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Bacterial endophthalmitis in the age of outpatient intravitreal therapies and cataract surgeries: Host-microbe interactions in intraocular infection

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Abstract

Bacterial endophthalmitis is a sight threatening infection of the interior structures of the eye. Incidence in the US has increased in recent years, which appears to be related to procedures being performed on an aging population. The advent of outpatient intravitreal therapy for management of age-related macular degeneration raises yet additional risks. Compounding the problem is the continuing progression of antibiotic resistance. Visual prognosis for endophthalmitis depends on the virulence of the causative organism, the severity of intraocular inflammation, and the timeliness of effective therapy. We review the current understanding of the pathogenesis of bacterial endophthalmitis, highlighting opportunities for the development of improved therapeutics and preventive strategies.

Keywords

Endophthalmitis; *Staphylococcus aureus*; *coagulase-negative staphylococci*; *Streptococcus pneumoniae*; *Enterococcus faecalis*; *Bacillus*

Bacterial endophthalmitis is a sight threatening intraocular infection. Endophthalmitis may arise exogenously or endogenously. In exogenous bacterial endophthalmitis, bacteria enter the eye through a breach in the globe, such as surgery, intraocular injection, penetrating trauma, or intraocular extension of infection of the cornea (keratitis) or a glaucoma filtering bleb (blebitis). Endogenous bacterial endophthalmitis stems from bacteremic seeding of the eye; the source of bacteremia may be transient (e.g. from intravenous drug abuse) or persistent (e.g. endocarditis). In this paper, we review the current understanding of the pathogenesis of bacterial endophthalmitis to aid the ultimate goal of developing better therapeutic and preventive strategies.

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1. The problem of endophthalmitis

The rate of intraocular procedures is increasing, especially cataract removal and lens replacement, now one of the most commonly performed surgeries in the developed world (Brian and Taylor 2001). There has also been a marked increase in the number of intravitreal injections for treatment of neovascular eye disease and intraocular inflammation (Peyman *et al.* 2009). This has been accompanied by a commensurate increase in the number of injection-related complications. The incidence of endophthalmitis after intravitreal injection ranges from 0.006% to 0.16% per injection, or between 0.07% and 1.3% per patient treatment period (Diago *et al.* 2009, Klein *et al.* 2009, Sampat and Garg 2010, VEGF Inhibition Study in Ocular Neovascularization (V.I.S.I.O.N.) Clinical Trial Group *et al.* 2006). Endophthalmitis is the leading infectious complication of cataract surgery, with an incidence of 0.01% to 0.3% (Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons 2007, Taban *et al.* 2005) and the rate has increased in recent years (West *et al.* 2005). Infection also often follows traumatic injury to the globe, with an incidence of posttraumatic bacterial endophthalmitis ranging from 0.9% to 17% (Jonas *et al.* 2000, Thompson *et al.* 1993, Thompson *et al.* 1995).

Complicating the rise in endophthalmitis, antibiotic resistance is increasing among common causes of endophthalmitis, resulting in more resistance-related treatment failure (Juarez-Verdayes *et al.* 2006, Major *et al.* 2010, Tang *et al.* 2007). Methicillin resistant *Staphylococcus aureus* (MRSA) endophthalmitis represents approximately 40% of *S. aureus* endophthalmitis cases in some centers (Deramo *et al.* 2008, Major *et al.* 2010). Intermediate vancomycin resistance has been reported in staphylococcal infections of the eye (Juarez-Verdayes *et al.* 2006), and full vancomycin resistance in enterococci is common (Tang *et al.* 2007). Recently, full vancomycin resistance has transferred from the enterococci to *S. aureus* (Centers for Disease Control and Prevention (CDC) 2002, Finks *et al.* 2009), but these strains have yet to cause eye infection. Resistance to newer fluoroquinolones is also on the rise (Deramo *et al.* 2008, Miller *et al.* 2006).

Visual prognosis after bacterial infection depends greatly on 1) the virulence of the causative organism, 2) visual acuity at presentation, and 3) efficacy of treatment (EVS 1996). Although infection resolves well in about 2/3 of cases using current intravitreal antibiotic regimens, and occasionally anti-inflammatory agents and vitrectomy, significant visual loss occurs in the remaining 1/3 of cases. In an effort to prevent infection and improve outcome, considerable effort is being invested in understanding the pathogenesis of endophthalmitis, and identifying critical points in the process that represent opportunities for intervention.

The most common microbes isolated from cases of post-surgical endophthalmitis are coagulase-negative staphylococci, principally *Staphylococcus epidermidis*, and most of these infections resolve well (Lalwani *et al.* 2008, Miller *et al.* 2007). *Staphylococcus aureus* is the second most common cause of acute postoperative infection following cataract and glaucoma surgeries, and vitrectomy. Following traumatic injury, *Bacillus cereus* is a leading concern, in part because of the explosiveness of infection (Table 1). *Bacillus*, *S. aureus*, and streptococcal endophthalmitis are associated with significant visual loss (Lalwani *et al.* 2008, Major *et al.* 2010).

2. The relationship between bacterial virulence and outcome: Progress toward an understanding

The main concern in endophthalmitis is that in infection caused by virulent organisms, visual loss often results despite effective antimicrobial therapy. Improved therapeutic strategies may result from a better understanding of exactly what constitutes virulence in the

host pathogen interaction. The pathophysiology of infection in the unique anatomical and immunological environment of the eye is beginning to be investigated. In other cases, we must extrapolate from experiments performed at other anatomical sites, and *in vitro*.

2.1 Staphylococcus aureus

2.1.1 *S. aureus* cell wall components—*S. aureus*** is a gram-positive bacterium and leading cause of postoperative and posttraumatic endophthalmitis, often associated with vision loss (Kattan *et al.* 1991, Pijl *et al.* 2010, Shirodkar *et al.* 2010). Its pathogenicity for the eye is believed to stem from the variety of virulence traits that it expresses, and from the host response to its presence. *S. aureus* cell wall components, including peptidoglycan, lipoproteins and teichoic acids, play important roles in virulence by contributing to immuno-stimulation and immune evasion (Bera *et al.* 2007, Hashimoto *et al.* 2006). Lipoteichoic acid and peptidoglycan in the cell wall are each capable of activating complement causing the release of cytokines and chemokines by monocytes and macrophages (Howes *et al.* 1994, Timmerman *et al.* 1993). Recently, wall teichoic acids (WTA) have been studied to understand their role in *S. aureus* endophthalmitis (Suzuki *et al.* 2011). WTA, a major polyanionic polymer component of *S. aureus* cell wall, is essential for the manifestation of virulence in endophthalmitis, and has been targeted with small molecule inhibitors of its biosynthesis (Suzuki *et al.* 2011). Cell wall anchored protein A binds the Fc region of immunoglobulin G, coating the cell surface and preventing neutrophils from binding, thus interfering with phagocytosis (Cedergren *et al.* 1993, Patel *et al.* 1987). Protein A also appears to be employed by *S. aureus* to evade an antigen-specific B cell response (Bekeredjian-Ding *et al.* 2007). It was identified as a sensitizer of B cells for the recognition of TLR2-active lipopeptides promoting T-cell independent B cell proliferation, without inducing secretion of IgM (Bekeredjian-Ding *et al.* 2007). It also activates a specific clone of T cells (Sinha *et al.* 1999). Protein A has also been described to elicit release of IL-1 and increase production of TNF-α and nitric oxide *in vivo* through activation of macrophages (Singh *et al.* 1992, Sinha *et al.* 1999).

2.1.2 Quorum sensing system and biofilm formation—*S. aureus* exists in alternate physiologic states depending upon environmental conditions/stressors, and number of bacteria: Planktonic (free-living, mobile) and sessile (stationary, biofilm-forming) states correlate with changes in bacterial physiology and virulence expression. We are starting to understand the many regulatory mechanisms involved in the transition from planktonic to biofilm phenotypes.

At low cell density, *S. aureus* expresses cell surface proteins including protein A, coagulase and fibronectin binding proteins and other adhesins, that are thought to promote colonization and evasion of the immune system (Goerke and Wolz 2004, Novick 2003). This state of upregulation of adhesion molecules correlates also with the initiation of biofilm formation that is thought to allow bacteria to survive conditions hostile to single cell planktonic growth (Beveridge *et al.* 1997). At higher cell densities, gene expression shifts to production of secreted factors, such as hemolysins and proteases that are associated with tissue damage and tissue invasion (Dunman *et al.* 2001).

The accessory gene regulator (*agr*) system is a main determinant of cell density-dependent regulation of gene expression by *S. aureus* (Fig. 1). The *agr* operon encodes an autoinducer peptide (AIP). Four AIP structural subgroups have been identified, each synthesized as a precursor and post translationally modified and processed to an8 amino acid cyclic peptide containing a conserved thiolactone ring (Jarraud *et al.* 2000, Ji *et al.* 1997). AIPs are species and strain specific, and exhibit cross interference such that one AIP can serve as an antagonist of another (Novick 2003, Otto *et al.* 1999). The *agr* system is transcribed in two

RNAs, RNA II and RNA III. Each is divergently transcribed from promoters P2 and P3 respectively. RNA II encodes the four structural genes; *agrA*, *B*, *C* and *D*. *agrD* encodes the precursor of the AIP that matures through proteolyticcleavage by a membrane anchored protein, *agrB,* into the active form capable of binding the cell surface exposed domain of the trans-membrane sensor kinase, AgrC. This leads to the activation of the response regulator, AgrA, triggering increased transcription of RNA II and RNA III. RNA III, which is a regulatory RNA that also encodes delta toxin, regulates expression of other virulence factors. Its 5' end has been shown to positively regulate alpha toxin expression from the *hla* gene (Morfeldt *et al.* 1995), and its 3' end represses the synthesis of protein A (Huntzinger *et al.* 2005).

