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Endophthalmitis Caused by *Enterococcus faecalis*: Clinical Features, Antibiotic Sensitivities, and Outcomes

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Abstract

Purpose—To report the clinical features, antibiotic sensitivities, and visual acuity (VA) outcomes of endophthalmitis caused by *Enterococcus faecalis*.

Study Design—Retrospective, observational case series.

Methods—A consecutive case series of patients with culture-positive endophthalmitis caused by *E. faecalis* between January 1, 2002 and December 31, 2012 at an academic referral center.

Results—Of 14 patients identified, clinical settings included bleb-associated (n=8), post-cataract surgery (n=4), and post-penetrating keratoplasty (n=2). All isolates were vancomycin sensitive. When comparing isolates in the current study to isolates from 1990–2001, the minimal inhibitory concentration required to inhibit 90% of isolates (MIC 90, μg/ml) increased for ciprofloxacin (4 from 1), erythromycin (256 from 4), and penicillin (8 from 4), indicating higher levels of resistance. The MIC 90 remained the same for vancomycin (2) and linezolid (2). Presenting VA ranged from hand motion to no light perception. Initial treatment strategies were vitreous tap and intravitreal antibiotic injection (n=12) and pars plana vitrectomy with intravitreal antibiotic injection (n=2). VA outcomes were ≤ 20/400 in 13 (93%) of 14 patients.

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Conclusions—Although all isolates were sensitive to vancomycin and linezolid, higher MIC 90s for isolates in the current study, compared to isolates from 1990 to 2001, occurred with ciprofloxacin, erythromycin, and penicillin. Despite prompt treatment, most patients had poor outcomes.

Introduction

Enterococcus faecalis is a gram positive bacterium that is part of the normal human gastrointestinal track flora.[1,2] Enterococci are the second most common cause of nosocomial catheter-associated infections of the bloodstream and urinary tract, and skin/soft-tissue infections.[1,2] *E. faecalis*, a relatively rare cause of endophthalmitis, accounted for approximately 1% of culture positive acute post-cataract surgery endophthalmitis cases in the Endophthalmitis Vitrectomy Study.[3] The most common clinical settings for *E. faecalis* endophthalmitis include acute-onset post-cataract surgery, delayed-onset bleb-related cases, and trauma.[4–7] In previous reports, patients with endophthalmitis caused by *E. faecalis* have worse visual outcomes than coagulase-negative *Staphylococcus* species, the most common cause of postoperative endophthalmitis overall.[3–11]

Enterococci have high rates of resistance to many commonly used antibiotics, including clindamycin, cephalosporins and aminoglycosides.[1,2,5,12] Additionally, the incidence of vancomycin-resistant enterococci (VRE) infections during hospitalizations rose from 4.68 per 100,000 in 2000 to 9.48 per 100,000 in 2006.[13] There are higher rates of vancomycin resistance among *E. faecium* species compared to *E. faecalis*.[13] The only cases reported in the literature of endophthalmitis due to *E. faecalis* resistant to vancomycin originated in Asia.[6,14,15]

A previous study from 1990 to 2001 from our institution reported clinical settings, antibiotic sensitivities, and treatment outcomes for endophthalmitis caused by *E. faecalis*.[5] There have been more recent studies of *E. faecalis* endophthalmitis from Asia.[4,6] However, there is variation in prevalence and antibiotic resistance patterns of *E. faecalis* from different geographical areas.[16,17] Additionally, the cause of vancomycin resistance differs among different geographic regions; in the United States (U.S.), it is attributed to antibiotic use in the hospital setting, while in Europe and Asia it is attributed to antibiotic use for livestock.[16,17] Prior reports from the U.S. and other geographic areas have not analyzed the minimal inhibitory concentration for 90% (MIC 90) of *E. faecalis* isolates for different antibiotics, which is an indicator of the level of antibiotic resistance.

The purpose of this study is to provide an update on the clinical settings, antibiotic sensitivities, and visual acuity (VA) outcomes in a more recent series of culture-proven endophthalmitis caused by *E. faecalis* in the United States. This is the first study (based on a PubMed search) to compare MIC 90 data between time periods for cases of endophthalmitis caused by *E. faecalis*.

Methods

The study protocol for a retrospective review of medical and microbiology records for all patients treated at Bascom Palmer Eye Institute with vitreous and aqueous fluid culture-

proven endophthalmitis caused by *E. faecalis* species between January 1, 2002 and December 31, 2012 was approved by the Institutional Review Board of the University of Miami Miller School of Medicine Medical Sciences Subcommittee for the Protection of Human Subjects. Isolates were identified using standard microbiological procedures. Shifting trends in *in vitro* MIC 90 (μg/ml) were analyzed using the E test (Biomeriuex, Raleigh, NC). The treatment strategies were determined by the individual treating physicians and did not follow a standardized protocol.

