Evaluation of Therapeutic Measures for Treating Endophthalmitis Caused by Isogenic Toxin-Producing and Toxin-Nonproducing *Enterococcus faecalis* Strains

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Purpose. Management of endophthalmitis typically includes antibiotic combinations to arrest bacterial growth and antiinflammatory agents to limit inflammatory damage to sensitive tissues. Little research has been reported that systematically evaluates the contribution of each therapeutic component for treating infections caused by organisms of varying virulence. The authors determined the relative value of the antiinflammatory corticosteroid, dexamethasone, as an intravitreal therapeutic adjunct for the treatment of infection caused by either *Enterococcus faecalis* expressing a cytolytic toxin previously shown to contribute to the course and severity of infection, or an otherwise identical strain of *E. faecalis* specifically attenuated in expression of the cytolytic toxin.

Methods. Endophthalmitis in rabbits was monitored using electroretinography (ERG). Eyes were infected with 100 colony forming units of either the cytolytic or the noncytolytic *E. faecalis* strain. Intravitreal ampicillin and gentamicin were administered at postinfection day 1, and intravitreal dexamethasone was either omitted or administered at day −1, 1, or 1.5.

Results. ERG B-wave amplitude declined precipitously throughout the course of infection with cytolytic toxin-producing *E. faecalis,* despite the administration of antibiotics and regardless of the time of dexamethasone administration. In fact, the ultimate course of infection caused by cytolytic *E. faecalis* did not differ from the course in untreated controls. In contrast, infections caused by specifically attenuated, noncytolytic strains of *E. faecalis* responded well to antibiotics augmented by antiinflammatory therapy when the latter was administered either 1 or 1.5 days after the initiation of infection. In these cases, no loss in ERG B-wave response was observed.

Conclusions. These results underscore the importance of bacterial toxins in infectious diseases of the eye and their contribution to treatment failures. These results further suggest that in cases of endophthalmitis caused by toxin producing bacteria, significant improvement in clinical outcome will require specific therapeutic targeting of the toxins involved. Invest Ophthalmol Vis Sci. 1995;36:9–15.

Endophthalmitis is a devastating complication of intraocular surgery or penetrating ocular injury. The most common etiologic agent of bacterial endophthalmitis is *Staphylococcus epidermidis,*[1,2] and these infections generally respond well to therapeutic measures.[3,4] However, endophthalmitis resulting from infection byother common causes, including *Staphylococcus aureus, Streptococcus spp, Pseudomonas spp,* and *Bacillus cereus,* is associated with a much poorer visual outcome.[5–7] In a previous study, we used transposon insertional mutagenesis to inactivate the gene encoding a cytolytic toxin expressed by some strains of *Enterococcus faecalis.*[8] Derivation of such mutants allowed us to demonstrate directly that the cytolytic toxin makes a major contribution to the course and severity of enterococcal endophthalmitis.[9] Similar direct tests have yet to be performed on the toxins expressed by other bacteria associated with fulminant or destructive endophthalmitis, but it has been speculated that toxin production contributes to the poor prognosis observed for other bacteria as well.[10]

In addition to bacterial toxins, the host inflamma-

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tory response makes a measurable contribution to the damage that results from bacterial endophthalmitis. Intraocular fibrocellular proliferation, membrane formation, and traction retinal detachment have all been described as secondary complications of the host response that requires aggressive management to limit visual loss.[11] Dexamethasone has been found to be a safe and effective adjunct to broad-spectrum antibiotics for suppressing the inflammatory response during treatment for endophthalmitis.[3,12,17] Despite aggressive therapy with synergistic antibiotic combinations augmented with antiinflammatory agents, endophthalmitis remains a sight-threatening condition with frequently poor outcome.[5-7] To define the basis for endophthalmitis treatment failure, we systematically analyzed the value of intravitreal antiinflammatory therapy in treating infections by isogenic toxin-producing and nontoxigenic bacteria. The results of this study highlight the importance of devising new therapies that directly target contributory toxins expressed by toxigenic organisms if the prognosis for endophthalmitis caused by the latter is to be improved.