The Staphylococcal Accessory Regulator (SarA) protein family supplements *agr* in regulating expression of virulence genes. SarA is a DNA-binding protein that activates target genes by binding to a conserved A/T-rich recognition motif of select promoters. SarA promotes synthesis of fibronectin- and fibrinogen-binding proteins involved in adhesion of bacteria, and synthesis of α-, β- and δ-toxins involved in tissue lysis and spread of infection (Chien *et al.* 1999, Dunman *et al.* 2001). Expression of SarA peaks during the late exponential phase and coincides with *agr* activation (Rechtin *et al.* 1999). SarA, is required for full *agr* regulation, as it influences expression of RNA III, the *agr* effector molecule. Several *sarA* homologs have been identified and their role in regulating gene expression is being studied. SarR, for instance, peaks during post-exponential phase and represses *sarA* transcription during the late exponential and stationary phases (Manna and Cheung 2001). SarS, repressed by *agr* and *sarA*, activates transcription of *spa* encoding surface protein A and it represses the expression of the alpha toxin gene (Tegmark *et al.* 2000). SarT that is repressed by *sarA* and *agr,* represses alpha toxin expression (Schmidt *et al.* 2001), highlighting the complexity of virulence regulation in *S. aureus*.

Some work has been done to evaluate the role of *agr* and *sarA* in the pathogenesis of endophthalmitis. A *sarA* mutant, which exhibits decreased extracellular protein and cell surface protein expression but increased production of lipolytic and proteolytic proteins, shows surprisingly little change by itself in virulence in an endophthalmitis model compared to its wild type parent (Booth *et al.* 1997). Mutations in *agr*, however are highly attenuated (Booth *et al.* 1995, Booth *et al.* 1997, Giese *et al.* 1999). The *agr*-deficient strain expresses decreased levels of alpha, beta, gamma and delta toxins, TSST-1 and staphylococcal enterotoxins B and C, with increase in protein A and fibronectin-binding protein expression (Booth *et al.* 1995, Morfeldt *et al.* 1988). An *agr/sar* double mutant is almost completely attenuated (Booth *et al.* 1997). Evaluating the role of the individual cytolysins revealed that their contribution to the severity of endophthalmitis disease progression is complex and partly additive (Booth *et al.* 1995). Among the different toxins, a significant role for the alpha and beta toxins was identified. Infections with strains deficient in these toxins retained significantly more retinal function and showed less inflammation (Callegan *et al.* 2002b). Alpha toxin is a well characterized pore-forming toxin that, in addition to its direct lytic effect, causes ATP and calcium ion leakage at sub-lytic levels, triggering the arachidonic acid cascade in endothelial cells and causing the inflammatory reaction (Walev *et al.* 1993). The beta toxin is a magnesium-dependent sphingomyelinase C that degrades sphingomyelin in the outer leaflet of erythrocytes, decreasing viability and eventually lysing monocytes and lymphocytes, with accompanying cytokine release (Huseby *et al.* 2007, Marshall *et al.* 2000). Culture fluids containing these toxins are highly inflammatory and toxic to the retina (Callegan *et al.* 1999a).

The Agr and the SarA regulators control staphylococcal gene expression under changing environmental conditions, including the transition from planktonic to biofilm growth. Generally, the transition from planktonic to biofilm growth (and back) requires cell

attachment, proliferation, biofilm maturation and finally cell detachment. Loss of *agr* function leads to upregulation of surface features that facilitate attachment to polystyrene surfaces (Vuong *et al.* 2000) and increased propensity to form biofilms, whereas mutations in *sarA* result in reduction in the capacity for biofilm formation (Beenken *et al.* 2010). These findings are supported by time-lapse confocal microscopic examination, which shows that detachment of cells from a biofilm coincides with *agr* expression (Yarwood *et al.* 2004). Thus, Agr activation reduces biofilm formation and enhances cell detachment, which is believed to contribute to dissemination of the microbe following establishment of a nidus of infection (Kong *et al.* 2006). This inability of cells to detach in *agr* mutants results in thicker biofilms than those formed by the wild type parental strain (Vuong *et al.* 2000, Vuong *et al.* 2004). Regulation of biofilm formation by *agr* is not entirely straight forward, however. Alpha-toxin expression, which is positively regulated by *agr*, enigmatically contributes to biofilm formation under static and flow conditions (Caiazza and O'Toole 2003). In the final stages, detachment from the biofilm is thought to be mediated in part by the surfactant properties of δ-hemolysin, encoded by the *agr* locus itself (Vuong *et al.* 2000).

The polysaccharide intercellular adhesion (PIA) that forms part of the extracellular biofilm matrix, is encoded by the *icaADBC* operon, that promotes biofilm formation (Cramton *et al.* 2001, Jefferson *et al.* 2004). Increased expression of *icaADBC* is triggered by environmental stress factors. This polymeric matrix contributes a physical barrier to penetration of some antimicrobials (Xu *et al.* 2000) and appears to offer an environment whereby *S. aureus* can deactivate reactive oxygen species (ROS) produced by the immune system (De Beer *et al.* 1994). The biofilm matrix chemistry is complex and includes proteinaceous material, extracellular DNA and polysaccharides. Thus enzymes such as DNase, trypsin and proteinase K, and other biofilm dispersing compounds may aid in the treatment of infections caused by the persistence of bacteria on abiotic surfaces (Boles and Horswill 2011). After intraocular lens (IOL) insertion, biofilm formation is of particular concern as it has the potential of promoting the survival of bacteria, and rendering them resistant to clearance.

2.1.3 The stress regulator, σ^B—Another regulatory factor involved in the stress response is σ^B. The σ^B regulon includes more than a 100 genes involved in stress response, cell envelope biosynthesis, intermediary metabolism, and other signaling pathways (Bischoff *et al.* 2004). Among σ^B regulated genes related to virulence are those that contribute to bacterial aggregation and protection against the type of oxidative stress that can result from PMN engulfment and exposure to antibiotics (Bischoff *et al.* 2004, De Lencastre *et al.* 1999, Gertz *et al.* 2000, Kullik *et al.* 1998). Based on microarray analysis of the transcriptional profile of different *S. aureus* strains and their respective isogenic σ^B mutants, σ^B appears to fine tune virulence factor production in response to changing environments (Bischoff *et al.* 2004). σ^B was found to upregulate expression of many adhesins, and repress exoprotein and toxin production, and is thus likely to be acting conversely to RNA III, the effector molecule of *agr* (Bischoff *et al.* 2004).

2.1.4 Nutritional environment and virulence—Recently, CodY has been found to connect *S. aureus* virulence to metabolic state (Sonenshein 2007), and similar regulators likely exist for most pathogens. CodY is a GTP-binding global regulator, first identified in *Bacillus subtilis* (Sonenshein 2005). In that host, it senses the nutritional environment and regulates catabolic enzyme biosynthesis, and production of competence factors for DNA uptake (Hendriksen *et al.* 2008). In *S. aureus*, CodY influences regulation of RNA II and RNA III expression in the *agr* operon, and as a result, affects expression of alpha-toxin and likely other toxins. It also regulates production of PIA (Majerczyk *et al.* 2008), in addition to its role in regulating capsule production (Majerczyk *et al.* 2010). In addition to an indirect role in regulating virulence gene expression through *agr*, *codY* also directly regulates numerous transcription units associated with amino acid biosynthesis, transport of

macromolecules, and virulence (Majerczyk *et al.* 2010). CodY is responsive to GTP and branched chain amino acid (BCAA) concentration in the environment. Isoleucine is a major ligand for CodY, and when present above a critical threshold, causes CodY to repress transcription of target genes (Pohl *et al.* 2009). Based on studies in other organisms, such as *S. pyogenes*, it was suggested that the requirements for CodY activation may be satisfied in the bloodstream and other tissues, resulting in a CodY-induced lag in expression of virulence, perhaps in an effort to stably co-exist with the host (Camargo and Gilmore 2008). We are beginning to examine on the role *codY* plays in ocular infection, given the presence of BCAA in the aqueous humor. Promoting CodY repression of virulence in infection could open new therapeutic opportunities for limiting ocular damage, perhaps using only non-toxic amino acids administered or restricted at the site of infection.

2.1.5 *S. aureus* pathogenesis atextraocularsites—Much of what is known about the role of quorum sensing and nutritional variables has been determined in the context of infection at other anatomical sites. For *S. aureus* to survive in the blood, they first need to protect themselves from killing by neutrophils and to that end they employ factors like carotenoid staphyloxanthin (Pelz *et al.* 2005), which scavenges reactive oxygen species; phenol soluble modulins, which disrupt the plasma membrane integrity of neutrophils (Wang *et al.* 2007); and clumping factor (ClfA) that binds fibrinogen, triggering staphylococcal agglutination reducing the effectiveness of phagocytosis (Palmqvist *et al.* 2004). ClfA is also believed to enable staphylococci to adhere to fibrin on the vascular endothelium, contributing to vegetation formation and endocarditis pathogenesis (Moreillon *et al.* 1995). The chemotaxis inhibitory protein of *S. aureus* (CHIPS) acts as a specific and potent inhibitor of neutrophil anaphylatoxin C5a, which plays a crucial role in the early recruitment of neutrophils to the infection site (Postma *et al.* 2004). High levelC5a can be deleterious in inflammatory and autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease and reperfusion injury (Bunschoten *et al.* 2011). Specific inhibition of C5a activation through modification of CHIPS is considered a promising strategy to treat such conditions (Allegretti *et al.* 2005, Bunschoten *et al.* 2011).

