

Results of the Endophthalmitis Vitrectomy Study

A Randomized Trial of Immediate Vitrectomy and of Intravenous Antibiotics for the Treatment of Postoperative Bacterial Endophthalmitis

Endophthalmitis Vitrectomy Study Group

Objective: To determine the roles of immediate pars plana vitrectomy (VIT) and systemic antibiotic treatment in the management of postoperative endophthalmitis.

Design: Investigator-initiated, multicenter, randomized clinical trial.

Setting: Private and university-based retina-vitreous practices.

Patients: A total of 420 patients who had clinical evidence of endophthalmitis within 6 weeks after cataract surgery or secondary intraocular lens implantation.

Interventions: Random assignment according to a 2×2 factorial design to treatment with VIT or vitreous tap or biopsy (TAP) and to treatment with or without systemic antibiotics (ceftazidime and amikacin).

Main Outcome Measures: A 9-month evaluation of visual acuity assessed by an Early Treatment Diabetic Retinopathy Study acuity chart and media clarity assessed both clinically and photographically.

Results: There was no difference in final visual acuity or media clarity with or without the use of systemic antibiotics. In patients whose initial visual acuity was hand motions or better, there was no difference in visual outcome whether or not an immediate VIT was performed. However, in the subgroup of patients with initial light perception–only vision, VIT produced a threefold increase in the frequency of achieving 20/40 or better acuity (33% vs 11%), approximately a twofold chance of achieving 20/100 or better acuity (56% vs 30%), and a 50% decrease in the frequency of severe visual loss (20% vs 47%) over TAP. In this group of patients, the difference between VIT and TAP was statistically significant ($P < .001$, log rank test for cumulative visual acuity scores) over the entire range of vision.

Conclusions: Omission of systemic antibiotic treatment can reduce toxic effects, costs, and length of hospital stay. Routine immediate VIT is not necessary in patients with better than light perception vision at presentation but is of substantial benefit for those who have light perception–only vision.

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CERTAIN ASPECTS of the management of bacterial endophthalmitis after cataract extraction, such as injection of intravitreal antibiotics, have been widely accepted. Other aspects of management are controversial. There have been no clear data as to whether pars plana vitrectomy (VIT) should be used in the initial management of endophthalmitis. Immediate VIT for endophthalmitis offers several theoretical advantages, including removal of the infecting organisms and the toxins they produce, removal of vitreous membranes that could lead to subsequent detachment of the retina, clearing of vitreous opacities, collection of abundant material for culture, and possibly better distribution of intravitreal antibiotics. In some experimental animal studies, VIT offered advantages over the use of intraocular antibiotics alone.¹⁻³ However, past

data from human studies have not shown VIT with intravitreal antibiotics to be superior to treatment with intravitreal antibiotics alone. In these studies, eyes that underwent VIT were not randomly selected and were those with the worst clinical presentation.⁴⁻⁸ Because of this selection bias, the place of pars plana VIT in the initial treatment of patients with endophthalmitis after cataract surgery remained in doubt.

Although the intraocular penetration of most antibiotics is poor after systemic administration, drugs given by this route have remained part of the routine management of bacterial endophthalmitis.⁹ Although

Participants and clinical and support centers of the Endophthalmitis Vitrectomy Study trials are listed on pages 1493 to 1495.

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METHODS

PROTOCOL AND PROCEDURES

Study Organization

Twenty-four centers across the United States participated in this clinical trial. Patients were enrolled between February 1990 and January 1994, and follow-up was completed in December 1994. Statistical design, data management, study communications, and data analysis were carried out by the Coordinating Center (University of Pittsburgh, Pa). A Photographic Reading Center (University of Wisconsin, Madison) was responsible for evaluating fundus photographs. Scientific direction for the study was the responsibility of the Study Chair in collaboration with the Executive Committee. An independent Data and Safety Monitoring Committee met annually and reported to the National Eye Institute. The research protocol was approved by institutional review boards at each participating clinical center.

Patient Selection

Patients were eligible for study entry if they had clinical signs and symptoms of bacterial endophthalmitis within 6 weeks after cataract surgery or secondary intraocular lens implantation. Eligibility required the following: visual acuity of light perception (LP) or better and worse than 36 letters at 4 m (equivalent to approximately 20/50 or worse) on an Early Treatment Diabetic Retinopathy Study (ETDRS) acuity chart¹⁴; cornea and anterior chamber of the involved eye clear enough to allow visualization of at least some part of the iris; the cornea clear enough to perform pars plana VIT; and a hypopyon or sufficient clouding of the anterior chamber or vitreous to obscure a view of second-order retinal arterioles. Patients were excluded for any of the following reasons: known eye disease limiting visual acuity to 20/100 or worse before the development of cataract, prior intraocular surgery other than cataract or intraocular lens surgery, prior penetrating ocular trauma, previous injection of intravitreal antibiotics, prior pars plana VIT, retinal detachment or choroidal detachment that was moderately high as judged by indirect ophthalmoscopy or ultrasound, probable intolerance to any study drugs (with the exception of penicillin allergy, in which case alternatives to β -lactam drugs were used), strong suspicion of fungal endophthalmitis, age younger than 18 years, unsuitability for surgery, or likelihood that the patient would not return for follow-up visits. A total of 1283 patients with endophthalmitis were screened, 855 of whom had endophthalmitis within 6 weeks after cataract extraction or secondary lens implantation. Of these, 510 met eligibility criteria, and 420 agreed to participate and were enrolled. Written informed consent was obtained from each patient.

Examination

The initial examination was performed before randomization. Best refracted vision was determined using an ETDRS acuity chart. If no letters could be read on the chart at 4 m, then at 1 m, vision was tested for the ability to count fingers. If the patient was unable to count fingers, vision was tested for the ability to recognize hand motions. For this, the patient's opposite eye was occluded, and a light source, such

as a lamp used for near vision, was directed from behind the patient to the examiner's hand that either was stationary or was moved at one motion per second in a horizontal or vertical direction at a distance of 60 cm from the eye. The patient was asked to identify whether the examiner's hand was still, moving sideways, or moving up and down. The presentation was repeated five times, and hand-motion visual acuity was considered present if the patient was able to identify the examiner's action on at least four of the presentations. If the examiner was not convinced that hand motions could be detected, LP was tested at 0.9 m with an indirect ophthalmoscope set at maximum intensity.

Treatment Assignment

Eligible patients who provided consent were immediately randomly assigned according to a 2x2 factorial design to one of four treatment groups: initial VIT with IV antibiotics, initial VIT without IV antibiotics, initial TAP with IV antibiotics, or initial TAP without IV antibiotics.

Initial Procedure

Treatment was begun within 6 hours of the initial examination. Eyelid cultures were obtained from the affected eye. All the patients had a 0.1-mL anterior chamber sample obtained with a 25- to 27-gauge needle and syringe. Patients assigned to the VIT groups underwent a three-port pars plana VIT. An initial undiluted vitreous specimen was obtained after placing all sclerotomies, but before turning on the infusion fluid. The VIT cutter was introduced into the midvitreous, and 0.2 to 0.5 mL of vitreous gel was excised and aspirated into a syringe, using manual suction with a high cutting rate. Once this sample was obtained, the infusion was turned on and the VIT procedure was continued with automated suction and collection into a VIT cassette. When necessary for visualization, the anterior chamber was cleared using any one of a variety of techniques.¹⁵ If there was no posterior vitreous separation, no attempt was made to induce a vitreous detachment, and the posterior cortical vitreous was not aggressively removed. It was a goal of surgery to remove at least 50% of the vitreous gel in eyes with no vitreous separation.

Patients assigned to the TAP groups had, at the discretion of the operating surgeon, a vitreous specimen collected either by trans-pars plana vitreous needle aspiration or by vitreous biopsy through a single sclerotomy using a VIT instrument.¹⁶ A vitreous sample of 0.1 to 0.3 mL was collected. If the surgeon chose needle aspiration and an adequate sample could not be safely obtained with that technique, a vitreous biopsy using a VIT instrument was performed.

Study Medications

All the study patients received a standard antibiotic regimen that was chosen by agreement among the investigators and infectious disease consultants before recruitment began. The EVS was not designed to test the efficacy of specific antibiotics or other drugs. The goal was to use what were judged to be the best available drugs. The antibiotic choices were reviewed annually, and on each occasion the investigators chose to continue using the same drugs throughout the course of the study.

After the initial VIT or TAP procedure, all the patients received intravitreal injection of amikacin (0.4 mg in 0.1 mL [volume of normal saline solution])

and vancomycin hydrochloride (1.0 mg in 0.1 mL). Vancomycin hydrochloride (25 mg in 0.5 mL), ceftazidime (100 mg in 0.5 mL), and dexamethasone sodium phosphate (6 mg in 0.25 mL) were administered by subconjunctival injection. If the patient was allergic to penicillin, subconjunctival amikacin (25 mg in 0.5 mL) was substituted for ceftazidime. Topical antibiotics (vancomycin hydrochloride, 50 mg/mL, alternating with amikacin, 20 mg/mL) were administered as frequently as one drop per hour if there was evidence of wound infection or leak, and every 4 hours otherwise. Topical cycloplegics (1% atropine sulfate or 1/4% scopolamine hydrobromide) and topical corticosteroids (1% prednisolone acetate) were also administered after surgery. Systemic corticosteroids (prednisone, 30 mg twice a day for 5 to 10 days) were administered orally.