MATERIALS AND METHODS

Bacterial Strains and Media

E. faecalis strain JH2SS harboring transposon Tn*917* insertional mutations in the cytolysin-encoding plasmid pAD1 was used in this study.[8] JH2SS(pAM771) harboring Tn*917* insertion in the cytolysin-encoding region of pAD1 was selected as the noncytolytic mutant. JH2SS(pAM714) contains Tn*917* insertion in a region of pAD1 not affecting cytolysin function and was chosen as the isogenic, cytolysin-producing strain (see ref. 9 for physical map of pAD1 and phenotype of strains used in this study). *E. faecalis* strains were routinely propagated overnight at 37°C in brain–heart infusion broth (BHI; Difco, Detroit, MI) supplemented with streptomycin (500 μg/ml), spectinomycin (500 μg/ml), and erythromycin (10 μg/ml) (Sigma, St. Louis, MO). Before intraocular inoculation, organisms were harvested by centrifugation, washed twice in sterile balanced salt solution (BSS; Dey Laboratories, Napa, CA), and resuspended in BSS at a final concentration of approximately 100 colony forming units (cfu)/0.1 ml, as previously described.[9,13] Viable organisms were enumerated at the conclusion of the experiments by plating vitreal contents on BHI agar (1.5% agar) supplemented with 5% human erythrocytes, as previously described.[9,13]

Vertebrate Animals

New Zealand White rabbits (each weighing 2 to 4 kg) were housed and cared for at the Dean A. McGee Eye Institute (Oklahoma City, OK) animal care facility in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Intraocular Injections

Intravitreal inoculation of anesthetized animals was performed as previously described.[9,13] General anesthesia consisted of intramuscular ketamine and xylazine. Proparacaine was used as topical anesthesia. Briefly, pupils of anesthetized rabbits were dilated, and approximately 0.1 ml of aqueous humor was aspirated with a tuberculin syringe to relieve intraocular pressure. Approximately 100 cfu (0.1 ml) of *E. faecalis* were introduced intravitreally through the pars plana approximately 3 mm from the limbus with a 25-gauge needle and a 1-ml syringe. Experimental day 0 was defined as the time of injection of 100 cfu *E. faecalis* JH2SS(pAM771) or JH2SS(pAM714). Combination antimicrobial therapy consisting of ampicillin (1 mg/0.1 ml) and gentamicin (200 μg/0.1 ml) was administered intraocularly on experimental day 1 (24 hours after infection) in all animals. This antimicrobial combination has been described as effective therapy for a variety of infections caused by beta-lactam–aminoglycoside-sensitive enterococci.[14] Dexamethasone (400 μg/0.1 ml) was either omitted or injected intravitreally at experimental day −1 (24 hours before infection), +1 (24 hours after infection), or +1.5 (36 hours after infection). Eyes receiving no injections served as absolute controls, whereas surgical control eyes received 0.1 ml sterile BSS.

Electroretinography

The course of infection was monitored using scotopic electroretinography (ERG), an objective measure that was shown previously to parallel clinical observations.[9,13] ERG was performed, as previously described,[9,13] on experimental days −1, +1, +3, and +5. B-wave amplitude measurements were expressed as mean percent of retained baseline (pre-experimental) B-wave amplitude ([experimental B-wave amplitude baseline B-wave amplitude] × 100) ± standard error of the mean. Immediately after the final ERG, anesthetized animals were killed with pentobarbital and phenytoin, and eyes were enucleated for bacterial quantitation as described above.