In an abscess model, it was found that administration of an inhibitory auto-inducing peptide delayed *agr* activation for 2–4 hours only (Wright *et al.* 2005). However, this was sufficient to limit formation of the abscess, suggesting that *agr* expression is required early in infection (Wright *et al.* 2005). Abscess formation in the kidney was recently shown to be restricted by the host protein, calprotectin, which chelates divalent metals including Mn^{+2} and Zn^{+2} (Corbin *et al.* 2008). Specifically, restriction of Mn^{+2} was shown to be the critical factor in limiting *S. aureus* abscess formation. Furthermore, *S. aureus* surface protein A, and coagulation factors like coagulase (Coa) and von Willebrand factor-binding protein (vWbp), are essential for abscess formation (Cheng *et al.* 2011). Questions that are unresolved with respect to the pathogenesis of *S. aureus* endophthalmitis include: Why does *S. aureus* make such a plethora of exotoxins? Do most of these induce subtle changes in host cell behavior at sub-toxic levels during asymptomatic colonization and carriage? To what extent does immune privilege alter the course of infection or abscess formation – particularly with respect to factors, such as CHIPS and Eap that target immune cells? How exactly does *S. aureus* damage the retina? Does it need to translocate from the anterior chamber to the vitreous when the posterior capsule is intact, or are the toxins produced along with the inflammation mounted by the host sufficient to cause the damage?

2.2 Coagulase-negative staphylococci (CoNS)

Coagulase-negative staphylococci (CoNS) are primary colonizers of the keratinized and wet epithelium of humans, but can cause infection when introduced into a sterile site. As a result of this proximity, they are leading causes of medical implant and device-related infections.

The increased uses of medical devices, along with the spread of antibiotic resistance, have heightened interest in better understanding this microbe in the context of infection (Raad *et al.* 1998). In the eye, CoNS, mainly *S. epidermidis* (although it is often not identified to the species level), are the most common causes of postoperative endophthalmitis, accounting for 70% of cases following cataract extraction. Most cases resolve well with treatment, with little visual loss. The rise in methicillin and fluoroquinolone resistance, as well as reduced glycopeptide susceptibility in *S. epidermidis*, is of concern (Giacometti *et al.* 2000, Raad *et al.* 1998, Villari *et al.* 2000).

2.2.1 Virulence in *S. epidermidis*—*S. epidermidis* possesses gene regulatory mechanisms that are similar to *S. aureus*, including an *agr* quorum sensing system. However, *S. epidermidis* lacks many of the toxins expressed by *S. aureus*. Its ability to form biofilms is important in the pathogenesis of infection, likely including endophthalmitis (Bainbridge *et al.* 1998, Garzozi and Harris 2000). Biofilm production by *S. epidermidis* involves synthesis and secretion of a β-1,6-linked N-acetylglucosamine polysaccharide intercellular adhesion (PIA) similar to that expressed by *S. aureus*. Biofilm formation involves adhesive surface proteins, such as ClfA (Heilmann *et al.* 1997) mediating bacterial binding to fibrinogen, and the AtlE autolysin and Spp1 holin (Gotz 2002) which release bacterial DNA into the biofilm, in addition to PIA biosynthesis (Gotz 2002, Heilmann *et al.* 1997). The type of IOL used affects the extent of bacterial binding, with the greatest binding being observed to hydrophilic acrylic polymer, followed by poly-(methyl methacrylate), hydrophobic acrylic, and then silicone (Baillif *et al.* 2008).

S. epidermidis, like *S. aureus,* expresses several surface proteins, termed MSCRAMMs (microbial surface components recognizing adhesive matrix molecules), that bind matrix proteins of basement membranes and provisional wound matrix. SdrG, a fibrinogen-binding protein, has been found to be important for adhesion and central venous catheter-associated infection (Guo *et al.* 2007, Hartford *et al.* 2001, Nilsson *et al.* 1998). Besides binding to prosthetic devices and wounds, *S. epidermidis* like *S. aureus*, produces short hydrophobic peptides termed phenol soluble modulins, that appear to function as proinflammatory agents and thus contribute to tissue damage and host evasion (Otto 2009). Despite the incidence of *S. epidermidis* as a causative agent of endophthalmitis, few studies have examined virulence in the context of the eye.

2.2.2 Methicillin resistance in staphylococci poses a serious challenge to treatment—Following the introduction of methicillin in 1960, antibiotic resistance emerged quickly (Jevons *et al.* 1963). Methicillin resistant *S. aureus* (MRSA) are now leading causes of invasive infection and death in the US (Klevens *et al.* 2007). First being confined to the hospital environment, MRSA emerged in the community in the US in the mid 90's, causing infection in children and others with no prior healthcare contact (Zetola *et al.* 2005). Community associated MRSA (CA-MRSA) appear to be more virulent than hospital associated (HA-MRSA) strains (Kazakova *et al.* 2005, Tenover *et al.* 2006). A main distinguishing feature of community associated strains is the presence of a mobile genetic element that encodes an arginine catabolic mobile element (ACME) (Diep *et al.* 2006). This mobile element, located adjacent to the methicillin resistance determinant, is thought to have been horizontally transferred to *S. aureus* from *S. epidermidis,* and to confer enhanced skin colonization (Miragaia *et al.* 2009).

Methicillin is a beta-lactam antibiotic that inhibits bacterial cell wall synthesis by binding and inhibiting the activities of penicillin binding proteins (PBPs) on the cell wall. PBPs catalyze transpeptidation of the cell wall, creating essential peptidoglycan crosslinks. Methicillin resistance in staphylococci is conferred by the product of the *mecA* gene, which encodes an unusual auxiliary penicillin binding protein, PBP2A, that fails to bind

methicillin, and thus renders methicillin and other structurally related β-lactam antibiotics incapable of blocking cell wall biosynthesis (Chambers 1997). In both *S. aureus* and *S. epidermidis*, *mecA* occurs on the staphylococcal cassette chromosome *mec* (SCC *mec*) element (Katayama *et al.* 2000). There are 8 organizational classes of SCC *mec* among CoNS and *S. aureus* (Zhang *et al.* 2009). CoNS positive for *mecA* are believed to serve as a reservoir for methicillin-resistance determinants (Barbier *et al.* 2010, Garza-Gonzalez *et al.* 2010). Strains carrying SCC *mec* tend to be resistant to multiple antibiotics (Diep *et al.* 2006, Holden *et al.* 2004).

MRSA has been isolated from ocular infections, including endophthalmitis, bleb-associated infection, trauma associated infection, and endogenous endophthalmitis (Fukuda *et al.* 2002, Major *et al.* 2010, Pierre and Tang 2010). Resistance of staphylococcal ocular pathogens to penicillin and methicillin is as high as 42.9% in recent reports (Cavuoto *et al.* 2008, Haas *et al.* 2011). MRSA strains arealso becoming resistant to even advanced fluoroquinolones used in prophylaxis and treatment of ocular infections (Major *et al.* 2010). Data from the Tracking Resistance in the United States Today (TRUST) study of ocular isolates, the Surveillance Network for ocular *S. aureus* isolates, and the Antibiotic Resistance Monitoring in Ocular MicRorganisms (ARMOR) study, all show continued erosion in beta-lactam susceptibility among CoNS and *S. aureus* (Asbell *et al.* 2008a, Asbell *et al.* 2008b, Haas *et al.* 2011). Staphylococci have proven particularly adept at acquiring resistance to every antibiotic that has been introduced, including vancomycin, highlighting the importance of the judicious use of antibiotics.

2.3 Enterococcus faecalis

E. faecalis is mainly a commensal organism of the gastrointestinal tract, but it has emerged as a leading cause of hospital acquired and postoperative infections that are especially difficult to treat, in part because of the high level of intrinsic antibiotic resistance (Murray BE 2000). Enterococci are rare causes of eye infections, but are usually associated with poor visual outcome. In addition to complicating cataract extraction, enterococci are occasionally isolated from infected glaucoma filtering blebs (Leng *et al.* 2011).

2.3.1 The role of the cytolysin—A cytolysin or cytolytic toxin expressed by some *E. faecalis* strains renders infections refractory to combined antibiotic and anti-inflammatory therapy (Jett *et al.* 1995). In fact, experimental endophthalmitis initiated with cytolysin-positive *E. faecalis* showed no difference in disease course, regardless of whether antibiotic and or anti-inflammatory treatment was given. In contrast, parallel infections using isogenic mutants specifically defective in cytolysin expression were successfully treated with a combination of antibiotics and anti-inflammatory agents, but not with antibiotics alone, highlighting the contribution of inflammation to the course of endophthalmitis (Jett *et al.* 1995) (Fig. 2). This illustrates the importance of not only killing the bacterium causing infection, but also neutralizing toxins and controlling inflammation during the course of infection.

The *E. faecalis* cytolysin is encoded within a chromosomal pathogenecity island, or by large pheromone-responsive plasmids, such as pAD1 (Shankar *et al.* 2004). The cytolysin operon, regulated by a quorum sensing system, consists of eight genes arranged in two divergent transcripts. One transcript encodes the two toxin subunit precursors, $CylL_L$ and $CylL_S$ (Fig. 3). Both toxin subunits are post-translationally modified by the product of the next gene in the operon, *cylM*. That modification includes the removal of hydroxyl groups from all serine and threonine residues in the subunits, and intramolecular ring formation with adjacent cysteines, resulting in the formation of the modified amino acids lanthionine and β-methyllanthionine. The post-translationally modified subunits, $CylL_L$* and $CylL_S$* are

secreted by the product of the next gene in the transcript, *cylB*, an ATP-binding cassette transporter. Both subunits are proteolytically trimmed co-secretionally, resulting in the extracellular forms $CylL_L$' and $CylL_S$'. At this stage in maturity, neither subunit possesses detectable cytolytic activity. Both subunits are finally activated extracellularly by an additional proteolytic trimming step catalyzed by the product of the next gene in the operon, *cylA*, which encodes an independently secreted serine protease (Haas *et al.* 2002). $CylL_L$", the fully processed form of the larger toxin subunit, upon final proteolytic trimming, readily inserts into the membrane of target cells. $CylL_S$", the fully processed form of the smaller subunit, has a lower affinity for target cell membranes, so transiently occurs in the free form in stoichiometric excess. This excess is sensed by the products of the cytolysin regulatory genes, CylR1 and CylR2, encoded on a divergent transcript. Detection of increased $CylL_S$" results in derepression of the operon and increased cytolysin expression. In the absence of target cells, $CylL_S$" and $CylL_L$" avidly bind to each other, rendering them incapable of insertion into membranes, and $CylL_S$" incapable of signaling. By this mechanism, the cytolysin is only expressed at high levels when target cells are present (Coburn *et al.* 2004). Conceivably, therapeutics could be designed around dominant negative forms of $CylL_L$" that would bind $CylL_S$" but be incapable of membrane insertion, or CylA may be targeted to block toxin maturation.

