This guest editorial is one of a series looking back at landmark articles published in the *JCRS*. This special series commemorates the 25th anniversary of the joint *Journal of Cataract & Refractive Surgery*. This issue: Prophylaxis of postoperative endophthalmitis following cataract surgery: ESCRS Endophthalmitis Study Group. Results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg* 2007;33:978–988.

So, you completed the cataract surgery flawlessly in your one-eyed patient, and she could already see a big improvement in the recovery area! You are excited to see the outcome the next day, when the patient examination note states she has suffered pain and decreasing vision. With one look you know this is likely postoperative endophthalmitis (POE); indeed that is what it is, and looking this bad the day after surgery likely means a bad bacteria (it is) and a bad outcome (sadly, yes). This is the cataract surgeon’s nightmare! Thus, anything we can do to prevent this calamity is important, and even as rare as such events are today—occurring per 10 000 surgeries—it is still a big international problem because of the sheer number of such surgeries done in the world today.

So, let’s wander back 15 or so years and consider what the state of the art was in POE prophylaxis at the time. Sureless corneal incisions were becoming popular, and there was concern that this was prompting more POE. The only generally agreed prophylaxis step was preoperative topical povidone–iodine with advocates for many antibiotic regimens, and some skeptics who doubted that any antibiotic routine made a difference. The studies that proved they did were certainly not definitive. Some papers were coming out suggesting that intracameral (IC) antibiotics might be a superior approach, but which antibiotic and by which route (a bolus at the end of the case or antibiotic in the irrigating solution were the two most popular) was unclear. Sweden had a registrar and impressive results for a bolus of IC cefuroxime at the end of surgery, but to say the controversy raged wildly is an understatement. Nothing less than a prospective, randomized study was going to solve this controversy. I think all agree that Peter Barry, FRCS, FRCOphth, was the driving force behind just such a study, the ESCRS multicenter effort. Such a study was a daunting task (Figure 1).

The design was straightforward with the following 4 cohorts: (1) placebo drops and no IC antibiotic; (2) placebo drops and IC 1 mg of cefuroxime; (3) levofloxacin 0.5% drops and no IC antibiotics; and (4) both levofloxacin 0.5% and 1 mg of intravenous cefuroxime. The plan was to enroll up to 35 000 patients; however, the results were so clear the study was terminated early with 16 603 patients enrolled. The results? The topical regimen had no statistically significant impact when compared with placebo in preventing POE, whereas IC cefuroxime cut the rate about fivefold (*P* = .001 for culture +/− cases). Wait, there was more! Corneal incisions increased POE risk 5.9-fold (*P* = .019 for culture +/− cases). The clear cornea crowd were not amused. Surgical complications increased POE risk about fivefold (*P* = .004 also for culture +/− cases), and there was enough other support for this finding in the literature; this was not controversial. The next one, however, drove the silicone intraocular lens (IOL) crowd crazy: silicone IOLs increased POE risk about threefold (*P* = .003 also for culture +/− cases). So, controversy solved? Not by a long shot.

The main complaints about the IC cefuroxime findings were (1) The non-IC cefuroxime cohorts had POE rates many times higher than several good reports using topical antibiotics alone, so something had to be amiss; (2) the topical regimen with drops postoperatively and then not until the next day was inferior to other reported topical approaches at the time; (3) there were topical regimens that reported better than the IC cefuroxime groups; and (4) cefuroxime had a lot of resistant bacterial strains out there so had to be a poor choice. Sadly, because of these concerns, the study was not well accepted in large parts of the United States, and so, the routine use of IC antibiotics lagged. Europe and other parts of the world were more receptive, and a series of reports on POE incidence as different groups moved to IC antibiotic generally supported the ESCRS study, with particularly impressive results from Kaiser and Aravind, with very large numbers and thus the power to show a difference. Critics will still say that none of these are prospective randomized trials, so the controversy remains unanswered. Although true, with incidence now in the 0.05% level or less, a definitive study is even more daunting, and most would consider the preponderance of the evidence so strong for IC antibiotics that even considering such a study is probably unethical today. Furthermore, I doubt anyone could support a cohort today where no antibiotic of any kind is used.
What about the finding that topical antibiotics have no role to play in POE prevention? At about this time, we had a prospective quality control program looking at POE and retrospectively created a large cohort with no POE for comparison. Indeed, we found that only antibiotics right after surgery vs frequent drops the day of surgery increased the incidence of POE 13.7-fold ($P = .001$), more than IC cefuroxime had done to prevent POE in the ESCRS study (Figure 2).6 Others also showed impressive results with topical regimens alone.7 Thus, the impact of topical antibiotics is not clear but likely can make some difference, while using no antibiotics at all would be difficult to defend today. The fact is, however, most studies looking at these issues show IC antibiotics superior to topical prophylaxis alone.

What about cefuroxime as outdated and a poor choice? No study I can find shows it inferior to other choices, such as moxifloxacin, and the most recent Kaiser study suggests it still may be the best choice even today.7 I was often called to debate Peter Barry about this controversy and Peter said it best; I am paraphrasing here but the gist is: Resistance is relative and related to what levels you can get into tissues. One milligram of cefuroxime is a lot of antibiotic, and many resistant strains still fall to this onslaught. Still, the most recent Kaiser study shows where POE occurs in the face of cefuroxime prophylaxis; the bacteria are resistant. Of interest, this was not so for moxifloxacin.

So, what about the other big controversies? Implying clear corneal incisions were not safe created an uproar, with clear corneal advocates showing impressive results of low POE numbers at meetings. Our own study, right at this inflection point, did confirm that clear corneal incisions are very unforgiving, with the risk of POE going up 44-fold if that clear corneal incision is seen to leak on postoperative day 1!6 So I agree with their conclusions, but the answer is scrupulous attention to incision closure; such that will result in excellent POE rates such as those as we have been able to show in later studies at our institution.7

So that leaves the silicone IOL controversy. The ESCRS paper points out the many studies at that time showed silicone IOL POE risk and others showed no risk. Our own cohort study did not show a difference, and so this conclusion remains controversial, but my sense is that most do not accept that silicone IOL optics per se result in a POE risk.6 Furthermore, this controversy is largely moot with so few silicone IOLs being used presently.

So, what can we conclude? Peter Barry bemoaned the animus this study created; however, consider this: such a large multicenter trial is a beast and no one has pulled off a larger prospective randomized trial in ophthalmology to date! I wish Peter was still with us to savor the judgement of history as very favorable to this work. For all the pioneers in this great effort, kudos to you and a hearty job well done! I personally feel the move to IC antibiotic prophylaxis, which was certainly encouraged by this landmark study, has saved thousands of cases of needless blindness, and we all owe a debt of gratitude to the pioneeers who made this happen!
REFERENCES

Disclosures: R.J. Olson is a shareholder in Eyegate Pharmaceuticals, Inc. and Perfect Lens LLC; in the latter, he also serves on the Medical Advisory Committee; he is a shareholder and serves on the Board of Directors of Voyant-Oriole, LLC.

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