Prophylaxis of postoperative endophthalmitis following cataract surgery: Results of the ESCRS multicenter study and identification of risk factors

ESCRS Endophthalmitis Study Group

PURPOSE: To identify risk factors and describe the effects of antibiotic prophylaxis on the incidence of postoperative endophthalmitis after cataract surgery based on analysis of the findings of the European Society of Cataract & Refractive Surgeons (ESCRS) multicenter study.

SETTING: Twenty-four ophthalmology units in Austria, Belgium, Germany, Italy, Poland, Portugal, Spain, Turkey, and the United Kingdom.

METHODS: A prospective randomized partially masked multicenter cataract surgery study recruited 16 603 patients. The study was based on a 2 × 2 factorial design, with intracameral cefuroxime and topical perioperative levofloxacin factors resulting in 4 treatment groups. The comparison of case and non-case data was performed using multivariable logistic regression analyses. Odds ratios (ORs) associated with treatment effects and other risk factors were estimated.

RESULTS: Twenty-nine patients presented with endophthalmitis, of whom 20 were classified as having proven infective endophthalmitis. The absence of an intracameral cefuroxime prophylactic regimen at 1 mg in 0.1 mL normal saline was associated with a 4.92-fold increase (95% confidence interval [CI], 1.87-12.9) in the risk for total postoperative endophthalmitis. In addition, the use of clear corneal incisions (CCIs) compared to scleral tunnels was associated with a 5.88-fold increase (95% CI, 1.34-25.9) in risk and the use of silicone intraocular lens (IOL) optic material compared to acrylic with a 3.13-fold increase (95% CI, 1.47-6.67). The presence of surgical complications increased the risk for total endophthalmitis 4.95-fold (95% CI, 1.68-14.6), and more experienced surgeons were more likely to be associated with endophthalmitis cases. When considering only proven infective endophthalmitis cases, the absence of cefuroxime and the use of silicone IOL optic material were significantly associated with an increased risk, and there was evidence that men were more predisposed to infection (OR, 2.70; 95% CI, 1.07-6.8).

CONCLUSIONS: Use of intracameral cefuroxime at the end of surgery reduced the occurrence of postoperative endophthalmitis. Additional risk factors associated with endophthalmitis after cataract surgery included CCIs and the use of silicone IOLs.

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Cataract surgery has become one of the most prevalent surgical procedures due to changes in population structure and increased life expectancy. With the population in Europe aging faster than on any other continent, increasing numbers of patients have cataract surgery procedures that may result in impaired and lost vision due to postoperative infective endophthalmitis. The European Society of Cataract & Refractive Surgeons (ESCRS) recognized the need for a multicenter study to investigate whether the incidence of endophthalmitis could be significantly reduced by the use of antimicrobial treatments. It was planned that up to 35 000 patients having cataract surgery would be recruited from centers across Europe. Each patient was randomized to 1 of 4 treatment groups to assess the prophylactic effect on the incidence of endophthalmitis of intracameral cefuroxime (1 mg in 0.1 mL normal saline) and/or topical levofloxacin 0.5% administered perioperatively. The study was funded by ESCRS, with Santen GmbH supplying

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levofloxacin and placebo drops free of charge along with an unrestricted educational grant. Further details on the rationale of the study can be found in Seal et al.,[1] while the formal registration of the study and its protocol can be found at http://www.clinicaltrials.gov/ct/show/NCT00136344?order=2 (accessed March 15, 2007).

The ESCRS European multicenter study of postoperative endophthalmitis was initiated in September 2003 when recruitment commenced in Belgium and Austria. Final patient recruitment took place at centers in Poland and the United Kingdom on January 13, 2006, following a decision to close the study on January 6, 2006, when the Data Monitoring Committee (DMC) was informed that there were significant findings on the prophylactic use for 1 of the 2 antibiotics. The DMC advised that it would be unethical to withhold the use of prophylactic intracameral cefuroxime any longer from the 2 groups not receiving it. A preliminary report was published in March 2006[2] that clearly showed the use of intracameral cefuroxime administered at the time of surgery significantly reduced the risk for cataract patients developing postoperative endophthalmitis. In practice, treatment effects were so marked that fewer than 17 000 patients were sufficient for valid conclusions to be obtained and to continue the study would have been futile. The final acquisition of outstanding data has been performed to estimate the incidence of postoperative endophthalmitis, risk associated with the antibiotic prophylaxes under test, and to identify further risk factors associated with the occurrence of endophthalmitis. These findings are presented here.

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From the European Society of Cataract & Refractive Surgeons, Dublin, Ireland, and the University of Strathclyde, Glasgow, United Kingdom.

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The members of the ESCRS Endophthalmitis Study Group are given in the Appendix.

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Corresponding author: Peter Barry, ESCRS, Temple House, Temple Road, Blackrock, County Dublin, Ireland. E-mail: escrs@agenda-comm.ie.