2.3.2 The role of the proteases—*E. faecalis* possesses another quorum regulated system that regulates expression of proteases GelE and SprE, and is organizationally similar to the staphylococcal *agr* locus (Qin *et al.* 2000) (Fig. 1). Termed the *fsr* locus, four *agr* homolgs, *fsrA, B, C* and *D* are endoded by the operon. FsrD is ribosomally synthesized, post-translationally processed, and secreted, and the mature quorum signal is termed gelatinase biosynthesis-activating pheromone (GBAP). The FsrD propeptide is processed by a cysteine protease domain on FsrB in a manner similar to the processing of *S. aureus* autoinducing peptide, AgrD. FsrD is then transported outside the cell for quorum sensing (Nakayama *et al.* 2006). GBAP accumulates outside the cell until it reaches a threshold level, at which point transcription of the *gelE-sprE* operon is induced generating GelE/gelatinase and the serine protease SprE, and also autoinducing transcription of the *fsr* operon itself (Nakayama *et al.* 2001). GelE, a zinc metalloprotease capable of hydrolyzing collagen, casein, hemoglobin and other polypeptides, is produced mainly in late log to early stationary phases (Barrett *et al.* 1998). In experimental endophthalmitis, deleting *gelE*, *sprE* or both resulted in measurable attenuation of endophthalmitis, with *gelE* deletion having a greater effect than deleting *sprE* alone. However, *fsr*-deficient mutants showed a greater degree of attenuation suggesting additional effects of *fsr* (Engelbert *et al.* 2004). GelE and SprE recently have been shown to have specific roles in mediating *E. faecalis* autolysis and biofilm formation (Thomas *et al.* 2008). *E. faecalis* can form biofilms on intraocular lens material (Kobayakawa *et al.* 2005). The contribution of the *fsr* system to biofilm formation was first shown by Hancock and Perego (Hancock and Perego 2004), who systematically knocked out each of the non-lethal two component signaling systems of *E. faecalis*. An interplay between GelE and SprE, and an *E. faecalis* autolysin, results in the release of high molecular weight extracellular (e)DNA, a by-product of cell lysis that is an important structural component of enterococcal biofilms (Thomas *et al.* 2008). The contribution of *fsr* and gelatinase to biofilm formation *in vivo* was supported by the observation of smaller vegetations produced by defective mutants in an endocarditis model (Hancock and Perego 2004). GelE also appears to modulate the immune response to *E. faecalis* in an endocarditis infection model through its ability to cleave the anaphylatoxin complement C5a causing decreased neutrophil migration to the infection sites (Thurlow *et al.* 2010). We believe that the contribution of the proteases to cell lysis also likely enhances inflammation, which may explain some of the additional attenuation noted above for the *fsr* mutant in the endophthalmitis model. Some evidence suggests that these proteases also may play a role in

the translocation of *E. faecalis* from the anterior chamber to the posterior segment, and contributing to retinal damage (Suzuki *et al.* 2008).

2.4 *Streptococcus pneumonia* and other *streptococci*

Streptococci are important causes of eye infections, especially endophthalmitis, with oral streptococci referred to as “viridians streptococci” or alpha hemolytic streptococci being especially common and severe (Chen *et al.* 2011, Mao *et al.* 1992). Streptococci accounted for almost 10% of post-cataract endophthlamitis cases in the Endophthalmitis Vitrectomy Study, and those cases had an especially poor outcome (EVS 1996). This included for historic reasons group D streptococci, the enterococci, as well as oral streptococci (often termed viridians streptococci) and pathogenic streptococci, including *S. pyogenes*, *S. agalactiae*, and *S. pneumoniae*. It remains unclear why streptococci produce such fulminant infections in the eye, while they often exist among the commensal flora of the oral cavity and nasopharynx. Viridans streptococci, such as *S. mutans, S. sanguis, and S. mitis*, have been reported to reach the eye endogenously after dissemination from endocarditis (Seles and Lang 2007), from local contamination following eye surgeries, and following ocular trauma complicating dental procedures (Blum-Hareuveni *et al.* 2006, Lamont and Booth 2006). Despite the blinding potential of this class of organisms, not much is known about their pathogenecity for the eye and this represents an important knowledge gap.

2.4.1 Pathogenesis of *S. pneumoniae* endophthalmitis—*Streptococcus pneumoniae*

is evolutionarily related to the oral streptococci, and there is some understanding of the pathogenesis of endophthalmitis due to this species. *S. pneumoniae* endophthalmitis can occur following any insult to the eye, but is most commonly encountered as a leading cause of bleb-associated endophthalmitis (Leng *et al.* 2011, Mac and Soltau 2003). Filtering blebs are surgically created defects in the sclera that allow excess aqueous humor to leak out of the eye in cases of glaucoma that are unresponsive to medical therapy. Bleb-related endophthalmitis typically occurs abruptly, months to years postoperatively, often after the bleb appears inflamed and the visual outcome is usually very poor even with prompt treatment (Leng *et al.* 2011).

S. pneumoniae expresses several virulence factors. The two most studied in relation to eye infection are pneumolysin and a cell wall hydrolase, autolysin. Pneumolysin is a member of the cholesterol-dependent, thiol-activated cytolysin family (Kanclerski and Mollby 1987), with structural similarities to other members of the family secreted by other gram positive pathogens (Tweten 2005), but is unique in lacking a signal peptide for secretion. This cytolysin binds to the host cell cytoplasmic membrane in a cholesterol-dependent manner, followed by formation of macromolecular assemblies and then pore formation resulting in lysis of neutrophils, red blood cells and platelets (Paton *et al.* 1997, Tweten 2005). At low doses, it can inhibit the respiratory burst of neutrophils and phagocytic capacity. It inhibits neutrophil chemotaxis and migration (Paton and Ferrante 1983). Independent from its cytolytic role, pneumolysinalso activates complement through the classical activation pathway by binding the Fc region of IgG (Paton *et al.* 1997), and interferes with opsonization, phagocytosis and killing. Pneumolysin is unusual in being produced in the cytoplasm and released by a process termed allolysis, where by competent cells cause the lysis of the noncompetent cells in the vicinity (Guiral *et al.* 2005, Gilmore and Haas 2005). Allolysis requires a two-peptide bacteriocin, CibAB that causes lysis through three cell wall hydrolases. For the pneumolysin to be released, it was found that a quorum sensor termed competence-stimulating peptide (CSP) is required (Guiral *et al.* 2005, Havarstein *et al.* 1995a) (Fig.1). Upon accumulation in the medium, CSP stimulates ComDE (Pestova *et al.* 1996), a two-component regulator, inducing the expression of the competence regulon. *ComC* encodes pre-CSP that is cleaved by an ATP-binding transporter, ComAB, during

export. CSP now can bind the membrane-kinase ComD and activate, through phosphorylating itself and ComE, gene transcription (Havarstein *et al.* 1995b, Hui *et al.* 1995). Autolysin is another enzyme involved in inflammation. It is located in the cell envelope and is involved in the metabolism and degradation of the peptidoglycan backbone of the cell wall. It also causes the liberation of inflammation-inducing cell wall fragments during infection (Ng *et al.* 2002).

Studies to characterize the role of pneumolysin and autolysin in endophthalmitis showed that strains deficient in pneumolysin expression resulted in infections with reduced intraocular inflammation early in infection, but with few differences from the wild type after 48 hours. Autolysin deficient strains caused a lower level of inflammation throughout (Ng *et al.* 2002). The contribution of these two virulence factors has been demonstrated in meningitis, where strains deficient in either showed significantly attenuated disease (Hirst *et al.* 2008).

2.4.2 Other pneumococcal factors—In addition to pneumolysin and autolysin, other pneumococcal factors such as neuraminidase and hyaluronatelyase may also contribute to the pathogenesis of endophthalmitis. Neuraminidase exists in two forms, NanA and NanB, that cleave the terminal sialic acid residues of glycoproteins and glycolipids on the cell surfaces, exposing receptors and enhancing adhesion (Krivan *et al.* 1988). In a murine meningitis model, it was shown that NanA is necessary and sufficient to promote *S. pneumoniae* adherence and invasion of the brain microvascular endothelial cells (Uchiyama *et al.* 2009). Hyaluronatelyase hydrolyzes hyaluronan, which is prevalent in the retina, choroid, trabecular meshwork, aqueous and vitreous humor (Lerner *et al.* 1997, Murata and Horiuchi 2005). Moreover, hyaluronan was identified as part of a signaling system that is involved in maintaining the functional structure of the retina and choroid (Murata and Horiuchi 2005). In meningitis, the laminin-receptor was found to be important for *S. pneumoniae* to bind cells that form the blood-brain-barrier, and consequently for invasion (Orihuela *et al.* 2009). It is interesting to speculate that polymorphisms in laminin may predispose to blood barrier infections, such as meningitis and endogenous endophthalmitis. Much can be learned from meningitis studies, including the importance of inflammation management when there is a high index of suspicion of the offending organism. Dexamethasone before or concurrent with the first dose of intravenous antibiotics, for example, decreased the mortality in adults with acute pneumococcal meningitis (van de Beek 2009). Whether the addition of corticosteroids improves outcome in acute bacterial endophthalmitis is not yet clear.

2.5 Bacillus

Bacillus species cause an explosive, rapidly blinding endophthalmitis usually following trauma, with 70% of the eyes losing all useful vision (David *et al.* 1994). The presence of *Bacillus* in the eye results in an intense and rapid inflammatory reaction.