Patients assigned to the IV antibiotic groups received two drugs. The first was ceftazidime, 2 g every 8 hours, in most patients (1.5 g for patients weighing less than 50 kg). Patients who were allergic to penicillin were given ciprofloxacin instead, 750 mg orally twice a day. The second systemic drug was amikacin given in a 7.5-mg/kg initial IV dose, followed by 6 mg/kg every 12 hours. If the patient's serum creatinine concentration exceeded 177 $\mu\text{mol/L}$ (2 mg/dL), subsequent doses of amikacin were based on serum concentrations of the antibiotic. In all patients, serum concentrations were obtained and doses were adjusted to maintain peak amikacin concentrations of 25 $\mu\text{g/mL}$ and trough concentrations of less than 5 $\mu\text{g/dL}$. The rationale for these drug choices has been previously reported.¹⁷ Patients were maintained on treatment with the systemic antibiotics for 5 to 10 days at the physician's discretion.

Cultures and Stains

Cultures of the anterior chamber fluid and undiluted vitreous were plated on chocolate agar (37°C in carbon dioxide) in freshly reduced, enriched thioglycolate liquid (aerobic at 37°C) (Baltimore Biological Laboratories, Cockeysville, Md), designated BBL 1135, and fresh Sabouraud dextrose agar (incubated at 25°C). Gram stains were prepared from the anterior chamber and undiluted vitreous specimens. The VIT effluent (collected in the VIT cassette) was filtered through a sterile 0.45- μm membrane filter. The filter was subsequently divided under sterile conditions into three pieces. One piece was placed on chocolate agar for culture at 37°C in 5% to 10% carbon dioxide and one was placed on fresh Sabouraud dextrose agar for culture at 25°C. Anaerobic culture of the filtered material was performed in either enriched thioglycolate broth or anaerobic blood agar enriched with hemin and vitamin K at 37°C.

Additional Procedures During Initial Hospitalization

The protocol allowed patients in the TAP groups to have VIT and reinjection of intravitreal antibiotics if the eye was doing poorly 36 to 60 hours after the initial surgery. For such additional surgery to be recommended, an eye had to meet all the following criteria: (1) visual acuity of less than 5/200 but LP or better; (2) an absent red reflex or an increase in media opacification compared with initial presentation; (3) at least an equivocal growth from the initial culture; and (4) one or more of the following: (a) a 1-mm increase in the height of the hypopyon, (b) a corneal ring infiltrate, or (c) worsening pain. Similarly, patients assigned to the VIT group who

met the same criteria 36 to 60 hours after the initial procedure could have repeated VIT (or vitreous aspiration) and reinjection of intravitreal antibiotics. Patients whose eyes did not meet the criteria for reoperation could still undergo additional surgery if their physician thought it to be in the patient's best interest. Conversely, patients who met criteria for additional surgery were not required to have such surgery if it was thought not to be in their best interest.

Late Additional Surgery

At the 3- and 9-month follow-up examinations, patients were assessed for remediable factors that limited visual acuity, such as vitreous opacities, macular pucker, or opacified posterior capsule. If clinically appropriate, additional surgery was encouraged to improve these conditions.

Outcome Evaluation

Primary study end points were visual acuity and clarity of the ocular media. All patients had end-point assessment at 3- and 9-month follow-up visits. An additional assessment was made at a 12-month visit for those patients who had additional procedures, based on the results of the 9-month visit. Best corrected visual acuity was measured after manifest refraction using the ETDRS visual acuity charts. Measurement was obtained by a certified technician masked to treatment assignment. Before data analysis, three thresholds of visual outcome were chosen to reflect different levels of functional vision: 20/40 or better, 20/100 or better, and 5/200 or better.

Media clarity was assessed both clinically and photographically. Clinical assessment of media clarity was performed with indirect ophthalmoscopy to classify the media as one of the following: (1) better or equal to a 20/40 view to the retina; (2) clarity worse than a 20/40 view, with a second-order retinal vessel visible; (3) inability to see a second-order retinal vessel, but with some retinal vessel visible; (4) inability to see a retinal vessel, but with a red reflex; and (5) no red reflex visible.

Photographic grading of media clarity was based on the 3-month and final (9- or 12-month) follow-up evaluations. The photographs consisted of (1) a stereo pair focused on the retina and centered halfway between the disc and macula; (2) a single clearest possible photograph of the retina centered in the same location; and (3) a stereoscopic anterior segment photographic pair to document the status of the cornea, anterior chamber, intraocular lens (if present) as well as to show the appearance of the fundus red reflex. A masked observer at the EVS Photographic Reading Center graded the photographs by comparison with two preselected standard photographs.

STATISTICAL METHODS

Sample Size Considerations

To determine sample size, the primary end point used to define success was a visual acuity of 20/400 or better at final follow-up. A success rate of 60% with TAP was assumed. A one-tailed test was used because a physician would want to recommend VIT only if it were better than TAP alone. Given a sample size of 420 patients, if there were

Continued on next page

60% success in the TAP group, the rate in the VIT group that could be detected with 80% power would be 72%, and that with 90% power, 74%.¹⁸

Treatment Group Comparisons

The distribution of baseline characteristics and follow-up events were compared among the four treatment groups using χ^2 tests or Brown-Mood median tests as appropriate.¹⁹ Because the trial used a 2×2 factorial design, logistic regression models for each visual acuity threshold were fitted with each of the two experimental factors and their interaction as explanatory variables. Since there was no evidence of an interaction between surgical treatment and systemic antibiotic treatment, these analyses are not reported. For each threshold of visual acuity, dichotomous outcome differences among the four treatment groups were tested with a χ^2 statistic. In addition, two-way tests were performed to compare the VIT and TAP groups and the IV and NOIV groups. The *P* values reported were not adjusted for multiple comparisons; therefore, the nominal *P* values must be interpreted with this in mind.

Outcome Evaluation

To examine the full range of visual acuity outcomes, we considered the visual acuity score based on the ETDRS acuity chart. The visual acuity scores among EVS patients were not normally distributed, so linear models that require an assumption of normality were not appropriate. A Mantel-Haenszel log rank analysis was used with each visual acuity score as a stratum. This allowed outcome comparisons of the proportion of patients with visual acuity scores of more than one letter, more than two letters, more than three letters, and so on. This analysis of outcome is parallel to the usual life-table analysis, in which one compares treatment according to the proportion of patients alive at more than 1 year, more than 2 years, more than 3 years, and so on. Figures were constructed to present the cumulative proportion of patients according to the final visual acuity score achieved. The figures are presented parallel to usual "survival curves." After verifying the assumption of proportional hazards, a Cox regression model was used to extend analysis of visual acuity outcome to take into account baseline characteristics.

Safety Monitoring

For issues of safety, the visual acuity score at the 3-month follow-up visit was used as the end point for the interim monitoring. A threshold of 5/200 visual acuity was used to compare the VIT and TAP treatment groups. For interim monitoring, the statistic described by O'Brien and Fleming²⁰ was calculated after 140, 280, and 420 patients had entered the trial, and these were reported to the Data and Safety Monitoring Committee. Formal interim statistical testing was not performed for patients treated with systemic antibiotics vs those who were not; however, tabulations comparing these patients were part of the presentation at the regular Data and Safety Monitoring Committee meetings.

Subset Analysis

To determine whether one surgical treatment was superior to the other for any subset of patients, outcome was examined by surgical treatment for each subgroup defined by clinical presentation. This was carried out for each of the four definitions of successful outcome based on the three visual acuity thresholds and media clarity level of 20/40 view or better. A logistical model was fitted with three explanatory variables. These three explanatory variables were VIT treatment, an individual risk factor defining the subgroup, and an interaction term of VIT with the risk factor. An interaction *P* value was calculated. A statistically significant coefficient for the interaction term was interpreted to mean that the association of VIT with outcome differed in the subgroup defined by the risk factor. To examine further whether VIT treatment was more effective than TAP for a particular subgroup, the Cox model was used with the same variables as were used in the logistic model described in the previous paragraph. To examine the consistency of the subgroup findings, a model was fitted to adjust for additional factors, once appropriate interaction terms were determined.

Risk Factors for Visual Acuity Outcome

To examine the relation of baseline characteristics to outcome, we performed tabulations for each visual outcome by each baseline factor. To determine which of these variables were independent risk factors for poor visual outcome, logistic regression models were fitted using a backward stepping procedure. Four separate models were fitted for the three threshold definitions of visual acuity and for media clarity outcome. A fifth model using the entire range of vision as an outcome was fitted using Cox regression analysis.

Patients Analyzed

Baseline characteristics are reported for the 420 EVS patients enrolled. Outcome is reported for the 396 patients who completed a final follow-up visit. Twenty-four patients did not have final follow-up data: 12 died, five withdrew consent to be followed up, and seven were not willing to return for the visit. These patients had been assigned in nearly equal numbers to all treatment groups. Among the 396 with final visit data, two were missing visual acuity data and four were missing a clinical assessment of media clarity. Thus, final visual acuity is reported in 394 patients, and media clarity in 392. Included in the reports was information on patients with enucleated eyes whose vision was classified as no LP. Also included is one patient who died before a scheduled 12-month visit; therefore, 9-month data were considered as final. Three patients who were entered into the trial were subsequently noted to have had exclusionary criteria. Based on the principle of "intention to treat," these patients were considered in the analysis, although one was among the patients who did not have a final follow-up visit.

some newer drugs, eg, the fluoroquinolones, given intravenously and even orally have greater penetration into the human vitreous, they still do not reach sufficient intraocular concentrations to be considered efficacious against many

common bacteria that are responsible for postoperative endophthalmitis.¹⁰ The β -lactam drugs and vancomycin hydrochloride, which are agents of choice for infections caused by gram-positive cocci, penetrate relatively poorly, and it

is not clear that they offer additional benefit over intravitreal injections. Disadvantages of systemic antibiotic treatment include adverse effects that may be severe,^{11,12} the cost of antibiotics, and the hospitalization required for their administration. In a nonrandomized study, Pavan and Brinser¹³ successfully treated several patients with endophthalmitis without using systemic antibiotics. Considering their uncertain efficacy, possible toxic effects, and high cost, the role of systemic antibiotics in postoperative endophthalmitis was also examined.

