

# REDUCTION OF PREOPERATIVE CONJUNCTIVAL BACTERIAL FLORA WITH THE USE OF MUPIROCIIN NASAL OINTMENT

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## ABSTRACT

**Purpose:** To determine whether the use of mupirocin ointment for preoperative eradication of nasal bacterial carriage was effective in reducing conjunctival bacterial flora.

**Methods:** Prospective, double-arm, blinded clinical trial of 37 eyes of 37 patients undergoing intraocular surgery (cataract extraction or pars plana vitrectomy) randomized to either control or mupirocin treatment groups. Treated patients received mupirocin nasal ointment twice daily for 5 days prior to surgery. Nasal cultures were obtained in all patients. All patients received a standard 5% povidone-iodine preparation before the surgical procedure, and conjunctival cultures were obtained in all patients before and after the povidone-iodine preparation.

**Results:** All 37 patient nasal swabs were positive for bacterial growth (cultures were obtained prior to the use of mupirocin ointment in the treatment group). One of 15 eyes (6.7%) in the treatment group had positive conjunctival cultures prior to povidone-iodine preparation, compared with nine of 22 eyes (41%) in the control group ( $P < .05$ ). Even after povidone-iodine preparation, eight of 22 eyes (36%) in the control group demonstrated persistent positive cultures, whereas one (6.7%) of the treatment eyes exhibited growth ( $P < .05$ ).

**Conclusions:** Prophylactic use of mupirocin nasal ointment resulted in significant reduction of conjunctival flora with or without preoperative topical 5% povidone-iodine preparation. The use of mupirocin nasal ointment prior to intraocular surgery or intravitreal injections is a novel method for reducing conjunctival contamination rates, which theoretically should reduce the incidence of endophthalmitis.

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## INTRODUCTION

Bacterial endophthalmitis is a rare, but serious, complication of intraocular surgery. The reported incidence varies depending on the type of surgery, with culture-positive endophthalmitis in one study observed in 0.30% of secondary intraocular lens implantations and 0.051% of vitrectomy cases.<sup>1</sup> A number of different sources have been implicated as origins of possible infection. Some of these include the eyelids, eyelashes, conjunctiva, and nasal secretions. One study demonstrated that organisms isolated from the vitreous were genetically indistinguishable from those recovered from the eyelids, conjunctiva, or nose in 14 of 17 cases of endophthalmitis.<sup>2</sup> Gram-positive organisms are part of the normal flora of the skin, nares, and conjunctiva, and interestingly the Endophthalmitis Vitrectomy Study demonstrated that 94% of isolates recovered from eyes with postoperative endophthalmitis had gram-positive organisms, 70% of which were due to coagulase-negative staphylococci.<sup>3</sup>

Mupirocin (Bactroban) is a unique antibiotic that exerts bactericidal action by interfering with the action of isoleucyl-transfer RNA synthetase. Mupirocin is active against gram-positive organisms, including *Staphylococcus* and *Streptococcus* species. It is available as a nasal ointment and is used for the eradication of methicillin-resistant *S aureus*.<sup>4</sup> Nasal carriage of *S aureus* was eliminated in 91% of colonized healthcare workers 2 to 4 days following treatment with mupirocin ointment.<sup>5</sup>

Nasal carriage of gram-positive organisms is a well-established risk factor for surgical site infections. In a large multicenter study of *S aureus* bacteremia, greater than 80% of the blood isolates were identical to those from the anterior nares.<sup>6</sup>

Perioperative elimination of nasal carriage using mupirocin ointment significantly reduced the surgical site infection rate in one study of cardiothoracic surgery patients.<sup>7</sup> Additionally, the use of mupirocin nasal ointment was effective in reducing the incidence of *S aureus* infections in hemodialysis patients, as well as in those patients who undergo continuous ambulatory peritoneal dialysis (CAPD).<sup>8,9</sup>

There is evidence in the literature of nonophthalmologic specialties that the rates of surgical site infections can be reduced with mupirocin nasal ointment. Therefore, we sought to determine if using mupirocin ointment to eliminate nasal bacterial carriage prior to intraocular surgery was effective in reducing conjunctival bacterial flora. If successful, we hypothesize that rates of postoperative endophthalmitis could be reduced with improved sterilization of the ocular surface.

