Title - Endophthalmitis After Clear Corneal Cataract Surgery: Outcomes Over Two Decades

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INTRODUCTION

Large nationwide surveys and case series in different countries estimate that the incidence of post-cataract endophthalmitis is between 0.012% and 1.3%.¹ Although infrequent, acute-onset endophthalmitis after cataract surgery may cause substantial morbidity. The purpose of the current study was to describe the causative organisms and visual outcomes associated with acute-onset endophthalmitis occurring between 2006 and 2015. Furthermore, this data was compared to the prior retrospective study from 1996-2005 conducted at the same institution.² Finally, the sensitivities of the bacterial isolates to commonly used prophylactic antibiotics were analyzed and reported.

METHODS

The study was approved by the Institutional Review Board (IRB) of the University of Miami School of Medicine. Clinical and microbiology records were reviewed for all patients who presented to Bascom Palmer Eye Institute between January 1, 2006 and December 31, 2015 with clinically diagnosed, culture-positive endophthalmitis occurring after clear corneal cataract surgery. The study included patients who had cataract surgery at Bascom Palmer Eye Institute as well as those who underwent surgery at outside hospitals or community practices and were referred for endophthalmitis. In the current and prior studies, endophthalmitis was defined by clinical diagnosis, a positive culture, and treatment with intravitreal antibiotics. Patients were excluded if they had non-clear corneal cataract surgery or combined procedures. Treatment at the time of diagnosis was at the discretion of the treating physician with influence from the results of the Endophthalmitis Vitrectomy Study (EVS).³ Presenting features and outcomes in the current series were then compared to the series from the prior decade.²

Cultures were obtained either by direct vitreous aspiration with a 23 or 25 gauge needle or sent from the vitrectomy cassette. There were no dry taps. Direct vitreous cultures were inoculated directly onto chocolate, 5% sheep blood agar (anaerobic), Sabouraud Dextrose Agar and Thioglycollate broth in the clinic or delivered to the laboratory in a syringe for direct plating. Vitrectomy wash samples were transferred to the microbiology lab for processing. From the vitrectomy bag, 30-50cc was passed through a 0.45 filter, sectioned, and placed on chocolate agar, 5% sheep blood agar, anaerobic blood agar, Sabouraud Dextrose Agar, Thioglycollate broth, and glass slide for smear. An additional 10cc was injected into a 70cc blood culture bottle. Chocolate and blood agar plates were kept for 7 days. Thioglycollate and Sabouraud Dextrose Agar were kept for 14 days. Chocolate agar, 5% sheep blood agar and Thioglycollate broth were incubated at 35 degrees Celsius in carbon dioxide. Sabouraud Dextrose Agar plates were incubated at 35 degrees Celsius without carbon dioxide. All statistical comparisons between categorical variables were conducted by using a Fisher's exact or Pearson's test. Continuous variables such as logMAR visual acuity (VA) were compared using a two-

sample t-test. For the purposes of calculating average logMAR VA, numerical values for count fingers, light perception, or no light perception vision were assigned as described previously.⁴⁻⁵ All analyses were performed in SPSS Version 22 (SPSS Inc., Chicago, IL).

RESULTS

Current Decade, 2006-2015

In the current study, there were 63 eyes of 63 patients. Thirty-six (57%) of 63 were right eyes. Thirty-five (56%) of 63 patients were male. The average age at diagnosis was 75 (range, 51-95). Nine (14%) of 63 eyes received their surgery at Bascom Palmer Eye Institute, while the remaining 54 (86%) eyes were referred. The average length of follow-up after endophthalmitis was 13.8 months (median 5.5 months, range 1 day – 64.3 months). Corneal wound sutures were present in 7 (11%) of 63 eyes at the time of diagnosis. Posterior capsule rupture was documented in 6 (10%) of 63 eyes. Hypopyon was present in 57 (90%) of 63 eyes. Presenting VA was 5/200 or better in 7 (11%) of 63 eyes and light perception only in 14 (22%). The average time from cataract surgery to presentation with endophthalmitis was 8 days (median 6, range 1-34). Of the 63 eyes, 40 (63%) presented within 7 days after surgery, 21 (33%) presented between 8 and 24 days after surgery, and 2 (3%) presented more than 24 days after surgery. There was no difference between the average time to presentation of eyes that ended with visual acuity of 20/100 or better and those that ended with visual acuity of worse than 20/100 (7.5 days versus 7.8 days, $p=0.850$). Additional presenting features can be found in Table 1.