The Endophthalmitis Vitrectomy Study (EVS), a randomized, multicenter, clinical trial supported by the National Eye Institute of the National Institutes of Health, Bethesda, Md, was designed to determine the role of immediate pars plana VIT and, separately, the role of systemic antibiotics in the management of endophthalmitis after cataract extraction or secondary intraocular lens insertion. The study subjects were 420 patients in whom clinical signs of endophthalmitis developed within 6 weeks after cataract surgery or secondary lens implantation. They were randomly assigned to treatment with either immediate pars plana VIT or vitreous tap or biopsy (TAP). They also were randomly assigned to either intravenous (IV) antibiotic treatment or no intravenous (NOIV) antibiotic treatment. Outcome was evaluated by visual acuity and clarity of ocular media at 3 months and at 9 to 12 months. This article reports the main results of the EVS.

RESULTS

BASELINE CHARACTERISTICS

Table 1 presents baseline characteristics for the four treatment groups. Statistical testing indicated that the treatment groups were balanced. Statistics for all patients combined (last column) describe the study patient profile. The median age was 75 years, and less than half the patients (43%) were men. There was a history of diabetes mellitus in 14% and systemic hypertension in 40%. In this population, cataract surgery (with lens implantation in all but two patients) preceded the clinical diagnosis of endophthalmitis in 95% of cases, and secondary lens implantation preceded in the remaining 5%. The median time from the cataract extraction or secondary lens implantation until presentation to a study center was 6 days. Presentation within 3 days of the initiating procedure occurred in 24%, within 4 to 7 days in 37%, within 8 to 13 days in 17%, and within 2 to 6 weeks in the remaining 22%. Almost all the patients had symptoms, with blurred vision being the most common. Pain was reported by 74% of patients.

Study patients had poor initial vision, with 86% having acuity of less than 5/200. Initial visual acuity was LP only in 26% of patients. An afferent pupillary defect was present in 12%, corneal ring ulcer or infiltrate in 5%, and hypopyon in 86%. For patients with a hypopyon, the median height was 1 mm, with 30% being higher than 1.5 mm. Media clarity at the initial visit was poor. A second-order retinal vessel could be seen by indirect ophthalmoscopy in only 10% of patients, and in almost 80% of patients, no retinal vessel of any type could be seen with indirect ophthalmoscopy. A red reflex was absent in 67% of patients.

To analyze microbiology results, "laboratory confirmed growth" was defined as at least semiconfluent growth on a solid medium, any growth on two or more media, or growth on one medium supported by a positive Gram stain. Results showed no growth in 18% of patients, "equivocal growth" (defined as growth less than laboratory-confirmed growth) in 13%, and laboratory-confirmed growth in the remainder. Laboratory-confirmed organisms were grouped as gram-positive coagulase-negative (47% of patients), other gram-positive (16% of patients), and gram-negative (4% of patients). More than one species grew in 3% of patients, either gram-positive coagulase-negative plus other gram-positive or gram-positive coagulase-negative plus gram-negative. The type of organism was evenly distributed across treatment groups (Table 1).

ADVERSE EVENTS AND ADDITIONAL PROCEDURES

To monitor the safety of treatments used in the EVS, events during follow-up were compared by treatment (**Table 2**). At the 36- to 60-hour examination, five eyes had no LP, four from the TAP group and one from the VIT group. Immediate complications associated with the initial EVS procedures were few and did not vary substantially by treatment. Two patients suffered from a dislocated intraocular lens and one patient experienced an expulsive hemorrhage. Macular infarction was observed in one patient who had undergone VIT with IV antibiotics. Renal complications were assessed by a change in serum creatinine levels, although these data were missing in a substantial number of patients assigned to the NOIV group. Five percent of patients showed an increase in serum creatinine level of 26 $\mu\text{mol/L}$ or greater (≥ 0.3 mg/dL), and less than 1% showed an increase of 53 $\mu\text{mol/L}$ or greater (≥ 0.6 mg/dL). There was no statistical difference in creatinine rise in patients in the IV group vs the NOIV group.

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As noted above, the protocol allowed for additional surgery in the immediate postoperative period if the involved eye was doing poorly. At the 36- to 60-hour examination, 29 (7%) of the 420 patients met study guidelines to be considered for an additional procedure (Table 2). These included 6% (14/218) of eyes in the VIT group and 7% (15/202) of eyes in the TAP group. Of eyes that met criteria for additional surgery, 86% (25/29) had such a procedure, with no statistical difference between the VIT and TAP groups. The clinician had the option of performing surgery outside the guidelines if in his or her judgment it was in the best interest of the patient. Additional procedures were performed in 4% (14/390) of patients who did not meet the guidelines, consisting of 2% (5/203) of eyes in the VIT group and 5% (9/187) of eyes in the TAP group (nonsignificant difference). Thus, in total, based on the 36- to 60-hour assessment, an additional procedure was actually performed in 9% of patients, representing 7% (16/218) of eyes in the VIT group and 11% (23/202) of eyes in the TAP group. The above

Table 1. Baseline Characteristics by Treatment Group

Characteristic	% of Patients*				Total No. (%) (N=420)
	Vitrectomy With IV Antibiotics (n=106)	Vitrectomy With No IV Antibiotics (n=112)	Tap/Biopsy With IV Antibiotics (n=100)	Tap/Biopsy With No IV Antibiotics (n=102)	
Age, y					
Median (range)	74.3 (24-95)	74.6 (36-91)	74.9 (24-91)	75.3 (32-92)	74.8 (24-95)
Right eye	44.3	50.9	44.0	49.0	198 (47.1)
Male	40.6	39.3	48.0	43.1	179 (42.6)
Black	7.6	8.0	7.0	5.0	29 (6.9)
History of diabetes	15.1	14.3	15.0	10.8	58 (13.8)
History of hypertension	38.7	35.7	45.0	40.2	167 (39.8)
History of glaucoma	7.6	6.3	13.0	8.8	37 (8.8)
Symptoms	98.1	99.1	98.0	100	415 (98.8)
Red eye	84.0	76.8	83.0	85.3	345 (82.1)
Pain	76.4	75.9	69.0	75.5	312 (74.3)
Blurred vision	90.6	98.2	94.0	94.1	396 (94.3)
Swollen lid	38.7	32.1	35.0	32.4	145 (34.5)
Days from cataract surgery to presentation (vitreous surgeon's office)					
Median (range)	6 (1-42)	7 (1-63)	6 (1-43)	6 (1-43)	6 (1-63)
Visual acuity					
Light perception	28.3	26.8	25.0	24.5	110 (26.2)
Hand motions	45.3	45.5	41.0	44.1	185 (44.1)
Counting fingers, <5/200	14.2	16.1	21.0	11.8	66 (15.7)
≥5/200	12.3	11.6	13.0	19.6	59 (14.1)
Afferent pupillary defect					
Yes	15.1	13.4	8.0	9.8	49 (11.7)
No	51.9	50.0	58.0	56.9	227 (54.1)
Unknown	33.0	36.6	34.0	33.3	144 (34.3)
Pupil size at maximum dilation, mm					
Median (range)	5.0 (2-10)	5.0 (1.5-10)	5.0 (1-9)	5.0 (1.5-9.5)	5.0 (1-10)
Pupil size of 5 mm	42.5	34.8	41.0	38.2	164 (39.1)
Corneal infiltrate or ring ulcer	4.7	5.4	3.0	5.9	20 (4.8)
Cataract surgical wound abnormality†	8.5	6.3	2.0	3.9	22 (5.2)
Wound leak present at presentation‡	13.2	8.9	7.0	5.9	37 (8.8)
Hypopyon present	87.7	85.7	81.0	88.2	360 (85.7)
Median (range), mm	1.0 (.3-6)	1.0 (1-9)	1.0 (.5-8)	1.1 (1-4)	1.0 (1-9)
Intraocular pressure, mm Hg					
Median (range)	16 (2-46)	15 (0-45)	15.5 (3-48)	17 (4-50)	15.5 (0-50)
0-5 mm Hg	2.9	4.6	2.1	3.1	13 (3.2)
6-25 mm Hg	84.6	78.9	81.3	79.2	328 (80.6)
>25 mm Hg	12.5	16.5	16.7	19.8	66 (16.2)
Media clarity (indirect ophthalmoscopy)					
Clarity ≥20/40 view to retina	0.9	0.0	0.0	0.0	2 (0.5)
Clarity worse than 20/40 view, but second-order retinal vessel seen	7.6	7.1	7.0	16.7	40 (9.5)
Cannot see second-order retinal vessel, but some vessel seen	10.4	10.7	13.0	9.8	46 (11.0)
Unable to see retinal vessel	81.1	82.1	79.0	73.5	332 (79.1)
Red reflex present	34.9	37.5	27.0	30.4	137 (32.0)
Choroidal detachment					
Yes	3.8	1.8	3.0	1.0	10 (2.4)
No	88.7	92.9	91.0	94.1	385 (91.7)
B-scan not done	7.6	5.4	6.0	4.9	25 (6.0)
Lens capsule intact (by examination)					
Yes	37.7	40.2	37.0	41.2	164 (39.1)
No	10.4	9.8	15.0	11.8	49 (11.7)
Unknown	52.0	50.0	48.0	47.1	207 (49.3)
Rubeosis irides present					
Yes	2.8	2.7	3.0	2.9	12 (2.9)
No	87.7	84.8	85.0	92.2	367 (87.4)
Unknown	9.4	12.5	12.0	4.9	41 (9.8)