## METHODS

The study was carried out with the approval of the University of Chicago School of Medicine Institutional Review Board. Thirty-seven adult patients, age range 26 to 83 years ( $57 \pm 14$  years), undergoing elective cataract or pars plana vitrectomy surgery between

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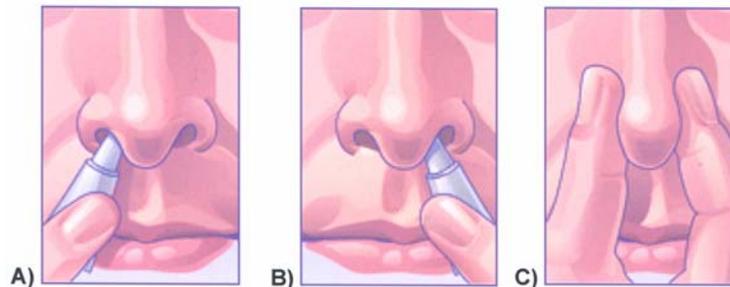
**Bold** type indicates **AS** member.

November 2005 and April 2006 at the University of Chicago were included in this prospective, blinded, randomized study (Table). Exclusion criteria included the following: known sensitivity or allergy to any of the constituents of mupirocin ointment, active ocular infection at the time of surgery, or concurrent use of any antibiotic (systemic or topical). The 37 eyes in this study were randomized to either control or treatment groups.

**TABLE. PATIENT DEMOGRAPHICS WITH BREAKDOWN OF THOSE WHO DID NOT USE MUPIROCIN NASAL OINTMENT (CONTROL GROUP) AND THOSE WHO RECEIVED NASAL OINTMENT (TREATMENT GROUP) PRIOR TO OCULAR SURGERY**

VARIABLE	CONTROL GROUP	TREATMENT GROUP
No. of patients	22	15
Age, mean (range)	55 (26-83)	59 (41-80)
Gender		
Male	11	6
Female	11	9
Surgical procedure	Vitrectomy (19/22) Cataract surgery (3/22)	Vitrectomy (9/15) Cataract surgery (6/15)

After informed consent was obtained, 22 patients were enrolled in the control group and received no nasal medication. Fifteen patients were enrolled in the treatment group and were asked to self-administer mupirocin ointment to each nostril twice daily for 5 days prior to surgery (Figure 1). Nasal cultures were obtained in all patients using a cotton swab moistened with sterile balanced saline solution (BSS, Alcon Laboratories, Inc). In the treatment group, nasal cultures were obtained prior to the administration of mupirocin ointment.



**FIGURE 1**

Technique for administering mupirocin nasal ointment prior to ocular surgery. A, Apply one-half the contents of a tube in one nostril. B, Apply the other half of tube contents in other nostril. C, Press nostrils together. Massage for approximately 1 minute

A standard povidone iodine scrub was performed in all patients. Prior to placement of sterile drapes, sterile gauze dipped in 5% povidone-iodine was used to cleanse the periocular region and eyelids three times. Povidone-iodine solution was then flushed over the ocular surface using a bulb syringe. Cotton-tipped swabs dipped in the povidone-iodine solution were then used to cleanse the upper and lower eyelashes and eyelid margins three times. Lastly, sterile gauze dipped in 5% povidone-iodine was once again used to cleanse the periocular region and eyelids prior to placement of the sterile drapes.

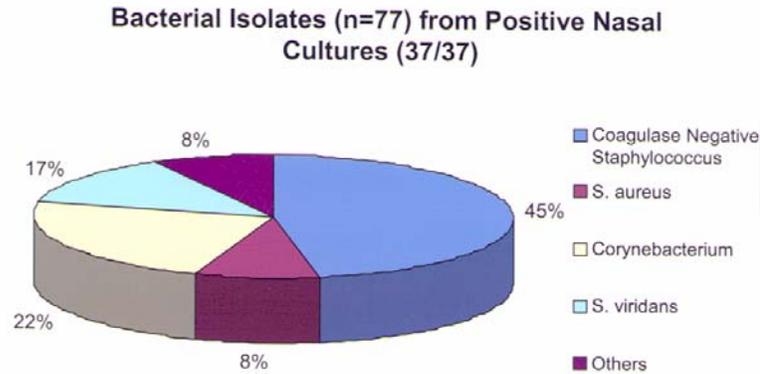
Two conjunctival cultures were obtained in all patients in the operating room, the first before application of 5% povidone-iodine scrub and the second immediately before surgery. BSS was used to rinse the ocular surface of any residual povidone-iodine to ensure culture swabs were free of povidone-iodine. Conjunctival cultures were obtained from the inferior fornix using a cotton swab moistened with sterile BSS. Care was taken to avoid touching the eyelid margin or lashes. Patients did not received topical antibiotics prior to conjunctival cultures.

