Pathogenesis of Gram-Positive Bacterial Endophthalmitis

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The severity of endophthalmitis has been associated generally with the virulence of the offending pathogen. However, precisely what constitutes the virulence in intraocular infections remains ill defined. We therefore sought to identify the basis for virulence for three common ocular pathogens (Bacillus cereus, Enterococcus faecalis, and Staphylococcus aureus) in terms of intraocular growth rates, bacterial localization patterns, and the contribution of cell walls and secreted products to the pathogenesis of endophthalmitis. Rabbit eyes were injected intravitreally with (i) viable B. cereus, E. faecalis, or S. aureus, (ii) metabolically inactive B. cereus, E. faecalis, or S. aureus, (iii) sacculus preparations from each strain, or (iv) culture fluid containing products secreted by each strain. Eyes were assessed at various times following injection by slit lamp biomicroscopy, electroretinography (ERG), bacterial and inflammatory cell enumeration, and histology. B. cereus endophthalmitis followed a more rapid and virulent course than E. faecalis or S. aureus endophthalmitis, eliminating retinal responsiveness, as measured by ERG, by 12 h. Analysis of bacterial localization revealed that B. cereus uniquely migrated rapidly from posterior to anterior segment during infection. Although injection of neither metabolically inactive bacteria nor cell wall sacculi greatly affected ERG, significant intraocular inflammation was observed. Injection of B. cereus or S. aureus culture fluids caused both significant reductions in retinal responsiveness and significant intraocular inflammation, paralleling that seen in natural infections. The results demonstrate that toxins, intraocular localization, and, to a lesser extent, the intraocular host response to cell walls all contribute to the pathogenesis of B. cereus, S. aureus, and E. faecalis endophthalmitis in a pathogen-specific manner. The key pathophysiologic differences in these intraocular diseases highlight opportunities for optimizing conventional therapies and deriving new ones.

Endophthalmitis is a vision-threatening disease that usually results from microbial infection of the interior of the eye. The course of bacterial endophthalmitis varies widely depending on the etiologic agent involved, ranging from relatively avirulent and therapeutically responsive infections caused by Staphylococcus epidermidis to the challenging and often sight-threatening infections caused by more virulent pathogens such as Bacillus cereus, Enterococcus faecalis, and Staphylococcus aureus. Although the outcome of severe endophthalmitis cases has been associated broadly with the virulence of particular bacterial species, precisely what constitutes virulence in these infections remains to be defined. Specific bacterial components that trigger aggressive intraocular inflammatory responses may represent candidate therapeutic targets for limiting visual loss in endophthalmitis. The emergence of multidrug-resistant organisms further highlights the importance of developing new therapeutic strategies.

Toward defining bacterial virulence in endophthalmitis, recent studies have centered on the specific contributions of bacterial toxins to disease severity. Attenuation of an organism’s ability to produce a single toxin (the E. faecalis cytolysin) or several toxins (S. aureus pore-forming toxins) resulted in significant reductions in infection severity, demonstrating that the production of toxins in situ in these two infection models measurably contributes to the course of endophthalmitis. The specific mechanisms by which these toxins induce intraocular tissue damage and inflammation are unclear. Despite attenuation resulting from insertional inactivation of toxin genes, substantial intraocular inflammation was observed, indicating that bacterial components other than exotoxins contribute to endophthalmitis pathogenesis. Furthermore, attenuation of the B. cereus derrnolysin toxin, hemolysin BL, did little to alter the course of experimental B. cereus endophthalmitis, suggesting that additional factors likely contribute to this highly virulent infection

Evidence from a number of experimental systems indicates the likelihood that a multitude of proteolytic or superantigenic proteins, chemoattractants, or other inflammatory mediators secreted by the bacterium during infection can contribute to an aggressive inflammatory response.

There exists a modest but rapidly emerging body of evidence highlighting the importance of gram-positive cell wall components in inflammation. Metabolically inactive organisms, cell walls, and individual envelope components (peptidoglycan, lipoteichoic acid, and capsular polysaccharide) stimulated inflammatory cell chemotaxis, cytokine production, and cellular toxicity in several ocular (17, 18, 32, 38, 39) and nonocular (4, 13, 19, 20, 23, 29–31, 33, 36, 46, 47, 54, 59, 61, 62) experimental systems. In the single report documenting the intraocular inflammation of gram-positive cell walls, Fox et al. (17) noted that peptidoglycan provoked chronic inflammation and retinal necrosis similar to that observed in eyes injected with lipopolysaccharide. However, due to the crude nature of the cell wall extracts injected, the specific basis for cell wall-induced inflammation was not determined.