Table 1. Baseline Characteristics by Treatment Group (cont)

Characteristic	% of Patients*				Total, No. (%) (N=420)
	Vitrectomy With IV Antibiotics (n=106)	Vitrectomy With No IV Antibiotics (n=112)	Tap/Biopsy With IV Antibiotics (n=100)	Tap/Biopsy With No IV Antibiotics (n=102)	
White blood cell count, $\times 10^9/L$					
Median (range)	9.1 (3.4-72.0)	9.3 (3.5-76.0)	9.2 (1.3-84.0)	9.7 (3.3-87.0)	9.3 (1.3-87.0)
$>10.0 \times 10^9/L$	32.1	33.0	30.0	39.2	141 (33.6)
$>14.0 \times 10^9/L$	9.4	10.7	9.0	10.8	42 (10.0)
Creatinine level, $\mu\text{mol/L}$ [mg/dL]					
Median (range)	88 (35-354) [1.0 (0.4-4.0)]	88 (35-168) [1.0 (0.4-1.9)]	88 (44-362) [1.0 (0.5-4.1)]	88 (44-628) [1.0 (0.5-7.1)]	88 (35-628) [1.0 (0.4-7.1)]
$>115 \mu\text{mol/L}$ ($>1.3 \text{ mg/dL}$)	11.3	10.7	17.0	10.8	52 (12.4)
Microbiology					
No growth	10.4	12.5	26.0	23.5	75 (17.9)
Equivocal only growth	20.8	12.5	8.0	9.8	54 (12.9)
Confirmed culture results					
Gram-positive coagulase-negative growth	44.3	49.1	45.0	49.0	197 (46.9)
Other gram-positive growth	16.0	19.6	15.0	10.8	65 (15.5)
Gram-negative growth	4.7	3.6	4.0	3.9	17 (4.1)
Polymicrobial§	3.8	2.7	2.0	2.9	12 (2.9)

*Except for median (range) data. IV indicates intravenous.

†Includes one or more of the following: vitreous incarceration, iris prolapse or incarceration, stitch abscess, or infected bleb.

‡Includes wound dehiscence, positive Seidel test.

§Polymicrobial results include gram-positive, coagulase-negative plus other gram-positive or gram-negative, coagulase-negative plus gram-negative growth.

procedures included reculture of the vitreous during the 36- to 60-hour period in 6% (24/420) of patients, 5% (10/218) in the VIT group and 7% (14/202) in the TAP group. Similarly, 7% (31/420) of patients had reinjection of intravitreal antibiotics, 6% (14/218) in the VIT group and 8% (17/202) in the TAP group.

Particular attention was paid to major adverse effects. By the final study visit, 5% had retinal detachment, 1% had an intraocular pressure of 30 mm Hg or higher, 3% had phthisis, and 1% had had enucleation or evisceration (Table 2). During the entire course of the study, additional surgery was performed on 35% of patients, 32% in the VIT group and 39% in the TAP group.

During the study there were 13 deaths distributed among all the treatment groups. Three of the deaths were due to myocardial infarction; two were due to congestive heart failure; three were due to cancer; and one each were due to ventricular arrhythmia, stroke, complications of diabetes, and pneumonia. In one 89-year-old patient, the cause of death was unknown. Of the 13 deaths, two (from myocardial infarction) occurred within the first week of the initial EVS procedure, but the remainder occurred longer than 1 month from the initial EVS procedure, and one occurred after 9 months but before a scheduled 12-month visit.

MEDIA CLARITY OUTCOME

Data from the trial show that the media cleared more quickly after VIT. At the 3-month follow-up visit, a 20/40 view to the retina by indirect ophthalmoscopy was found in 86% of VIT eyes, but in only 75% of TAP eyes ($P=.004$). At the same examination, there was no difference in media clarity by antibiotic treatment group. **Table 3** presents data regarding media clarity at the final examination analyzed by treatment type. More than 85% of all patients had clear

media (20/40 or better view with indirect ophthalmoscopy), 90% in the VIT group and 83% in the TAP group, not a statistically significant difference. For patients receiving IV antibiotics, 88% had 20/40 media clarity, similar to the rate of 85% of patients not receiving IV antibiotics.

Photographic assessment of media clarity was used to further evaluate patients with the best media clarity (the group with 20/40 or better view to the retina with indirect ophthalmoscopy). Slightly more patients in the VIT group (43% [85/200]) than in the TAP group (33% [63/192]) showed the best category of media clarity as assessed photographically ($P=.06$). No differences in photographic assessment of media clarity were seen between the IV and NOIV groups.

VISUAL ACUITY OUTCOME

At 3 months, 41% of patients achieved 20/40 or better visual acuity and 69% had 20/100 or better acuity. At 9 to 12 months, 53% of patients achieved visual acuity of 20/40 or better, 74% achieved 20/100 or better, and 15% had acuity worse than 5/200. Five percent of patients had no LP at the final follow-up visit.

The visual results over the entire visual acuity range examined for differences based on treatment assignment revealed no statistically significant differences. This finding was based on a Cox regression model that compared VIT with TAP and IV with NOIV as well as an interaction term that examined whether there was synergism between the two treatment arms, surgery and antibiotic use. This was the case both at 3 months and at the final study follow-up.

Figure 1 shows the cumulative percentage distribution of visual acuity scores in the VIT and TAP groups. Note that the graphs are similar except that fewer patients in the VIT group had a visual acuity score of 0 (could read none of the 5/200 letters). **Figure 2** shows the cumulative per-

Table 2. Patients With Events by Treatment Group*

Event	No. (%) of Patients			
	Vitrectomy With IV Antibiotics (n=106)	Vitrectomy With No IV Antibiotics (n=112)	Tap/Biopsy With IV Antibiotics (n=100)	Tap/Biopsy With No IV Antibiotics (n=102)
Surgical complications of the initial procedure				
Expulsive hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Microhyphema	2 (1.9)	0 (0.0)	2 (2.0)	3 (2.9)
Wound leak	2 (1.9)	3 (2.7)	0 (0.0)	0 (0.0)
Dislocated intraocular lens	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Choroidal detachment	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
Macular infarction during initial hospitalization	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Visual acuity of no light perception (at 36- to 60-h examination)	0 (0.0)	1 (0.9)	3 (3.0)	1 (0.9)
Creatinine level during initial hospital stay†				
Increase ≥26 μmol/L (≥0.3 mg/dL)	6 (6.0)	1 (3.1)	4 (4.2)	2 (6.5)
Increase ≥53 μmol/L (≥0.6 mg/dL)	0 (0.0)	0 (0.0)	1 (1.1)	1 (3.2)
Additional procedures within 36-60 h‡				
Met guidelines	9 (8.6)	5 (4.5)	7 (7.0)	8 (7.8)
Procedure	8 (7.6)	3 (2.7)	7 (7.0)	7 (6.9)
Vitrectomy	0 (0.0)	0 (0.0)	3 (3.0)	5 (4.9)
Tap/biopsy	8 (7.6)	3 (2.7)	4 (4.0)	1 (1.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
No procedure	1 (1.0)	2 (1.8)	0 (0.0)	1 (1.0)
Did not meet guidelines	96 (91.4)	107 (95.5)	93 (93.0)	94 (92.2)
Procedure	4 (3.8)	1 (0.9)	5 (5.0)	4 (3.9)
Vitrectomy	0 (0.0)	0 (0.0)	2 (2.0)	1 (1.0)
Tap/biopsy	3 (2.9)	1 (0.9)	0 (0.0)	2 (2.0)
Other	1 (1.0)	0 (0.0)	3 (2.0)	1 (1.0)
No procedure	92 (87.6)	106 (94.6)	88 (88.0)	90 (88.2)
Total Procedures	12 (11.3)	4 (3.6)	12 (12.0)	11 (10.8)
Vitrectomy	0 (0.0)	0 (0.0)	5 (5.0)	6 (5.9)
Tap/biopsy	11 (10.4)	4 (3.6)	4 (4.0)	3 (2.9)
Other	1 (0.9)	0 (0.0)	3 (3.0)	2 (2.0)
Death				
≤7 d after initial procedure	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)
>7 d after initial procedure	4 (3.8)	2 (1.8)	4 (4.0)	1 (1.0)
Follow-up surgery§	29 (27.4)	30 (26.8)	28 (28.0)	33 (32.4)
Enucleation of involved eye	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)
Phthisis	4 (3.8)	1 (0.9)	4 (4.0)	4 (3.9)
Intraocular pressure ≥30 mm Hg at final follow-up	1 (0.9)	3 (2.7)	2 (2.0)	0 (0.0)

*IV indicates intravenous.

†Creatinine data missing for 162 patients: vitrectomy with IV group (n=6), vitrectomy with no IV group (n=80), tap/biopsy with IV group (n=5), and tap/biopsy with no IV group (n=71).

‡One patient with missing data regarding additional procedures guidelines in the vitrectomy with IV group.

§Procedure performed more than 60 hours from the initial procedure.

percentage distribution of visual acuity scores in the IV and NOIV groups. Note that the two treatment groups are similar throughout the entire range of visual acuity.

Table 4 shows the visual acuity distribution and the results of statistical tests comparing the outcome of the various treatments at three acuity thresholds. There was no significant difference in the visual outcome for any of the three visual thresholds for patients in the IV vs the NOIV group. There was no significant advantage of either VIT or TAP in achieving 20/40 or better or 20/100 or better acuity. However, the proportion of severe visual loss (5/200 or worse acuity) was halved from 15% in the TAP group to 8% in the VIT group ($P=.03$).