RESULTS

As a first step in assessing the efficacy of standard regimens for treatment of endophthalmitis, two parameters were systematically analyzed, the administration of the antiinflammatory corticosteroid dexamethasone and the timing of administration and the virulence of the organism causing endophthalmitis. The first set of experiments examined the value of dexamethasone as an adjunct to antimicrobial therapy in

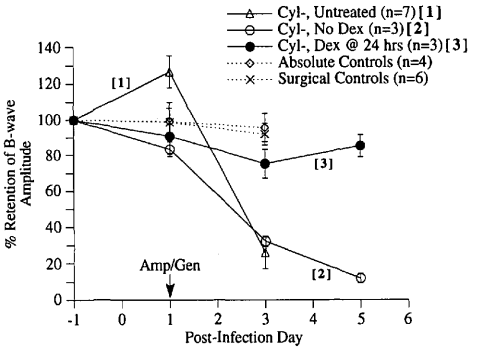

FIGURE 1. B-wave amplitude retention in eyes infected with noncytolytic *Enterococcus faecalis*. Amp (ampicillin, 1000 μg) and Gen (gentamicin, 200 μg) were administered at postinfection day 1 except untreated animals, absolute control animals, and surgical control animals. Dex (dexamethasone, 400 μg) was administered as described on graph. No Dex = ampicillin/gentamicin alone at postinfection day 1. Cyl− = noncytolytic *E. faecalis*. Absolute controls = no injection. Surgical controls = saline injection only. Numbers in boldface brackets are referred to in text as curves 1, 2, 3, and so on. Absolute and surgical control data are included only in Figure 1 for clarity of graphs.

treatment of endophthalmitis caused by a specifically attenuated, noncytolytic strain of *E. faecalis*, JH2SS(pAM771).

The data presented in Figure 1 show that, irrespective of treatment group, eyes infected with attenuated, noncytolytic *E. faecalis* JH2SS(pAM771) exhibited no significant loss in ERG B-wave amplitude 24 hours after infection. These findings are consistent with previous observations on the kinetics of untreated endophthalmitis caused by noncytolytic *E. faecalis*.[9,13] Treatment with the antibiotic regimen that included 1 mg ampicillin and 200 μg gentamicin 24 hours after infection did little to alter the ensuing precipitous decline in ERG responsiveness. As shown in Figure 1 (curves 1 and 2), ERG loss at day 3 in eyes treated with combined antibiotics without the antiinflammatory agent was virtually identical to that observed for eyes that received no treatment at all. In contrast, eyes that received combined antibiotic therapy augmented by simultaneous administration of 400 μg of dexamethasone exhibited no significant loss in ERG at 3 or 5 days after infection when compared to surgical and absolute controls (day 1, $P > 0.5$; day 3, $P > 0.1$; Student's *t*-test). These results clearly illustrate the value of the inclusion of antiinflammatory agents in the therapeutic regimen for treatment of organisms that are deficient in production of a cytolytic virulence factor.

Repeating this line of experimentation with isogenic *E. faecalis* strain JH2SS(pAM714) that expresses wild-type levels of the cytolysin yielded a strikingly different result. As shown in Figure 2, a substantial reduction in ERG B-wave amplitude for all groups occurred by 24 hours after infection with the cytolysin expressing *E. faecalis* strain, as has been described previously.[9,13] After the administration of combined antibiotic therapy alone (that is, without dexamethasone), ERG responsiveness was lost at a rate that was not significantly different from eyes receiving no treatment (Fig. 2, curves 1 and 2; $P > 0.5$). In contrast to the above results with attenuated organisms, eyes infected with the cytolytic strain and treated with combined antibiotics and dexamethasone at 24 hours after infection showed no moderation in the loss of ERG B-wave amplitude. This result indicates that although dexamethasone was completely effective in limiting loss of retinal function in eyes infected with an attenuated strain, it was of surprisingly little value in the treatment of infections caused by the isogenic, cytolysin-producing strain. Moreover, there was no difference in outcome whether or not any therapy was provided.

