Endophthalmitis Isolates and Antibiotic Sensitivities: A 6-year Review of Culture-proven Cases

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• PURPOSE: To investigate the spectrum of organisms causing culture-proven endophthalmitis and their sensitivities to commonly used antimicrobial agents.
• DESIGN: Retrospective, noncomparative, consecutive case series.
• METHODS: Medical records were reviewed of all patients with culture-proven endophthalmitis at a single institution between January 1, 1996, and December 31, 2001. Endophthalmitis categories included postoperative, posttraumatic, endogenous, and miscellaneous (for example, keratitis). The outcome measures included intravitreal isolates identified, antibiotic sensitivities, and category of endophthalmitis.
• RESULTS: In all, 313 organisms were isolated from 278 patients during the study interval. The most common organisms identified were *Staphylococcus epidermidis* in 27.8% (87/313), *Streptococcus viridans* group in 12.8% (40/313), other coagulase-negative staphylococci in 9.3% (29/313), *Staphylococcus aureus* in 7.7% (24/313), and *Propionibacterium acnes* in 7.0% (22/313). Overall, 246 of 313 (78.5%) isolates were gram-positive organisms, 37 (11.8%) were gram-negative organisms, and 27 (8.6%) were fungi. For gram-positive organisms, sensitivities were the following: vancomycin 100%, gentamicin 78.4%, ciprofloxacin 68.3%, ceftazidime 63.6%, and cefazolin 66.8%. For gram-negative organisms, sensitivities were the following: ciprofloxacin 94.2%, amikacin 80.9%, ceftazidime 80.0%, and gentamicin 75.0%. Fungal isolates were *Candida* species (9/313), *Aspergillus* species (9/313), and other molds (9/313). Among the endophthalmitis categories, the most frequent organisms were the following: (1) acute-onset postoperative: *S epidermidis*, 46.9%; (2) delayed-onset postoperative: *S epidermidis*, 22.7%; (3) delayed-onset bleb-associated: fastidious gram-negative rods, 20.4%; (4) posttraumatic: *S epidermidis*, 20.8%; (5) endogenous: *Aspergillus* species, 20.8%; and (6) miscellaneous: molds (other), 36.4%.
• CONCLUSIONS: In considering antibiotic treatment of endophthalmitis, it is important to recognize that no single antibiotic provided coverage for all of the microbes isolated from eyes with endophthalmitis. Combination therapy is recommended as the initial empiric treatment of suspected bacterial endophthalmitis. Appropriate history and characteristic clinical features may justify the use of initial antifungal agents. Knowledge of the most frequent causative organisms in various categories will help direct appropriate initial therapy. (Am J Ophthalmol 2004;137:38–42. © 2004 by Elsevier Inc. All rights reserved.)

ENDOPHTHALMITIS IS A SERIOUS, SIGHT-THREATENING condition. Strategies for reducing the incidence of postoperative endophthalmitis include careful attention to preoperative preparation of the operative site with antiseptic agents such as povidone–iodine, preoperative hand scrubbing by surgeons and associated personnel involved in the case, perioperative maintenance of a sterile operative field, and use of selected prophylactic antibiotics. Treatment of endophthalmitis usually includes identification of the etiologic organisms through culture of intraocular fluids and prompt initiation of antibiotic therapy.

In previous studies of infectious agents causing endophthalmitis, the microbiologic spectrum has been reported to vary depending upon the clinical setting (for example, acute-onset postoperative, delayed-onset postoperative, bleb-associated, trauma, endogenous, miscellaneous).[1,2] Strategies for both prevention and treatment of endophthalmitis include evaluation of emerging bacterial strains resistant to frequently employed antibiotics and evaluation of the microbial spectrum of newer antimicrobial medications.

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The purpose of the current study is to investigate the spectrum of organisms causing culture-proven endophthalmitis (overall and by category of endophthalmitis) and their sensitivities to commonly used antimicrobial agents at the Bascom Palmer Eye Institute between 1996 and 2001.

DESIGN

THIS WAS A RETROSPECTIVE, NONCOMPARATIVE, CONSECUTIVE case series. The microbiology and medical records were reviewed of all patients with culture-proven endophthalmitis (positive culture from the vitreous cavity) at the Bascom Palmer Eye Institute between January 1, 1996, and December 31, 2001.