CAUSES OF DECREASED VISUAL ACUITY

Table 5 presents the causes for visual acuity of less than 5/200 and less than 20/40 but better than 5/200 by surgi-

cal treatment and initial vision. Among the subgroup of patients with baseline acuity better than LP, there was no substantial difference in the distribution of causes between eyes undergoing VIT vs TAP. The most common cause of impaired vision was an abnormality of the macula, accounting for about half of patients with visual acuity of less than 20/40.

Among the patients with initial LP-only vision and impaired final vision, there was a trend for enucleation or phthisis to be a more common cause of visual loss in the TAP group than in the VIT group (23% vs 7%). Similarly, media opacities tended to be a more frequent cause in the TAP group (15% vs 2%). In no cases were vitreous opacities judged to be the principal cause of impaired vision. As with patients who initially had better than LP vision, macular abnormalities were the most common cause of impaired vision in those with initial LP-only vision.

Table 3. Media Clarity at the Final Visit by Treatment Type*

	No. (%) of Patients			
	Vitrectomy	Tap/Biopsy	IV Antibiotics	No IV Antibiotics
Clinical clarity 20/40 view to retina	179 (89.5)	160 (83.3)	168 (88.0)	171 (85.1)
No decreased photographic clarity	85 (42.5)	64 (33.3)	75 (39.3)	74 (36.8)
Questionable decrease in photographic clarity	38 (19.0)	37 (19.3)	39 (20.4)	36 (17.9)
Photographic clarity decreased less than standard photograph 2	23 (11.5)	30 (15.6)	23 (12.0)	30 (14.9)
Photographic clarity decreased less than or equal to standard photograph 2, but greater than standard photograph 3	13 (6.5)	11 (5.7)	11 (5.8)	13 (6.5)
Photographic clarity decreased greater than or equal to standard photograph 3	1 (0.5)	3 (1.6)	3 (1.6)	1 (0.5)
Photographs missing	19 (9.5)	15 (7.8)	17 (8.9)	17 (8.5)
Clinical assessment of clarity <20/40 view to retina, but visible second-order retinal vessel	6 (3.0)	12 (6.3)	6 (3.1)	12 (6.0)
No visible second-order retinal vessel, but some visible retinal vessel	2 (1.0)	0 (0.0)	1 (0.5)	1 (0.5)
No visible retinal vessel	13 (6.5)	20 (10.4)	16 (8.4)	17 (8.5)
Total	200 (100.0)	192 (100.0)	191 (100.0)	201 (100.0)

*IV indicates intravenous.

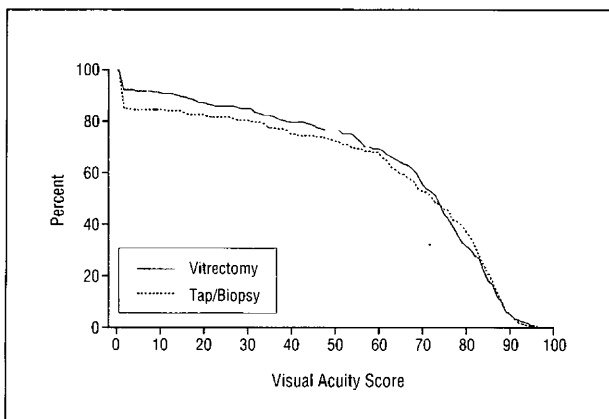


Figure 1. Cumulative visual acuity scores at the final follow-up by surgery type. Snellen equivalents for selected visual acuity scores are as follows: 20/20=85, 20/40=70, 20/100=50, 20/200=35, and 5/200=5.

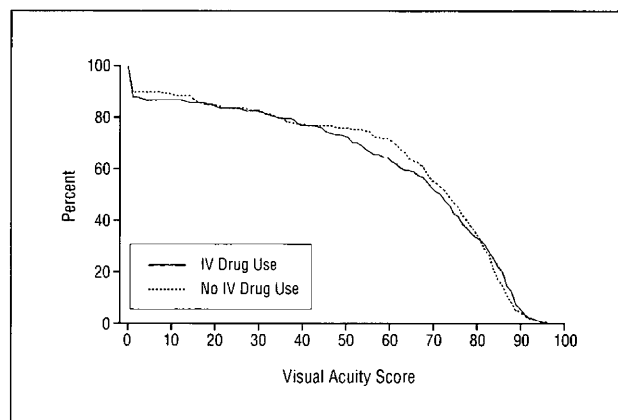


Figure 2. Cumulative visual acuity scores at the final follow-up by intravenous (IV) drug use. Snellen equivalents for selected visual acuity scores are as follows: 20/20=85, 20/40=70, 20/100=50, 20/200=35, and 5/200=5.

RISK FACTORS FOR DECREASED VISUAL ACUITY OUTCOME

The percentage of cases with various outcomes at the final visit was correlated with baseline characteristics regardless of treatment assignment. Potential risk factors for decreased final visual acuity outcome or decreased media clarity were assessed. Risk factors, listed in **Table 6**, are those for which the *P* value was .05 or less for at least one visual acuity threshold or for decreased media clarity. Four baseline factors that were strongly associated ($P \leq .001$) with poor outcome at all four outcome determinants were worse initial vision, small pupil size after maximal dilatation, presence of rubeosis irides, and absence of a red reflex. Other important risk factors at the initial examination that were associated with poor final outcome included history of diabetes or glaucoma; findings of the examination, including afferent pupillary defect, corneal infiltrate, or ring ulcer; abnormal intraocular pressure; inability to see any retinal vessels by indirect ophthalmoscopy; and type of organism grown in culture.

Because the baseline characteristics associated with poor outcome were often interrelated (eg, limited view to the retina

was related to poor initial vision), independent risk factors were determined, ie, factors related to outcome even after their association with other factors was taken into consideration. **Table 7** gives the odds ratios for risk factors for decreased media clarity that were significant after adjusting for other factors (based on a logistic regression model). It also shows the relative risks for significant independent baseline factors (based on a Cox regression analysis) for a decrease over the entire range of visual acuity (as distinct from individual visual acuity thresholds). In both the Cox and logistic regression models, the table only includes a number in the appropriate column for the variable if it was statistically significant after controlling for other factors for either decreased acuity or for decreased media clarity. However, the treatment variables VIT, TAP, IV, and NOIV were included, although they were not significant, since assessment of their effect was the study goal.

To interpret **Table 7**, as an example, note that after adjustment for other factors, older age is a risk factor for decreased visual acuity but not for decreased media clarity. A patient of any age had a 1.04 risk for decreased vision compared with a patient who was 1 year younger. The

Table 4. Cumulative Final Visual Acuity by Treatment Type*

Snellen Equivalent	Visual Acuity Score (No. of Letters)	No. (%) of Patients		P	No. (%) of Patients		P
		Vitrectomy (n=201)	Tap/Biopsy (n=193)		IV Antibiotics (n=193)	No IV Antibiotics (n=201)	
20/25 or better	≥80	60 (29.9)	67 (34.7)		62 (32.1)	65 (32.3)	
20/40 or better	≥70	108 (53.7)	101 (52.3)	.78	99 (51.3)	110 (54.7)	.50
20/50 or better	≥65	127 (63.2)	114 (59.1)		114 (59.1)	127 (63.2)	
20/100 or better	≥60	154 (76.6)	139 (72.0)	.30	140 (72.5)	153 (76.1)	.42
20/200 or better	≥35	165 (82.1)	150 (77.7)		154 (79.8)	161 (80.1)	
10/200 or better	≥20	175 (87.1)	159 (83.4)		163 (84.5)	171 (85.1)	
5/200 or better	≥5	185 (92.0)	164 (85.0)	.03	168 (87.1)	181 (90.1)	.35
LP or better	≥LP	193 (96.0)	183 (94.8)		182 (94.3)	194 (96.5)	

*IV indicates intravenous; LP, light perception.

Table 5. Reasons for Moderate and Severe Visual Acuity Impairment at Final Follow-up by Initial Vision and Treatment*