Evidence suggests that the tertiary configuration of pepti-
Preparation of bacterium-free supernatants. Overnight cultures of each organ-
ism were diluted 1:100 in sterile BHI and incubated with aeration for 8 h at
37°C to an early stationary phase of growth. Cultures were centrifuged, and
cell-free supernatants filtered through Acrodisc 0.2-μm filter units (Gelman Sci-
ences, Ann Arbor, Mich.), adjusted to equivalent protein concentrations, and
stored at −70°C prior to injection.

Experimental endophthalmitis. New Zealand White rabbits (2 to 3 kg) were
maintained in accordance with institutional guidelines and the Association for
Research in Vision and Ophthalmology Statement on the Use of Laboratory
Animals in Ophthalmic Research. Prior to intravitreal injections, eyes were
dilated with topical 1% tropicamide and 2.5% phenylephrine HCl. Rabbits were
anesthetized generally by intramuscular injection of ketamine (Ketavet; Phoenix
Scientific, St. Joseph, Mo.) and xylazine (Rompun; Bayer Corp., Shawnee Missi-
nion, Kan; 5 mg/kg body weight) and topically in each eye with proparacaine HCl (Ophthalmic; Allergan, Horgmuersos, Puerto Rico; 0.5%).

Prior to intravitreal injection, aqueous humor (100 μl) was aspirated to relie-
ve intraocular pressure. Bacterial suspensions or cell-free supernatants (100 μl)
were injected into the midvitreous via a 0.15-mm needle attached to a 1.0-ml
syringe introduced through the pars plana approximately 3 mm from the limbus.
The contralateral eye was injected with PBS or sterile BHI (surgical controls) or
was left undisturbed (absolute control). Before postinfection, the course of in-
fec tion and inflammation were assessed by (i) slit lamp biomicroscopy, (ii)
electroretinography (ERG), (iii) intraocular bacterial growth, (iv) anterior chamber
inflammatory cell enumeration, and (v) thin-
section histology, as described above. Quantities of bacteria injected and times of
tissue recovery for analysis are listed in Results.

Slit lamp examination. To quantify intraocular inflammation, rabbits were
observed by slit lamp biomicroscopy (Topcon SL-5D; Kogaku K.K., Tokyo,
Japan) before and at various times during infection. Ocular inflammation was
scored by masked observers based on the scoring of progressive inflammation in
the cornea, anterior chamber, vitreous, and retina (11, 44). Each area of the eye
was scored independently on a scale of 0 (no inflammation) to 4 (maximal
inflammation). With regard to the anterior chamber, intraocular inflammation
was measured in parameters termed cell and flare. “Cell” corresponds to inflam-

matory cells appearing as flecks within the slit lamp beam, while “flare” corre-
dsponds to protein leakage into anterior chamber, giving a dusty appearance to
the slit lamp beam (40). The fundus reflex was assessed by the extent of red reflex
observed when the eye was exposed to an open slit-lamp beam. Vitreous and
retinal clarity were each scored based on the extent of progressive haze, exudate
and fibrin clump formation, and cellular reactions observed under thin slit-lamp
beam conditions.

Analysis of retinal function. ERG was used to measure the extent of retinal
function during the course of infection. Retinal responses are generally divided
into A-wave maximum and B-wave minimum values, with the B-wave amplitude
being the difference between the two responses. After dilation and 30 min of
dark adaptation, a ground electrode is placed on the rabbit’s ear, while bipolar
contact lens electrodes that record the flash response are placed in each eye. A
monopolar electrode is placed on the forehead. Retinas are illuminated with a
single, low-intensity flash (one flash per second), and the resulting B-wave am-
plitude is measured (in millivolts). Baseline B-wave amplitude was established
before each fundus reflex was assessed by the extent of red reflex observed
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beam conditions.

Analysis of anterior segment inflammation. Anterior segment inflammation
was assessed by counting infiltrating inflammatory cells in anterior chamber
fluid, using a hemocytometer.

Analysis of bacterial growth. To enumerate organisms in specific ocular tis-
sues, whole globes were surgically removed, rinsed with sterile PBS, and
placed cornea side up on sterile surgical dressing. Aqueous humor was recovered
from the anterior chamber by aspiration. The cornea, iris, lens, and vitreous were
each dissected away and placed separately into sterile tubes. The remaining outer
tunic was minced into small pieces and placed into a sterile tube. After each solid
tissue was weighed 0.5 ml of sterile PBS was added. All samples were then
homogenized with 1-0.1-mm-diameter glass beads in a Mini-BeadBeater (5,000
rpm, 30 s; Biospec Products, Bartlesville, Okla.). Bacterial CFU were quantified
by plating triplicate serial 10-fold dilutions on BHI.