PATIENTS AND METHODS

Study Design

All patients taking part in the study had phacoemulsification cataract surgery with placement of an intraocular lens (IOL) as a single procedure without additional surgery. All operations took place within a modern operating room with assisted ventilation and full sterile and aseptic techniques. Each patient gave informed consent and was supplied with an information sheet in his or her own language. All recruited patients were screened for eligibility based on the inclusion and exclusion criteria listed in the protocol.[1] Twenty-four hospitals took part in the study, based in 9 countries: Austria (1), Belgium (5), Germany (1), Italy (2), Poland (1), Portugal (1), Spain (4), Turkey (1), and the United Kingdom (8).

The study was planned as a factorial design to test for the effects of 2 prophylactic interventions: (1) cefuroxime injected into the anterior chamber at the end of surgery as 1 mg in 0.1 mL normal saline, and (2) levofloxacin 0.5% administered 1 drop 1 hour before surgery, 1 drop 30 minutes before surgery, and 3 drops at 5-minute intervals commencing immediately after surgery.

The patients were randomly assigned to 1 of 4 treatment groups of approximately equal sizes (Figure 1). Group A received no perioperative antibiotic prophylaxis, Group B received the intracameral cefuroxime treatment only, Group C received the topical levofloxacin treatment only, and Group D received both intracameral cefuroxime and topical levofloxacin treatments. The levofloxacin treatment was masked; with patients receiving placebo or antibiotic drops from bottles supplied as part of the study. The use of cefuroxime was not masked; surgeons were requested to give patients who had been randomly allocated to Groups B and D the intracameral injection at the end of surgery.

All patients received povidone–iodine 5% drops (Betadine) into the conjunctival sac and onto the cornea for a minimum of 3 minutes before surgery, and all patients were requested to use levofloxacin 0.5% eyedrops (Oftaquix) 4 times daily for 6 days starting the day after surgery.

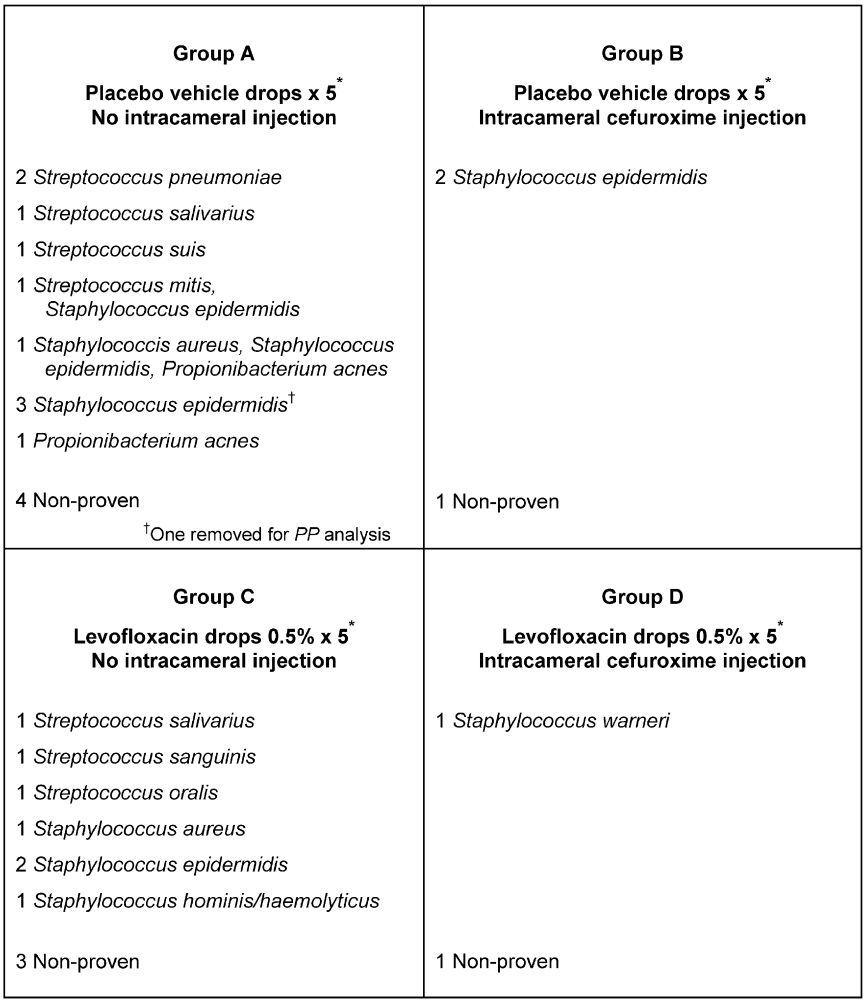
Case Definition

Clinicians were alert for the signs and symptoms associated with endophthalmitis.[3] A diagnosis of presumed endophthalmitis was made for any patient presenting with pain or loss of vision thought to be due to infection. Samples of aqueous and vitreous were collected from these patients and investigated using Gram staining, culture, and polymerase chain reaction testing using nonspecific microbial primers. Any case in which at least 1 of these tests yielded a positive result was classified as proven infective endophthalmitis. The total endophthalmitis cases constituted these proven cases together with those identified by the clinicians but for which no positive proof of infection was found. Each unproven case was reviewed for evidence of toxic anterior segment syndrome (TASS)[4] or noninfective uveitis.

