



# Intracameral antibiotics: Safety, efficacy, and preparation

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Endophthalmitis is a rare but potentially devastating complication of cataract surgery. This article presents an overview of endophthalmitis prophylaxis and the use of intracameral antibiotics. It highlights available intracameral antibiotics with respect to pharmacology, spectrum of activity, dosage and preparation, safety, and efficacy profiles, as well as toxic anterior segment syndrome risks to better define the potential use of these medications in the prevention of endophthalmitis.

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Endophthalmitis is a potentially devastating complication of cataract surgery that occurs in 0.04% to 0.2% of cases.<sup>1,2</sup> Historically, most options for chemoprophylaxis against bacterial endophthalmitis have been topical and subconjunctival antibiotics and povidone-iodine preparation and instillation on the ocular surface before surgery. Practice patterns vary worldwide. In the United States, the most common form of chemoprophylaxis has been topical fluoroquinolones prescribed 1 to 3 days preoperatively and resumed immediately postoperatively for 1 week.<sup>1</sup> The use of preoperative povidone-iodine preparation appears to be nearly universal, whereas most European surgeons now favor intracameral antibiotics over subconjunctival antibiotics or topical antibiotics alone.<sup>1</sup> Increasing evidence supports the use of intracameral antibiotics to prevent postoperative bacterial endophthalmitis.<sup>3–6</sup> However, the use of intracameral antibiotics is considered off-label in the U.S.

In this review, we summarize the current literature regarding the options, use, and efficacy of intracameral antibiotic prophylaxis during cataract surgery. The European Society of Cataract and Refractive Surgery's (ESCRS) landmark study<sup>3</sup> of antibiotic prophylaxis for cataract surgery was a prospective multicenter randomized clinical trial. It reported a statistically significant 5-fold decrease in endophthalmitis following cataract surgery when cefuroxime was injected directly into the anterior chamber. The ESCRS study compared 4 treatment groups: Group A received no topical or intracameral antibiotics, Group B received intracameral cefuroxime, Group C received topical levofloxacin only, and Group D received both topical levofloxacin and intracameral cefuroxime. The rates of culture-proven endophthalmitis were 0.226% and 0.173% in the groups that did not receive intracameral cefuroxime (A and C) compared with 0.049% and 0.025% in the groups that received intracameral prophylaxis (B and D). The latter rates are similar to the previously reported 0.06% rate of endophthalmitis in a Swedish study<sup>6</sup> of more than 32 000 cases that used intracameral cefuroxime without additional topical antibiotic prophylaxis.

A Spanish group<sup>7</sup> reported that endophthalmitis following cataract surgery decreased from a mean rate of 0.59% to a mean rate of 0.043% after prophylactic use of intracameral cefuroxime was instituted. Additionally, a Singapore study<sup>5</sup> found a 6-fold reduction in postoperative endophthalmitis with the use of intracameral cefazolin.

The first large-scale comparative U.S. study found a significant reduction in postoperative endophthalmitis

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rates with the routine use of intracameral cefuroxime, particularly following posterior capsule rupture.<sup>4</sup> This study, which analyzed rates over a 5-year period, showed an initial 2.2-fold decline in endophthalmitis rates during the first 2 years (2008 and 2009) of the 5-year retrospective study in patients without a penicillin/cephalosporin allergy. A further 10-fold decline was observed during the next 2 years of the study, when all patients, including those with posterior capsule rupture, received intracameral cefuroxime, moxifloxacin, or vancomycin.

## REVIEW OF INTRACAMERAL ANTIBIOTICS

There is neither strong evidence nor consensus as to which medication is superior. Thus, the decision about which intracameral antibiotic to use is left up to the surgeon and can be based on various factors. Aprakam is a powdered solution of cefuroxime that is mixed with 0.9% sterile sodium chloride for intracameral use. This single-use commercial product is approved for endophthalmitis prophylaxis in numerous European countries but not in the U.S., where use of any intracameral antibiotic is off-label. The following section compares characteristics of moxifloxacin, cephalosporin, and vancomycin, 3 antibiotics whose general safety for intracameral prophylaxis is supported by the literature.<sup>6,8-13</sup>

### Basic Pharmacology

Newer fourth-generation fluoroquinolones such as moxifloxacin have an improved spectrum of coverage, higher potency, delayed antibiotic resistance, better tissue penetration, and excellent efficacy, especially against gram-positive bacteria.<sup>14</sup>

Cefuroxime is a second-generation cephalosporin that offers concentration-dependent bactericidal activity. Similar to other beta-lactam antibiotics, it inhibits cell-wall synthesis. Cefuroxime's bactericidal activity is concentration-dependent and occurs at concentrations that are 4 to 5 times higher than the minimum inhibitory concentrations (MICs). It is a broad-spectrum antibiotic that covers most gram-positive and gram-negative organisms commonly associated with postoperative infectious endophthalmitis, with the exception of methicillin-resistant *Staphylococcus aureus* (MRSA).