Histopathological analysis. All eyes recovered for thin-section histopathology
were enucleated and fixed in 4% formalin for 24 h. Eyes were sectioned
and stained with either hematoxylin and eosin or tissue Gram's stain (53). Stained
tissue sections were analyzed by masked observers based on the extent of
inflammation in the cornea, anterior chamber, vitreous, and retina (11, 43).

Statistical analysis. All values represent the mean ± standard error of the
mean. Data for >2 eyes per treatment group and inflammatory response were
compared using the Wilcoxon's rank sum test. Statistical significance was
determined for P values ≤ 0.05.
RESULTS

Strain-to-strain variation in natural experimental endophthalmitis. Experimental infections with viable organisms were initiated by injection of the following inocula (log$_{10}$): B. cereus, 2.06 ± 0.04 CFU; E. faecalis, 1.99 ± 0.07 CFU; and S. aureus, 2.07 ± 0.07 CFU (mean ± SEM, p = 0.08). The natural courses of experimental endophthalmites were then analyzed as described in Materials and Methods. Sham-injected and uninfected control eyes were all normal, as measured by all inflammatory parameters.

(i) Intraocular inflammation. In B. cereus-infected eyes, intraocular inflammation was observed as early as 3 h, with mild to moderate conjunctival edema and minimal cell and flare in the anterior chamber. At 6 h, inflammatory symptoms progressed, with moderate anterior chamber cell and flare, vitreous haze, and a significant decrease in fundus reflex. From 12 to 18 h, inflammatory symptoms were severe in all animals, with anterior chamber hyphema, severe iritis, and peripheral corneal ring abscesses present. Fundus reflex was absent. Gross examination of enucleated globes and surrounding tissues showed severe periorbital inflammation, indicating a developing panophthalmitis. No B. cereus infections were allowed to progress further.

The evolution of experimental E. faecalis and S. aureus endophthalmitis occurred over a slower time course than that of B. cereus. Briefly, anterior and posterior chamber inflammatory changes and a significant loss of fundus reflex were evident by 24 h in both infection groups. Moderate to severe inflammation (severe anterior chamber cell and flare, vitreous opacities, white fundus reflex) was observed by 36 h in both infection groups. No additional evolution of disease occurred from 36 to 72 h in either infection group.

(ii) Bacterial growth and distribution in the eye. The numbers of viable B. cereus per eye increased steadily from 0 to 12 h. After reaching maximal levels (B. cereus, 8.07 ± 0.12 log$_{10}$ CFU), bacterial numbers were sustained until the termination of infection. The numbers of B. cereus per eye were significantly greater than those of E. faecalis and S. aureus per eye at 6 and 12 h (P ≤ 0.03) (Fig. 1A). B. cereus was recovered in both posterior and anterior segment tissues. At 3 h, the majority of viable bacilli were recovered from the vitreous (Fig. 2). At 6 and 9 h, greater numbers of bacilli were recovered from the outer tunic tissues than from the isolated vitreous. After 9 h, B. cereus populations recovered demonstrated a migration of organisms toward and into the anterior segment. Microscopic examination of aqueous humor samples recovered after 9 h showed bacilli moving about vigorously and clinging to fibrin clots within the sample.

The numbers of viable E. faecalis per eye increased from 0 to 24 h to 8.98 ± 0.03 log$_{10}$ CFU, with no significant intraocular growth thereafter. The numbers of viable S. aureus per eye increased from 0 to 36 h to approximately 6.14 ± 0.32 log$_{10}$ CFU, with no significant intraocular growth observed thereafter. Bacterial counts were higher in eyes infected with E. faecalis than in S. aureus-infected eyes from 12 to 72 h (P ≤ 0.04) (Fig. 1A). E. faecalis and S. aureus were recovered exclusively from posterior segment tissues.