2.5.1 *B. cereus* and the eye—*Bacillus cereus* is the most common *Bacillus* species identified in cases of endophthalmitis. Available evidence points to a complex interplay between secreted factors and the host response, with a yet unidentified link to explain the rapid course of the disease. *B. cereus* has 4 identified membrane damaging toxins: hemolysin BL, phosphatidylinositol-specific phospholipase C, sphingomyelinase and phosphatidylcholine-specific phospholipase C. The sphingomyelinase and phospholipase C are part of the cereolysin AB toxin that act sequentially to cause lysis of the cell membrane (Gilmore *et al.* 1989). The multi subunit hemolysin BL is a membrane-lytic toxin that also causes vascular permeability, ocular toxicity, and contributes to enteric disease (Callegan *et al.* 2002a, Callegan *et al.* 2002c, Callegan *et al.* 2003). In endophthalmitis, however,

hemolysin BL only contributes measurably to pathogenesis early in the course of eye infection (Callegan *et al.* 1999b). Phosphatidylcholine-phospholipase C, part of the cytolyic unit of cereolysin AB, was found to have no effect on the course or severity of experimental endophthalmitis. The role of other lipases, enterotoxins and proteases expressed by *B. cereus* remain to be determined. After ocular infection with *B. cereus*, neutrophils, emerging from the vasculature of the optic nerve head, were identified as early as 4 hours post infection (Ramadan *et al.* 2006). In addition, an increase in blood ocular barrier permeability was found where leakage of albumin and fibrin occurred as early as 8 hours after infection, and the tight junction disruption at the level of the retinal pigment epithelium began after 4 hours, accompanied by an increase in cytokines along the course of the infection (Moyer *et al.* 2009).

2.5.2 Quorum sensing in *B. cereus*: *plcR*—*B. cereus*** virulence is clearly multifactorial, and it has proven challenging to dissect specific roles for various factors. To attempt to address a number of virulence factors *en bloc*, mutants in the quorum sensing system *plcR*, which regulates expression of membrane damaging toxins, cell surface proteins and enzymes, were tested in rabbit endophthalmitis (Callegan *et al.* 2003). The *plcR* mutant was found to be significantly attenuated with decreased toxin expression, decreased motility, and significantly slower evolution of disease; however retinal damage was still evident and severe (Callegan *et al.* 2003). The quorum regulator PapR, a 48 amino acid autoinducer peptide, regulates the *plcR* regulon, leading to a decrease in hemolytic activity and virulence for insects, the natural host for *B. cereus* infection (Slamti and Lereclus 2002). Cytolysins regulated by *plcR* did not detectably affect retinal pigment epithelium cytotoxicity, indicating that *B. cereus*-induced permeability of the blood retina barrier is largely independent of *plcR*-regulated toxins (Moyer *et al.* 2008).

2.5.3 Motility and its contribution to virulence—*Bacillus cereus* is unique among the common causes of endophthalmitis because of its motility – it can migrate from the site of injection to involve all layers of the eye, from retina to anterior segment, within 12 hours (Callegan *et al.* 2002a). Non-motile strains injected into the vitreous do not migrate to the anterior segment, but posterior segment disease and retinal inflammation are still explosive (Callegan *et al.* 2006). Non-motile strains deficient in toxin production, proved less virulent and elicited slower evolution of retinal function loss and intraocular inflammation (Callegan *et al.* 2005, Callegan *et al.* 2006). At the cellular level, toxin production by *B. cereus* near or within the retina results in loss of retinal architecture and disruption of Müller cells, the major glial cells of the retina involved in structural support and retinal homeostasis control (Ramadan *et al.* 2006). *Bacillus cereus* strains capable of swarming express the highest level of hemolysin, suggesting that swarming and virulence factor production are related (Ghelardi *et al.* 2007). Oxygen is likely the substance driving *B. cereus* chemotaxis, attracting them away from the a cellular central vitreous to the highly vascularized periphery of the eye including the retina (Callegan *et al.* 2006). In summary, there appears to be a close association between motility, swarming and virulence factor production, but the basis for the unique virulence of *B. cereus* in endophthalmitis is far from solved.

3. Host factors

Despite the wealth of research on the molecular pathogenesis of infections at other anatomical sites, such as endocarditis and meningitis, our understanding of host/microbe interactions in the immune privileged eye is still in its infancy but holds considerable promise for the development of new therapeutic approaches for endophthalmitis. Optimization of the expression and activity of endogenous antimicrobial factors of the innate immune system could provide a path for improved therapy. For example, RegIIIγ, a secreted lectin active against gram-positive bacteria expressed by intestinal cells (Cash *et al.*

2006) and possibly others, regulates the abundance of gram positive flora on mucosal surfaces. Interestingly, it has been found to be downregulated in the intestines of mice after treatment with antibiotics (Brandl *et al.* 2008) as the result of the elimination of flagellated gram negatives, which gratuitously stimulate its production through TLR5 (Kinnebrew *et al.* 2010). Similar host antimicrobials are present at various anatomical sites, including the ocular surface, but little is known of their occurrence or role in the uveal tract.

3.1 Anterior Chamber Acquired Immune Deviation

The aqueous humor is contaminated by bacteria at a high rate after cataract surgeries as shown by some studies (Bausz *et al.* 2006, Dickey *et al.* 1991, Parmar *et al.* 2006), yet the rate of endophthalmitis after this procedure remains as low as 0.01–0.3% (Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons 2007, Miller *et al.* 2005, Taban *et al.* 2005). This is *prima facie* evidence that despite immune privilege, which has been well studied in other contexts, innate defense to bacterial establishment and growth, remains at least partially intact. Immune privilege of the eye is achieved by the concerted actions of immune modulators including TGF-β, Fas ligand, α-MSH and others, thus limiting inflammatory reactions in the eye and preserving clarity of the visual axis during infection elsewhere in the body (Streilein 2003), but potentially leaving the eye vulnerable to infection. Immune privilege has both systemic and localized mechanisms of modulation. An arc of systemic suppressive mechanisms has been organized into what has been termed anterior chamber-associated immune deviation (ACAID). ACAID is established first by F4–80 macrophages acquiring antigen within the immune privileged eye, migrating to the spleen and presenting intraocular antigens to lymphocytes. As a result of experiencing the immunomodulatory environment of the eye, the macrophage orchestrates antigen-specific immunological tolerance mediated by efferent suppressor CD8 T cells, and potential afferent regulatory T cells. The soluble immunomodulating factors of the immune privileged ocular microenvironment themselves inhibit the activation of effector T cells and cytotoxic T cell activity, while promoting the induction and activation of regulatory T cells. These systemic and localized mechanisms of immunomodulation protect the eye from the inflammation, and from the induction of autoimmune disease targeting the retinal proteins expressed within its sequestered microenvironment (Taylor 2009). The precise mechanisms by which antimicrobial defenses function in this carefully regulated milieu is largely unexplored, but there is evidence for low level expression of defensins.

Maintenance of ocular immune privilege is required for preserving a clear visual axis free of inflammation, however, imbalances that lead to inflammation happen not only following infection but also as a consequence of systemic autoimmune and inflammatory disease (some of which are now being associated with infection, such as sarcoidosis (Song *et al.* 2005), Behcet's disease (Yanagihori *et al.* 2006), and inflammatory bowel diseases (Friswell *et al.* 2010)). The innate immune system is believed to play an important role in triggering systemic autoimmune diseases as well as development of uveitis. Most eye tissues express toll-like receptors (Chang *et al.* 2006). Eyes injected with TLR agonists induce uveitis through the induction of cytokine synthesis (Allensworth *et al.* 2011). In addition to the presence of microbial component receptors, macrophages and dendritic cells in the uveal tract are part of the innate immune system (McMenamin *et al.* 1994). Typically, uveitis is induced in experimental models using endotoxin, specifically lipopolysaccharides (LPS) that are a major component of the cell wall of gram-negative bacteria. Inflammation usually occurs 24h following LPS injection, with the posterior compartment also being susceptible (Koizumi *et al.* 2003). The relevance of experimental endotoxin induced uveitis to human uveitis is debated, although evidence is emerging that systemic diseases associated with uveitis, including IBD and ankylosing spondylitis, might be due to shifts in bowel flora (Friswell *et al.* 2010, Strober 2010), and that infections by microbes such as *Salmonella*,

Yersinia and *Chlamydia* (Huhtinen *et al.* 2001, Wakefield *et al.* 1990) are associated with reactive arthritis in HLA-B27-positive patients. It is clear that even the most basic components of bacterial cells contribute to ocular inflammation in bacterial endophthalmitis as well as other inflammatory conditions.

3.2 Defense of the posterior segment despite immune privilege

Despite the restricted immunity of the eye, several lines of defense against infection have been defined. The anatomic barrier provided by an intact lens posterior capsule is important for limiting the spread of bacteria to the vulnerable posterior segment (Beyer *et al.* 1984). The lens capsule is held by zonules that are porous and likely allow for communication between anterior and posterior compartment fluids, especially when pressure in the anterior chamber rises such as during a cataract surgery. Defensins are expressed in the vitreous, but appear to occur at too low a level to be antimicrobial (Haynes *et al.* 2000). Although complement had been proposed to play a role in posterior segment defense, direct experimentation using $C3^{-/-}$ knockout mice found no increase in susceptibility to infection compared to wild type mice (Engelbert and Gilmore 2005). Fas ligand (FasL) was found to enhance defense, potentially by activating either resident cells or the first wave of neutrophils (Engelbert and Gilmore 2005). This conclusion was based on the observation that FasL deficient B6 mice exhibited susceptibility to infection at infective doses to which wild type mice were resistant.