Based on these case definitions, separate analyses of the study data were performed on (1) total endophthalmitis cases (including both the proven and unproven cases), and (2) proven infective endophthalmitis cases only.

Data Capture and Management

The study required that data were collected in 24 centers across Europe from clinicians working in 9 different



*One drop 1 hour before surgery, 1 drop half an hour before surgery, 1 drop immediately postoperation, 1 drop 5 minutes later, and 1 drop 5 minutes later again. All groups received povidone–iodine 5% (Betadine) before surgery and were prescribed levofloxacin 0.5% eyedrops from days 1 to 6 after surgery 4 times daily.

Figure 1. Study design and bacteriological results relating to all endophthalmitis cases (proven and non-proven) in patients recruited to the study.

languages (English, Flemish, French, German, Italian, Polish, Portuguese, Spanish, and Turkish). A multilingual database with study-specific data-entry forms was thus developed and installed in most centers. In 3 centers, existing database systems were adapted for study use. As the study database was made accessible within each operating room, it was possible to use the system to notify the surgeon which of the patients had been randomly assigned to receive a cefuroxime injection as well as to capture data at time of surgery. A parallel system was put in place at each location to handle follow-up data. The data were uploaded to a central server at the University of Strathclyde in Glasgow each week, making it possible to run data quality checks to monitor study collection and to perform interim analyses for evidence of early efficacy as well as for safety thresholds. The database application was implemented using Microsoft Access 2000. Further details on aspects of data management have been published.[1]

Per-Protocol and Intent-to-Treat Data Sets

The design of the study gave rise to few departures from the protocol, and consequently there was little difference between the composition of the per-protocol (PP) and intent-to-treat (ITT) data sets. Data from patients meeting the inclusion and exclusion criteria as stated in the study protocol and whose treatment fully conformed to the study protocol formed the PP data set.

Patients excluded from the PP data set were considered for inclusion in the ITT data set.

Identification of Key Risk Factors Using Logistic Regression Analyses

A list of variables identified as potential risk factors for proven and total endophthalmitis was extracted from the data sets as suitable for analysis and organized according to whether the factors were associated with time, environment, patient, disease, clinician, follow-up, treatment, surgical procedure, or surgical material factors. Each factor was screened individually using logistic regression and chi-square tests. All factors with a likelihood ratio test P value of 0.25 or less were made available for final multivariable binary logistic regression analyses. In addition, 2 demographic factors (age and sex of patients) were included as forced covariates in the final regression analysis along with the key design factors;

that is, whether or not patients received intracameral cefuroxime injection or topical levofloxacin at the time of surgery.

Using the variables selected in this way, successive models were constructed using backward elimination by considering the contribution of each factor and the significance of the variable in the model. Risk factors were eliminated until a model for each case definition type was obtained after consideration of interactions between factors. The odds ratios (ORs) and their significance were further examined in the absence of each factor to confirm that the models obtained were satisfactorily stable.

The likelihood ratio test statistical significances of each factor in the final regression model are reported with their ORs and associated 95% confidence intervals (CIs).

The influence of each center that recruited more than 850 patients into the study was investigated by examining the estimates of ORs and significance of risk factors associated with the final regression model when records from each such center were omitted from the data in turn. This provided information on how robust the results were to the exclusion of particular centers.

RESULTS

Intent-to-Treat and Per-Protocol Data Sets

There were 16 603 patients recruited to the study, of which 324 (2%) were lost to follow-up. Reasons for patients being lost to follow-up included failure to attend scheduled appointments, death, and incomplete data reports. A further 68 patients were omitted because they did not have the planned surgery or they withdrew their consent, resulting in an ITT data set that consisted of 16 211 patients. This set included 240 patients who could not be included in the PP data set due to protocol deviation such as the use of extracapsular cataract extraction (ECCE) rather than phacoemulsification, allergy to penicillin, and the inclusion of patients younger than 18 years of age. In both data sets, the majority of patients were women (58%) with a median age of 75 years; the median age of the men was 73 years. Results are summarized for both the ITT and PP data sets; however, detailed information is only provided for the ITT data set as the results were very similar.

Cases of Endophthalmitis Within the Study and Incidence Rates

A summary of all 29 cases (20 proven) in each of the 4 treatment groups, together with the results for identification of bacteria in proven cases, is shown in Figure 1. (Further details of the microbiological results will be presented in a future publication.) One additional unproven case presented evidence of TASS at the same time as 3 non-study cases in 1 unit. This case was reclassified as TASS and was excluded from analysis.