Vancomycin is a bactericidal antibiotic with virtually 100% coverage of gram-positive endophthalmitis-causing organisms. The MIC of vancomycin for gram-positive pathogens causing endophthalmitis is 4.0 mg/1.0 mL or less and in most cases is in the range of 0.5 to 1.0 mg/1.0 mL.<sup>15,16</sup> In vitro studies have reported<sup>17</sup> that vancomycin was bacteriostatic for the first 6 hours and became bactericidal only after 8 hours,

a finding that is consistent with its mechanism of action that blocks cell-wall synthesis.<sup>17,18</sup>

### Spectrum of Activity

Gram-positive bacteria are the most common cause of postoperative endophthalmitis.<sup>1,19-23</sup> However, the prevalence of certain pathogens may vary by geographic region. According to the Endophthalmitis Vitrectomy Study,<sup>19</sup> 94.2% of culture-positive endophthalmitis cases involved gram-positive bacteria; 70.0% of isolates were gram-positive *S epidermidis*, 9.9% were *S aureus*, 9.0% were *Streptococcus* species, 2.2% were *Enterococcus* species, and 3.0% were other gram-positive species. Gram-negative species were involved in 5.9% of cases.<sup>8</sup> In endophthalmitis, coagulase-negative staphylococci (CoNS) are the most frequently recovered pathogens.

Fluoroquinolones remain the most commonly used antimicrobials for the prevention and management of bacterial endophthalmitis.<sup>24</sup> Compared with earlier generation fluoroquinolones, moxifloxacin has good activity against gram-negative bacteria and improved coverage of gram-positive cocci and atypical pathogens.<sup>25,26</sup> It is active against many anaerobes and against typical and atypical upper- and lower-respiratory pathogens such as *Mycobacteria* spp. and *Legionella*. It is one of the most active fluoroquinolones against *pneumococci*, including penicillin- and macrolide-resistant strains.<sup>26,27</sup>

Asena et al.<sup>28</sup> reported that moxifloxacin used in an endophthalmitis rabbit model reached a higher concentration than the MIC of all common endophthalmitis pathogens and exceeded the mutant prevention concentration levels for *Streptococcus pneumoniae*, *S viridans*, fluoroquinolone-susceptible CoNS, and fluoroquinolone-susceptible *S aureus* for 6 hours. They concluded that perioperative intracameral moxifloxacin injection for endophthalmitis prophylaxis is safe and effective. Furthermore, because moxifloxacin's efficacy is concentration-dependent, high drug concentrations (ie, above the MIC) might result in faster and more extensive bacterial eradication, assuming that the pathogen is sensitive.<sup>29</sup> Several studies have found moxifloxacin to have superior potency.<sup>29-32</sup> It has the lowest MIC for most bacterial endophthalmitis isolates.

Cephalosporins are divided into 4 generations. In general, first-generation cephalosporins have better activity against gram-positive bacteria than against gram-negatives. In contrast, third- and fourth-generation cephalosporins have better gram-negative activity than gram-positive activity. The earlier generations are often used for community-acquired or uncomplicated infections, whereas the later generations are used for hospital-acquired or complicated infections.

There are 2 types of second-generation agents, the “true” second-generation cephalosporins (cefuroxime and cefamandole) and the cephamycins (cefoxitin, cefotetan, and cefmetazole). The 2 groups differ in their spectrum of activity and adverse-reaction profile.<sup>A</sup>