Reasons	Baseline >LP, Vitrectomy (n=146)			Baseline >LP, Tap/Biopsy (n=146)			Baseline=LP, Vitrectomy (n=55)			Baseline=LP, Tap/Biopsy (n=47)		
	<20/40 to ≥5/200		Total (<20/40)	<20/40 to ≥5/200		Total (<20/40)	<20/40 to ≥5/200		Total (<20/40)	<20/40 to ≥5/200		Total (<20/40)
	to	<5/200		to	<5/200		to	<5/200		to	<5/200	
Phthisis or enucleation	0	1	1 (0.7)	0	1	1 (0.7)	0	4	4 (7.3)	0	11	11 (23.4)
Media opacities	8	2	10 (6.8)	7	1	8 (5.5)	0	1	1 (1.8)	3	4	7 (14.9)
Cornea opacities	3	2	5 (3.4)	0	1	1 (0.7)	0	1	1 (1.8)	2	2	4 (8.5)
Posterior capsule or IOL opacities	4	0	4 (2.7)	4	0	4 (2.7)	0	0	0 (0.0)	1	2	3 (6.4)
Vitreous opacities	1	0	1 (0.7)	3	0	3 (2.1)	0	0	0 (0.0)	0	0	0 (0.0)
Macular abnormalities	25	1	26 (17.8)	22	2	24 (16.4)	20	2	22 (40.0)	14	2	16 (34.0)
Macular or ERM distortion	3	0	3 (2.1)	7	0	7 (4.8)	3	1	4 (7.3)	2	0	2 (4.3)
Macular edema	11	0	11 (7.5)	6	0	6 (4.1)	6	1	7 (12.7)	6	2	8 (17.0)
Pigmentary degeneration of the macula	10	0	10 (6.8)	8	2	10 (6.8)	8	0	8 (14.5)	5	0	5 (10.6)
Macular ischemia	1	1	2 (1.4)	1	0	1 (0.7)	3	0	3 (5.5)	1	0	1 (2.1)
Miscellaneous	3	1	4 (2.7)	8	3	11 (7.5)	3	4	7 (12.7)	1	4	5 (10.6)
BRVO, CRVO, or diabetic retinopathy	0	0	0 (0.0)	2	0	2 (1.4)	0	1	1 (1.8)	0	0	0 (0.0)
Retinal detachment	1	1	2 (1.4)	0	2	2 (1.4)	0	3	3 (5.5)	0	2	2 (4.3)
Optic nerve pathology	2	0	2 (1.4)	6	1	7 (4.8)	2	0	2 (3.6)	1	1	2 (4.3)
Others (cytomegalovirus, myopia)	0	0	0 (0.0)	0	0	0 (0.0)	1	0	1 (1.8)	0	1	1 (2.1)
Unknown	15	0	15 (10.3)	6	0	6 (4.1)	3	0	3 (5.5)	2	1	3 (6.4)
Total With Impaired Visual Acuity	51	5	56 (38.4)	43	7	50 (34.2)	26	11	37 (67.3)	20	22	42 (89.4)

*Data are number (percentage) of patients. LP indicates light perception; IOL, intraocular lens; ERM, epiretinal membrane or macular pucker; BRVO, branch vein occlusion; and CRVO, central vein occlusion.

model was also used to determine that a patient of any age had a 1.5 risk for decreased final vision compared with a patient who was 10 years younger. A patient with diabetes was 1.6 times as likely to have decreased vision compared with a patient without diabetes. The odds ratio for decreased media clarity at final follow-up was about 3.0 for a patient who had pain at the initial examination compared with a patient without symptoms of pain.

The risk factors at the initial ocular examination that were related to decreased media clarity at the final follow-up were presence of pain, LP-only visual acuity, corneal infiltrate and/or ring ulcer, a greater hypopyon height, and presence of rubeosis.

After adjustment, statistically significant risk factors at the initial ocular examination that were predictive of de-

creased final vision were LP-only visual acuity, corneal infiltrate and/or ring ulcer, posterior capsule not intact as determined by initial examination results, low or high intraocular pressure (<5 mm Hg or >25 mm Hg), afferent pupillary defect, rubeosis, and absent red reflex. The risk for decreased vision for patients with LP-only acuity at presentation was 2.0 times the risk for patients with better than LP vision at presentation.

VISUAL ACUITY OUTCOME FOR SUBGROUPS OF PATIENTS

Analyses were done to determine whether there were any interactions between the type of treatment (VIT vs TAP or IV vs NOIV) and baseline characteristics. A benefit from the

Table 6. Outcomes at Final Visit by Baseline Characteristics*

Characteristic	N	VA ≥70 Letters (20/40 or Better)		VA ≥50 Letters (20/100 or Better)		VA ≥5 Letters (5/200 or Better)		≥20/40 View to Retina	
		%	P	%	P	%	P	%	P
Total	394	53.1		74.4		88.6		86.5	
Age			<.001		.002		.12		.17
≥75 y	193	42.0		67.4		86.0		88.8	
<75 y	201	63.7		81.1		91.0		84.0	
History of diabetes			.03		.001		.03		.10
Yes	54	38.9		55.6		79.6		79.3	
No	340	55.3		77.4		90.0		87.6	
History of hypertension			.02		.16		.26		.06
Yes	158	44.9		69.6		85.4		81.5	
No	234	58.1		77.4		90.6		89.7	
Unknown	2	100		100		100		100	
History of glaucoma			.05		.01		.58		.21
Yes	35	37.1		57.1		85.7		79.4	
No	359	54.6		76.0		88.9		87.1	
Symptoms present			.02		.77		.42		.37
Yes	389	53.7		74.3		88.4		86.3	
No	5	0.0		80.0		100		100	
Pain			.10		.07		.01		.003
Yes	289	50.5		72.0		86.2		83.3	
No	105	60.0		81.0		95.2		95.2	
Blurred vision			.02		.06		.03		.09
Yes	370	54.6		75.4		89.5		87.2	
No	24	29.2		58.3		75.0		75.0	
Swollen lid			.74		.02		.02		.002
Yes	133	51.9		66.9		83.5		78.8	
No	261	53.6		78.2		91.2		90.4	
Visual acuity			<.001		<.001		<.001		<.001
Light perception	102	22.6		44.1		67.7		66.0	
Hand motions	173	55.5		83.2		96.0		92.4	
Counting fingers, <5/200	62	74.2		87.1		95.2		96.8	
≥5/200	57	77.2		87.7		96.5		93.0	
Afferent pupillary defect			.01		<.001		.01		.008
Yes	47	38.3		57.5		78.7		80.8	
No	214	59.4		82.7		92.5		91.4	
Unknown	133	48.1		66.9		85.7		80.6	
Pupil size at maximum dilation			.001		<.001		<.001		<.001
≤5 mm	235	46.0		66.4		83.4		81.1	
>5 mm	159	63.5		86.2		96.2		94.3	
Corneal infiltrate or ring ulcer			.03		<.001		<.001		<.001
Yes	20	30.0		35.0		55.0		50.0	
No	374	54.3		76.5		90.4		88.4	
Cataract surgical wound abnormality†			.16		<.001		.004		.008
Yes	21	33.3		33.3		71.4		68.2	
No	347	54.5		77.2		90.5		88.4	
Unknown	26	50.0		69.2		76.9		76.0	
Wound leak at initial visit‡			.71		.03		.08		.08
Yes	34	50.0		58.8		79.4		76.5	
No	360	53.3		75.8		89.4		87.4	
Hypopyon height			.06		.002		.004		<.001
0 mm-1.5 mm	282	56.0		78.7		91.5		91.0	
>1.5 mm	112	45.5		63.4		81.3		75.0	
Intraocular pressure			.007		.02		.01		.008
0-5 mm Hg	13	38.5		76.9		92.3		84.6	
6-25 mm Hg	310	56.8		77.1		91.0		89.3	
>25 mm Hg	59	35.6		59.3		78.0		74.1	
Media clarity (able to see any retinal vessel)			<.001		<.001		.001		.003
Yes	83	74.7		90.4		98.8		96.4	
No	311	47.3		70.1		85.9		83.8	
Red reflex			<.001		<.001		<.001		<.001
Yes	270	61.5		82.6		95.2		93.3	
No	124	34.7		56.5		74.2		71.1	
Lens capsule intact (by examination)			<.001		<.001		.002		<.001
Yes	154	68.2		87.0		95.4		94.8	
No	47	38.3		61.7		87.2		87.2	
Unknown	193	44.6		67.4		83.4		79.6	
Rubeosis irides present			<.001		<.001		<.001		<.001
Yes	12	41.7		58.3		83.3		81.8	
No	346	56.7		78.3		92.2		90.4	
Unknown	36	22.2		41.7		55.6		50.0	
White blood cell count			.46		.40		.007		.05
≤10.0×10 ⁹ /L	263	54.4		75.7		91.6		88.9	
>10.0×10 ⁹ /L	131	50.4		71.8		82.4		81.7	

*VA indicates visual acuity.

†Includes one or more of the following: vitreous incarceration, iris prolapse or incarceration, stitch abscess, or infected bleb.

‡Includes wound dehiscence, positive Seidel test.

Table 7. Independent Risk Factors for Media Clarity and Visual Outcome at Final Follow-up*

Variable	Odds Ratio for <20/40 View to Retina	Relative Risk for Decrease in Vision
Vitrectomy (vs tap/biopsy)	0.45	(0.90)†
IV antibiotics (vs no IV antibiotics)	(0.79)†	(1.03)†
Age (per year)	...	1.04
Diabetes (yes vs no)	...	1.6
Pain symptom (present vs absent)	3.0	...
Visual acuity (LP only vs >LP)	4.8	2.0
Corneal infiltrate and/or ring ulcer	4.4	1.7
Capsule (not intact vs intact)	...	1.9
Capsule (unknown vs intact)	...	1.3
IOP (<5 mm Hg vs 5-25 mm Hg)	...	1.2
IOP (>25 mm Hg vs 5-25 mm Hg)	...	1.4
Afferent pupillary defect (present vs absent)	...	1.03
Afferent pupillary defect (unknown vs absent)	...	1.3
Hypopyon height (in mm, continuous)	1.4	...
Rubeosis (present vs absent)	3.2	1.2
Rubeosis (unknown vs absent)	3.5	1.8
Red reflex (absent vs present)	...	1.3

*For independent risk factors the odds ratio and relative risks listed were significant at $P < .05$. Ellipses indicate there was no statistically significant odds ratio or relative risk. Factors that were considered based on their univariate relation to outcome, but not independently significant for either end point: swollen lid, glaucoma initial media clarity, hypertension, wound leak by examination, type of lens implanted, viscoelastic material, operative complications at inciting surgery, wound abnormalities, pupil size, and white blood cell count. IV indicates intravenous; LP, light perception; and IOP, intraocular pressure.