METHODS

THE STUDY WAS APPROVED BY THE INSTITUTIONAL REVIEW Board of the University of Miami School of Medicine Medical Sciences Subcommittee for the Protection of Human Subjects. All causative organisms were identified, and the clinical setting in which endophthalmitis developed was recorded. Susceptibility testing of the intraocular isolates was performed using an automated system—the VITEK (Automatic Microbial System; Biomerieux Vitek, Hazelwood, Missouri, USA) or the E test (A. B. Biodisk; NA, Remel, Lenexa, Kansas, USA).

RESULTS

IN THIS STUDY, 278 PATIENTS WITH CULTURE-PROVEN ENdophthalmitis were identified from the microbiology records of the Bascom Palmer Eye Institute; some of these patients had polymicrobial infections and, therefore, a total of 313 infecting organisms were identified during the 6-year study period. Overall, the most common organisms identified were *Staphylococcus epidermidis* in 87 of 313 (27.8%), *Streptococcus viridans* group in 40 of 313 (12.8%), other coagulase-negative staphylococci in 29 of 313 (9.3%), *Staphylococcus aureus* in 24 of 313 (7.7%), and *Propionibacterium acnes* in 22 of 313 (7%; Table 1). Study isolates included gram-positive organisms in 78.5%, gram-negative isolates in 11.8%, and fungi in 8.6%.

The antibiotic sensitivities of the most commonly identified endophthalmitis-causing organisms are shown in Table 2. Among the 246 gram-positive organisms identified, the sensitivities were the following: vancomycin 100%, gentamicin 78.4%, ciprofloxacin 68.3%, cefazolin 66.8%, and ceftazidime 63.6%. Among the 37 gram-negative organisms, the sensitivities were the following: ciprofloxacin 94.2%, ceftazidime 80%, amikacin 81%, and gentamicin 75%.

TABLE 1. Isolates From the Vitreous of Patients With Clinically Diagnosed Endophthalmitis

Vitreous Isolates, BPEI 1996–2001	Percent of Total	Number (n = 313)
Staphylococcus epidermidis	27.8%	87
Streptococcus viridans group	12.8%	40
Coagulase-negative *Staphylococcus* (other)	9.3%	29
Staphylococcus aureus	7.7%	24
Propionibacterium acnes	7.0%	22
Gram-negative rods (other)	5.1%	16
Enterococcus species	4.8%	15
Fastidious gram-negative rods	4.5%	14
Aerobic gram-positive rods	3.2%	10
Streptococcus pneumoniae	2.9%	9
Molds (other)	2.9%	9
Aspergillus species	2.9%	9
Candida albicans	2.9%	9
Streptococcus (other)	2.6%	8
Pseudomonas aeruginosa	2.2%	7
Mycobacteria species	1.0%	3
Corynebacterium species	0.6%	2

BPEI = Bascom Palmer Eye Institute.

Streptococcus viridans group: *S. salivarius, S. salivarius2, S. mitis, S. acidominimus, S. constellatus, S. anginous, S. intermidius.* Coagulase negative *Staphylococcus* (other): *S. haemolyticus, S. simulans, S. cohnii, S. warnerii, S. xylosus, S. sciuri, S. auricularis, S. hominis.* Fastidious gram-negative bacteria: *Moraxella* species, *Neiserria mucosa, Haemophilus influenzae, M. osolensis, N. meningitides. Enterococcus* species: *E. faecalis, E. gallinarium.* Aerobic gram-positive rods: *Corynebacterium minutissimum, Corynebacterium species, Bacillus cereus, Bacillus species, C. xerosis.* Gram-negative rods (other): *Proteus mirabalis, Serratia marcescens, Alcaligentes xylosoxidans, Pseudomonas maltophilia, Achromobacter species, P. cepacia. Aspergillus* species: *A. fumigatus, A. glaucus, A. terreus, A. niger. Streptococcus* species (other): *S. bovis, nonhemolytic Streptococcus, S. morbillorum.* Molds (other): *Philaphora veruccosa, Cladosporium* species, *Fusarium oxysporum, Fusarium species, Fonseca pedrosoi.* Mycobacteria species: *M. triplex, M. chelonae.*

Among the endophthalmitis categories, the microbiologic spectra of organisms are shown in Table 3. Gram-positive organisms make up the majority of organisms isolated in most settings. The bleb-associated category of endophthalmitis shows a high percentage of gram-negative isolates, however, and the endogenous category of endophthalmitis shows a significant percentage of fungi.