Cefuroxime is a second-generation cephalosporin and is the only cephalosporin available in intramuscular, intravenous, and oral forms.<sup>33,34</sup> Cefuroxime (Zinacef, Kefurox) intramuscular, intravenous, and oral formulations are somewhat less potent against *S aureus* and more potent against *S pneumoniae* and *S pyogenes* than first-generation cephalosporins. Cefuroxime is active against *Haemophilus influenzae*; *Moraxella catarrhalis*; *Escherichia coli*; *Proteus mirabilis*; *Klebsiella*;  $\beta$ -lactamase-producing penicillinase-positive and -negative strains of *Neisseria gonorrhoeae*; and the Enterobacteriaceae *Salmonella*, *Citrobacter*, *Enterobacter*, and *Shigella* species.<sup>34,35,A</sup> It has activity against *Borrelia burgdorferi*, the bacteria responsible for Lyme disease, and against some anaerobic bacteria such as *Peptococcus* species.<sup>34</sup> Cefuroxime has adequate activity against methicillin-sensitive *S aureus* but is inactive against MRSA and enterococci.<sup>A</sup> One potential gap in the coverage of cefuroxime is multidrug-resistant enterococci. Although uncommon, endophthalmitis caused by this pathogen carries a poor prognosis.

Vancomycin is the therapy of choice for serious gram-positive cocci infections when the penicillins and cephalosporins cannot be used or when the organism is resistant to multiple drugs. Vancomycin is active against *S epidermidis*, *S aureus* (methicillin sensitive and resistant), and most strains of *Streptococcus*.<sup>36,37,B</sup> Vancomycin is also effective against the anaerobes, diphtheroids, and the *Clostridium* species, including *C difficile*.<sup>B</sup>

In a review of endophthalmitis isolates,<sup>38</sup> 100% of the gram-positive organisms were susceptible to vancomycin but fewer were susceptible to other antibiotics (gentamicin 88.0%, sulfamethoxazole/trimethoprim 77.5%, levofloxacin 58.5%, oxacillin 54.7%, ciprofloxacin 51.0%, gatifloxacin 51.0%, and moxifloxacin 47.0%). The authors found that no single antibiotic covered all the microbes isolated from eyes with endophthalmitis, and they therefore recommended a combination therapy.<sup>38</sup>

## DOSAGE AND PREPARATION

Espiritu et al.,<sup>9</sup> Lane et al.,<sup>10</sup> Arbisser,<sup>11</sup> and O'Brien et al.<sup>39</sup> reported using the commercial preparation of self-preserved moxifloxacin eyedrops (Vigamox 0.5% ophthalmic solution) for topical and direct intracameral prophylaxis.<sup>9-11,39</sup> Although such use is clearly off-label, they reported their methods of preparation and dilution as summarized in Table 1.

Whether to use topical antibiotics in lieu of or in addition to intracameral antibiotic prophylaxis is a controversial topic and beyond the scope of our review.

Cefuroxime is used as an intracameral injection in a concentration of 1.0 mg/0.1 mL. However, to date there is no commercially available preparation, so it must be freshly prepared by reconstituting the parenteral drug in balanced salt solution to achieve the desired concentration.

The clinically recommended dose of intracameral vancomycin is 1.0 mg/0.1 mL balanced salt solution. Murphy et al.<sup>40</sup> prepared vancomycin for intracameral injection in the hospital pharmacy as follows: The unpreserved vancomycin 500 mg powder is reconstituted with 10 mL balanced salt solution. The resultant 10 mL solution is diluted in 40 mL balanced salt solution to give a final concentration of 10.0 mg/1.0 mL vancomycin. This is then filtered into 1.0 mL syringes to a volume of 0.5 mL and 0.1 mL (1 mg) of this is administered intracamerally.

## EFFICACY

Several studies support the theoretical or actual clinical efficacy of intracameral antibiotic prophylaxis, depending on what antibiotic is being used. Intracameral injection of moxifloxacin achieves much higher aqueous levels than does topical application.<sup>41</sup> Concentrations vary depending on whether regimens commence in the days before surgery, on the day of surgery, or a combination of these.<sup>42-48</sup> With applications that start several days before surgery, reported values ranged from 0.11  $\mu\text{g/mL} \pm 0.05$  (SD) to 2.28  $\pm 1.23$   $\mu\text{g/mL}$  in aqueous.<sup>42,44,47</sup> With applications that start on the day of surgery, reported values ranged from 1.50  $\pm 0.75$   $\mu\text{g/mL}$  to 1.80  $\pm 1.21$   $\mu\text{g/mL}$ .<sup>45,46,48</sup> With combined regimens, reported concentrations ranged from 0.97  $\pm 0.63$   $\mu\text{g/mL}$  to 2.16  $\pm 1.12$   $\mu\text{g/mL}$ .<sup>45-47</sup> By comparison, intracameral injection of 250  $\mu\text{g}$  of moxifloxacin is expected to produce approximate aqueous humor concentrations of 710 to 1250  $\mu\text{g/mL}$ .<sup>10</sup>

By extrapolating results of laboratory experiments, Espiritu et al.<sup>9</sup> approximated that the initial anterior chamber moxifloxacin levels after injection of 0.1 mL of solution containing 500  $\mu\text{g}$  moxifloxacin was at least 300 times the median MIC of endophthalmitis-causing organisms.