Incidence rates and their associated CIs for the ITT and the PP data sets are shown in Figure 2. For the ITT data set, the highest incidence rates were in Group

Group A	Group B
Intent to Treat Number of patients 4054 ***Incidence Rates (%)*** Total: 0.345 (95% CI, 0.119-0.579) Proven: 0.247 (95% CI 0.118-0.453) **Per Protocol** Number of patients 3990 ***Incidence Rates (%)*** Total: 0.326 (95% CI, 0.174-0.557) Proven:0.226 (95% CI, 0.103-0.428)	**Intent to Treat** Number of patients 4056 ***Incidence Rates (%)*** Total: 0.074 (95% CI, 0.015-0.216) Proven: 0.049 (95% CI, 0.006-0.178) **Per Protocol** Number of patients 3997 ***Incidence Rates (%)*** Total: 0.075 (95% CI, 0.016-0.219) Proven: 0.050 (95% CI, 0.006-0.181)
Group C	**Group D**
Intent to Treat Number of patients 4049 ***Incidence Rates (%)*** Total: 0.247 (95% CI, 0.119-0.454) Proven: 0.173 (95% CI, 0.070-0.356) **Per Protocol** Number of patients 3984 ***Incidence Rates (%)*** Total: 0.251 (95% CI, 0.120-0.461) Proven: 0.176 (95% CI, 0.071-0.362)	**Intent to Treat** Number of patients 4052 ***Incidence Rates (%)*** Total: 0.049 (95% CI, 0.006-0.178) Proven: 0.025 (95% CI, 0.001-0.137) **Per Protocol** Number of patients 4000 ***Incidence Rates (%)*** Total: 0.050 (95% CI, 0.006-0.181) Proven: 0.025 (95% CI, 0.001-0.139)

Figure 2. Total patient numbers and endophthalmitis incidence rates in each of the 4 groups in the study based on ITT and PP analysis (CI = confidence interval).

A (placebo drops, no intracameral injection), where the observed rate for total endophthalmitis was 0.345% and for proven endophthalmitis, 0.247%. The associated 95% CIs were 0.119% and 0.579% for total endophthalmitis and 0.118% and 0.453% for proven endophthalmitis. These intervals may be interpreted as lower and upper interval estimates of the current background incidence rate in Europe of infective postoperative endophthalmitis after phacoemulsification cataract surgery when no perioperative antibiotic prophylaxis was given. The lowest observed incidence rates were in Group D, which received both the intracameral cefuroxime and perioperative topical levofloxacin. These rates were 0.049% for total endophthalmitis and 0.025% for proven endophthalmitis.

The PP data set had almost identical incidence rates as the ITT data set in all treatment groups except for the group receiving no perioperative antibiotic prophylaxis, in which 1 additional proven case of endophthalmitis that did not comply fully with the protocol was present in the ITT data set.

Risk Factors

From the patient report forms, many factors were available for investigation as potential sources of risk associated with the incidence of endophthalmitis (Table 1). In addition to comparisons of prophylactic regimen, over 40 factors, including surgical procedures and materials, were explored as potentially significant risk factors.

The results of the initial screening of these risk factors for an association with total endophthalmitis for the ITT data set are shown in Table 2. The effects of patient age and sex were included as forced covariates; the effects of the absence and presence of the 2 antibiotic treatments being tested in the study were also included. Each center (Hospital ID) and country were not included as risk factors as the associated regression analysis for each factor on its own failed to converge due to insufficient case numbers in each of the many subcategories for these variables. The remaining risk factors left for model building were those found on their own to be significantly associated with endophthalmitis at a P value less than 0.25. From Table 2, it can be seen that surgeon experience level, site of incision, type of IOL insertion, any surgical complications, IOL optic material, and IOL construction were thus initially identified as potential risk factors. Table 2 also shows the results when the analysis was restricted to proven cases. A similar set of potential risk factors was obtained at this initial screening with the exception of any surgical complications.

Table 3 shows the final results of the logistic regression analysis that, in addition to the forced covariates (age and sex) and the prophylactic interventions, lists key risk factors that were significantly ($P<.05$) associated with total endophthalmitis. The ORs obtained for factors were found to be stable in the absence of any other factor and robust in the absence of any single center. Factors found to be significant were site of incision, with patients receiving the clear corneal procedure being 5.88 times more likely to experience endophthalmitis than patients receiving a scleral tunnel; any surgical complications, with patients experiencing complications at time of surgery being 4.95 times more likely to experience endophthalmitis; cefuroxime injection, with patients not receiving cefuroxime being 4.92 times more likely to experience endophthalmitis than patients receiving cefuroxime; IOL optic material, with patients receiving a silicone IOL being 3.13 times more likely to experience endophthalmitis than patients receiving an acrylic (or other material) IOL; and surgeon experience level, with experienced surgeons being twice as likely to participate in an endophthalmitis case.

The results for proven endophthalmitis cases are also shown in Table 3. The same risk factors are identified as those for total endophthalmitis cases with the exception of surgical complications, which was no longer found to be significant. In addition, patient sex became significant, with men being 2.70 times more likely than women to have a proven endophthalmitis. In general, the ORs associated with proven cases were higher than those for total endophthalmitis cases. Identical risk factors with minor variations to the ORs were obtained for the PP data set.

DISCUSSION

When this study began, the only proven method of prophylaxis against infective endophthalmitis after cataract surgery was the administration of povidone–iodine preoperatively. The use of postoperative antibiotic drops was also considered to be of benefit. The results in this study indicate that for patients in Europe for whom these are the only methods of prophylaxis used, the incidence of total endophthalmitis is centered on a rate as high as 0.35%. This may be regarded as high for a "background" rate; however, rates reported in other studies have often been for patients receiving various additional forms of prophylaxis, some of which have, no doubt, been of benefit. The results presented here also indicate that with the prophylactic use of intracameral cefuroxime, the incidence rate can be reduced to a level below 0.08%.