All culture samples were immediately inoculated on Columbia agar with 5% sheep blood and chocolate II agar plates (BD Diagnostics System). Plates were incubated overnight in 5% to 10% CO<sub>2</sub> and examined the next day. Plates were then reincubated and reexamined daily until issuing final reports. The microbiologists (S.B. or K.T.) and surgeons (S.M.H., M.S., S.K., and W.F.M.) were masked with regard to treatment vs control group.

**RESULTS**

Indications for operation in the 37 patients were as follows (Table): cataract extraction with posterior chamber intraocular lens implantation (nine patients) and pars plana vitrectomy (28 patients).

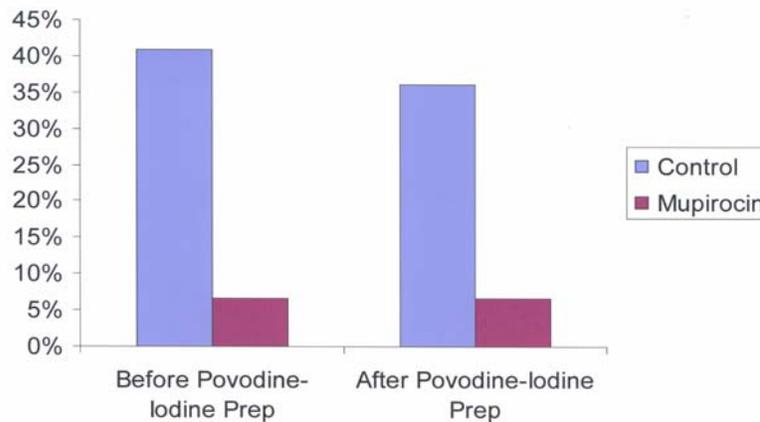
All 37 patients (100%) demonstrated bacterial growth on nasal swabs. A total of 77 bacterial isolates were yielded from the 37 nasal cultures. Coagulase-negative *Staphylococcus* was the most commonly cultured organism, accounting for 35 of 77 isolates (45%), followed by *Corynebacterium* (22%) and *Streptococcus viridans* (17%). Six (16%) of the 37 nasal cultures were positive for *S aureus*, with methicillin-resistant *S aureus* accounting for three of the six positive cultures (Figure 2).



**FIGURE 2**

Nasal culture isolates from all 37 patients included in control and treatment groups prior to ocular surgery: coagulase-negative *Staphylococcus* (35/77); *S aureus* (3 methicillin-sensitive *S aureus*, 3 methicillin-resistant *S aureus* (6/77); *Corynebacterium* (17/77); *S viridans* (13/77) ; others (6/77).

Baseline conjunctival cultures revealed that nine of 22 eyes (41%) in the control group had bacterial growth, yielding 13 isolates. Baseline conjunctival cultures in the mupirocin-treated group were positive for bacterial growth in one of the 15 eyes (6.7%). Following povidone-iodine preparation, eight (36%) of 22 eyes in the control group demonstrated persistent positive cultures, yielding 10 bacterial isolates. In the study group, cultures after povidone-iodine preparation again were positive in one of the 15 eyes (6.7%) (Figure 3).



**FIGURE 3**

Conjunctival culture positivity in control group vs nasal mupirocin-treated group before and after povidone-iodine preparation for ocular surgery.

Differences in baseline and final conjunctival culture positivity rates between the two groups were statistically significant ( $P < .05$ ). Conjunctival bacterial isolates from the control and study group included coagulase-negative *Staphylococcus*, *Corynebacterium*, *S viridans*, and *S aureus*. Each positive conjunctival culture was associated with the same species in the nasal culture of the same patient.

Mupirocin was well tolerated in the treatment group, with no patients reporting any adverse reactions.