(iii) ERG. The significant reductions in retinal responses of B. cereus-infected eyes observed as early as 3 h evolved rapidly to a >97% loss of B-wave activity by 12 h (Fig. 1B). Super-normal ERG responses were observed in E. faecalis-infected eyes and S. aureus-infected eyes at 12 and 6 h, respectively. Significant reductions in B-wave responses were observed at 24 h, with >90% loss of B-wave activity by 36 h in both E. faecalis- and S. aureus-infected eyes (Fig. 1B).
(iv) Anterior segment inflammation. Inflammatory cells were recovered from the aqueous humor of *B. cereus*-infected eyes as early as 6 h (Fig. 1C). By 12 h, the numbers of inflammatory cells recovered from *B. cereus*-infected eyes were greater than that recovered from *E. faecalis*- or *S. aureus*-infected eyes (*P* ≤ 0.02). Inflammatory cells were recovered from the aqueous humor of *E. faecalis* and *S. aureus*-infected eyes as early as 12 and 6 h, respectively (Fig. 1C), with similar inflammatory cell numbers recovered from infected eyes in both groups from 36 to 72 h (*P* ≥ 0.08).

(v) Histology. At 6 h, bacilli were observed primarily at posterior segment structural interfaces. Retinal detachment and photoreceptor layer folding and disruption were observed as early as 9 h. Bacilli were observed in the spaces between the outer limiting membrane and the retinal pigment epithelium (Fig. 3A) and at the posterior/anterior segment interface (Fig. 3B). Marked cell infiltration advanced from the optic nerve head into the vitreous. Bacilli were observed in the anterior segment at the posterior corneal surface. By 12 h, greater numbers of infiltrating cells and bacilli were interspersed within fibrin in the anterior chamber, and migration of cells into the cornea from the limbus and anterior chamber was observed. Bacilli appeared to invade the corneal endothelium and stroma (Fig. 3C). A similar but more severe inflammatory reaction was observed in the vitreous, with moderate disruption of the retinal architecture. At 18 h, eyes demonstrated maximal inflammation in all parts of the eye, including periorcular tissues.

Histological changes of eyes infected with *E. faecalis* and *S. aureus* were broadly similar to previous findings (8, 9, 27, 55). At 6 and 12 h, retinal and anterior segment tissues appeared histologically normal, and organisms were observed in the midvitreous in both infection groups. By 24 h, marked inflammatory cell infiltration advanced from the optic nerve head into the vitreous, and the outermost retinal layers were slightly

![Image](http://iai.asm.org/ on October 14, 2017 by guest)
inflamed in both infection groups. Enterococci associated with vitreous structures, including the anterior hyaloid membrane (Fig. 4A), while staphylococci adhered primarily to midvitreous fibrinous exudate and within small inflammatory cell clusters (Fig. 4B). The cornea, iris, and anterior chamber of E. faecalis-infected eyes were histologically normal, while inflammatory cells were observed in the anterior chamber and cornea of S. aureus-infected eyes.

At 36 h, the number of inflammatory cells in the vitreous increased, and fibrin and inflammatory cells were observed in the anterior chamber in both infection groups. Enterococci were associated with fibrinous exudate and vitreous structures, and significant retinal layer disruption was observed. The few staphylococci visualized were associated with fibrinous exudate or with inflammatory cell clusters in the vitreous. Anterior segment changes of S. aureus-infected eyes also included inflammatory cells in the cornea. By 48 h, retinal layers were indistinguishable in E. faecalis-infected eyes, and infiltrating cells filled the vitreous cavity. In S. aureus-infected eyes, significant retinal layer disruption and extensive abscess formation in the vitreous were observed. Anterior segment inflammation was more severe, with erythrocyte infiltration into the anterior chamber in both infection groups. The histological changes observed at 48 and 72 h were similar. Neither enterococci nor staphylococci were observed in the anterior segment in these histological sections.

**Contribution of secreted bacterial products to intraocular inflammation.** To assess the relative contributions of secreted bacterial products to intraocular inflammogenicity, supernatants of early-stationary-phase cultures of B. cereus, E. faecalis, and S. aureus were each injected intravitreally, and inflammation was assessed as described in Materials and Methods. Results are shown in Fig. 5 and 6. For clarity, in the discussion of results that follows, the individual data sets are designated by bracketed numbers which correspond to those in Fig. 5 and 6.

(i) **B. cereus.** In general, intravitreal injection of B. cereus supernatant significantly reduced ERG values and induced influx of inflammatory cells into the aqueous humor in numbers approaching that of the natural infection (live organisms [1] to supernatants [2] [Fig. 5A and live organisms [13] to supernatants [14] [Fig. 6A]). Histological examination of eyes injected with B. cereus supernatant exhibited retinal photoreceptor layer folding similar to that observed in the early stages of natural B. cereus infection (Fig. 3D).