The techniques used in this study for determining whether an infective organism was present or not are the best currently available. However, no methods for detecting infection are infallible and any specimen

Table 1. Study demographics showing variables explored as potential risk factors associated with endophthalmitis in patients recruited to the study.

Grouping and Potential Risk Factors	Class (% Patients)
Environmental	
Country	Austria (15), Belgium (9), Germany (3), Italy (6), Poland (2), Portugal (15), Spain (11), Turkey (5), U.K. (34)
Hospital ID	1 … 24 centers
Theater air flow	<6 (2.5), 6–13 (5), 13-34 (57.5), >34 (28), unknown (7) changes hr^{-1}
Time	
Date of operation	Day, month, and year
Time operation started	24-hour clock
Operation duration	Minutes
Patient data	
Age	Years
Sex	Female (58), male (42)
Diabetic (patient self-report)	No (86), yes (14)
Disease data	
Cataract cause	Senile (82), induced (3), other (5), unknown (10)
Cataract type	Mixed (39), nuclear sclerosis (27), other (24), unknown (10)
Clinician data	
Surgeon sex	Male (80), female (20)
Surgeon age range	20–29 (7), 30–39 (40), 40–49 (25), >50 (28) years
Surgeon experience level	[1] <100 (15), [2] 100–500 (20), [3] >500 (65) cataract operations performed in career
Treatment data	
Treatment group	A (25), B (25), C (25), D (25) (see Figure 1)
Cefuroxime injection vs none	B + D (50) vs A + C (50)
Periop levofloxacin vs none	C + D (50) vs A + B (50)
Surgical procedure	
Shared operation	No (93), yes (7)
Day/overnight case	Day (72), overnight (18), unknown (10)
Left or right eye	Left (50), right (50)
First or second cataract	First (60), second (30), unknown (10)
Anesthesia procedure	Topical (50), retrobulbar (18), sub-Tenon's (16), other (16)
Number of OVDs	One (66), two (34)
Incision size	Millimeters
Incision site	Clear corneal (82), scleral tunnel (18)
Incision position	Superior (43), temporal (35), oblique (22)
Type of IOL insertion	Injector (55), forceps (45)
Wound closure type	None (91), single stitches (7), other (2)
Occlusion	Yes (56), no (34), unknown (10)
Additional intraocular drugs	Yes (52), no (38), unknown (10)
Surgical complications	No (95), yes (5)
Surgical materials	
OVDs	Healon group (25), Provisc (23), other (52)
Tubing system	Disposable (70), reusable (20), unknown (10)
Irrigation fluid	BSS (59), Ringer's (20), BSS Plus (11), unknown (10)
IOL type	Multipiece (52), 1-piece (48)
IOL optic material	Acrylic (74), silicone (25), PMMA (0.5), unknown (0.5)
IOL haptic material	PMMA (49), acrylic (48), PVDF (2.8), unknown (0.5)
IOL power	Diopters
Hydrophobic/hydrophilic IOL	Hydrophobic (80), hydrophilic (19), unknown (1)

BSS = balanced salt solution; BSS Plus = fortified balanced salt solution; Healon = sodium hyaluronate 1.0%; IOL = intraocular lens; OVD = ophthalmic viscosurgical device; PMMA = poly(methyl methacrylate); Provisc = sodium hyaluronate 1.0%; PVFD = polyvinylidene fluoride

Table 2. Results after univariate screening of all variables based on the ITT data set showing all those identified as potential risk factors ($P < .25$) for total and proven endophthalmitis and made available for binary logistic regression analysis.

Variable	Categorical (C) or Scale (S) (Number of Levels)	Levels	Total Endophthalmitis			Proven Endophthalmitis		
			Numbers of Patients		Likelihood Ratio Test *P* Value	Numbers of Patients		Likelihood Ratio Test *P* Value
			Cases	Non Cases		Cases	Non Cases	
Patient age*	S	Years	29	16173	.254	20	16182	.739
Patient sex*	C	Female	13	9446	.142	7	9452	.034
		Male	16	6727		13	6730	
Surgeon experience level	S	1,2,3	29	16173	.040	20	16181	.016
Site of incision	C	Scleral tunnel	2	3018	.069	1	3019	.071
		Clear corneal	27	13143		19	13151	
Type of insertion	C	Forceps	17	7213	.136	12	7218	.173
		Injector	12	8895		8	8899	
Any surgical complications†	C	Absent	25	15444	.048			
		Present	4	717				
IOL optic material	C	Acrylic etc	16	12009	.024	10	12015	.019
		Silicone	13	4100		10	4103	
IOL construction	C	1 piece	10	7712	.145	7	7715	.245
		Multipiece	19	8395		13	8401	
Cefuroxime injection††	C	Present	5	8103	< .0005	3	8105	.001
		Absent	24	8079		17	8086	
Perioperative levofloxacin eye drops††	C	Present	12	8089	.353	8	8093	.371
		Absent	17	8093		12	8098	