The retina appears to possess an intrinsic ability to protect itself from inflammatory damage. Alpha-B crystalline, a heat shock protein constitutively expressed in the neural retina and retinal pigment epithelium, appears to contribute to host defense by preventing apoptosis of retinal cells, by inhibiting the activation of caspase 3. *S. aureus* appears to be able to overcome this protection by inducing the cleavage and inactivation of alpha B crystalline (Whiston *et al.* 2008).

3.3 Toll-like receptor (TLR) involvement in host response

TLRs that trigger innate immunity in response to bacterial ligands have begun to be examined in the context of endophthalmitis. *S. aureus* and the TLR-2 ligand Pam-3-Cys induce inflammatory cytokine expression in mice, as well as trigger responses specifically in Müller cells (Chang *et al.* 2006, Shamsuddin and Kumar 2011). TLR-2 also plays an important role in the initial ocular response to *B. cereus* endophthalmitis (Shamsuddin and Kumar 2011). Immunomodulatory factors involved in maintaining immune privilege, such as α-MSH (Taylor *et al.* 1992), have been found to modify some TLR-mediated signaling. α-MSH, a neuropeptide involved in blocking inflammation in the eye and maintaining immune privilege, antagonizes TLR-4 signaling by triggering interleukin-1 receptor-associated kinase M (IRAK-M) to bind IRAK-1 in the TLR signaling pathway, preventing activation of the inflammatory cascade (Taylor 2005).

3.4 Tumor necrosis factor alpha (TNF-α)

TNF-α contributes to the explosive host response to *B. cereus*, resulting in blood-retina barrier breakdown. It is secreted by macrophages and neutrophils, and results in the upregulation of cell adhesion molecules, particularly selectins, on vascular endothelial cells (Rosen 2004, Rosenfeld *et al.* 2006, Whiston *et al.* 2008). TNF-α increases vascular permeability and induces mononuclear phagocytes to produce cytokines IL-1 and IL-6. As a result, neutrophils rapidly chemotax through the reduced blood-retina barrier into the vitreous (Bazzoni and Beutler 1996, Crane and Liversidge 2008). TNF-α is upregulated in parallel with neutrophil influx in *B. cereus* endophthalmitis. *B. cereus* experimental endophthalmitis in homozygous TNF-α knockout mice replicated faster that in the wild type

mice, elicited less neutrophil infiltration into the vitreous, and precipitated a more severe drop in electroretinographic response (Ramadan *et al.* 2008).

4. Anti-inflammatory therapy: Thecontroversy

The value of corticosteroids and other anti-inflammatory drugs for treating endophthalmitis continues to be debated. Anti-inflammatory agents function by inhibiting migration of macrophages, stabilizing vascular membranes, and blocking inflammatory mediators. In endophthalmitis, a correlation has been demonstrated between the level of expression of inflammatory mediators TNF-α, IL-1β and IFN-γ and endophthalmitis clinical inflammation scores (Petropoulos *et al.* 2006). In acute bacterial meningitis – a condition with parallels to bacterial endophthalmitis – adjunctive corticosteroids are beneficial (de Gans *et al.* 2002). These factors establish a rationale for the potential benefit of using corticosteroids as adjunctive treatment of bacterial endophthalmitis. However, demonstration of efficacy has met with mixed results with respect to reducing postoperative inflammation, improving visual outcome, and influencing potency and availability of co-administered antibiotics. Response to intravitreal anti-inflammatories has been directly examined in rabbit models of endophthalmitis caused by staphylococci, streptococci, bacilli and enterococci. These studies have assessed clinical scores, histology and sometimes electroretino graphic changes. Results vary widely, with some studies demonstrating benefit, others showing no effect, and still others showing worse outcomes:

1. Use of steroids alone without antibiotics was found to render the eye more susceptible to infection, and impedes the immune response (Bucher *et al.* 2005).
2. Early administration of intravitreal corticosteroids with vancomycin and other antibiotics for the treatment of gram positive bacterial infection was found to help resolve inflammation and infection, and salvage vision (Bucher *et al.* 2005, De Kaspar *et al.* 2008, Jett *et al.* 1995, Liu *et al.* 2011, Liu *et al.* 2008) (Fig. 2). The use of biodegradable polymers mixed with vancomycin, amikacin, and dexamethasone as scleral plugs for treatment of endophthalmitis was found to deliver high concentrations of drugs *in vivo* in experimental endophthalmitis over an extended period of time without any major complications (Peng *et al.* 2010).
3. Use of corticosteroids as adjuncts to antibiotics including fluoroquinolones was found not to influence outcome (Ermis *et al.* 2005, Ermis *et al.* 2007, Yildirim *et al.* 2002)
4. Use of adjunctive steroids in some endophthalmitis models was found to reduce the efficacy of antibiotics (Smith *et al.* 1991, Wiskur *et al.* 2008), and in some cases contributed to an increase in ocular inflammation and retinal necrosis following injection (Meredith *et al.* 1996).

Clinical studies have similarly failed to reach consensus on the benefit of adjunctive anti-inflammatory use. Inconsistency stems from differences in study design, sample size, causative organism, and treatment methods used. A retrospective study of endophthalmitis due to coagulase negative staphylococci found that good visual outcome was associated with intensive topical corticosteroid during the symptomatic period (Ormerod *et al.* 1993). A prospective placebo controlled series of 29 patients with acute postoperative endophthalmitis was conducted where half received 0.4 mg of intravitreal dexamethasone in addition to the intravitreal antibiotics (0.2 mg vancomycin and 0.05 mg gentamicin) received by all patients. Those receiving the antibiotic with dexamethasone showed a trend toward better visual outcome, although this did not achieve statistical significance (Gan *et al.* 2005b). Vancomycin levels were similar in both groups and did not appear to be affected by dexamethasone co administration (Gan *et al.* 2005a). Das *et al.* (Das *et al.* 1999)

conducted a prospective randomized trial on 63 patients to evaluate the efficacy of intravitreal dexamethasone co-administered with antibiotic, along with vitrectomy, for treating exogeneous bacterial endophthalmitis. Dexamethasone was found to reduce inflammation early, but had no independent influence on the visual outcome (Das *et al.* 1999). A more recent prospective double blind trial randomized 62 patients with endophthalmitis following cataract surgery, bleb infection and other causes, to receive intravitreal ceftazidime (2.225 mg/0.1 ml) and vancomycin (1 mg/0.1 ml), plus either dexamethasone (0.4 mg/0.1 ml) or placebo. No significant difference in visual outcome was observed, however subgroup analysis found a trend to better visual acuity in the postcataract/dexamethasone-treated subgroup (Albrecht *et al.* 2011). In contrast, Shah *et al.* (Shah *et al.* 2000) conducted retrospective analysis of 57 patients with postoperative endophthalmitis who received intravitreal amikacin (0.4 mg/0.1 ml) and vancomycin (1 mg/0.1 ml) at the time of vitrectomy or vitreous aspirate, and analyzed cohorts based on whether or not they had also received dexamethasone (0.4 mg/0.1 ml). They found that patients who received intravitreal dexamethasone had a significantly reduced probability of a three-line improvement in visual acuity (Shah *et al.* 2000). Patient treatment was non-random and depended on physician preference, which raises the possibility of bias in administering anti-inflammatory therapy in more severe cases where the chances of improvement may have been lower *a priori*. In summary, it is difficult to draw unambiguous conclusions about the value of anti-inflammatory adjunctive treatment for acute bacterial endophthalmitis based on existing animal and human studies. A large, well-constructed randomized trial will be necessary to resolve this question.

5. Prophylaxis

Prophylaxis is an important consideration for any globe penetrating surgical procedure, including intravitreal injection and intraocular surgery, given the potential consequence of bacterial endophthalmitis. However, the low incidence of endophthalmitis, the rapid evolution of surgical techniques, and the difference in practice patterns, all make it difficult to perform or compare controlled studies that attempt to measure efficacy of prophylactic measures. Prophylactic measures generally fall into two categories: 1) Use of mainly topical antiseptics with a broad antimicrobial activity, and 2) Use of perioperative antibiotics that have a targeted antimicrobial spectrum. The value of preoperative, intraoperative and postoperative prophylactic measures has been studied in humans as well as in animals, although there are few randomized prospective trials.

5.1 Evidence from clinical studies

The use of 5% povidone-iodine in the conjunctival *cul de sac* was found to be effective for preventing postoperative endophthalmitis (Ferguson *et al.* 2003, Mino de Kaspar *et al.* 2005, Speaker and Menikoff 1991) through decreasing conjunctival bacterial numbers (Ferguson *et al.* 2003, Wu *et al.* 2006), and is included among best practices by the American Academy of Ophthalmology (American Academy of Ophthalmology 2011). Systemic, topical, subconjunctival and intracameral antibiotics are also used for prophylaxis, but there have been few randomized controlled studies that unambiguously prove benefit. Topical antibiotics for surgical prophylaxis have been widely used, but there have been no randomized placebo-controlled trials (Chang *et al.* 2007). Fluoroquinolones, such as moxifloxacin and gatifloxacin, are most widely used, and have good ocular penetration with few side effects (Gungor *et al.* 2011, Ong-Tone 2007). Besifloxacin, a recently approved fluoroquinolone developed for ophthalmic use, has been approved for treatment of conjunctivitis, and appears also to achieve good ocular penetration (Yoshida *et al.* 2010). When comparing an immediate application of povidone-iodine with or without a pre-injection antibiotic, no additional benefit was found in adding the antibiotic (Moss *et al.* 2009). As antimicrobial resistance in the conjunctival flora was found to increase after

repeated antibiotic exposure (Kim and Toma 2011), there is some concern for the selection of resistant organisms through the extensive use of prophylactic antibiotics.