Gram-positive organisms were isolated in 61 (97%) of 63 eyes, while two eyes (3%) showed gram-negative organisms. The most common isolates were coagulase-negative *Staphylococcus* (39/63 eyes, 62%), *Streptococcus* species (7/63 eyes, 11%), and *S. aureus* (7/63 eyes, 11%). Other isolates included other *Staphylococcus* species (3/63 eyes, 5%), *Enterococcus* (3/63 eyes, 5%), *Propionibacterium* (2/63 eyes, 3%), *Pseudomonas* (1/63 eyes, 2%), and *Serratia* (1/63 eyes, 2%). There were no cases caused by multiple culture-positive organisms. Of note, the median time to presentation for coagulase-negative *Staphylococcus* was 6 days, *S. aureus* 6 days, *Streptococcus* species 7 days, gram-negative organisms 7 days, and other gram-positive organisms 4 days.

All 57 isolates which were tested for vancomycin were sensitive. Twenty-six of 51 isolates (51%) were sensitive to Ceftazidime. Twenty-four of 49 isolates (49%) were sensitive to Cefazolin, Cephalothin, and Cefuroxime. Sensitivity to fluoroquinolones included 22/52 (42%) to levofloxacin, 20/54 (37%) to ciprofloxacin, 16/47 (34%) to moxifloxacin, and 3/13 (23%) to gatifloxacin. Of the eyes where sensitivities were reported, 60/60 (100%) were sensitive to at least one of the initially chosen antibiotics.

Intravitreal vancomycin (1mg/0.1mL) and ceftazidime (2.25mg/0.1mL) were used for treatment in 59 (94%) of 63 eyes. Four (6%) of 63 eyes were treated with intravitreal vancomycin and amikacin (0.4mg/0.1mL). Fifty (79%) of 63 eyes also received intravitreal dexamethasone (0.4mg/0.1mL). Fifty-seven (90%) of 63 eyes were treated with initial vitreous tap and injection of intravitreal antibiotics while 6 (10%) of 63 eyes were treated with initial pars plana vitrectomy (PPV) and intravitreal antibiotics.

Twenty-four (38%) of 63 eyes had VA better than or equal to 20/40 at last follow up. Forty-five eyes (71%) had VA of 5/200 or better at last follow up. Visual outcomes are summarized in Table 2. Visual acuity outcomes were most favorable with coagulase-negative *Staphylococcus* with 20 (51%) of 39 eyes achieving 20/40 or better. In contrast, eyes that had *S. aureus* or *Streptococcus* species achieved less favorable visual outcomes with 1 (14%) of 7 eyes and 3 (43%) of 7 eyes with 5/200 or better respectively (Table 3). Of the 57 eyes treated initially with tap and inject, 23 (40%) achieved vision of 20/40 or better in comparison to only 1 (17%) of 6 eyes treated with PPV as the initial treatment (Table 4). Average logMAR VA at initial presentation was worse in the eyes treated with PPV and inject than with tap and inject (2.63 versus 2.12 logMAR eq., $p=0.032$). While average final logMAR VA was worse in the eyes treated with PPV in comparison to those treated with tap and inject, the difference was not statistically significant (1.55 logMAR eq. versus 0.96, $p=0.17$). Furthermore, while the absolute change in logMAR VA between initial presentation and last follow up was greater in the eyes treated with tap and inject than those treated with PPV and inject, this difference was also not statistically significant (1.16 logMAR eq. versus 1.08, $p=0.851$).

Comparison to Prior Decade, 1996-2005

The number of patients presenting with 5/200 or better was similar in the prior and current study (Table 1), but mean time to presentation was shorter in the current decade (8 versus 13 days). The overall distribution of organisms was similar between the two decades with coagulase-negative *Staphylococcus* comprising the majority of cases. While 19 (26%) of 73 eyes were treated with PPV as the initial treatment in the prior decade, only 6 (10%) of 73 eyes were treated with PPV as the initial treatment in the current decade ($p=0.013$). Final visual outcomes were slightly more favorable in the prior decade with a larger proportion of patients achieving 20/40 and 20/100 or better although these differences were not statistically significant ($p=0.189$ and $p=0.058$ respectively) as shown in Table 2. There was, however, a statistically significant difference in the percentage of eyes ending with 5/200 or better (63 of 73 eyes, 86%, in the prior decade versus 45 of 63 eyes, 71%, in the current decade, $p=0.032$). Of the eyes with coagulase-negative *Staphylococcus* 31 (62%) of 52 eyes achieved 20/40 or better in the prior study in comparison to 20 (51%) of 39 in the current study, $p=0.310$ (Table 3). Both patients treated with tap and inject as the initial treatment and those treated with PPV and inject as the upfront treatment fared slightly worse than the prior study with fewer achieving 20/40 or 20/100 or better (Table 4).