## DISCUSSION

Endophthalmitis is a serious complication of intraocular surgery. The eyelids and conjunctiva have been implicated as the most common source of bacteria causing postoperative endophthalmitis. Various methods of prophylaxis have been attempted, including preoperative lash trimming, irrigation with saline solution, topical antibiotics, irrigating solutions containing antibiotics, postoperative subconjunctival antibiotic injection, and postoperative collagen shields presoaked in antibiotics.<sup>10-13</sup> The goal of all these interventions is to decrease the incidence of postoperative endophthalmitis. In an evidence-based update, it was found that only preoperative povidone-iodine preparation received an intermediate clinical recommendation, indicating that povidone-iodine use is only moderately important to clinical outcome.<sup>14</sup> Nonetheless, povidone-iodine is currently the “gold standard” of preoperative ocular surface sterilization.

Speaker and associates<sup>2</sup> demonstrated that organisms isolated from the vitreous were genetically indistinguishable from those recovered from the eyelids, conjunctiva, or nose in 14 of 17 cases of endophthalmitis. In our study, each patient with positive conjunctival cultures had a nasal culture positive for the same organism. The anterior nares serve as a reservoir for gram-positive bacteria. All 37 patients in our study were positive for bacterial growth on nasal culture. Coagulase-negative *Staphylococcus* accounted for 45% of isolates (35/77), *S aureus* for 8% (6/77), and *S viridans* for 17% (13/77). These organisms are a frequent cause of bacteremia and have been implicated as the source of surgical site infections in various surgical populations.

Mupirocin is an antibiotic with bactericidal activity against gram-positive organisms, including methicillin-resistant *S aureus*. Treatment with mupirocin ointment to eliminate nasal bacterial carriage has been successful in reducing surgical site infections in cardiothoracic surgical patients and decreasing exit site infections in CAPD patients.<sup>7,8</sup> Our study results demonstrate a significant reduction of conjunctival bacterial flora with preoperative nasal application of mupirocin ointment. This reduction was observed with or without the use of povidone-iodine. Conjunctival contamination rates before povidone-iodine use were 41% (9/22) in the control group and 6.7% (1/15) in the treatment group ( $P < .05$ ). Of great interest was that even after povidone-iodine application, the mupirocin-treated group still had strongly lower rates of conjunctival contamination compared to the control group.

The proximity of the nose to the sterile eye field raises another potential benefit of treating the nares with mupirocin ointment. It has been proposed that nasal secretions may breach the sterile drape and enter the operative field, serving as a source of conjunctival contamination during surgery.<sup>15</sup> Kuhn and associates<sup>16</sup> describe two cases where what was believed to be vitreous reaccumulating on the conjunctiva was in fact clear mucous nasal secretions. They suggest that this may not be so rare an occurrence. This observation needs to be investigated further; however, if indeed nasal secretions are contaminating the operative field during surgery, then preoperative treatment with mupirocin ointment is even more logical.

There is increasing evidence that endophthalmitis is on the rise. A review of recent literature suggests that the incidence of postoperative endophthalmitis has increased.<sup>17</sup> This may be due to changes in surgical technique, rising number of intravitreal injections performed, sutureless vitrectomy, or other causes. We need to develop new strategies for the management of intraocular infection with creative use of antibiotics, with a goal of limiting the impact of proven infection, or ideally eliminating the development of endophthalmitis in a cost-effective manner.

The use of mupirocin nasal ointment prior to intraocular surgery or intravitreal injections is a novel method for reducing conjunctival contamination rates. Lower conjunctival contamination rates should theoretically reduce the incidence of postoperative endophthalmitis. Future studies will be needed to precisely define the role of mupirocin nasal ointment for prophylaxis against intraocular infections.

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## PEER DISCUSSION

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DR RICHARD K. FORSTER: Mupirocin nasal ointment has been demonstrated to reduce nasal carriage of bacterial organisms, and to reduce surgical site infection due to methicillin-resistant *S. aureus* in both cardiothoracic and hemodialysis patients. Based on a prospective, randomized study using nasal mupirocin in 37 patients undergoing intraocular surgery, the authors report a significant reduction in positive cultures, with or without preoperative topical povidone-iodine prep.

One hundred percent of patients demonstrated bacterial growth on nasal swabs prior to initiation of the treatment with 77 bacterial isolates from 37 nasal cultures, including 45% of isolates positive for coagulase-negative staphylococci, and 16% for *S. aureus*, with 3 of 6 positive cultures for methicillin-resistant *S. aureus*. Of interest, 36% of eyes in the control group not receiving mupirocin demonstrated positive cultures after povidone-iodine prep, and only one of 15 eyes in the mupirocin study group was culture positive. In addition, each positive conjunctival culture was associated with the same species from the nasal culture of the same patient.