In 2002, in a retrospective review of 32 000 cases, Montan et al.<sup>6</sup> reported that intracameral injection of 1 mg cefuroxime appeared to effectively inhibit sensitive bacterial strains and was associated with a low frequency of postoperative endophthalmitis. Subsequently, the large multicenter prospective ESCRS randomized trial<sup>3</sup> provided the strongest evidence of

**Table 1.** The impact of intracameral injection of self-preserved moxifloxacin to intraocular structures in the literature.

Author*	Concentration	Study Characteristics	Cornea Evaluation	Anterior Chamber Inflammation	Macular Evaluation
Espiritu <sup>9</sup>	0.5 mg/0.1 mL (undiluted)	Prospective study; 65 eyes analyzed 1 mo postop	On POD1, no corneal edema; mean CCT increase of 17.80 $\mu\text{m}$ at 1 mo; endothelial cell loss mean difference of 70.06 cells/ $\text{mm}^2$ from baseline	On POD1, flare ranged from 0 to +2 and cells from 0 to +2 in all eyes; quiet on other follow-up	Not evaluated
Arbisser <sup>11</sup>	0.1 mg/0.1 mL (diluted)	Retrospective comparison; 200 eyes with moxifloxacin versus 100 eyes without moxifloxacin; analyzed 6 wk postop	Corneal edema present in no moxifloxacin eyes versus 1 control eye <sup>†</sup>	On POD1, cells >3+ in 2% of moxifloxacin eyes versus 11% in control eyes	Not evaluated
Arbisser <sup>11</sup>	0.1 mg/0.1 mL (diluted)	Prospective study; 31 eyes analyzed 6 wk postop	Not evaluated	Not evaluated	Increase in macular thickness of <3% and in macular volume of <4%
Lane <sup>10</sup>	250 $\mu\text{g}$ /0.05 mL	Prospective randomized trial; 26 eyes with moxifloxacin versus 31 control eyes; analyzed 3 mo postop	CCT comparable; corneal edema trace in 1 moxifloxacin eye versus no control eyes; ECC comparable	Trace cells noted in 9 (34.6%) moxifloxacin eyes versus 15 (48.4%) control eyes	At 3 mo postop, 15% increase in macular thickness in 2 moxifloxacin eyes versus 5 control eyes

CCT = central corneal thickness; ECC = endothelial cell count; POD1 = postoperative day 1

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<sup>†</sup>Patient had preexisting anterior membrane dystrophy

the efficacy of intracameral cefuroxime in reducing the endophthalmitis rate. Overall, direct intracameral cefuroxime injections resulted in more than a 5-fold decrease (95% confidence interval [CI], 1.72-20.0) in the risk for culture-positive endophthalmitis. Several subsequent European studies have reported a reduction in endophthalmitis rates with the adoption of intracameral injection of cefuroxime, including 3 nationwide prospective registry studies in Sweden that collected endophthalmitis cases that followed more than 800 000 cataract surgeries over 12 years.<sup>7,49-56</sup>

The results of a large retrospective study suggest that direct intracameral injection of vancomycin is efficacious.<sup>8</sup> Mendívil and Mendívil<sup>57</sup> reported that cataract patients who received intracameral vancomycin (20 g/mL) had significantly fewer positive cultures (from aspirates drawn at the end of surgery) than those who did not receive vancomycin. They observed that 2 hours after surgery, 47% of the initial concentration of vancomycin remained in the anterior chamber.

These values are greater than the MIC (4  $\mu\text{g}/\text{mL}$ ) for most bacteria that cause postoperative endophthalmitis.