(ii) **E. faecalis.** Intravitreal injection of E. faecalis supernatant significantly reduced ERG values compared to controls at 24 and 48 h ($P \leq 0.03$), but not to the extent of that observed during the natural infection (live organisms [5] to supernatants [6] [Fig. 5B]). Histological analysis demonstrated transient in-
flamatory cells in the vitreous and a normal retina. The numbers of aqueous humor inflammatory cells recovered were similar to that induced by the natural infection at 24, 48, and 72 h ($P \geq 0.29$) (Fig. 6B, live organisms [17] to supernatants [18]).

(iii) *S. aureus*. Intravitreal injection of *S. aureus* supernatant significantly reduced retinal responsiveness similar to that of the natural infection at 48 and 72 h ($P \geq 0.22$) (Fig. 6C, live organisms [9] to supernatants [10]). Histological analysis demonstrated transient inflammatory cells in the vitreous and a normal retina. Aqueous humor inflammatory cell numbers approached that induced by the natural infection (Fig. 6C, live organisms [21] to supernatants [22]).

(iv) Strain-to-strain variation in supernatant inflammogenicity and retinal toxicity. ERG values of eyes injected with *B. cereus* and *S. aureus* supernatants were similar ($P = 0.43$) and were lower than those of eyes injected with *E. faecalis* supernatants at 24 and 48 h ($P \leq 0.04$) (Fig. 5 [2, 6, 10]). ERG values of eyes injected with *S. aureus* supernatant were lower than those injected with *E. faecalis* supernatant at 72 h ($P = 0.02$) (Fig. 5 [10, 6]).

Intravitreal injection of *B. cereus* supernatant caused an influx of greater numbers of inflammatory cells into the aqueous humor compared to that of *E. faecalis* or *S. aureus* supernatant at 24 h. ($P \leq 0.03$) (Fig. 6 [14, 18, 22]). Aqueous humor inflammatory cell numbers recovered from eyes injected with *E. faecalis* and *S. aureus* supernatants were similar at 48 and 72 h ($P \geq 0.08$) (Fig. 6 [18, 22]).

**Contribution of cell wall constituents to virulence.** To assess the relative inflammogenicity of gram-positive cell walls in endophthalmitis, metabolically inactive cells and sacculi of *B. cereus*, *E. faecalis*, and *S. aureus* were each injected intravitreally, and inflammation was assessed as described in Materials and Methods. Sacculi were tested to specifically assess potential differences in the inflammogenicity of the cell wall structural components in the absence of surface proteins to intraocular inflammation.

(i) Metabolically inactive organisms. The numbers of metabolically inactive bacteria injected were chosen based on the number of viable organisms present when early signs of inflammation were observed in the natural infection. The following inocula (log$_{10}$ CFU) were used: *B. cereus*, 7.96 ± 0.07; *E. faecalis*, 7.07 ± 0.12 (mean ± SEM; *E. faecalis* significantly greater [$P \leq 0.01$]).

Metabolically inactive *E. faecalis* and *S. aureus* caused slight but significant reductions in ERG values at 24 h ($P \leq 0.01$) (Fig. 5 [8, 12]), which returned to preoperative levels by 48 h ($P \geq 0.59$). ERG values of eyes injected with metabolically inactive *B. cereus* remained at preoperative levels at all time points ($P \geq 0.08$) (Fig. 5A [3]). Significant increases in the numbers of aqueous humor inflammatory cells following intravitreal injection of metabolically inactive *B. cereus*, *E. faecalis*, or *S. aureus* were observed ($P \leq 0.01$) (Fig. 6 [15, 19, 23]). At 72 h, the numbers of inflammatory cells induced by metabolically inactive *E. faecalis* were greater than those induced by either metabolically inactive *S. aureus* or *B. cereus* ($P \leq 0.04$) (Fig. 6 [15, 19, 23]).

(ii) Sacculi. The numbers of sacculi injected were chosen based on the inflammogenicity observed in assays using metabolically inactive organisms and to compare the inflammogenic potential of the three organisms to themselves. The following inocula (log$_{10}$ CFU) were used: *B. cereus*, 5.92 ± 0.08; *E. faecalis*, 6.02 ± 0.19; and *S. aureus*, 6.14 ± 0.21 (mean ± SEM, $P \geq 0.42$).

ERG values of eyes injected with sacculi of *B. cereus*, *E. faecalis*, or *S. aureus* remained at preoperative levels throughout the assay period ($P \geq 0.39$) (Fig. 5 [3, 7, 11]). There were, however, increases in the numbers of aqueous humor inflammatory cells from 24 to 72 h that were similar among the three infection groups throughout the assay period ($P \geq 0.13$).