*Forced demographic covariates
†Not a candidate factor for proven infective endophthalmitis cases
††Primary study objectives

collection process is prone to error; therefore, the 9 unproven cases represent an area of uncertainty in which it is likely that some cases were infected while others were not. The authors are confident that none was likely to be due to TASS as this was actively monitored and the 1 unproven case linked to a TASS incident was removed from the group. Thus, the rate of endophthalmitis infection occurring within Europe under the mix of interventions present within this study is estimated to lie between that reported for the proven infective cases (0.12%) and that reported for the total cases (0.18%). It is of interest that in a recent retrospective cohort study reported from the United States, involving patients given a range of antibiotic prophylaxis, almost identical overall incidence rates were reported for total and proven infective endophthalmitis cases.[5]

In this study a clear result was obtained in that 1 of the 2 prophylactic regimens being investigated, namely intracameral injection of cefuroxime 1 mg in 0.1 mL normal saline, was shown to have a statistically significant beneficial effect in reducing the risk for endophthalmitis after cataract surgery by phacoemulsification. The finding, that in the absence of cefuroxime administration there is a 5- to 6-fold increased risk for endophthalmitis, is in line with results reported from Sweden.[6] In addition, the rate of infection reported from Sweden based on 151 874 operations with administration of intracameral antibiotics from 1999 to 2001 was 0.053%,[7] which is consistent with the rates of 0.037% and 0.062% observed in the study reported here for patients receiving intracameral cefuroxime for proven and total endophthalmitis infections, respectively.

In addition to the administration of intracameral cefuroxime at the time of surgery, other important factors associated with a reduction in the risk for endophthalmitis were the use of acrylic material for the IOL optic and the choice of scleral tunnel as the site of incision.

The finding that silicone as the IOL optic material was associated with a significantly increased risk for

Table 3. Final binary logistic regression models of the risk factors for total and proven endophthalmitis cases based on the ITT data set showing the forced covariates and primary study objectives included in the model together with other significant risk factors. Categorical factors included in the model (all binary) are shown with their estimated ORs (including a 95% CI) and the associated *P* values. Scaled covariates included are shown with their estimated ORs and the associated 95% CIs per unit of scale.

Risk Factor	Categorical (C) (Referent Category First) or Scaled (S)	Total Endophthalmitis Cases		Proven Endophthalmitis Cases	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Patient age*	S (years)	1.02 (0.98-1.06)	.311	1.01 (0.96-1.05)	.773
Patient sex*	C (female, male)	1.79 (0.86-3.75)	.121	2.70 (1.07-6.8)	.035
Surgeon experience level	S (1,2,3)	2.01 (1.02-4.0)	.046	2.86 (0.99-8.28)	.053
Site of incision	C (scleral tunnel, clear corneal)	5.88 (1.34-25.9)	.019	7.43 (0.97-57.0)	.054
Any surgical complications	C (absent, present)	4.95 (1.68-14.6)	.004	—	—
IOL optic material	C (acrylic, silicone)	3.13 (1.47-6.67)	.003	4.10 (1.66-10.1)	.002
Cefuroxime injection†	C (present, absent)	4.92 (1.87-12.9)	.001	5.86 (1.72-20.0)	.005
Levofloxacin perioperative eyedrops†	C (present, absent)	1.41 (0.67-2.95)	.368	1.51 (0.62-3.7)	.368

CI = confidence interval; IOL = intraocular lens; OR = odds ratio
*Forced covariate
†Primary study objective

endophthalmitis (between 3- and 4-fold) is of particular interest because this factor is clearly under the control of the clinician. The suggestion that such an association might exist dates back to the early 1990s.[8] This was supported by work of Bainbridge et al.,[9] who in providing a comprehensive summary of both clinical and experimental investigations state that "the findings in this series add weight to existing evidence supporting an association between the use of SPP (silicone polypropylene) IOLs and an increased risk of postoperative endophthalmitis." More recently, a randomized trial in Japan[10] appeared to find that silicone IOLs were not associated with increased risk. Unfortunately, the design of this trial was unbalanced and did not allow for proper assessment of IOL optic material as a risk factor. Another recent study of endophthalmitis infections in Asian patients[11] found a similar result to that reported here, with operations using silicone IOLs being associated with increased rates of infection of 4.3 times and 8.0 times for total cases and culture positive cases, respectively. The work of Montan et al.[12] in Sweden sounds a note of caution with respect to IOL optic material as a risk factor. In their study of endophthalmitis cases in 1998, they found that acrylic IOLs were associated with significantly lower rates than other IOL types, including silicone. However, on reviewing the situation over the succeeding 3 years, they concluded that "no IOL material was associated with a significantly increased risk of postoperative endophthalmitis."[7]