The prophylactic use of intraocular antibiotics received support from the results of the European Society of Cataract and Refractive Surgeons (ESCRS) study (Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons 2007). This study was a prospective, randomized, partially masked, multicenter trial that examined the effect of intracameral cefuroxime injected at the end of the surgery, with or without perioperative levofloxacin. The study included 8,103 patients who received prophylactic intracameral cefuroxime, and as many who did not. The arm not receiving intracameral cefuroxime had a 4.92 fold increased risk of developing postoperative endophthalmitis (C.I. 1.87–12.9) (Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons 2007). The study was terminated early because of this beneficial effect. Other studies in Europe also reported a benefit from the use of intracameral cefuroxime orcefazolin in reducing the incidence of postoperative endophthalmitis (Montan *et al.* 2002, Romero *et al.* 2006, Wejde *et al.* 2005, Yu-Wai-Man *et al.* 2008). Among intracameral antibiotics tested, cefuroxime was found in one study to be the most cost-effective for prevention of postoperative endophthalmitis (Sharifi *et al.* 2009). Intracameral cefuroxime prophylaxis is now common in Europe, with 61% of surveyed ophthalmologic units in the United Kingdom using it in 2010 (Murjaneh *et al.* 2010). It is unclear how the rates of endophthalmitis in the ESCRS, and some of the other studies, which were higher than those routinely reported in the US, might have affected the outcomes of these studies. The use of intracameral cefuroxime in the USA is less common, partly because of the lack of commercially available ophthalmic formulation, and because of difference in the incidence of postoperative endophthalmitis (Wykoff *et al.* 2010).

5.2 Animal studies and novel approaches

New approaches for prophylaxis are being tested. An intracameral vancomycin microparticle injection at the time of insertion of a contaminated intraocular lens into the anterior chamber of a rabbit, was found to reduce the rate of endophthalmitis without detectable toxic effect, and showed maintenance of antibiotic concentrations above MIC levels for at least 6 hours (Kodjikian *et al.* 2010). Subconjunctival injection of triamcinolone with ciprofloxacin hydrochloride as compared to 0.3% topical ciprofloxacin hydrochloride showed equal efficacy when used in experimental *S. aureus* endophthalmitis in rabbits suggesting that the subconjunctival route of antibiotic delivery might be a way to decrease non-compliance (Cardillo *et al.* 2010). Other experimental therapies that are being studied include the application of bacteriophage lysins to rapidly decontaminate an environment after surgery. Bacteriophages produce lysins that rupture the bacterial cell wall, leading to release of its phage progeny (Vandersteegen *et al.* 2011). Staphylococcal phage lyins are being explored for therapy as well as eradication of *S. aureus* from different sites of infection (Pastagia *et al.* 2011). Antipneumococcal lysins have also been used to treat experimental *S. pneumoniae* pneumonia (Witzenrath *et al.* 2009) and meningitis (Grandgirard *et al.* 2008). With a current rate of postoperative endophthalmitis ranging from 0.01 – 0.3 %, depending on center (Endophthalmitis Study Group, European Society of Cataract & Refractive Surgeons 2007, Taban *et al.* 2005), an extremely large study would be required to prove efficacy of a prophylactic measure. This poses a formidable barrier to proving the value of prophylaxis in an era of evidence-based medicine.

6. Future directions and perspectives

Research questions that still need to be addressed include among others:

1. Factors related to the host/bacterial relationship in the eye

a. What are the critical determinants of outcome in endophthalmitis? Since bacteria vary widely in virulence, are any of the principles generalizable? How exactly is the blood-retinal barrier maintained and regulated, and can it be manipulated to manage the course of disease? How do retinal cell death pathways differ when the effector is inflammation versus bacterial toxins?

b. In an increasingly aged patient population, with growing rates of type-2 diabetes, what aspects of the host response contribute to susceptibility to bacterial endophthalmitis?

c. How is host response to infection in the immune privileged eye similar and different from the response at other sites of infection?

2. Clinical research

a. Given the rarity of the postoperative endophthalmitis, randomized controlled trials evaluating different antimicrobial prophylaxis protocols require a very large study population (usually thousands of patients in each study arm). Are there reasonable surrogate approaches for answering the question of optimal prophylaxis? Does vision loss resulting from treatment failure associated with antibiotic resistant microbes stem only from delay in eradication, or do these microbes exhibit increased virulence as well, as has been suggested for CA-MRSA?

3. Pharmacology research

a. How can our understanding of virulence and expression regulation aid in developing novel antimicrobials? Conceivably, therapeutics could be designed around many of the things discussed earlier in the review like: changes in the nutritional environment that can regulate virulence production as is the case with *codY* in *S. aureus*; the use of *agr* inhibitors in staphylococci to control virulence and biofilm formation/detachment and spread of infection; targeting CylA in *E. faecalis* to block toxin maturation; blocking hyaluronatelyase in *S. pneumoniae* from breaking hyaluronan that is abundant in ocular parts.

b. To what extent do new cell wall agents (inhibitors of *S. aureus* wall teichoic acid biosynthesis, phage lysin mediated release of bacterial DNA) mitigate or exacerbate inflammation, and to what extent does rapid bacterial killing limit damage in endophthalmitis?

7. Conclusion

Rapid growth in globe-penetrating procedures performed on an outpatient basis is fueling increased concern for intraocular infection. Because of proximity to the retina, endophthalmitis is always a therapeutic crisis and many cases result in significant vision loss. Research into microbial pathogenesis that can lead to better targeted strategies for preventing vision loss is therefore very important. A better understanding of the critical events in the pathogenesis of endophthalmitis could lead to new approaches for prevention and treatment that target bacterial quorum development, attachment, virulence factor expression, mechanisms of migration from anterior to posterior segment, and the host response. Technical advances in our ability to manipulate the microbe as well as model hosts are bringing us to the threshold of this understanding.

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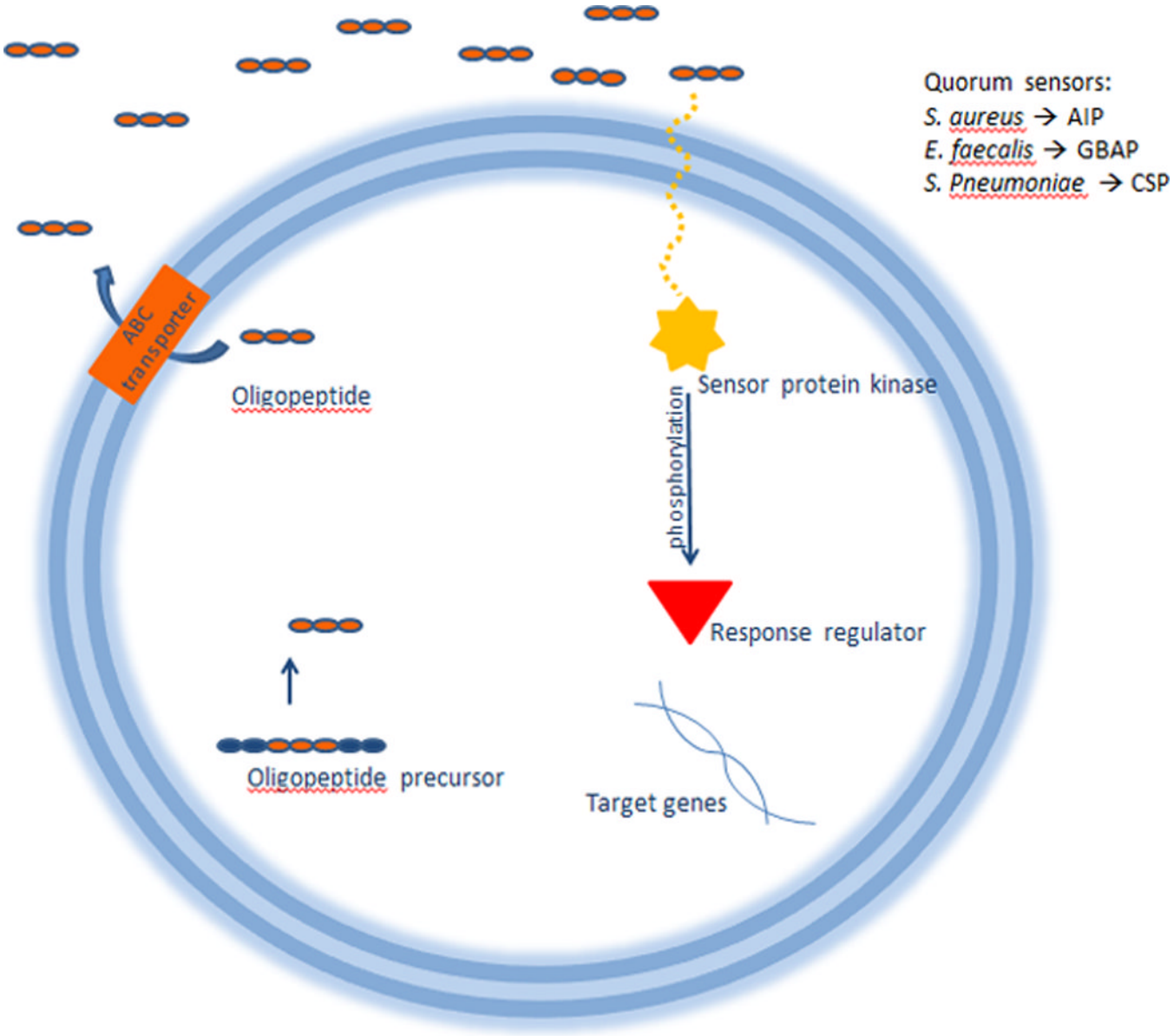

Figure 1.

Peptide-based quorum sensing in gram positive bacteria. A precursor peptide co-secretionally processed into mature form by an ABC transporter. The peptide accumulates outside the cell as function of bacterial cell density. A threshold level detected by the cognate sensor histidine protein kinase transduces the signal to a response regulator through phosphotransfer. This leads to a shift in global regulation of virulence gene expression. Competence-stimulating peptide (CSP); gelatinase biosynthesis-activating pheromone (GBAP); auto inducing peptide (AIP).