Povidone-iodine has been demonstrated to reduce both the quality—that is the genus and species of organisms—and the quantity of organisms isolated at the time of intraocular surgery. This treatment, as part of preoperative prep along with topical antibiotics, has probably contributed to a reduction of an acute postoperative endophthalmitis. However, other factors such as organisms from the skin or oral mucosa may contribute to the contamination of intraocular contents. This report is encouraging by demonstrating the significant reduction in conjunctival bacterial flora with preoperative nasal application of mupirocin ointment.

However, I have one major concern about the methodology of the study and several observations that should be considered by the authors. Povidone-iodine has also been shown to reduce the type of organisms in conjunctival cultures, as well as the quantity of isolated organisms. This current study apparently did not quantitate bacterial isolation from the nasal cultures before treatment, nor the numbers of organisms at the time of the preoperative cultures—before and after povidone-iodine prep. Perhaps the authors could comment on whether quantitation was attempted in order to, more thoroughly analyze the results of the study. In addition, it is important to know whether the reduction of organisms was greater for any particular species, especially for *S. aureus* and coagulase negative staph. The authors do not report organisms and numbers comparing pretreatment nasal cultures to the immediate preoperative post treatment cultures of the conjunctiva.

I would encourage the authors to consider comparing povidone-iodine alone to mupirocin alone in order to compare their relative efficacy in reducing conjunctival flora. It may also be useful to compare nasal mupirocin alone to a five-day topical antibiotic and obtain quantitative cultures preoperatively. The later is important because in order to make such preoperative treatment practical and to expect compliance from patients it should be demonstrated that mupirocin nasal ointment is superior to povidone-iodine and/or topical antibiotics. Finally, enlarging the number of patients enrolled probably would make the study more significant. I congratulate the authors in bringing to our attention this novel approach to reduce the incidence of postoperative endophthalmitis.

DR MARK W. JOHNSON: The issue of prophylactic antibiotics, in terms of endophthalmitis, is a difficult one. There was a paper published in Germany several years ago actually showing that pre-operative use of topical antibiotics seemed to be a risk factor for the development of endophthalmitis. Is a period of five days enough time where, by inhibiting one group of organisms, one could actually encourage the growth of another group of resistant organisms? Or is that even a theoretical concern in pre-operative prophylaxis of this duration?

DR DAN B. JONES: I am assuming you did not do pre-Mupirocin conjunctival cultures before you started the study. My suggestion would be to do that in any future studies and maybe even sequentially over time to see how long it takes to reduce the conjunctival flora. Since the efficacy of Mupirocin in other infections reduces organisms where they do not normally occur, I would like the authors to speculate on the mechanism, since the conjunctiva has normal flora, as opposed to these other sites.

DR ALLAN J. FLACH: Almost all of us who speak about endophthalmitis begin by saying “we’ll never have a prospective double-masked randomized study that shows endophthalmitis is affected in any way.” There is a preliminary report in the Journal of Cataract and Refractive Surgery, thanks to our European colleagues, that involves thousands of patients from at least a dozen or more separate countries, that compares topical antibiotic therapy prophylactically, topical plus intracameral, and povidone iodine, in all three. So, we’ve got a placebo-controlled povidone iodine, plus topical, plus intracameral. They showed that the intracameral treatment had an effect on endophthalmitis. It is only a preliminary report, but do you have any comments about that study.

DR JAMES P. MCCULLEY: Antiseptics are time and heat dependant and have to be left for two to three minutes at a minimum or are not going to be effective. How long did you leave the antiseptic in place before you irrigated it away? Many of us see patients with chronic or recalcitrant Staph blepharitis. In children with chronic unilateral Staph blepharitis they are not uncommonly either thumb suckers or nose pickers. They have been very difficult to deal with and I've actually seen that in some adults. Your approach in those patients might be the key to us bringing them under control as it is difficult to get them to stop their habit of thumb sucking or nose picking.

DR THOMAS O. WOOD: Have you tried putting mupirocin directly on the ocular surface?

DR W. BANKS ANDERSON, JR: In this day and age of increasing medical costs, do you have any feel for the number necessary to treat in order to avoid one case of vision losing endophthalmitis? And what would that cost?