It has been suggested that the apparent increased risk for endophthalmitis incurred by the use of silicone as the IOL optic material may be due to the hydrophobic nature of silicone.[11] The hydrophobic characteristics of IOLs was investigated after determining which IOLs used in the study with acrylic as the optic material were hydrophilic and which were hydrophobic. The data provided no evidence ($P = .82$ and $P = .66$ for total and proven endophthalmitis cases, respectively) that this characteristic of the IOL optic material, when separated from its association with silicone, is a significant risk factor for endophthalmitis. The explanation is likely more subtle, involving an understanding of how differing biofilms are formed based on the surface properties of varying types of IOLs.[9]

The currently popular clear corneal incision (CCI) was found to be associated with a significantly higher risk for endophthalmitis, a result supported by other recent findings.[10,13–15] An excellent survey of the evidence to date is provided by Nichamin et al.[16] However, there was no evidence in the current study to support the hypothesis that temporal incision placement was associated with an increased risk.[10,16] Although the risk associated with CCIs remains an important finding in this study, the result must be treated with caution. Only 2 participating centers used scleral tunnel incisions routinely, with none of the others using it more than occasionally. It is therefore conceivable that the reduced risk associated with the scleral tunnel technique is due to some other unidentified factor common to both centers but absent from most other centers in the study.

In the course of analysis, consideration was given to type of IOL insertion (ie, forceps or injector). However, in this study, type of insertion was highly correlated

with the site of incision (scleral tunnel or clear corneal). Careful examination of these factors in models including each separately, as well as both together, clearly showed that the evidence pointed to site of incision as the more important risk factor. Type of insertion was not therefore retained as a risk factor in the final model. This contrasts with the finding reported by Mayer et al,[17] that injectable IOLs can lower incidence rates. This retrospective study attempted to consider factors over a 10-year period during which several related variables altered, and in the light of evidence from the current study, it seems likely that some level of confounding would be present.

Surgical complications during surgery were strongly associated with total endophthalmitis cases. This is perhaps not a surprising finding and is in agreement with reports in several other recent studies.[5,11] However, in both studies, the specific complication noted was a torn posterior capsule. There was no evidence of this specific association in the present study, in which approximately 330 torn posterior capsule incidents were recorded but was linked to an endophthalmitis infection in only 1 case. In addition, the surgical complications association did not hold when only proven cases were considered.

It was also shown that surgeon experience had a marginally significant association with the incidence of total and proven endophthalmitis. This may suggest that experienced surgeons are more likely to be involved in more complicated cases, including those that result in endophthalmitis.

The sex of the patient showed some evidence of being a risk factor, with men almost twice as likely to experience proven endophthalmitis. This is in contrast to an earlier finding based on an outbreak at a Scottish hospital,[18] in which women were more at risk, which was also the case for culture-positive cases in a case-control study in Singapore.[11]

Several variables that have been shown or suggested by previous studies to be risk factors were not found to be so in the present study. One of the earliest large-scale epidemiological reviews of postoperative endophthalmitis[19] found a significantly higher rate of infection after ECCE in diabetic patients. However, in common with several recent studies based on populations of Asian patients,[10,11] no evidence was found in the current study that diabetic status was a risk factor. Wound closure and the use of sutures has also been suggested as a potential risk factor[5,16]; however, as in another recent study[11] there was no evidence of an association in the data analyzed here.

Although increased age is associated with an increased prevalence of cataract,[20] the age of patients was not found to be a risk factor for endophthalmitis. It has been suggested that outpatient versus inpatient surgery or IOL design might be risk factors,[13] but no evidence of such associations was found in this study. In addition, the use of levofloxacin 0.5% eyedrops perioperatively was not found to reduce the risk for endophthalmitis. The study was not designed to assess the effectiveness of using levofloxacin postoperatively as all groups were administered this antibiotic. That 2 of the groups (A and C) had what would be considered to be relatively high incidence rates might suggest that levofloxacin used postoperatively confers little benefit. Alternatively, it may be that had this antibiotic not been included in this study, the rates across all groups would have been higher.

In summary, the results clearly show that endophthalmitis is a multifactorial problem with associations to risk factors that depend on the attributes of the patient, the clinician, the antibiotic treatment, the surgical procedure, and the IOL materials used. Given this complexity, it is gratifying to find that whether total cases or only the proven cases are considered, the main substantive findings in the study remain unchanged and there are only small changes to the final estimates of risk. Assuming a conservative average of 2.5 million cataract operations per year[21,22] and a background incidence rate (without the use of perioperative antibiotics) of 0.3%, 75 000 cases of endophthalmitis could be expected to occur in Europe during the next 10 years. Based on these assumptions, the introduction of perioperative intracameral cefuroxime in cataract surgery across Europe could reduce the number of endophthalmitis infections by approximately 60 000 cases over the coming decade. If the additional factors identified are causes of increased risk, avoidance of silicone IOLs and the use of a scleral tunnel incision rather than a CCI would result in an even more marked reduction.

APPENDIX

The ESCRS Endophthalmitis Study Group

Study Investigators and Management Team Peter Barry (study chairman), Royal Victoria Eye & Ear Hospital and St. Vincent's University Hospital, Dublin, Ireland; George Gettinby, Fiona Lees, Magnus Peterson, Crawford Revie, Department of Computer and Information Sciences/Department of Statistics and Modelling Science, University of Strathclyde, Glasgow, Scotland; David Seal (study coordinator), Applied Vision Research Centre, City University, London, England; Mary D'Ardis, Betsan Bradley (study administration), ESCRS, Dublin, Ireland.