In the only study of its kind, Murphy et al.<sup>40</sup> used serial aqueous taps after cataract surgery in human patients to measure the aqueous concentration of vancomycin at different time intervals following a single intracameral injection of 1 mg in 0.1 mL saline. The mean concentrations of vancomycin at 1 hour and 23 hours after injection were 5385.2 mg/1.0 mL and 41.1 mg/1.0 mL, respectively. At 26 hours after injection, the concentration in the anterior chamber still exceeded the MIC for most gram-positive organisms by a factor of 4. It was estimated to have remained above the MIC for 32 hours. In this study, the prolonged high concentration of vancomycin in the anterior chamber following bolus injection might enable effective bacterial killing to be achieved, especially because its bactericidal activity is greater during the logarithmic bacterial growth phase than during the stationary growth phase.<sup>58</sup> However, there are no published,

large trials that evaluate the clinical efficacy of antibiotic prophylaxis with moxifloxacin or vancomycin. Therefore, the strongest evidence for clinical efficacy in endophthalmitis prophylaxis is for intracameral cefuroxime.

## RESISTANCE

The use of intracameral antibiotics prophylactically to increase antimicrobial resistance is a controversial issue and has been reviewed in detail by Gordon.<sup>59</sup> Prophylactic use has been of particular concern with vancomycin, which is considered the agent of last resort for multidrug-resistant bacteria. Systemic use of vancomycin is generally restricted for this reason. However, the anterior chamber is a closed compartment that is normally sterile, and intracameral antibiotic injection should not lead to significant systemic levels. In our opinion, although not supported by published evidence, it is unlikely that routine intracameral antibiotic prophylaxis will promote drug resistance.

Experimental studies have reported inadequate antibiotic coverage for human (CoNS) endophthalmitis isolates, with vancomycin being more effective than fourth-generation fluoroquinolones (gatifloxacin and moxifloxacin).<sup>60</sup> Finally, the incidence of MRSA ocular infections is rising, both in total numbers and as a percentage of all *S aureus* infections.<sup>61,62</sup> Vancomycin is the most effective antibiotic for MRSA.

## SAFETY AND TOXIC ANTERIOR SEGMENT SYNDROME

Aside from European markets where Aprokam is approved, the lack of a commercially available injectable solution approved for intracameral prophylaxis raises important issues for surgeons and their patients. Corneal endothelial toxicity and toxic anterior segment syndrome (TASS) are potential concerns following intracameral injection of any drug. Toxicity may result not only from the drug itself, but also from preservatives and abnormal pH or osmolality.<sup>63</sup> Toxic anterior segment syndrome is an acute sterile postoperative inflammation that can follow anterior segment surgery. A frequent cause is toxicity from medications or solutions injected into the anterior chamber during surgery.<sup>63,64</sup>

Intracameral antibiotics other than Aprokam must be mixed, diluted, or prepared for intracameral administration. As such, these formulations must be sterile and unpreserved and must be of the proper concentration and dose. Dilution errors are more likely when multiple steps are required to prepare the antibiotic solution. Both anterior and posterior segment inflammation were reported in a group of patients who, because of dilution error, inadvertently were

given a high dose of intracameral cefuroxime at the conclusion of uneventful cataract surgery.<sup>65</sup> In addition to iridocyclitis, optical coherence tomography showed extensive macular edema associated with a large serous retinal detachment. Fortunately, the patients in this study eventually recovered satisfactory vision with resolution of their macular edema. There has been 1 case report of macular infarction and associated cystoid macular edema following an inadvertent intracameral injection of approximately 62.5 mg of cefuroxime<sup>66</sup> and 4 reported cases of hemorrhagic retinal infarction caused by inadvertent overdose of cefuroxime in cases of complicated cataract surgery.<sup>67</sup> Even when the cefuroxime is mixed according to a relatively strict protocol, it is difficult to prepare a consistent dilution for intracameral injection. A study carefully evaluated the mixing of a solution using potassium chloride as a surrogate for cefuroxime and found that the mean dose after dilution ranged from 0.62 to 7.25 mg, even when a proper protocol was followed.<sup>68</sup>

There are also potential pH and osmolality issues whenever intracameral drugs must be mixed or diluted. For example, vancomycin has an acidic pH that must be adequately buffered with balanced salt solution. An episode of TASS occurred when a compounding pharmacy improperly mixed vancomycin for injection, leading to it having a low pH of 4. Furthermore, osmolality errors caused by diluting the vancomycin with sterile water instead of balanced salt solution have led to severe corneal edema and glaucoma.<sup>C</sup>