Results

Patient demographics and clinical settings

Endophthalmitis caused by *E. faecalis* was identified in 14 eyes of 14 patients. The demographics and clinical setting for each case is summarized in Table 1. Of the 14 cases, eight (57%) were male and eight (57%) were right eyes. Mean age at presentation was 74 years (range: 54 to 86 years). Clinical settings included 8 bleb-associated (57%), 4 post-cataract surgery (29%), and 2 post-penetrating keratoplasty (PKP, 14%) cases. One of the bleb-associated cases was an inadvertent bleb created during an extracapsular cataract extraction (ECCE) surgery. One of the post-cataract surgery cases was due to a dehisced ECCE wound. One of the post-PKP cases was combined with a pars plana vitrectomy (PPV), scleral-fixated intraocular lens (IOL), and Baerveldt glaucoma implant (BGI) tube repositioning surgeries.

Microbiology and antibiotic resistance

E. faecalis was identified in vitreous samples in 13 (93%) of 14 patients and in the anterior chamber of one (7%) patient. All cultures were monomicrobial. The antibiotic susceptibilities and MIC 90 of *E.* isolates from the current study are summarized and compared to isolates from 1990 to 2001 in Table 2. All *E. faecalis* isolates tested were susceptible to vancomycin (13 of 13, 100%) and linezolid (13 of 13, 100%). There were low rates of resistance to ciprofloxacin (2 of 13, 15%), high level gentamicin (MIC >500 mg/l, 2 of 14, 14%), and penicillin (1 of 10, 10%). There were higher rates of resistance to erythromycin among isolates from 2002 to 2012 (7 of 10, 70%) compared to 1990 to 2001 (3 of 8, 38%). Similarly, there were higher rates of resistance to tetracycline among isolates from 2002 to 2012 (11 of 14, 79%) compared to 1990 to 2001 (8 of 11, 73%). The MIC 90 for isolates from 2002 to 2012 and 1990 to 2001 remained the same for vancomycin (2 μg/ml), linezolid (2 μg/ml), and tetracycline (16 μg/ml). The MIC 90 from 2002 to 2012 increased 2-fold for penicillin, 4-fold for ciprofloxacin, and 64-fold for erythromycin.

Clinical presentation and management

The initial and subsequent clinical management of patients are summarized in Table 3. The presenting VA was light perception (LP) in 10 (71%) of 14 patients, hand motion (HM) in 3 (21%) patients, and no light perception (NLP) in 1 (7%) patient. Pain was present in 13 (93%) of 14 patients. The mean intraocular pressure (IOP) was 34 (range: 11 to 56). A hypopyon was present in 13 (93%) of 14 patients. A view of the posterior pole was unobtainable in all of the patients due to severe anterior segment inflammation and media opacities.

Initial treatment consisted of a vitreous tap and intravitreal antibiotics in 12 (86%) of 14 patients and pars plana vitrectomy (PPV) and intravitreal antibiotics in 2 (14%). Endoscopic PPV was not performed in any patients. Additional treatments were administered within two weeks of initial treatment in 6 (50%) of the 12 patients treated with vitreous tap and intravitreal antibiotics, due to clinical evidence of worsening inflammation or infection (e.g., compared with initial presentation, an increase in media opacification, height of the hypopyon, corneal ring infiltrate, etc.). Three patients had a PPV with injection of intravitreal antibiotics, 2 received additional intravitreal antibiotics, and 2 patients underwent enucleation. The 2 patients initially treated with PPV and intravitreal antibiotics did not undergo additional treatment. One additional patient had additional interventions due to recurrent endophthalmitis due to *E. faecalis* 71 days after the initial infection. This patient was treated for the recurrent infection with a vitreous tap and injection of antibiotics initially, followed by a PPV with a pars plana lensectomy and capsulectomy 3 days later.

Vancomycin and ceftazidime were used initially for intravitreal antibiotic treatment in all patients. Additionally, 11 (79%) of 14 patients were treated with intravitreal dexamethasone as part of their initial treatment. All patients were started on topical antibiotic drops: 13 (93%) of 14 on fortified vancomycin (50 mg/ml) and a second antibiotic (fortified tobramycin (14 mg/ml), fortified gentamicin (14 mg/ml), fortified ceftazidime (50 mg/ml), or a fluoroquinolone), and 1 (7%) on polymyxin B/trimethoprim alone. A topical steroid drop was started within 48 hours of the initial treatment in 11 (79%) of 14 patients.