Clinical Partner Ophthalmologists

Austria: Guenther Grabner, Stefan F. Egger, Josef Ruckhofer, University Eye Clinic, Paracelsus Private Medical University, Salzburg.

Belgium: Johan Blanckaert, Jan Yperman Ziekenhuis, Campus Zwarte Zuster, Ieper; Camille Budo, Oogheelkunde, Melveren;

Albert Galand, Jessica Crommen, Jean Rakic, Gaël Xhauflaire, Centre Hospitalier Universitaire, Liège; Marie-José Tassignon, UZA Ophthalmology, Edegem; Hugo Verbraeken, Rita de Donker, Universitair Ziekenhuis, Gent.

Germany: Stefanie Schmickler, Augenklinik Ahaus, Ahaus.

Italy: Roberto Bellucci, Simonetta Morselli, Sandro Soldati, Ospedale Borgo Trento, Verona; Fausto Vigasio, Marco Bertelli, Andrea Bottoli, Marta Cassamali, Fabrizio Danieli, Samer Khuri, Luigina Rosa, Azienda Ospedaliera di Desenzano del Garda, Desenzano del Garda.

Poland: Jerzy Szaflik, Justyna Izdebska, Jacek P Szaflik, Department of Ophthalmology, Medical University of Warsaw, Warsaw.

Portugal: Conceição Lobo, José Cunha-Vaz, Joaquin Mira, Department of Ophthalmology, University Hospital, Coimbra.

Spain: Augusto Abreu, Jose Aguilar, Victor Arteaga, Luis Cordovés, Valentin T Díaz-Aleman, Manuel Gonzalez de la Rosa, Cristina Mantolan, Servicio de Oftalmologia, Hospital Universitario de Canarias, Tenerife; Pedro Abreu, Jorge Alvarez-Marin, Maria Antonia Gil, La Candelaria University Hospital, Tenerife; Jorge Alió, Instituto Oftalmologico VISSUM, Alicante; Miguel Teus, MT Alvarez, JM Román, Hospital Oftalmologico Internacional, Madrid.

Turkey: Süleyman Kaynak , Osman Saatcý, Ýsmet Durak, Üzeyir Günenç, Tülin Berk, Meltem Söylev, Hakan Öner, Nilüfer Koçak, Mehmet Ergin, Dokuz Eylul University, Izmir.

United Kingdom: David Allen, Peter Phelan, David Steel, Chris Wood, Sunderland Eye Infirmary, Sunderland; Carol Cunningham, Michael Miller, Ramesh Moorthy, Andleeb Zafar, Moorfields Eye Outreach Unit, Northwick Park Hospital, Harrow; Alex Ionides, Damian Lake, Graham Thompson, Moorfields Eye Outreach Unit, St. George's Hospital, London; John Jacob, Daniel Byles, Casper Gibbon, Andrew Kleinschmidt, Roland Ling, Anthony Quinn, Peter Simcock, George Sturrock, West of England Eye Unit, Royal Devon & Exeter Hospital (Wonford), Exeter and Axminster Hospital, Axminster; William Kiel, Ipswich Hospital, Ipswich; Denise Mabey, David Spalton, Anupma Kumar, Department of Ophthalmology, St. Thomas' Hospital, London; Paul Rosen, CK Patel, John Salmon, Oxford Eye Hospital, Oxford.

Ophthalmology Nurse Managers and Administrative Assistants

Belgium: Eveline Callens, Gent; Danny Mathysen, Antwerp; Françoise Molemans, Gérald de Rassenfosse, Christel Schenkeveld, Melveren.

Germany: Andrea Eckelmann, Andreas Haselhoff, Ahaus.

Poland: Renata Franczuk, Warsaw.

Portugal: Liliana Carvalho, Ana Catarina, Coimbra.

Spain: Laurent Bataille, Elena Jiménez, Alicante; Ana Martín de Nicolás, Madrid.

Turkey: Hakan Kuheylan, Izmir.

United Kingdom: Sue Bovill, Ian Tate, Sunderland; Suzanne Cabral, Tim Withers, London; Deborah Cox, Trudi Yeates, Exeter and Axminster; Jean Dash, Linda Lindsell, Rebecca Turner, Oxford.

Molecular and Microbiologists

Consuelo Ferrer, Instituto Oftalmologico VISSUM, Alicante, Spain; Roland Koerner, Sunderland Royal Hospital, Sunderland, England; Udo Reischl, Anke Behr, University of Regensburg, Regensburg, Germany.

Data Monitoring Committee

Stephen Barrett (chairman), Charing Cross Hospital, London, England; Susanne Gardner, Clinical Research, Atlanta, Georgia, USA; Susan Kennedy, National Ophthalmic Pathology Laboratory, Royal Victoria Eye and Ear Hospital, Dublin, Ireland; John Ludgate, London, England; Per Montan, St. Erik's Hospital, Stockholm, Sweden; Kirk Wilhelmus, Department of Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston, Texas, USA.

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