The timing of dexamethasone administration was varied to determine whether treatment could be optimized to salvage residual ERG responsiveness in eyes infected with cytolytic *E. faecalis*. A recommendation has been made previously that antiinflammatory therapy for infectious endophthalmitis be postponed for 12 hours after antibiotic administration to allow for efficient killing of the offending organism.[15] It was, therefore, of interest to determine whether postpon-

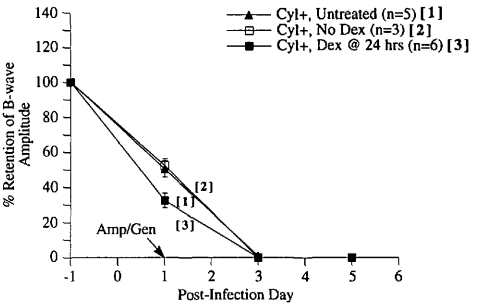

FIGURE 2. B-wave amplitude retention in eyes infected with cytolytic *Enterococcus faecalis*. Amp (ampicillin, 1000 μg) and Gen (gentamicin, 200 μg) at post infection day 1 except untreated animals, absolute control animals, and surgical control animals. Dex (dexamethasone, 400 μg) was administered as described on graph. No Dex = ampicillin/gentamicin alone at post infection day 1. Cyl+ = cytolysin-producing *E. faecalis*. Numbers in boldface brackets are referred to in the text as curves 1, 2, 3, and so on. Absolute and surgical control data are included only in Figure 1 for clarity of graphs.

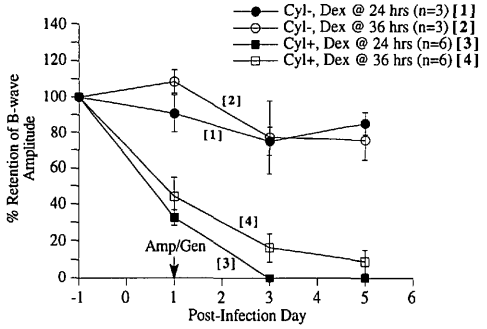

FIGURE 3. B-wave amplitude retention in eyes infected with cytolytic or noncytolytic *Enterococcus faecalis*. Amp (ampicillin, 1000 μg) and Gen (gentamicin, 200 μg) were administered at post infection day 1 except absolute control and surgical control animals. Dex (dexamethasone, 400 μg) was administered as described on graph. Cyl+ = cytolysin-producing *E. faecalis*. Cyl− = noncytolytic *E. faecalis*. Numbers in boldface brackets are referred to in text as curves 1, 2, 3, and so on. Absolute control and surgical control data are included only in Figure 1 for clarity of graphs.

ing dexamethasone administration by 12 hours would affect adversely the therapeutic efficacy of treating the infection caused by the attenuated noncytolytic *E. faecalis* strain or would enhance neuroretinal function in the treatment of infections of the cytolysin-producing organism. As shown in Figure 3, the delay in administration of dexamethasone by 12 hours after antibiotic treatment (36 hours after infection; curve 2) did not significantly alter the previously observed positive outcome from simultaneous antibiotic and antiinflammatory treatment of eyes infected with the attenuated *E. faecalis* strain (curve 1; $P > 0.2$ for all points). A slight enhancement in the retention of measurable ERG responsiveness was seen when eyes infected with the wild-type cytolytic strain JH2SS(pAM714) were treated with antibiotics at 24 hours and dexamethasone at 36 hours after infection (curve 4) over eyes treated simultaneously with antibiotics and dexamethasone at 24 hours (curve 3), but this enhancement was only marginally significant 3 days after infection ($P = 0.057$) and was not significant 5 days after infection ($P > 0.1$).