DISCUSSION

Presenting features and causative organisms of endophthalmitis with clear corneal cataract surgery have remained similar over the past two decades. Time to presentation was 8 days in the current study, slightly shorter than the prior decade but similar to the data reported from the EVS (6 days). Gram-positive infections continued to be the most prevalent with coagulase-negative *Staphylococcus* comprising over 50% of cases.

Previously unreported in the series from the prior decade were resistance patterns among isolates. Of note, all the isolates tested in the current series were sensitive to vancomycin but less than half of the isolates tested were sensitive to cephalosporins or a range of fluoroquinolones including moxifloxacin. A recent study from Taiwan also showed pan vancomycin sensitivity in acute postoperative cataract endophthalmitis cases, although fluoroquinolones were not widely tested. Furthermore, the series was predominantly *Enterococcus* (38%).⁶ Although vancomycin resistant organisms have been described post-cataract surgery, they remain rare.⁷

The use of intracameral antibiotics at the time of cataract surgery (vancomycin, cephalosporins, or fluoroquinolones) is controversial. Some studies have reported an association between the use of intracameral antibiotics and a lower rate of post-surgical endophthalmitis.⁸⁻¹² Potential complications associated with the use of intracameral antibiotics have also been described including postoperative hemorrhagic occlusive retinal vasculitis which may be associated with the use of intracameral vancomycin and although rare, has had poor visual outcomes.¹³ To our knowledge, none of the referred cases in the current series had received prophylactic intracameral antibiotics. However, complete operative reports were not available for all of these cases. In all of the cases originating at our institution, none had received intracameral antibiotics.

Data from the current study also shows a trend towards a lower rate of utilization of initial PPV. The rate of primary PPV was 64% lower than the prior decade. A range of factors could have contributed to this difference including medical comorbidities, operating room availability, and corneal opacities obscuring a view for PPV. The patients treated with PPV in the current series did not have better final VA or change in VA from initial presentation compared to the tap and inject group, but this was not a randomized study so other selection biases are possible. Although there was smaller percentage of patients in the current decade with final VA of 5/200 or better, it does not appear to be attributed to a lower utilization of PPV.

Differences in the distribution of comorbid glaucoma and macular disease between the two decades may have contributed to differences in outcomes. These patient characteristics could not be used as exclusion criteria as the information was not available for many of the referred cases both in this and the prior study. Data were not directly compared to that of the EVS due to the more extensive inclusion and exclusion criteria of that study (e.g. the inclusion of culture negative cases, the exclusion of eyes

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4 with pre-existing maculopathy reducing VA to < 20/100, and the exclusion of eyes with
5 corneal opacities interfering with a view for PPV). Other factors may have played a role
6 in the differences in visual acuity outcomes between the two decades, for instance the
7 shorter time to presentation in the current decade which could have represented more
8 virulent organisms.
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11 Limitations of the current study include the analysis of culture positive cases only, its
12 retrospective design, and the absence of complete information on the utilization of
13 perioperative or postoperative prophylactic intracameral or topical antibiotics in the
14 referred cases. In addition, there was incomplete data on ophthalmic comorbidities prior
15 to surgery as well as no defined protocol for determining whether to select initial tap and
16 inject or vitrectomy.
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20 In conclusion, the presenting clinical features, demographic patterns, causative
21 organisms, and visual outcomes of patients with acute onset postoperative
22 endophthalmitis following cataract surgery were similar over the past two decades.
23 Furthermore, in the current study, a number of isolates were found to have resistance to
24 cephalosporins and fluoroquinolones.
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References

