

Legacy of the Endophthalmitis Vitrectomy Study

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ENDOPHTHALMITIS FOLLOWING CATARACT surgery is one of the most feared complications in ophthalmology. It has been estimated that approximately 1 case per 1000 cataract operations will be associated with this complication. Because there are more than 1.7 million cataract operations per year performed in the United States,¹ the magnitude of this problem is significant. Under the leadership of Bernard Doft, MD, and the National Eye Institute, the Endophthalmitis Vitrectomy Study (EVS) Group was organized in the late 1980s to undertake a prospective clinical trial (the EVS) evaluating the roles of pars plana vitrectomy and systemic antibiotics in the management of acute-onset endophthalmitis following cataract surgery or secondary intraocular lens implantation.^{2,3}

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Following the introduction of pars plana vitrectomy in 1970, the role of this treatment modality for endophthalmitis was controversial.⁴ The theoretical advantages of pars plana vitrectomy include debriding the intravitreal infection, removing the vitreous opacities obstructing vision, collecting intraocular specimens for culture, and allowing better distribution of intravitreal antibiotics. Before the EVS, there were widely divergent opinions regarding the role of vitrectomy in endophthalmitis management, ranging from vitrectomy for all endophthalmitis cases to the use of vitrectomy for only the most severe cases with greater inflammation, worse visual acuity, and more rapid onset.

The role of systemic antibiotics was also widely debated.⁵ In the early 1970s, the mainstay of endophthalmitis management was the use of systemic antibiotics, which usually meant hospitalization for 5 days or more with intravenous antibiotics. In 1974, a series of experimental and clinical studies⁶⁻⁸ was published touting the use of intravitreal antibiotics to augment the effectiveness of systemic, topical, and periocular antibiotics. During the late

1970s, the use of intravitreal antibiotics (in addition to systemic antibiotics) became standard treatment for clinically suspected endophthalmitis. There was at least 1 report of favorable outcomes in endophthalmitis treated with intravitreal and subconjunctival antibiotics but without systemic antibiotics.⁵ Despite improved outcomes with intravitreal antibiotics, most clinical series included treatment outcomes of patients with complex pathologic conditions, making it difficult to interpret the effect of systemic antibiotics and vitrectomy on visual results. A study of eyes with similar expected visual outcomes randomized to different treatment regimens was needed to answer the major endophthalmitis treatment questions.

The EVS was a randomized, multicenter, clinical trial that recruited patients between February 1990 and January 1994. The 420 study subjects were patients in whom clinical signs of endophthalmitis developed within 6 weeks after cataract surgery or secondary intraocular lens implantation. The following 2 treatment randomizations were performed: (1) immediate pars plana vitrectomy or vitreous tap and biopsy and (2) intravenous antibiotics (ceftazidime and amikacin sulfate) or no intravenous antibiotics. All patients in the study received intravitreal antibiotic therapy (vancomycin hydrochloride, 1 mg, and amikacin sulfate, 0.4 mg) and topical and systemic corticosteroids. Standardized procedures and measurements were used to establish clear study end points. The main end point of the study was best-corrected visual acuity at 9 to 12 months after the initial visit. A secondary end point was media clarity.

The outcomes of the EVS were reported at the 1995 Annual Meeting of the American Academy of Ophthalmology and were subsequently published in a series of articles.^{2,3} In study subjects with endophthalmitis whose visual acuity when initially seen was hand motions or better, there was no difference in visual outcomes whether or not an immediate pars plana vitrectomy was performed.² However, in the subgroup of patients whose visual acuity was only light perception at the initial visit, immediate pars plana vitrectomy was associated with a 3-fold increase in the frequency of achieving 20/40 visual acuity or better, approximately a 2-fold chance of achieving 20/100 visual acuity or better, and a 50% decrease in the frequency of severe visual loss to worse than 5/200 visual acuity. The study also showed no difference in final visual acuity or media clarity with or with-

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out the use of systemic antibiotics.² In the EVS, the single most important predictor of visual outcomes was visual acuity at the initial study visit.²

The findings of the EVS had a substantial effect on the management of endophthalmitis. The EVS provided level I evidence-based data to establish guidelines that have been used for more than 10 years. Today, most patients having acute-onset endophthalmitis after cataract surgery or secondary intraocular lens implantation are managed without the cost and patient burden associated with intravenous antibiotics (and associated inpatient hospital stays) and without the expense associated with vitrectomy. Rather, most patients with endophthalmitis are treated as outpatients in an office setting with vitreous tap and intravitreal antibiotic injection.

The economic implications of the EVS have been reported.^{9,10} In an ancillary study,⁹ hospital charge data were collected retrospectively among 129 patients from 4 clinical centers (this represented 31% of the total EVS population). Analysis of variance was used to compare hospital charges across clinical centers and treatments, and a charge-effectiveness analysis was performed. The annual savings of hospital charges in the United States were estimated for a range of annual incidence rates of endophthalmitis. Assuming the results of the EVS were used as a guide for treatment of endophthalmitis, the authors estimated that the annual nationwide reduction in hospital charges would be \$7.6 to \$40 million. Authors of another study¹⁰ estimated that implementing the EVS treatment guidelines would be associated with a reduction in Medicare reimbursements of \$1.5 to \$7.8 million per year. These cost savings were estimated to cover the entire cost of the EVS in 3 years.¹⁰

Optimal strategies for the prevention and successful treatment of endophthalmitis depend on knowledge of the most common microbial isolates. The microbiologic results of the EVS showed that gram-positive micrococci (coagulase-negative *Staphylococcus*) were the most common organisms, occurring in approximately 70% of gram-positive cases.² Furthermore, 94% of isolates were gram-positive organisms. Because *Staphylococcus epidermidis* and *Staphylococcus aureus* were the most common subgroups, concern was raised about common methicillin resistance (cross-resistance to the cephalosporins). Although the cephalosporins can provide satisfactory coverage for some staphylococcal infections, a large percentage of staphylococcal isolates will be resistant to this antibiotic class and result in inadequate prophylaxis for cataract surgery.