Previous reports on the nature of endophthalmitis caused by cytolytic strains of *E. faecalis* showed that a loss in ERG responsiveness was easily observed by 24 hours,[9,13] an observation confirmed in the present study. To determine whether prophylactic antiinflammatory therapy would delay the initial rapid loss of ERG function or would otherwise enhance retention of retinal function, especially in infections of the cytolytic strain, the following experiment was performed. Two groups of animals were treated 24 hours *pre*infection with dexamethasone. One group was infected with the cytolytic strain JH2SS(pAM714), and the other group was infected with the isogenic, attenuated noncytolytic strain JH2SS(pAM771). Both groups were then treated with combined antibiotic therapy at 24 hours *post*infection, and the course of infection was followed by ERG. As shown in Figure 4, eyes infected with the attenuated, noncytolytic strain JH2SS(pAM771) and treated preemptively with dexamethasone lost ERG responsiveness (curve 2) to a significantly greater degree than eyes similarly infected with the attenuated strain but treated simultaneously at 24 hours after infection with antibiotics and dexamethasone (curve 1; $P < 0.04$, days 3 and 5). In this case, preadministration of dexamethasone before infection provided no benefit because the outcome was not significantly different from that observed for eyes that were infected with the attenuated strain and received no therapy or that received antibiotics alone ($P > 0.3$). Significant differences in ERG B-wave amplitudes were observed at postinfection day 1 for dexamethasone-pretreated eyes infected with the cytolytic strain JH2SS(pAM714) (curve 3; $P = 0.009$). However, this initial enhancement of ERG responsiveness did not persist, and no significant differences were noted between treatment groups infected with the cytolytic organism at day 3 or 5 (Fig. 4; $P > 0.16$).

Vitreous was examined for the presence of viable organisms at postinfection day 5. Vitreous from a single eye, belonging to the group infected with the attenuated strain JH2SS(pAM771) and receiving dexamethasone 24 hours before infection, grew a low num-

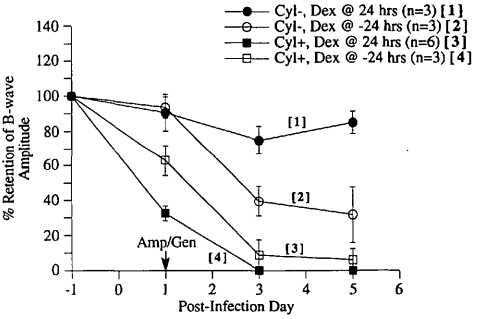

FIGURE 4. B-wave amplitude retention in eyes infected with cytolytic or noncytolytic *Enterococcus faecalis*. Amp (ampicillin, 1000 μg) and Gen (gentamicin, 200 μg) were administered at post infection day 1, except in absolute control and surgical control animals. Dex (dexamethasone, 400 μg) was administered as described on the graph. Cyl+ = cytolysin-producing *E. faecalis*. Cyl− = noncytolytic *E. faecalis*. Numbers in boldface brackets are referred to in text as curves 1, 2, 3, and so on. Absolute control and surgical control data are included only in Figure 1 for clarity of graphs.

ber of organisms at day 5 (fewer than 10^2 cfu/ml). All other eyes receiving antibiotics and dexamethasone in this study were sterile at postinfection day 5.

DISCUSSION

To identify the basis for treatment failure and associated catastrophic loss of vision, the value of intravitreal antibiotic and antiinflammatory therapies was compared systematically for treatment of endophthalmitis caused by isogenic strains of *E. faecalis*. To our knowledge, this is the first report comparing the efficacy of therapeutic regimens for the treatment of eye infections caused by bacteria specifically attenuated in expression of a virulence factor, in this case the cytolysin, using molecular biologic techniques.[8] The existence of strains identical genetically, except in the production of cytolysin, allowed us to determine the specific contribution of this virulence factor to treatment failure.

Previous studies characterizing the natural course of endophthalmitis demonstrated that the growth rate of cytolytic and noncytolytic *E. faecalis* strains in vivo is comparable, achieving numbers of approximately 10^8 cfu per gram of vitreous.[9] Histopathologic examination of tissues from these infections revealed that retinas from infections of the cytolytic strain exhibited substantial disorganization and lysis of cells in all retinal layers.[9] In contrast, retinas from infections of the attenuated, noncytolytic isogenic *E. faecalis* strain were structurally intact,[9] with the primary finding a substantial infiltration of immune cells into the vitreous.[13] These findings suggested that ERG loss in eyes infected with the wild-type cytolytic strain was the result of toxin-mediated destruction of the retina, whereas reduction in ERG in eyes infected with the noncytolytic strain was attributable to the inflammatory reaction, perhaps opacification of the vitreous, as previously reported.[13] Both deductions are supported by the findings of the present study.