The clinical settings in which culture-proven endophthalmitis occurred are shown in Table 4. The most common settings during the 6 years of the study were the following: acute postoperative in 103 of 278 (37%), chronic postoperative in 97 of 278 (35%), delayed-onset bleb-associated in 50 of 278 (18%), posttraumatic in 37 of 278 (13%), and endogenous in 22 of 278 (8%).

TABLE 2. Sensitivities of Endophthalmitis-causing Organisms to Commonly Used Antibiotics

Vitreous Isolates	Percent Sensitive							
BPEI 1996–2001	N*	Cefazolin	Ciprofloxacin	Amikacin	Ceftazidime	Gentamicin	Vancomycin	Levofloxacin†
Staphylococcus epidermidis	87	48	59	‡	57	72	100	55
Streptococcus viridans grp	40	97	100	‡	100	50	100	100
Coagulase-negative *Staphylococcus* (other)	29	81	93	‡	100	93	100	100
Staphylococcus aureus	24	65	58	‡	100	83	100	17
Gram-negative rods (other)	16	17	88	60	67	65	‡	100
Enterococcus species	15	33	60	0	0	86	100	100
Fastidious gram-negative rods	14	‡	100	100	100	100	‡	‡
Aerobic gram-positive rods	10	63	89	‡	33	89	100	‡
Streptococcus pneumoniae	9	100	‡	‡	100	‡	100	100
Streptococcus (other)	8	100	100	‡	50	100	100	‡
Pseudomonas aeruginosa	7	‡	100	100	100	100	‡	100
All vitreous isolates (excluding fungi)	286	65	73	77	70	78	100§	68

BPEI = Bascom Palmer Eye Institute.
*Number of isolates evaluated.
†Levofloxacin tested mid-2000–2001.
‡Not tested.
§Only gram-positive isolates tested.

TABLE 3. Endophthalmitis Isolates From Vitreous by Clinical Setting, Bascom Palmer Eye Institute 1996–2001

Clinical Setting	Total (%)	A (%)	B (%)	C (%)	D (%)	E (%)	F (%)	G (%)
Vitreous isolates (number)	313	115	47	54	49	24	11	13
Staphylococcus epidermidis	27.8	46.9	22.7	14.8	20.8	8.3	0	15.3
Streptococcus viridans group	12.8	10.4	15.9	18.5	12.5	8.3	18.2	7.7
Coagulase-negative *Staphylococcus* (other)	9.3	9.6	9.1	7.4	12.5	8.3	0	15.3
Staphylococcus aureus	7.7	13.9	2.3	1.9	2.1	16.7	9.1	0
Propionibacterium acnes	7.0	0	18.2	1.9	14.6	8.3	0	23.1
Gram-negative rods (other)	5.1	6.1	13.6	3.8	2.1	0	0	0
Enterococcus species	4.8	4.3	0	12.9	2.1	0	0	15.3
Fastidious gram-negative rods	4.5	0.9	0	20.4	4.2	0	0	0
Aerobic gram-positive rods	3.2	2.6	2.3	0	12.5	0	0	0
Streptococcus pneumoniae	2.9	0	4.2	5.6	0	4.2	18.2	7.7
Molds (other)	2.9	0	2.3	0	6.3	4.2	36.4	0
Aspergillus species	2.9	0	4.2	0	2.1	20.8	0	7.7
Candida albicans	2.9	0	2.3	3.8	4.2	12.5	0	7.7
Streptococcus (other)	2.6	0.9	2.3	3.8	4.2	4.2	0	7.7
Pseudomonas aeruginosa	2.2	4.3	2.3	0	0	0	9.1	0
Mycobacteria species	1.0	0	0	1.9	2.1	0	9.1	0
Corynebacterium species	0.6	0	0	3.8	0	0	0	0

A = acute-onset postoperative; B = delayed-onset postoperative; C = delayed-onset bleb-associated; D = posttraumatic; E = endogenous; F = miscellaneous; G = unknown.