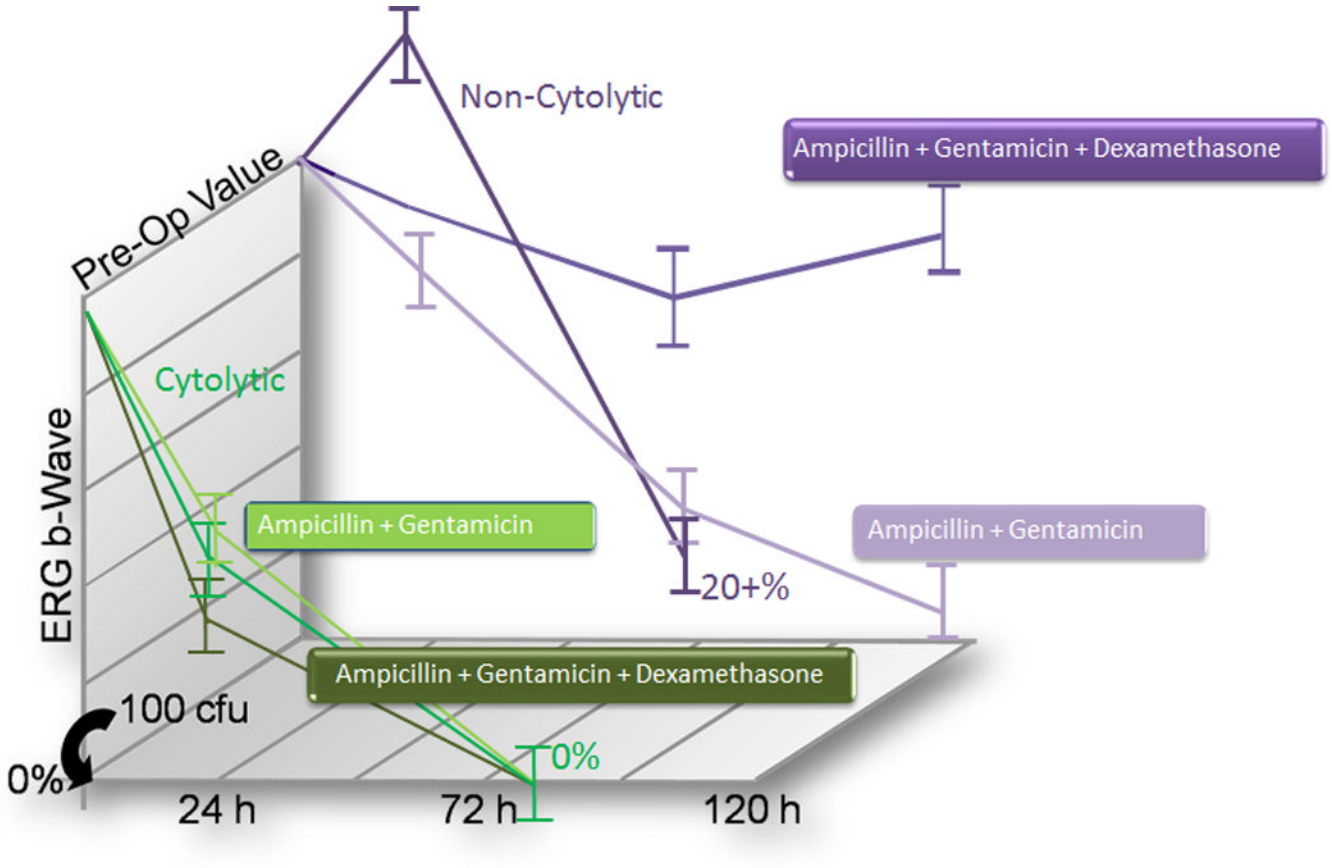

Figure 2.

Course of rabbit endophthalmitis as a function of treatment regimen, as measured by % ERG B-wave amplitude retention (b-wave in infected eye/b-wave in control eye ×100). Antibiotic therapy consisting of ampicillin (1 mg/0.1 ml) and gentamicin (200 ug/0.1 ml) for endophthalmitis from either cytolytic (in green) or non-cytolytic (in purple) *E. faecalis* provides little improvement over untreated controls. Inclusion of dexamethasone (400 ug/0.1 ml) results in complete recovery of retinal function in eyes infected with non-cytolytic *E. faecalis*, but provides no measurable benefit for eyes infected with the cytolytic *E. faecalis*.

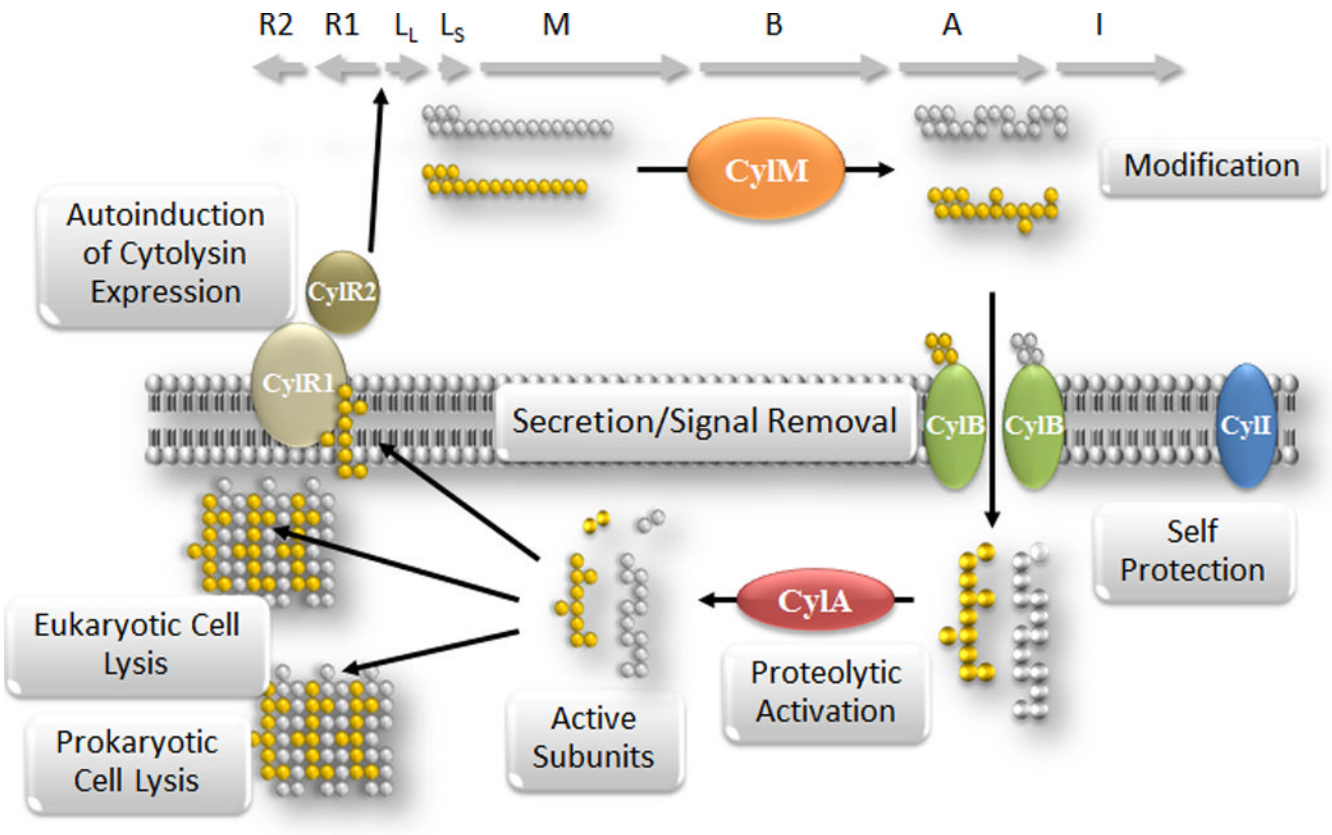

Figure 3.

The peptide subunits $CylL_L$ and $CylL_S$ are ribosomally synthesized in the cell. Following post-translational modification by CylM, they are cleaved and secreted to be activated extracellularly by CylA. This allows the fully active peptides to act together to lyse prokaryotic and eukaryotic cells, in addition to inducing expression of the cytolysin operon. CylR1 and CylR2 serve to repress expression of the operon. The cytolysin-producing cell itself is protected by CylI.

Table 1

Prevalence of microorganisms in endophthalmitis

Type of endophthalmitis	Common organisms
Exogenous (83–98%)	
Postoperative[a]	Bacteria
	Gram positive (~90%)
	Coagulase-negative staphylococci (70%)
	Staphylococcus aureus (10%)
	Streptococcus species (9%)
	Enterococcus species (2%)
	Gram negative (4–6%)
	Fungi (3–21%)
Post-traumatic[b]	*Staphylococcus* species
	Bacillus species
	Streptococcus species
	Gram- negative bacilli
	Fungi
Post anti-VEGF injections[c]	Coagulase-negative staphylococci
	Viridans streptococci *(e.g. Streptococcus mitis, Streptococcus salivarius)*
Endogenous[d] (2–17%)	Bacteria
	Gram positive
	Streptococcus species
	Staphylococcus aureus
	Gram negative
	Klebsiella
	Escherichia coli
	Pseudomonas
	Neisseria meningitidis
	Fungi
	Candida species
	Aspergillus
	Cryptococcus
	Fusarium

[a] In postoperative endophthalmitis, 90% of cases occur after cataract surgery

[b] *Staphylococcus* and *Bacillus* species are the most common causes of posttraumatic endophthalmitis with their incidence varying among studies

[c] Most reported cases do not list the causative organism so percentages were not included here

[d] Causative organisms of endogenous endophthalmitis vary widely with geographic location

Based on data from (EVS 1996, Anand *et al.* 2000, Chhabra *et al.* 2006, Diago *et al.* 2009, Klein *et al.* 2009, Leng *et al.* 2011, Nayak 2008, Smith *et al.* 2007)