophylaxis was nearly fivefold compared with groups receiving this treatment. It was deemed unethical to continue the trial and deny certain patients the benefits of cefuroxime prophylaxis. The robust evidence provided by the ESCRS study led to a change in practice patterns across Europe. For instance, 55% of surgeons surveyed in the United Kingdom in 2008 reported using intracameral cefuroxime, as compared with 10% in 2005 [45]. The major concerns cited by surgeons not using cefuroxime prophylaxis were lack of a preformulated preparation and risk of dilution errors, along with endothelial toxicity and possible bacterial contamination. Two-thirds of the surgeons not using cefuroxime would use it if a commercial preparation were available.

Subsequent to the results of the ESCRS study, multiple studies with large sample sizes from across Europe and Asia have reported decrease in endophthalmitis rates with the use of intracameral antibiotics (Table 1) [3,46–48,49▪▪,50,51]. Despite the inherent drawbacks of retrospective and observational study designs, lack of randomization or masking and possible selection bias, the statistical and clinical significance of the numbers from various centres is too consistent to be ignored. The antibiotics used have been cephalosporins (cefuroxime and cefazolin) as well as vancomycin. Interpreted in conjunction with the ESCRS trial outcomes, these studies constitute the largest cumulative body of evidence in favour of any single intervention for reducing the risk of postoperative endophthalmitis. From the public health perspective, routine use of intracameral antibiotics could possibly be one of the most cost effective measures to reduce endophthalmitis after cataract surgery. Sharifi *et al.* [52] in 2009 estimated the cost–effectiveness ratio for intracameral cefuroxime to be US$1403 per case of postoperative endophthalmitis prevented. According to them, fourth generation fluoroquinolones commonly used topically prior to surgery would have to be more than 19 times more effective than cefuroxime to achieve cost–effectiveness equivalence.

The impact of the ESCRS trial has been far less impressive on practice patterns across the Atlantic. In the 2007 ASCRS survey, 77% of respondent surgeons were not using any intracameral antibiotic [17]. However, 82% would do so if a reasonably

Table 1. A summary of recent studies on the efficacy of intracameral antibiotics in preventing postcataract surgery endophthalmitis

Authors	N	Type of study	Intracameral antibiotic used	Endophthalmitis rate (%)		
				With intracameral antibiotic	Without intracameral antibiotic	*P*-value
ESCRS endophthalmitis study group [3]	16211	Prospective, randomized, partially masked	Cefuroxime	0.062	0.296	<0.005
Garat *et al.* [46]	18579	Retrospective	Cefazolin	0.047	0.422	<0.0000001
García-Sáenz *et al.* [47]	13652	Prospective, observational	Cefuroxime	0.043	0.59	
Anijeet *et al.* [48]	16606	Retrospective	Vancomycin	0.008	0.3	<0.0001
Romero-Aroca *et al.* [49▪▪]	25001	Prospective, observational	Cefazolin	0.05	0.63	<0.001
Barreau *et al.* [50]	5115	Prospective, observational	Cefuroxime	0.044	1.238	<0.0001
Tan *et al.* [51]	50177	Retrospective	Cefazolin	0.01	0.064	<0.001

priced commercial preparation were available. In the 2011 survey, the number of surgeons not using intracameral antibiotics went up to 81.7% [18]. This finding clearly indicates that surgeons in the USA have serious concerns regarding intracameral antibiotic use. These concerns include risks associated with preparing the solution, including dilution errors, bacterial contamination or toxic anterior segment syndrome. To overcome these, intracameral use of moxifloxacin has been suggested as an alternative [19]. A broad-spectrum antibiotic, it is available commercially as a nonpreserved formulation that can be diluted by the surgeon or administered directly with no further preparation. The safety profile of intracameral moxifloxacin has been established in a rabbit model [53] as well as in human controls [54]. Larger, well constructed studies that determine the efficacy of intracameral moxifloxacin in reducing postoperative endophthalmitis may lead to this modality assuming an important role in the future.

NEWER APPROACHES TO DRUG DELIVERY SYSTEMS

Collagen shields presoaked in antibiotic solutions have been explored as a method of drug delivery to the eye for well over a decade [55–57]. Although adequate penetration into the aqueous has been documented, the utility of this approach compared with the much simpler topical instillation is questionable. In a rabbit model, no statistical difference was found in endophthalmitis prophylaxis using fourth generation fluoroquinolones delivered either using collagen shields or by the topical route [58].

A fascinating approach to drug delivery is the potential use of polymeric devices to achieve sustained release of antibiotics postcataract surgery. This may have several potential advantages over traditional topical application of antibiotics, including cost, elimination of toxicity to the ocular surface and reliance on compliance by the patient. In a recently published study [59▪], a polymeric drug-delivery device incorporating norfloxacin was able to achieve therapeutic concentrations of the antibiotic in rabbit eyes. The device was attached to haptics of a commonly used intraocular lens, which was implanted subsequent to cataract surgery using a routine injection system. In an experimental endophthalmitis model, this approach was found to be superior to topical antibiotics for infection control. Such innovations may provide low-cost solutions for effective endophthalmitis prophylaxis in the future.

CONCLUSION

Preoperative antisepsis using povidone–iodine is essential for cataract surgery. Topical antibiotic prophylaxis, particularly the use of fourth generation fluoroquinolones continues to remain popular among surgeons, although convincing evidence regarding efficacy of the same is unavailable. In the light of convincing data published in the last decade from various centres across the world, we feel compelled to recommend the use of intracameral antibiotic prophylaxis as a routine measure in cataract surgery. There are legitimate concerns regarding lack of a commercially available, ready-to-inject formulation of cefuroxime. Further studies exploring the role of intracameral moxifloxacin may

address these issues, and enhance greater adoption of this modality. Development of well tolerated, low-cost biocompatible devices for sustained antibiotic release is an exciting approach that merits further exploration.

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Conflicts of interest

There are no conflicts of interest.
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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 83–84).

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This experimental study provides useful pointers towards the future of drug delivery systems into the eye, raising the possibility of well tolerated, effective and low-cost biocompatible devices for sustained antibiotic release.