†For treatment variables, the odds ratios and relative risks are given but they were not statistically significant.

use of IV antibiotics was not found for any of the subgroups. However, there were subgroups for which visual outcome differed by VIT vs TAP treatment. Cox regression analysis was carried out over the entire visual range, focusing on one potential risk factor at a time to determine significant interaction terms. **Table 8** lists factors with interaction P values of less than .10, a liberal screening threshold. Visual acuity, absence of a red reflex, a positive Gram stain, systemic antibiotic treatment prior to presentation, and cataract or lens procedure performed at an outpatient surgical center were factors that, when examined one at a time, each suggested a benefit of VIT over TAP. Only for a baseline LP-only visual acuity was the interaction P value less than .01. While not shown in Table 8, the type of organism that grew in culture did not show an interaction with treatment group for visual outcome. The effect of microbiology class on visual outcome will be the topic of a separate publication.

Visual results for each treatment group are presented as a function of identified risk factors in Table 8. Eyes with LP-only visual acuity at presentation had a three times greater chance of achieving 20/40 vision with VIT compared with TAP (33% vs 11%). Corresponding results for eyes with LP-only acuity at presentation achieving 20/100 vision were 56% for VIT vs 30% for TAP, and for achieving 5/200 vision were 80% for VIT vs 53% for TAP.

Because patients with LP-only visual acuity constituted the subgroup that showed the strongest evidence of benefit

of VIT (as judged by the interaction P value of .0002), each of the other factors listed in Table 8 was paired with initial LP-only vision to determine if other risk factors defined subgroups in which VIT was efficacious over and above its efficacy among patients with LP-only vision. In each case, the other factor was no longer statistically significant at even the 0.1 level when LP-only vision was considered. Initial vision of LP only was significant at a P value of less than .005 for all the pairings. Thus, the apparent benefit of VIT that was present in the other subgroups of patients shown in Table 8 was owing to their association with LP-only vision at presentation.

Table 9 presents relative risks for decreased vision at the final follow-up visit based on a Cox regression analysis model. We used patients who initially had better than LP vision and received TAP as a reference group. For patients who initially had visual acuity better than LP, the risk (1.1) for decreased vision was not significantly higher in the VIT group compared with the TAP group. Among the patients assigned to receive TAP, the risk for decreased vision was 4.15 times greater in those having LP-only vision. Among patients with an initial visual acuity of LP only, the risk for decreased vision was about one half as great in patients in the VIT group compared with the TAP group ($1.92/4.15=0.46$).

Figure 3 shows the cumulative visual acuity scores for the VIT and TAP groups for both patients who initially had LP-only vision and patients who had better than LP vision. This figure best captures one of the most important findings of the EVS; patients who initially had LP-only vision showed benefit from VIT compared with TAP, whereas patients with better than LP vision did about as well with either VIT or TAP.

Final media clarity was also examined according to whether patients initially had LP-only or better than LP vision. There was no significant advantage of VIT for patients with better than LP vision. Of the VIT group, 94% achieved the best category of clinically assessed media clarity compared with 93% of those who underwent TAP. In contrast, among those who initially had LP-only vision, 78% of the VIT group achieved a 20/40 view to the retina compared with only 52% in the TAP group ($P=.007$). The evaluation based on photographic assessment reached similar conclusions. Among patients who initially had better than LP vision, 77% in the VIT group vs 71% in the TAP group had no or only a questionable decrease in photographic clarity, a nonsignificant difference. However, in the subgroup of patients who had LP-only vision, 63% of the VIT group compared with 48% of the TAP group were in the "no" or "questionably decreased" clarity category, also not statistically significant. Thus, the results for media clarity paralleled the results for visual acuity.

COMMENT

VISUAL AND MEDIA CLARITY RESULTS

Overall, the visual outcomes of the EVS patients were excellent, with more than one half of patients achieving 20/40 vision and three quarters achieving 20/100 or better visual outcome. Only 11% of patients had final visual acuities worse than 5/200. Current treatment approaches as

Table 8. Relation of Surgery Type to Visual Acuity (VA) Scores by Selected Characteristics at the Final Follow-up*

Characteristic	Interaction P Value*	Vitrectomy, N	Tap/Biopsy, N	VA Score \geq 70 (20/40 or Better), %		VA Score \geq 50 (20/100 or Better), %		VA Score \geq 5 (5/200 or Better), %	
				Vitrectomy	Tap/Biopsy	Vitrectomy	Tap/Biopsy	Vitrectomy	Tap/Biopsy
Visual acuity									
Light perception (LP)		55	47	32.7	10.6	56.4	29.8	80.0	53.2
Hand motions		91	82	52.8	58.5	82.4	84.2	97.8	93.9
Counting fingers, <5/200		31	31	77.4	71.0	90.3	83.9	96.8	93.6
\geq 5/200		24	33	75.0	78.8	83.3	90.9	91.7	100.0
LP only	<.001	55	47	32.7	10.6	56.4	29.8	80.0	53.2
>LP		146	146	61.6	65.8	84.2	85.6	96.9	95.2
Red reflex present	.05								
Yes		131	139	60.3	62.6	82.4	82.7	96.2	94.2
No		70	54	41.4	25.9	65.7	44.4	84.3	61.1
Positive Gram's stain	.10								
Yes		83	68	49.4	33.8	74.7	60.3	88.0	75.0
No		93	92	55.9	60.9	77.4	77.2	94.6	90.2
Systemic antibiotics before initial visit†	.06								
Yes		5	16	60.0	31.3	80.0	43.8	100	68.8
No		194	177	53.1	54.2	76.3	74.6	91.8	86.4
Initiating procedure performed in hospital	.06								
No		50	52	60.0	42.3	78.0	61.5	94.0	75.0
Yes		151	141	51.7	56.0	76.2	75.9	91.4	88.7

*The interaction P value is based on Cox regression analysis of entire range of vision.

†The use of systemic antibiotics before presentation was unknown for two patients in the vitrectomy group.

practiced in this and other studies⁷ can yield excellent visual results.

Looking at the entire range of vision, a significant difference between VIT and TAP was not found for the total group of patients. The visual results were also assessed at specific thresholds (determined a priori). There was no advantage of either treatment in achieving 20/40 or better or 20/100 or better acuity. However, VIT was of value compared with TAP in halving the chance of severe visual loss (<5/200 visual acuity) from 15% in the TAP group to 8% in the VIT group. When considering IV vs NOIV treatment, there was no difference by treatment group over the entire range of vision, or for any visual threshold.

Media clarity outcome was also compared by treatment. A significantly greater percentage of patients in the VIT group than in the TAP group (86% vs 75%) had clear media by the 3-month follow-up, with similar data at the final visit (VIT, 90%; TAP, 83%). There was no difference between the IV and NOIV groups. The more rapid clearing of media in the VIT group (even though not associated with concomitant rapid improvement in visual acuity) could be of clinical importance for certain patients, eg, a patient whose only eye had endophthalmitis, where more rapid improvement could be important.

VISUAL RESULTS ANALYZED BY TREATMENT FOR SUBGROUPS OF PATIENTS

VIT vs TAP

The data for all the study patients suggested a benefit of VIT vs TAP only in saving eyes from severe visual loss; however, when we examined the interaction of treatment with specific subgroups of patients, the benefit of

VIT was limited to the subgroup who initially had LP-only vision.

These data show that patients who had initial vision of LP only and underwent immediate VIT compared with those who underwent TAP had a three times greater chance of achieving 20/40 final visual acuity (33% vs 11%), almost double the chance of achieving 20/100 final visual acuity (56% vs 30%) and less than one half the risk for severe visual acuity loss of less than 5/200 (20% vs 47%). Therefore, the EVS findings strongly support the use of VIT after cataract or secondary lens implantation for patients with endophthalmitis who meet EVS entry criteria and who have LP-only vision at the initial visit. This finding is consistent with the recommendation of other authors that VIT be undertaken for eyes with the worst clinical appearance at the initial visit, including eyes with severe vision loss to a level of LP only,²¹ limited visibility of the fundus,²² loss of red reflex, afferent pupillary defect, corneal ring infiltrate, or loss of light projection.²³

Patients who initially had better than LP vision (ie, hand motions or better) had about the same chance of achieving 20/40 or better acuity (66% vs 62%) and 20/100 or better acuity (86% vs 84%) and a similar risk for visual acuity loss of worse than 5/200 (5% vs 3%), whether they had immediate VIT or immediate TAP. Therefore, the study found no advantage to routinely performing immediate VIT in patients who had better than LP vision at the initial visit. Our patients with vision greater than LP did just as well with TAP.

Although other factors showed interactions with treatment, none showed a significant interaction after taking into account whether the patient had LP-only vision at the initial visit. The apparent benefit of VIT in other subgroups of patients (Table 8) was owing to the association a subgroup had with having LP-only vision. For example,

Table 9. Relative Risks for Decreased Vision at Final Follow-up by Surgical Treatment and Initial Vision*

Treatment	Better Than LP-Only Vision at Initial Visit	LP-Only Vision at Initial Visit
Tap/biopsy	1.0†	4.15 (2.94-5.84)
Vitrectomy	1.10 (0.87-1.38)	1.92 (1.40-2.62)

*Data are relative risk (95% confidence interval) based on a Cox regression model with the outcome variable as the entire range of visual acuity, and the explanatory variables treatment (vitrectomy vs tap), initial visual acuity, and the interaction of treatment and initial visual acuity. LP indicates light perception.

†Reference category is tap/biopsy for patients with better than LP-only vision at presentation.

patients with no red reflex at the initial visit did better with VIT than with TAP. Once the data were adjusted for LP-only vision, there was no evidence that VIT was more beneficial than TAP for patients with no red reflex. This is not surprising since LP-only vision at the initial visit was highly correlated with an absent red reflex.

IV vs NOIV

There was no difference in visual acuity or media clarity outcome with or without the use of systemic antibiotic agents. This was not only true overall, but for all subgroups of patients examined.