Commercially available Vigamox eyedrops (moxifloxacin 0.5%) are preservative-free and isotonic, with a 6.8 pH and an osmolality of approximately 290 mOsm/kg. Because these values are similar to those of aqueous (pH 7.4, osmolality 305 mOsm./Kg.),<sup>39</sup> using this topical solution has not been associated with ocular toxicity at full strength or with a 50:50 dilution in balanced salt solution for intracameral injection.<sup>11,39</sup> However, the Intermountain Ocular Research Center recently became involved in an outbreak of TASS in which 12 patients received an inadvertent intracameral injection of a commercially available moxifloxacin 0.5% product, Moxeza. All 12 patients developed severe postoperative TASS. In addition to moxifloxacin, the topical drug Moxeza contains inactive ingredients such as xanthan gum, sorbitol, and tyloxapol. The latter has both detergent and mucolytic properties. The prescribing information for topical Moxeza specifically states that it should not be introduced into the anterior chamber.<sup>D</sup>

Kowalski et al.<sup>31</sup> also found that intracameral injection of commercial Vigamox was nontoxic and effective in preventing endophthalmitis from *S aureus* in a

rabbit model. Two U.S. patient studies<sup>39,69</sup> demonstrated a good safety profile of intracameral moxifloxacin given as a 100 µg/0.1 mL dose or a 250 µg/0.05 mL dose, diluted from Vigamox.

In several studies,<sup>6,70,71</sup> use of 1.0 mg intracameral cefuroxime did not cause endothelial cell loss or macular thickening. Furthermore, electroretinographic and histologic findings indicated that a dose of 1.0 mg cefuroxime, administered intravitreally, was not toxic to the rabbit retina.<sup>72</sup> There have been 2 reports of anaphylactic reactions following cefuroxime injection, 1 after intracameral injection<sup>73</sup> and 1 after intravitreal injection.<sup>74</sup> Fortunately, this reaction appears to be very rare.

Vancomycin powder is reconstituted with sterile water (10 mL for each 500 mg of vancomycin), and the sterile water must be preservative free (labeled “for injection”). The reconstituted vancomycin must be further diluted (at least 1:9) with balanced salt solution before injection.

## DISCUSSION

The ESCRS prospective randomized study demonstrated the efficacy of intracameral cefuroxime in the prevention of endophthalmitis.<sup>3</sup> There are several potential advantages to the use of intracameral antibiotics following cataract surgery, such as ease of delivery and reduction in or elimination of the use of topical eyedrops. Another advantage of an intracameral antibiotic injection is a higher drug concentration at the target site. Also, intracameral medications might eliminate some patient-compliance problems, such as the proper postoperative use and timing of eyedrops.

A Spanish study<sup>52</sup> looked at the cost of a dose of cefuroxime and the hospital costs of a case of endophthalmitis, using full-cost analysis and accounting for all hospital expenses of each case of endophthalmitis. Their analysis using analytic accounting showed that the potential savings was €1176.7 (US \$1549.40) for every 182 patients treated prophylactically with cefuroxime. Another study<sup>75</sup> reported that the cost savings for intracameral cefuroxime is US \$1403 per case of postoperative endophthalmitis prevented and that cefuroxime might be more cost effective than fluoroquinolones.

The peer-reviewed literature generally supports the safety of using intracameral preparations of vancomycin, moxifloxacin, and several cephalosporins.<sup>6,8-13</sup> However, in countries without access to commercially approved preparations, there are potential risks for incorrect dosing, formulation, and preparation. In a 2008 survey of ASCRS members in the U.S.,<sup>76</sup> 77% of respondents were not using intracameral antibiotics postoperatively at that time. However, 82% responded

that they would likely use it were a reasonably priced commercial preparation available.

We believe that approved commercial antibiotic preparations for intracameral injection ultimately should increase the safety of cataract surgery by providing better endophthalmitis prophylaxis and reduced risk for toxicity. We call on the pharmaceutical industry and the U.S. Food and Drug Administration to make the development and approval of such products a high priority.

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## FINANCIAL DISCLOSURES

Dr. Braga-Mele is a consultant to Alcon Laboratories Inc. and Abbott Medical Optics, Inc. Dr. Chang is a consultant to Abbott Medical Optics, Inc., Clarity, and Power Vision. Dr. Henderson is a consultant to Alcon Laboratories, Inc., Bausch & Lomb, Abbott Medical Optics, Inc., and Genzyme. Dr. Talley-Rostov is a consultant to Bausch & Lomb. Dr. Vasavada is a consultant to Alcon Laboratories, Inc. Dr. Mamalis has no financial or proprietary interest in any material or method mentioned.



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