Clinical outcomes

Clinical outcomes are summarized in Table 3. The VA outcome was NLP in 5 of (36%) 14 patients, LP in 4 (29%), HM in 3 (21%), 6/200 (7%) in 1, and 20/25 (7%) in 1. The mean follow-up period was 33 months (range: 6 days to 96 months). Retinal detachments occurred in 4 (29%) of 14 patients and enucleations were performed in 2 (14%) patients.

Discussion

The current study demonstrates that endophthalmitis due to *E. faecalis* has poor VA outcomes, despite prompt and appropriate intravitreal antibiotic treatment. Although cases of vancomycin-resistant *E. faecalis* from Asia have been reported, all *E. faecalis* isolates in the current study were sensitive to vancomycin.[6,14,15] Additionally, there is no change in the MIC 90 for vancomycin (2 μg/ml) between *E. faecalis* isolates in the current study and those from 1990 to 2001. Based on the methods published by the Clinical and Laboratory Standards Institute, the *E. faecalis* isolates with a MIC ≤ 4 μg/ml are sensitive to vancomycin.[18]

Previously reported cases of endophthalmitis due to vancomycin-resistant bacterial isolates (*Staphylococcus, Enterococcus, and Bacillus* species) were successfully treated with intravitreal daptomycin, fluoroquinolones, and quinupristin/dalfopristin, or systemic linezolid.[14,19–21] All 7 of the *E. faecalis* isolates tested in the current study were resistant to quinupristin/dalfopristin, which has been reported to be effective in the treatment of vancomycin resistant *Staphylococcusaureus* and *E. faecium* isolates.[14,19]

Of note, the isolates in the current study had higher MIC 90s for penicillin (8 μg/ml), ciprofloxacin (4 μg/ml), and erythromycin (256 μg/ml) than the isolates from 1990 to 2001. Based on the Clinical and Laboratory Standards Institute, *E. faecalis* isolates are sensitive to penicillin with a MIC ≤ 8 μg/ml, to ciprofloxacin with a MIC ≤ 1 μg/ml, and to erythromycin with a MIC ≤ 0.5 μg/ml.[18] A rise in the MIC 90s for these antibacterial agents indicates a rise in the level of resistance. Additionally, higher MICs, even when below the cutoff for resistance, are associated with decreased vancomycin treatment success rate for bacteremia with methicillin-resistant *Staphylococcus aureus*.[22] Bacterial isolates with higher MIC values may cause worse clinical outcomes in patients with endophthalmitis and may contribute to instances of persistently positive vitreous cultures after treatment with intravitreal antibiotics, which the isolate is sensitive to.[22,23] In the current study, only two (29%) of seven patients with isolates with vancomycin MIC of 2 μg/ml achieved final BCVA better than LP, while three (50%) of six patients with vancomycin MIC < 2 μg/ml achieved final BCVA better than LP. The only patient with a persistently positive vitreous culture also had an isolate with vancomycin MIC of 2 g/ml. There are no previous reports comparing the MIC 90s of isolates of *E. faecalis* causing endophthalmitis between different time periods (based on a PubMed search).

The clinical settings, initial treatment, and visual acuity outcomes of the current study and two previous studies on *E. faecalis* from our institution are compared in Table 4.[5,7] The most common etiology in the current series is bleb-associated compared to post-cataract surgery in the 1990–2001 series.[5] Furthermore, a larger proportion of patients in the current series had VA outcomes worse than 20/400 (13 of 14, 93%), compared to the 1990–2001 series (24 of 29, 83%), and the 1977–1990 series (6 of 13, 46%).[5,7] Likewise, enucleations were performed in a larger proportion of patients in the current series 2 of 14, 14%) compared to the 1990–2001 series (1 of 29, 3%) and 1977–1990 series (0 of 13, 0%).[5,7]

The tissue destructive effects of *E. faecalis* may explain the worse visual prognosis in endophthalmitis caused by *E. faecalis* compared to other organisms.[24,25] In a rabbit model of endophthalmitis, *E. faecalis* demonstrated prominent inflammatory cells in the non-cavitary tissues (cornea, iris, ciliary body, retina, choroid, optic nerve, sclera) and panophthalmitis.[24] In contrast, inflammation due to *Staphylococcus epidermidis* was mainly restricted to the ocular cavities (anterior chamber, posterior chamber, and vitreous).[24] This study demonstrated that *E. faecalis* is destructive to the ocular tissues early in the course of endophthalmitis, compared to *S. epidermidis*, which causes an inflammatory reaction that more confined to ocular cavities with relative sparing of the ocular tissues.[24] Additionally, in this model, the histopathologic inflammatory response to *E. faecalis* in untreated rabbit eyes was the same as rabbit eyes treated with intravitreal vancomycin 24 hours or 48 hours post-inoculation or eyes treated with vitrectomy (with or without intravitreal vancomycin).[24]