In the past, the use of IV antibiotics has been part of the standard of care in the management of postsurgical endophthalmitis. Systemically administered antibiotics can have serious adverse effects. Their use is expensive because of their cost and the cost of hospitalization required for IV administration. Thus, the finding that systemic antibiotics did not provide additional benefit may save patients with endophthalmitis from risk and may allow them to be discharged from the hospital earlier. In some cases, patients may not require hospitalization at all. The results of the EVS support omission of IV antibiotic treatment in the management of endophthalmitis occurring after cataract surgery.

While, strictly speaking, the findings regarding IV antibiotics apply only to the drugs used in this study, it is not unreasonable to extrapolate to other drugs. The amount of antimicrobial that can be delivered to the vitreous cavity is so great with intravitreal injection compared with the amount that can enter the eye from systemic administration that a systemically administered drug is not likely to provide additional benefit. Some other classes of drugs that are more lipid soluble than β -lactams and aminoglycosides (eg, quinolones, chloramphenicol, metronidazole, and trimethoprim-sulfamethoxazole) penetrate the vitreous relatively well but are not drugs of choice for the most common pathogens in postoperative endophthalmitis, namely, gram-positive cocci. Thus, it is unlikely that different systemically administered drugs, even if they penetrate the vitreous cavity to a greater extent than the ones used in this study, would provide benefit in acute endophthalmitis following cataract extraction. Since repeated doses of systemic drugs²⁴ may allow increased drug penetration after time, one can only speculate as to whether there may be a role for systemic administration in other types of endophthalmitis,

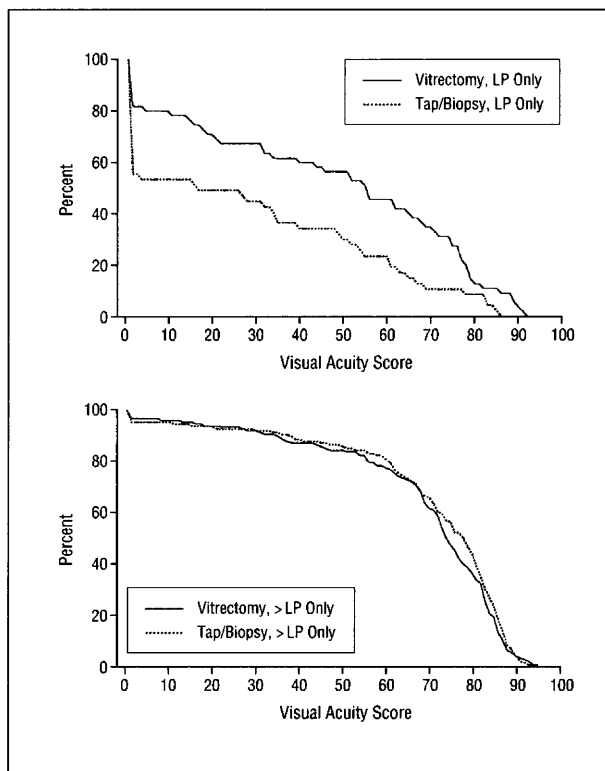


Figure 3. Cumulative visual acuity scores at the follow-up by surgery type and initial visual acuity. Snellen equivalents for selected visual acuity scores are as follows: 20/20=85, 20/40=70, 20/100=50, 20/200=35, and 5/200=5. LP indicates light perception.

endophthalmitis refractory to initial treatment, or prophylaxis. The EVS did not study these issues.

RISK FACTORS FOR POOR VISUAL RESULTS

The EVS assessed risk factors that might have been associated with poor outcome. Previous reports have shown that a positive culture, a more virulent organism, delay before initiation of treatment, the presence of concomitant ocular disease such as rubeosis and retinal detachment, and poor initial visual acuity are risk factors for worse visual acuity results.^{7,25,26} In one previous report, just 20% of patients with an initial acuity of LP only achieved a final 20/400 acuity, but almost all patients whose initial acuity was 20/400 or better achieved a final 20/400 acuity.²⁵ The EVS findings showed many similar risk factors for poor outcome. Because many of these were interrelated, we applied statistical models to determine which were independent risk factors for decreased final visual acuity. Older age, history of diabetes, corneal infiltrate or ring ulcer, abnormal intraocular pressure, rubeosis, an absent red reflex, an open posterior capsule, and visual acuity of LP only were all independent risk factors for decreased final visual acuity.

The most important risk factor for decreased final visual acuity was an initial visual acuity of LP only. Such patients had twice the risk for a worse acuity outcome compared with patients with better than LP acuity. Overall, 23% of patients who had acuity of LP only achieved 20/40 final acuity, compared with 64% of patients who had better than LP acuity.

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Continued on next page

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Executive Committee: *Members:* Matthew Davis, MD, Bernard H. Doft, MD, Donald Everett, MA, Sheryl F. Kelsey, PhD, Philip T. Nelsen, MD, Kirk H. Packo, MD, Thomas A. Rice, MD.

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Independent risk factors for decreased media clarity included corneal infiltrate or ring ulcer, greater hypopyon size, and visual acuity of LP only. Just as initial visual acuity of LP only was the strongest independent risk factor for decreased final visual acuity, it was also the strongest risk factor for decreased media clarity at the final examination, with an odds ratio of 4.8.

BASELINE FINDINGS IN THE STUDY POPULATION

The patient population of this study had advanced and severe disease. Only 14% of patients were able to see at least 5/200 at study entry, and fully one quarter of patients could only perceive light. The red reflex was absent in two thirds of patients. Approximately 5% of patients had a corneal infiltrate or ring ulcer, and 8.8% had a wound leak. Wound leak was detected slightly more often in patients who underwent VIT, possibly because of a greater ability to inspect the wound during a VIT procedure.

Other baseline patient characteristics are of interest. Pain has often been considered to be an important aspect of the symptom complex in endophthalmitis, but pain was absent in one quarter of the EVS patients. Its absence therefore should not dissuade physicians from the diagnosis of bacterial endophthalmitis. Although the median time from cataract or secondary lens implantation surgery to presentation with endophthalmitis was 6 days, approximately one quarter of patients were not

seen until more than 2 weeks after the inciting surgery. It is important for the clinician to realize that a high proportion of cases of acute bacterial endophthalmitis can occur this late after cataract surgery. Eligibility criteria prevented patients from entering the EVS more than 6 weeks after their inciting surgical procedure. However, previous data have shown that 88% of postcataract-induced endophthalmitis occurs within 6 weeks after surgery.⁵

COMPLICATIONS AND ADDITIONAL PROCEDURES

According to the EVS treatment strategy, a patient whose involved eye was doing poorly 36 to 60 hours after the initial procedure could have further surgery if suggested guidelines were met or if the physician thought it was in the best interest of the patient. Within this time frame, almost 9% of patients had an additional procedure performed. Since TAP is a less aggressive approach, it was not surprising to see a greater number of eyes in the TAP group than in the VIT group undergo further surgery during this period, but the difference between groups was small and not significant. During the entire course of follow-up, approximately one third of patients required an additional surgical or laser procedure, information that will be described in detail in another report.

Prior to this study, the literature had suggested that there might be a greater complication rate associated with

VIT than with TAP, but severe selection bias in those published reports made the data difficult to evaluate. Retinal detachment in particular was cited as occurring more frequently in eyes undergoing VIT, with an incidence as high as 21% reported in one series²⁷ and 18% in another.²⁸ In the EVS, retinal detachment occurred in 20 patients (5%), six in the VIT group and 14 in the TAP group ($P=.04$). Phthisis occurred in 2% of patients in the VIT group and 4% of patients in the TAP group, a non-significant difference, and visual acuity of no LP occurred in 5% of TAP and 4% of VIT eyes. Enucleation was performed on three study eyes, all in the TAP group. Previous reports that had suggested that eyes subjected to VIT might suffer a greater complication rate were therefore not supported by our results.

One potential risk with VIT was the theoretical possibility that the procedure could allow a greater amount of drug to the retina, thus resulting in a greater chance for retinal toxic effects from intravitreally administered antimicrobials such as aminoglycosides.²⁹ A single patient was observed to have macular infarction of an unknown cause. Since this trial did not assess the macula with fluorescein angiography, it remains possible that the frequency was actually higher.

CAUSES OF DECREASED VISION

Analysis of the causes of decreased vision suggested that the excess of eyes with poor outcome in the TAP group was explained mainly by phthisis, enucleation, or anterior segment media opacification (Table 5). There was no evidence that residual opacification of the vitreous was a factor in the poorer outcome in the TAP group. Overall, the most common cause of decreased vision in all subgroups was an abnormality of the macula.

CONCLUSIONS

In the EVS, treatment with systemic antibiotics did not provide benefit in the management of endophthalmitis that occurred after cataract surgery. Omission of these drugs can provide advantages in terms of reduction of toxic effects, costs, and length of hospital stay.

Vitreotomy did not provide benefit in the patients who had better than LP vision at the initial visit, a group who in general had a better visual outcome. Whether or not such patients had a VIT, more than 60% achieved 20/40 final visual acuity, and less than 5% suffered severe vision loss. There was no advantage to routinely performing immediate VIT in patients who met EVS criteria and had better than LP vision at the initial visit.

The EVS findings show that VIT is of substantial benefit over TAP for patients who have LP-only vision, increasing by threefold (33% compared with 11%) the frequency of achieving 20/40 final visual acuity, and decreasing by half (20% compared with 47%) the frequency of severe vision loss in the group of patients. Therefore, EVS findings support the use of VIT in patients who have EVS eligibility criteria and have LP-only vision.

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