1. Cao H, Zhang L, Li L, Lo S. Risk factors for acute endophthalmitis following cataract surgery: a systematic review and meta-analysis. *PLoS One*. 2013 Aug 26;8(8):e71731.
2. Lalwani GA, Flynn HW Jr, Scott IU et al. Acute-onset endophthalmitis after clear corneal cataract surgery (1996-2005). Clinical features, causative organisms, and visual acuity outcomes. *Ophthalmology*. 2008 Mar;115(3):473-6.
3. 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. *Arch Ophthalmol*. 1995 Dec;113(12):1479-96.
4. Bach M, Schulze-Bonsel K, Feltgen N, Burau H, Hansen L. Author response: Numerical imputation for low vision states [electronic letter] *Invest Ophthalmol Vis Sci*. 2007
5. Goldberg RA, Flynn HW, Jr. Isom RF, Miller D, Gonzalez S. An outbreak of streptococcus endophthalmitis after intravitreal injection of bevacizumab. *Am J Ophthalmol*. 2012;153(2):204-208. e1.
6. Teng YT, Teng MC, Kuo HK, et al. Isolates and antibiotic susceptibilities of endophthalmitis in postcataract surgery: a 12-year review of culture-proven cases. *Int Ophthalmol*. 2016 Jul 15.
7. Relhan N, Albin TA, Pathengay A et al. Endophthalmitis caused by Gram-positive organisms with reduced vancomycin susceptibility: literature review and options for treatment. *Br J Ophthalmol*. 2016 Apr;100(4):446-52.
8. Daien V, Papinaud L, Gillies MC et al. Effectiveness and Safety of an Intracameral Injection of Cefuroxime for the Prevention of Endophthalmitis After Cataract Surgery With or Without Perioperative Capsular Rupture. *JAMA Ophthalmol*. 2016 Jul 1;134(7):810-6.
9. Creuzot-Garcher C, Benzenine E, Mariet AS et al. Incidence of Acute Postoperative Endophthalmitis after Cataract Surgery: A Nationwide Study in France from 2005 to 2014. *Ophthalmology*. 2016 Jul;123(7):1414-20.
10. Herrinton LJ, Shorstein NH, Paschal JF et al. Comparative Effectiveness of Antibiotic Prophylaxis in Cataract Surgery. *Ophthalmology*. 2016 Feb;123(2):287-94.
11. Shorstein NH, Winthrop KL, Herrinton LJ. Decreased postoperative endophthalmitis rate after institution of intracameral antibiotics in a Northern California eye department. *J Cataract Refract Surg*. 2013 Jan;39(1):8-14.
12. Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons. Prophylaxis of postoperative endophthalmitis following cataract surgery: results of the ESCRS multicenter study and identification of risk factors. *J Cataract Refract Surg*. 2007 Jun;33(6):978-88.
13. Witkin AJ, Shah AR, Engstrom RE et al. Postoperative Hemorrhagic Occlusive Retinal Vasculitis: Expanding the Clinical Spectrum and Possible Association with Vancomycin. *Ophthalmology*. 2015 Jul;122(7):1438-51.

Tables

Table 1: Clinical Characteristics and Distribution of Isolates in Patients with Endophthalmitis After Clear Corneal Cataract Surgery

	Current Study 2006-2015 (n = 63)	Prior Study^a 1996-2005 (n = 73)
Baseline Visual acuity		
• >5/200 (%)	7 (11%)	12 (16%)
• Light Perception (%)	14 (22%)	11 (15%)
Presence of hypopyon (%)	57 (91%)	60 (82%)
Mean time to presentation (days)	8	13
PPV as initial treatment	6 (10%)	19 (26%) ^b
Causative organism		
• Coagulase-negative <i>Staphylococcus</i>		
• <i>Staphylococcus aureus</i>	39 (62%)	50 (68%)
• <i>Streptococcus</i> species	7 (11%)	5 (7%)
• Miscellaneous gram-positive organisms	7 (11%)	6 (8%)
• Gram-positive species	8 (13%)	5 (7%)
• Gram-negative species	61 (97%)	66 (90%)
• Gram-negative species	2 (3%)	7 (10%)

^a. Lalwani GA, Flynn HW Jr, Scott IU et al. Acute-onset endophthalmitis after clear corneal cataract surgery (1996-2005). Clinical features, causative organisms, and visual acuity outcomes. Ophthalmology. 2008 Mar;115(3):473-6.

^b. A chi-square test was used to compare the percentage of cases treated with PPV in the prior and current study (p=0.013).

VA = visual acuity, PPV = pars plana vitrectomy.