DISCUSSION

SUCCESSFUL TREATMENT OF ENDOPHTHALMITIS INCLUDES the prompt use of an effective antimicrobial regimen.[3,4] Treatment may be guided by recognizing differences among the various endophthalmitis categories and by utilizing knowledge of antibiotic effectiveness against possible causative organisms.

The current study reviews the spectrum of organisms causing endophthalmitis at a single, tertiary-care institution over a 6-year period. Gram-positive organisms were predominant (identified in 78.4% of overall cases). However, gram-negative organisms made up a larger portion of isolates (identified in 11.8% of overall cases) than were found in the Endophthalmitis Vitrectomy Study (EVS). The EVS reported 94% of identified microbiologic isolates

TABLE 4. Endophthalmitis Cases by Clinical Setting

Clinical Setting	Percentage of Endophthalmitis Cases	Number (n = 278)
Postoperative	72	200
Acute postoperative	37	103
Cataract	26	73
Pars plana vitrectomy	2	5
Filtering bleb	4	11
Other	5	14
Chronic postoperative	35	97
Cataract	11	31
Pars plana vitrectomy	0	0
Filtering bleb	18	50
Other	6	16
Traumatic	13	37
Endogenous	8	22
Miscellaneous (e.g., keratitis)	4	11
Unknown	3	8

to be gram positive and 6% to be gram negative.[1] This difference may be due, at least in part, to the EVS entry criteria including only acute-onset endophthalmitis associated with cataract surgery or secondary intraocular lens placement, whereas the current study included all categories of endophthalmitis. When reviewing only acute, postoperative cases in the current study from 1996 to 2001 (Table 3), 88.6% of cases were caused by gram positives, 11.3% of cases were caused by gram negatives, and no cases were caused by fungi. The microbiologic spectrum of the acute, postoperative cases in the current series contrasts with that found by both the EVS and by Kunimoto and associates.[5] In that series, the authors found only 53.1% of acute, postoperative cases caused by gram positives, 26.2% caused by gram negatives, and 16.7% caused by fungi. The differences in the results found by these three studies may be explained by differing inclusion criteria, geographic differences, or random variation.

Bleb-associated endophthalmitis has been reported to have a different spectrum of infecting agents with a greater incidence of streptococcal and gram-negative organisms than acute postoperative endophthalmitis after cataract surgery.[6,7] The causes of bleb-associated endophthalmitis in the current study confirmed those reports, with 28% of cases caused by streptococcal species and 25% of cases caused by gram-negative organisms (Table 3).

Despite information such as a recent evidence-based literature review showing a relatively low level of evidence justifying the use of topical antibiotic prophylaxis,[8] topical fluoroquinolones are commonly used for perioperative infection prophylaxis in patients undergoing cataract surgery in North America. In a survey of ophthalmologists performing cataract surgery in 2000, 79% reported use of a preoperative topical antibiotic, most commonly a fluoroquinolone.[9] Some studies have reported increasing microbial resistance to commonly used antibiotics, including an increased resistance to fluoroquinolones among gram-positive organisms.[10,11] In evaluating patients with postoperative endophthalmitis from India, one recent study showed a relatively high susceptibility of gram-positive organisms to ciprofloxacin (88%),[12] contrasting with the 68% susceptibility to ciprofloxacin of gram-positive organisms in the current study. During the period of the current study, there was a significant decrease in the sensitivity of gram-positive endophthalmitis-causing isolates to ciprofloxacin. In 1996, 21 of 29 (72%) gram-positive isolates tested against ciprofloxacin were found to be sensitive. However, in 2001, only 10 of 28 (36%) gram-positive isolates tested against ciprofloxacin were found to be sensitive. During the 6-year period of the study, gram-positive isolates showed a statistically significant trend to decreasing sensitivity to ciprofloxacin. In comparison, during the same period sensitivities of gram-positive endophthalmitis-causing organisms to gentamicin remained relatively stable. During the period of the study, gram-positive isolates did not show a statistically significant trend to decreasing sensitivity to gentamicin (Table 5). The widespread and routine use of third-generation fluoroquinolones (such as ciprofloxacin) as therapeutic and prophylactic medications in North America may have led to an increase in microbial resistance against them in this geographic location.