The EVS did not directly address the issue of antibiotic prophylaxis for cataract surgery. However, the EVS described 10 patients who developed endophthalmitis after receiving intracameral antibiotics in the irrigating fluid for cataract surgery.¹¹ The European Society of Cataract and Refractive Surgery study group reported that the use of intracameral cefuroxime reduced the rate of endophthalmitis from 23 cases per 6862 patients (0.34%) in the control group to 5 cases per 6836 patients (0.07%) in the treated group.¹² The study group noted alarmingly high rates of endophthalmitis among the control subjects, whereas rates associated with the use of intravitreal antibiotics were somewhat comparable to more recent published findings among patients undergoing cataract surgery without the use of in-

tracameral antibiotics.¹³ Cefuroxime is not generally effective for methicillin-resistant *Staphylococcus*, *Enterococcus*, and *Pseudomonas*.¹⁴ Finally, the use of intracameral cefuroxime requires reconstitution from a powder to a solution, which involves a small but definite risk of microbial contamination.

All patients in the EVS were treated with intravitreal amikacin and vancomycin, plus subconjunctival vancomycin, ceftazidime, and dexamethasone sodium phosphate.^{2,3} Subsequent studies^{15,16} reported that the omission of subconjunctival antibiotics does not seem to adversely affect the final visual outcomes. Today, many ophthalmologists do not follow the EVS guidelines for subconjunctival antibiotics and prefer to omit this form of treatment in cases of endophthalmitis associated with cataract surgery.

Cataract surgery has evolved from mostly extracapsular cataract extraction and scleral tunnel phacoemulsification at the time of the EVS to mostly clear corneal incision phacoemulsification today. A recent study¹⁷ of acute-onset endophthalmitis cases in the latter setting demonstrates initial clinical features, microbial spectra, and visual outcomes similar to those of the EVS cases. Differences identified were the time to endophthalmitis manifestation after cataract surgery (6 days in the EVS vs 13 days in the clear corneal series) and the absence of systemic antibiotic use in the clear corneal series.¹⁷ The recent report validates the findings and the importance of the EVS.

Before the EVS, many retinal surgeons believed that the rates of retinal detachment would be much higher in eyes undergoing needle tap and vitrectomy biopsy. Retinal detachment occurred in 8.3% of subjects in the EVS.¹⁸ The rates of retinal detachment were slightly higher in the vitreous tap and biopsy group (9.0% vs 7.8%), but these differences between groups were not statistically significant ($P = .66$). The EVS confirmed that the occurrence of retinal detachment during endophthalmitis treatment was a poor prognostic sign, and often this subgroup of patients had the worst visual outcomes. Only 27% of the EVS subjects with retinal detachment achieved 20/40 final visual acuity compared with 55% of patients who did not develop retinal detachment.

Certain limitations of the EVS should be recognized. First, the EVS recommendations regarding the use of vitrectomy in acute-onset endophthalmitis following cataract surgery or secondary intraocular lens implantation may not be directly applied to other forms of endophthalmitis. For example, although coagulase-negative *Staphylococcus* accounted for 70% of culture-positive cases in the EVS, bleb-associated, traumatic, and endogenous types of endophthalmitis are more likely to be caused by organisms of greater virulence. In such cases, the benefits of vitrectomy may be greater because of the mechanical removal of bacteria and toxins from the eye. Second, amikacin and ceftazidime were the only systemic antibiotics evaluated in the EVS. Although patients in the EVS derived no demonstrable benefit from these systemic antibiotics, the study made no recommendations regarding treatment with additional antimicrobial agents (eg, systemic fluoroquinolones) or systemic antimicrobial agents for other types of endophthalmitis (eg, chronic, bleb-associated, traumatic, fungal, and endogenous

forms). Third, potential study subjects with significant opacification of the anterior chamber or without light perception were excluded from the EVS. Because these eyes with more severe infection or involving more virulent organisms were excluded from the EVS, the effect might have shifted the EVS outcomes to more favorable results. Although the EVS provides general guidelines, the clinician ultimately must decide on the best treatment strategy for the individual patient.

In summary, the EVS has had a significant effect on the management of patients with acute-onset endophthalmitis following cataract surgery and secondary intraocular lens implantation, as well as on the cost associated with management of this disease. Most patients are treated in an office setting with vitreous tap and intravitreal antibiotic injection rather than in the operating room with pars plana vitrectomy, and most are managed as outpatients without intravenous administration of antibiotics.

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Correction

Error in "Methods" Section. In the Clinical Sciences article titled "Classification of Visual Field Abnormalities in the Ocular Hypertension Treatment Study," published in the May 2003 issue of the *Archives* (2003; 121[5]:643-650), on page 644, second column, line 1, the incorrect published statement reads "(2) 3 adjacent points (cluster) beyond normal limits ($P < .05$) and at least 1 point worse than the .01 probability level on the total and/or pattern deviation plots (a cluster is defined as ≥ 2 horizontally or vertically contiguous abnormal points with $P < .05$); and. . . ." The statement should read "(2) 2 adjacent points (cluster) beyond normal limits ($P < .05$) and at least 1 point worse than the .01 probability level on the total and/or pattern deviation plots (a cluster is defined as > 2 horizontally or vertically contiguous abnormal points with $P < .05$) and. . . ."