A specific hemolytic toxin, cytolysin, produced by some *E. faecalis* isolates is a potential cause for poor visual outcomes, despite prompt treatment with appropriate intravitreal antibiotics and corticosteroids.[25] A study comparing endophthalmitis caused by cytolysin-producing and non-producing *E. faecalis* strains in rabbit eyes treated with intravitreal antibiotics and corticosteroids found worse retinal function (99% vs. 74.2% loss) and greater histologic damage (near total destruction vs. no destruction) in the cytolysin producing *E*

faecalis infections.[25] One study found no difference in VA outcomes based on cytolysin expression in patients with endophthalmitis due to *E. faecalis*, but the sample size was only 20 patients, 15 of whom had VA outcomes <20/200.[26] There are no studies comparing the histology of enucleated specimens or electroretinograms of patients with endophthalmitis due to cytolysin-producing or non-producing *E. faecalis* isolates.

The limitations of the current study include its retrospective design, relatively small number of patients, and use of positive vitreous and aqueous cultures as the inclusion criteria for the study, which could potentially have excluded cases with false negative cultures. The current study does not include any *E. faecium* species which have been reported to have higher rates of vancomycin resistance.[13] Despite these limitations, this study provides important prognostic and antibiotic resistance and MIC 90 data for endophthalmitis caused by *E. faecalis*.

In conclusion, despite prompt vancomycin treatment, patients in the current study had poor VA outcomes and showed worse VA outcomes compared to previous reports.[5,7] The antibiotic susceptibility data from the current study further supports continued use of vancomycin. Rising antibiotic MICs for *E. faecalis* isolates raises concern about decreased clinical susceptibility to commonly used antibiotics now and in the future.

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Biography

Ajay E. Kuriyan, MD, is an ophthalmology resident at the Bascom Palmer Eye Institute, Miami, Florida. He received his undergraduate, master's, and medical degree from the University of Rochester. His research interests include, epiretinal membranes, ophthalmic imaging, proliferative vitreoretinopathy, and endophthalmitis. He will begin his vitreoretinal fellowship in July 2014 at the Bascom Palmer Eye Institute.

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Table 1

Clinical features of patients with endophthalmitis caused by *Enterococcus faecalis*.

Patient Number	Age	Eye	Gender	Clinical Setting	Time After Surgery
1	79	Left	Male	Bleb-Associated	10 years
2	68	Right	Female	Bleb-Associated	Unknown
3	67	Left	Female	Bleb-Associated	17 months
4	78	Right	Male	Bleb-Associated	2 months
5	77	Right	Male	Bleb-Associated	12 years
6	54	Left	Female	Bleb-Associated	8 years
7	80	Left	Female	Bleb-Associated (Seidel +)	30 years
8	86	Right	Male	Bleb-Associated[a]	16 years
9	82	Right	Female	Post-op Cataract (ECCE)[b]	31 years
10	78	Left	Female	Post-op Cataract (Phaco)	6 days
11	82	Right	Male	Post-op Cataract (Phaco)	2 days
12	64	Right	Male	Post-op Cataract (Phaco)[c]	14 days
13	73	Left	Female	Post-op PKP	8 days
14	71	Right	Female	Post-op PKP/PPV/Scleral Fixated IOL/BGI revision	8 days

Legend: BGI = Baerveldt glaucoma implant, ECCE = extracapsular cataract extraction, IOL = intraocular lens, PKP = penetrating keratoplasty, PPV = pars plana vitrectomy, Phaco = phacoemulsification.

[a] aIatrogenic bleb s/p ECCE,

[b] Dehisced complicated ECCE-wound,

[c] Symptoms for 1 week, diagnosis delayed due to outside hospitalization.

Table 2

Enterococcus faecalis antibiotic susceptibility and minimal inhibitory concentrations.