Table 2: Visual Acuity Outcomes at Last Follow-Up in Patients with Endophthalmitis After Clear Corneal Cataract Surgery

Visual Acuity	Current Study 2006-2015 (n = 63)	Prior Study^a 1996-2005 (n = 73)	p-value
≥ 20/40	24 (38%)	36 (49%)	0.189
≥ 20/100	35 (56%)	52 (71%)	0.058
≥ 5/200	45 (71%)	63 (86%)	0.032
NLP	4 (6%)	3 (4%)	0.704

- a. Lalwani GA, Flynn HW Jr, Scott IU et al. Acute-onset endophthalmitis after clear corneal cataract surgery (1996-2005). Clinical features, causative organisms, and visual acuity outcomes. Ophthalmology. 2008 Mar;115(3):473-6.

NLP = no light perception.

Table 3: Visual Acuity Outcomes by Causative Organism in Patients with Endophthalmitis After Clear Corneal Cataract Surgery

Current Study (2006-2015)				
Isolates (n)	≥ 20/40	≥ 20/100	≥ 5/200	NLP
Coagulase-negative <i>Staphylococcus</i> (39)	20 (51%)	27 (69%)	34 (87%)	0 (0%)
<i>Staphylococcus aureus</i> (7)	0 (0%)	1 (14%)	1 (14%)	2 (29%)
<i>Streptococcus species</i> ^a (7)	0 (0%)	1 (14%)	3 (43%)	1 (14%)
Other gram-positive species ^b (8)	4 (50%)	5 (63%)	6 (75%)	0 (0%)
Gram-negative species ^c (2)	0 (0%)	1 (50%)	1 (50%)	1 (50%)
Prior Study (1996-2005)^d				
Coagulase-negative <i>Staphylococcus</i> (50)	31 (62%)	43 (86%)	48 (96%)	0 (0%)
<i>Staphylococcus aureus</i> (5)	1 (20%)	0 (0%)	2 (40%)	1 (20%)
<i>Streptococcus species</i> (6)	0 (0%)	0 (0%)	4 (66%)	3 (50%)
Other gram-positive species (5) ^e	2 (40%)	2 (40%)	4 (80%)	0 (0%)
Gram-negative species (7) ^f	2 (29%)	3 (43%)	6 (86%)	0 (0%)

- Includes one unidentifiable *Streptococcus* species, *Streptococcus salivarius* (1), *Streptococcus sanguinis* (1), *Streptococcus constellatus* (1), *Streptococcus mitis* (2), and *Streptococcus viridans* (1).
- Includes *Pseudomonas aeruginosa* (1) and *Serratia marcescens* (1).
- Includes *Enterococcus faecalis* (3), *Propionibacterium acnes* (1), *Propionibacterium granulo-seem* (1), *Staphylococcus warneri* (1), and *Staphylococcus lugdunensis* (2)
- Lalwani GA, Flynn HW Jr, Scott IU et al. Acute-onset endophthalmitis after clear corneal cataract surgery (1996-2005). Clinical features, causative organisms, and visual acuity outcomes. Ophthalmology. 2008 Mar;115(3):473-6.
- Includes *Enterococcus faecalis*, *Gemella morbillorum*, and *Bacillus* species.
- Includes *Enterobacter*, *Stenotrophomoria maltophilia*, *Ochrobactrum*, *Moraxella catarrhalis*, and *Pseudomonas aeuroginosa*.

NLP = no light perception

Table 4: Visual Acuity Outcomes at Last Follow-up by Initial Treatment in Patients with Endophthalmitis After Clear Corneal Cataract Surgery

2006-2015				
Initial Treatment	≥ 20/40	≥ 20/100	≥ 5/200	NLP
Tap and inject (57)	23 (40%)	33 (58%)	42 (74%)	3 (5%)
PPV and inject (6)	1 (17%)	2 (33%)	3 (50%)	1 (17%)
1996-2005^a				
Tap and inject (54)	29 (54%)	41 (76%)	48 (89%)	2 (4%)
PPV and inject (19)	7 (37%)	11 (58%)	15 (79%)	1 (5%)

a. Lalwani GA, Flynn HW Jr, Scott IU et al. Acute-onset endophthalmitis after clear corneal cataract surgery (1996-2005). Clinical features, causative organisms, and visual acuity outcomes. Ophthalmology. 2008 Mar;115(3):473-6.

PPV = pars plana vitrectomy, NLP = no light perception