(iii) Comparative analyses: whole bacteria versus sacculi. ERG values of eyes injected with metabolically inactive organisms were similar to those of eyes injected with sacculi, regardless of the strain tested ($P \geq 0.07$) (Fig. 5). Overall, the numbers of aqueous humor inflammatory cells recovered from eyes injected with metabolically inactive organisms were greater than those recovered from eyes injected with their sacculi ($P \leq 0.03$) (Fig. 6).

(iv) Comparative analyses: whole bacteria versus supernatants and natural infections. ERG values of eyes injected with metabolically inactive *B. cereus* or *S. aureus* or their respective sacculi were greater than those of eyes injected with supernatants ($P \geq 0.03$) (Fig. 5A and C). ERG values of eyes injected with metabolically inactive *E. faecalis*, sacculi, or supernatant were similar at all time points ($P \geq 0.06$) (Fig. 5B). In general, ERG values of metabolically inactive *S. aureus* and *E. faecalis* and their sacculi were greater than those of the natural infections ($P \leq 0.01$) (Fig. 5B). In general, the numbers of aqueous inflammatory cells recovered from eyes injected with superna-
tants were greater than the numbers recovered from eyes injected with metabolically inactive organisms or sacculi preparations (P ≤ 0.03) (Fig. 6) but were lower than cell numbers recovered from natural infections (P ≤ 0.02) (Fig. 6).

**DISCUSSION**

Intraocular infection following the introduction of *B. cereus*, *S. aureus*, or *E. faecalis* into the posterior segment of the eye can follow one of two courses: (i) a highly inflammatory infection that is treated with aggressive therapy and in many cases salvages useful vision, or (ii) a highly inflammatory infection that is refractory to treatment, resulting in permanent vision loss, if not loss of the eye itself. The visual consequences of severe endophthalmitis cases caused by these ocular pathogens have been linked with virulence traits of the particular bacterial species. In most cases, however, the specific factors associated with virulence in these infections have not been characterized. It was, therefore, of interest to determine what cellular components (i.e., secretory products and/or cell wall constituents) and the intraocular behavior (i.e., growth patterns and tissue localization) of each organism contributed to the pathogenesis of endophthalmitis.

Reports correlating the intraocular virulence of these pathogens with visual outcome regularly list toxins as the proponents of a natural infection. Recently, we observed that culture supernatants of *S. aureus* and *B. cereus*, hav

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after 36 h). Bacilli were shown associating with and penetrating into the cornea, suggesting that corneal ring abscess formation may be attributed to the induction of a corneal inflammatory response to the bacterial invasion itself or to locally produced inflammatory mediators generated in response to the tissue invasion. Questions remain as to the cause of such an aggressive inflammatory response and almost certain loss of vision accompanying B. cereus endophthalmitis. B. cereus, unlike S. aureus and E. faecalis, is a soil saprophyte and therefore is not likely to have adapted to commensal existence within or on the surface of the human body. The intense inflammatory reaction observed with B. cereus endophthalmitis may therefore be attributable to a lack of coevolutionary history and therefore a lack of evolved tolerance.

The results of these studies revealed key differences in the pathophysiology of gram-positive bacterial endophthalmitis caused by different organisms. If B. cereus, S. aureus, and E. faecalis possessed similar general biochemical traits (i.e., cell wall composition and toxin production), one would expect such infections to be similar. B. cereus and S. aureus each produce multiple toxins, both pore forming and cell membrane destabilizing, that have been implicated as virulence factors in various animal models of infection (6, 14, 63). The cytolysin is the only toxin of E. faecalis reported to contribute to its virulence (27, 28, 55). Yet S. aureus and E. faecalis infections were clinically similar to one another, and B. cereus intraocular infections were more severe. Another important difference observed was that of B. cereus motility and migration into retinal tissues and into the anterior segment, a phenomenon observed for neither S. aureus nor E. faecalis. In any case, the ocular pathogenesis of these organisms has been demonstrated to be an organism-dependent contribution of toxins, intraocular localization and behavior, and, to a lesser extent, the host response to bacterial cell walls. The results suggest that conventional therapeutic approaches may not be adequate for all types of endophthalmitis due to key differences in the pathophysiology of each infection. Understanding the basis for these differences in these virulent infections will provide unique insights into endophthalmitis pathogenesis and advance the goal of developing new therapeutic strategies for these diseases.

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