TABLE 5. Gram-positive Isolates Tested (n) and Percentage Sensitive (%) to Ciprofloxacin and Gentamicin in Each Year From 1996 to 2001

Year	1996 n (%)	1997 n (%)	1998 n (%)	1999 n (%)	2000 n (%)	2001 n (%)
Ciprofloxacin	29 (72)	35 (91)	34 (82)	20 (60)	16 (56)	28 (36)
Gentamicin	28 (86)	38 (79)	26 (81)	21 (71)	13 (77)	27 (70)
P value	0.33	0.19	0.99	0.52	0.68	0.005

In gram-positive endophthalmitis-causing isolates from 1996 to 2001, there was a statistically significant trend to decreasing sensitivity to ciprofloxacin ($P < .001$).

Owing to its higher concentration of the active isomer, levofloxacin has been purported to show a broader spectrum of activity than older fluoroquinolones,[13] particularly against the gram-positive organisms recently developing more resistance to ciprofloxacin and ofloxacin. In addition, much like ciprofloxacin and ofloxacin, intravitreal levels of levofloxacin after oral administration have been reported to reach effective mean inhibitory concentrations for a number of endophthalmitis-causing organisms, although not *Pseudomonas aeroginosa*.[14–16] The combination of an expanded spectrum of activity against gram positives and good intravitreal levels after oral administration would seem to make oral levofloxacin a potential adjunctive antibiotic in treating endophthalmitis. From late 2000 until December 31, 2001, however, our testing of intravitreal isolates for sensitivity to levofloxacin has shown incomplete gram-positive coverage (Table 2). For example, recovered isolates of *Staphylococcus epidermidis*, the most common cause of endophthalmitis, had only 55% (11/20) sensitivity to levofloxacin during this time period. Although levofloxacin showed better activity in 2001 against gram-positive endophthalmitis-causing isolates than ciprofloxacin (62% vs 36%), it still had incomplete gram-positive coverage. The frequent use of fluoroquinolones as a perioperative prophylactic agent may have contributed to this resistance pattern.

In the current study, there were increasing levels of resistance of endophthalmitis-causing microbes to the commercially available third-generation fluoroquinolones (levofloxacin, ofloxacin, ciprofloxacin), particularly the gram-positive isolates. The gaps in gram-positive coverage presently seen in third-generation fluoroquinolones may be addressed by the fourth-generation fluoroquinolones, gatifloxacin and moxifloxacin. These medications have been shown in vitro to have an increased spectrum of activity against gram-positive organisms such as *S aureus*, coagulase-negative staphylococci, and *S viridans* group.[17] Orally administered gatifloxacin has also been shown to reach effective mean inhibitory concentrations for a number of endophthalmitis-causing organisms.[18] In addition, the addition of a methoxy group at the eighth position of the molecule allows the fourth-generation fluoroquinolones to bind to both DNA gyrase and topoisomerase IV in gram-positive organisms. This dual mechanism of action may decrease the likelihood that gram-positive bacteria will develop resistance to these new medications.

The ideal antibiotic to treat endophthalmitis would include the following characteristics: broad spectrum of coverage for all organisms, low incidence of toxicity, widespread availability, and low cost. There is no single antibiotic that adequately covers all infecting agents in this review of culture-proven endophthalmitis. The antibiotic with the greatest potency against gram-positive organisms is vancomycin. As was the case in the EVS, all of the gram-positive organisms identified were sensitive to vancomycin.[1] However, vancomycin has incomplete coverage against gram-negative organisms. Additionally, infectious disease authorities are encouraging the judicious use of vancomycin to prevent widespread microbial resistance to this antibiotic.[19]

Current recommendations for empirically treating suspected bacterial endophthalmitis involve combination therapy targeting both gram-positive and gram-negative organisms. Therapeutic combinations of antibiotics should be tailored to the clinical scenario in which endophthalmitis develops and should target the most common causative organisms. Fungal therapy is considered when clinical history and ocular features justify this approach.

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