The administration of the corticosteroid dexamethasone as an adjunct to antimicrobial therapy, consisting of a combination of ampicillin and gentamicin, was highly effective in preserving ERG response in eyes infected with the attenuated, noncytolytic strain of *E. faecalis*. The efficacy of dexamethasone was independent of the time of administration at the two times tested—24 or 36 hours after infection (simultaneous with or 12 hours after antibiotic administration, respectively). Prophylactic administration of dexamethasone 24 hours before infection provided no enhancement in ERG retention over control experiments where dexamethasone therapy was omitted.

The impact of the expression of a single virulence factor dramatically altered the therapeutic responsiveness of endophthalmitis in the model tested. When eyes were infected with *E. faecalis* strains differing only in the expression of the *E. faecalis* cytolysin (recognizable clinically by the occurrence of zones of hemolysis surrounding *E. faecalis* colonies cultured on agar containing erythrocytes from a source other than sheep), the resultant endophthalmitis was refractory to antibiotic treatment with or without coadministered dexamethasone. Manipulation of the timing of dexamethasone administration did not significantly affect the negative treatment outcome. However, a measurable, though short-lived, benefit was observed when cytolytic infections were *pre*treated with dexamethasone, arguing strongly against a delay in antiinflammatory therapy. With cytolytic infections, the observation that the ultimate outcome was not enhanced by any therapy over the results of untreated infection emphasizes the importance of characterizing the offending toxin and targeting it for therapeutic intervention.

Dexamethasone has been shown to be safe and efficacious in the treatment of human intraocular infections and in animal models.[3,12,16,17] Its use as an adjunct in the treatment of endophthalmitis was recently reviewed.[17] Graham and Peyman[12] observed a significant reduction in inflammatory response in the anterior and posterior chambers, vitreous, retina, and choroid in experimental *Pseudomonas* endophthalmitis when dexamethasone and gentamicin were administered within 5 hours of infection. More severe inflammatory reactions were seen in eyes treated with gentamicin alone or eyes in which the administration of the antibiotic–corticosteroid combination was delayed until 10 hours after infection. Although broadly similar in experimental design, the experiments of Graham and Peyman[12] differ from the present study in several respects. First, earlier studies used a considerably larger inoculum (20,000 cfu *Pseudomonas* versus 100 cfu *E. faecalis*), which may have accelerated the course of infection. Second, treatment of gram-negative endophthalmitis with antibiotics alone can result in the release of inflammatory endotoxin, thereby exacerbating inflammation-mediated ocular damage.[17] In the present study, the effects of dexamethasone administered 24 hours *pre*infection were minimal. This loss of protective activity may result from dexamethasone clearance before infection. The intravitreal half-life of dexamethasone has been reported to be approximately 3 hours, with an approximate 500-fold decrease in intravitreal concentration at 24 hours.[12]

The value of subconjunctival gentamicin or combination gentamicin–dexamethasone, when administered prophylactically, has been studied in a rabbit model of *Staphylococcus aureus* endophthalmitis.[18] Although the coadministration of dexamethasone did not adversely affect the outcome of gentamicin prophylaxis, it provided no observable benefit over prophylactic gentamicin alone. Meredith et al[3] used a

rabbit model of *Staphylococcus epidermidis* endophthalmitis to show that intramuscular corticosteroid provided a level of antiinflammatory activity that was comparable to the effect of intraocular administration. However, intraocular injection appears to be an effective route of administration.[17,19] It is unknown whether intramuscular corticosteroid would have been effective in the present study because intramuscular administration was not tested. Although corticosteroids appear to be a safe adjunct to endophthalmitis therapy, retinal toxicity has been observed with high dose (800 to 4000 μg) intravitreal dexamethasone.[20]