Antibiotic	2002 to 2012			1990 to 2001		
	No. of Isolates Tested	Resistant Isolates (%)	MIC 90	No. of Isolates Tested	Resistant isolates (%)	MIC 90
Erythromycin	10	7 (70)	256	8	3 (38)	4
Ciprofloxacin	13	2 (15)	4	14	1 (7)	1
Gentamicin[a]	14	2 (14)	NA	29	5 (17)	NA
Linezolid	13	0 (0)	2	29	0 (0)	2
Penicillin	10	1 (10)	8	21	2 (10)	4
Quinupristin/Dalfopristin	7	7 (100)	32	0	NA	NA
Tetracycline	14	11 (79)	16	11	8 (73)	16
Vancomycin	13	0 (0)	2	23	0 (0)	2

Legend: NA = not applicable, No. = number, MIC 90 = minimal inhibitory concentrations for 90% of isolates.

[a]High level gentamicin resistance (MIC >500 mg/l).

Table 3

Presentation, treatment strategies, and outcomes of patients with endophthalmitis caused by *E. faecalis*.

No.	Pre-infection VA	Initial VA	IOP	Initial Tx	Initial Intravitreal Injection(s)	Additional Tx (Days After Initial Tx)	Additional Intravitreal Injection(s)	Last VA	Follow-up Time
1	20/30	LP	28	PPV	VANC + CTZ+DEX	None	None	HM	7yrs
2	20/30	LP	UK	T + I	VANC + CTZ	None	None	NLP	4.5 yrs
3	20/200	LP	11	T + I	VANC + CTZ+DEX	PPV (9)	VANC + CTZ+DEX	LP	8 yrs
4	UK	LP	42	T + I	VANC + CTZ+DEX	None	None	LP	6 days
5	20/40	HM	51	T + I	VANC + CTZ + DEX	T + I (71)[a], PPV + PPL + capsulectomy (74)[a]	VANC + CTZ + DEX	HM	13 mos
6	20/100	LP	36	T + I	VANC + CTZ + DEX	Enucleation (8)	None	NLP	8 mos
7	CF	LP	32	PPV	VANC + CTZ + DEX	None	None	NLP	4.5 yrs
8	20/30	LP	40	T + I	VANC + CTZ + DEX	None	None	NLP	13 mos
9	20/20	LP	44	T + I	VANC + CTZ + DEX	PPV + ACIOL removal (1)	VANC + CTZ + DEX	LP	6 mos
10	20/40	NLP	44	T + I	VANC + CTZ+DEX	T + I (1), Enucleation (6)	VANC + DEX	NLP	12 mos
11	UK	HM	13	T + I	VANC + CTZ	T + I (1)	VANC + AMI	20/25	4.5 yrs
12	20/100	LP	22	T + I	VANC + CTZ + DEX	PPV (9)	VANC + CTZ + DEX	HM	13 mos
13	CF	HM	56	T + I	VANC + CTZ + DEX	None	None	6/200	3 yrs
14	4/200	LP	13	T + I	VANC + CTZ	None	None	LP	18 mos

Legend: ACIOL = anterior chamber intraocular lens, AMI = amikacin, CF = count fingers, CTZ = ceftazidime, DEX = dexamethasone, HM = hand motion, IOP = intraocular pressure, LP = light perception, NLP = no light perception, No. = number, mos = months, PPV = pars plana vitrectomy, PPL = pars plana lensectomy, T + I = vitreous tap + intravitreal injection, Tx = treatment, VAN = vancomycin, VA = visual acuity, UK = unknown, yrs = years.

[a]Additional treatment at time of recurrent infection.

Table 4

Comparison of studies of endophthalmitis caused by *Enterococcus faecalis*.

	Current Study 1/2002 – 12/2012 (n = 14)	Scott Study 6/1990 – 12/2001 (n = 29)	Mao Study 1/1977 – 5/1990 (n = 13)
	No. of Patients (%)	No. of Patients (%)	No. of Patients (%)
Clinical Setting			
Bleb-Associated	8 (57)	8 (28)	NR
Post-Cataract Sx	4 (29)	15 (52)	NR
Post-PKP Sx	2 (14)	4 (14)	NR
Miscellaneous	0 (0)	2 (7)	NR
Initial Treatment			
Vitreous Tap + Antibiotics	12 (86)	23 (79)	NR
PPV + Antibiotics	2 (14)	6 (21)	NR
Intravitreal Corticosteroids	11 (79)	NR	NR
Visual Acuity Outcomes			
≥ 20/50	1 (7)	2 (7)	3 (23)
≥ 20/400	1 (7)	5 (17)	7 (54)
<20/400	13 (93)	24 (83)	6 (46)
Enucleation/Evisceration	2 (14)	1 (3)	0 (0)

Legend: No. = number, NR = not reported, PKP = penetrating keratoplasty, PPV = pars plana vitrectomy, Sx = surgery.