DR SEENU M. HARIPRASAD: It was hard to evaluate compliance in this study. Few patients did not have an effect, calling compliance into question. We are considering moving forward with a three-day administration study instead of five days to see if efficacy is comparable. We based our five-day treatment on a previous study performed in another specialty.

As you are aware, this pilot study had several limitations which will hopefully be addressed in a larger study. Dr. Forster points out that quantification of organisms is very valuable and we will consider performing this in a larger study. Additionally, in a pilot study we were concerned about having a Mupirocin only alone arm because we did not know how effective this drug was. Based on the results of this pilot study, we feel more comfortable in having a "Mupirocin only" arm. Comparing efficacy of Mupirocin versus topical antibiotics in eradicating conjunctival bacterial flora could be investigated in another study as this was not specifically addressed in our pilot study.

Dr. Johnson asked if five days of Mupirocin treatment encourages the development of resistant organisms. Although this is a theoretical possibility, we are comforted by those patients on peritoneal dialysis who receive Mupirocin prophylactically to prevent peritonitis. These patients may be on Mupirocin for months at a time without any problems anecdotally. Our use is confined to under a week so it is unlikely that ophthalmic use would have a significant impact on resistance patterns.

Dr. Jones recommends performing conjunctival cultures even before the application of nasal Mupirocin ointment. This will certainly be considered as we move forward with a larger study as this data is useful. He also asks how Mupirocin gets to the sites of action. It is not precisely known, however, I believe it is through one of two ways. First, the nasal mucosa and capillaries are very friable and Mupirocin may be absorbed into the systemic circulation and taken to the sites of concern (i.e., peritoneum in dialysis patients). Another possibility relevant to our study may be one that is more direct. Perhaps Mupirocin applied nasally sterilizes the ducts between the nose and the eye. There have been studies done in the pre-Medline era that have shown that secretions from the nose can actually reach the eye. One of my residents will be beginning a research project where Fluorescein dye will be placed in the nares during general anesthesia cases to see if any dye is present on the ocular surface at the end of the case. If there is reflux of nasal secretions onto the ocular surface, we will have added to the increasing evidence that nasal bacteria are one source of ocular surface contamination during surgery. Studies have shown that organisms isolated in endophthalmitis are frequently genetically indistinguishable from those found in the nose in the same patient.

Dr. Flach asks for my comments regarding the recent European Society of Cataract & Refractive Surgeons (ESCRS) multicenter study of the prophylaxis of endophthalmitis after cataract surgery. I agree with him that this study represents an impressive undertaking by our European colleagues. A question that came to mind when reviewing the preliminary report of the study (not necessarily a criticism) is why the baseline endophthalmitis rate in this patient population was so high (.33 percent or 23 cases in 6862 patients) compared to what we see in the United States. I wonder if the recommendations of this study truly apply for our patients in the U.S. At the present time, I cannot comment on the role of intracameral cefuroxime.

Concerning Dr. McCulley's question, we left povidone iodine on the ocular surface for about two minutes as the true effect is typically seen after 90 seconds. We then rinsed the ocular surface of any residual povidone iodine before taking cultures. Dr. McCulley raises the interesting idea of using Mupirocin nasal ointment in children to control Staph blepharitis. That is a novel concept with great potential; however, the product label states that safety in children has not been fully assessed.

Dr. Wood brings up the possibility of using Mupirocin directly on the ocular surface. Unfortunately, in its current formulation, Mupirocin causes stinging and burning so it should probably not be used topically.

Lastly, Dr. Anderson asks about the cost to society. The number of intravitreal injections performed by retina specialists in this country has skyrocketed to over 200,000 injections per year; up from maybe 4,500 injections just five years ago. Therefore, Dr. Anderson's question about cost to society is very relevant. The decisions we make can have a great financial impact. If we were to use a topical fourth generation fluoroquinolone antibiotic in each patient, then the cost to society would be approximately \$60 a bottle times the number of procedures performed in the year. Mupirocin is relatively inexpensive and it comes in two formulations, a skin ointment and a nasal preparation. The skin ointment costs about \$15 per patient per treatment and the nasal preparation is closer to \$55. Because the nasal preparation is frequently back ordered at pharmacies the skin ointment is routinely used in its place and seems to work well. Anecdotally, nephrologists and cardiothoracic surgeons routinely use the skin ointment in the nose.