Optimal antimicrobial combinations and route of administration for treatment of endophthalmitis are subjects of continuing debate. Stern et al[21] observed that 5 of 7 culture-positive patients who were treated with a single antibiotic injection and no vitrectomy suffered either recurrence of their infection or did not respond to treatment. One patient who received repeated intravitreal antibiotic injections and all patients who received repeated intravitreal antibiotic injections in combination with vitrectomy experienced resolution of their infections. Forster et al[22] recommended that intravitreal antibiotics be injected repeatedly at approximately 48- to 96-hour intervals in patients whose cultures are positive. However, Oum et al[23] described toxic reactions in the retinas of rabbits, especially in the outer retina and retinal pigmented epithelium, after repeated intravitreal antibiotic injections. The present study found that a single injection of ampicillin–gentamicin was effective in sterilizing the vitreous of all but one eye by postinfection day 5.

The combination of ampicillin and gentamicin was chosen for the present study because this antimicrobial combination has been shown to be highly efficacious for the treatment of severe enterococcal infection.[14] Although the laboratory *E. faecalis* strain JH2SS used in this study is susceptible to combined ampicillin and gentamicin, this combination therapy is effective in the treatment of fewer enterococcal isolates because of the increase in strains producing aminoglycoside-modifying enzymes.[24] Because of the increase in gentamicin resistance and retinal toxicity, alternative combinations that include agents such as ceftazidime, amikacin, and vancomycin[25–28] appear to be preferred over formerly recommended combinations[29] for the initial treatment of endophthalmitis.

Patients with endophthalmitis often have a postoperative or posttraumatic emergency. Even though the incidence of endophthalmitis is low (0.12% to 0.16%)[1,30] in the United States, numerous organisms are able to establish infection rapidly and to destroy intraocular tissue. Many organisms, such as *Bacillus cereus, Staphylococcus aureus, Streptococcus spp,* and *Pseudomonas spp* liberate potent toxins and tissue-damaging enzymes that may contribute to virulence in intraocular infections.[5,6,31] The treatment of infections with such organisms is problematic because although the intraocular spaces may be sterilized with antibiotic infusions, significant amounts of bacterial debris and potentially toxic products remain. Aside from the direct demonstration of a role for *E. faecalis* cytolysin in contributing to the course and severity of endophthalmitis, the role of toxins expressed by other bacterial species remains speculative as the availability of control strains specifically deficient in production of the toxin of interest is limited. Based on the dramatic effect of cytolysin expression on treatment failure observed in the present study, however, it is likely that other bacterial toxins do play determinant roles in the outcome of endophthalmitis. We are actively testing this prospect for several of them.

Although many cases of postoperative endophthalmitis are caused by nontoxigenic, coagulase-negative staphylococci, most severe infections are caused by bacteria known to produce one or more toxins. Identifying toxins that contribute to the course, severity, and now therapeutic responsiveness of endophthalmitis caused by toxigenic organisms is critical if visual outcome in such cases is to be improved. Understanding at the molecular level of the structure and mechanism of the action of toxins found to be contributory will provide a basis for developing rational or information-based therapeutics. By comparing the structures and functions of several contributory toxins, it may be possible to derive new and general therapeutic principles that permit successful, empirical treatment of endophthalmitis even before the toxigenic nature of the offending organism is known. This analysis using isogenic strains of *E. faecalis* was facilitated by the fact that *E. faecalis* strains express, at most, a single recognized toxin, cytolysin. A similar analysis of virulence for *Staphylococcus aureus, Bacillus cereus,* or *Streptococcus pyogenes* will be much more formidable because each of these strains expresses a constellation of toxins.

Key Words

Enterococcus faecalis, endophthalmitis, dexamethasone, cytolysin, inflammation

Acknowledgments

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