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Endophthalmitis

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1. Introduction

Endophthalmitis is an infection of the anterior and posterior segments of the eye resulting from the introduction of microorganisms following a surgical procedure (postoperative), traumatic penetrating injury (posttraumatic), or metastasis from an infection of a distant site in the body (endogenous). Endophthalmitis can develop into panophthalmitis if the infectious agent invades the cornea and sclera. The vast majority of cases of endophthalmitis result from intraocular surgical procedures, in particular cataract surgery (West et al., 2005). Over the past several decades, the number of postoperative endophthalmitis cases has risen steadily, owing to the increase in the number of invasive ocular surgeries performed (West et al., 2005). The etiological agents responsible for endophthalmitis include both Gram-positive and Gram-negative bacteria and fungi. Cases of post-surgical endophthalmitis are usually a result of the introduction of members of the normal microbiota of the eyelid and skin surrounding the eye, the most common cause being coagulase-negative staphylococci (CNS) (West et al., 2005). Cases of posttraumatic endophthalmitis are more frequently caused by environmental bacteria, the most common being *Staphylococcus aureus* and *Bacillus cereus* (Jonas et al., 2000; Meredith, 1999; O'Brien & Choic, 1995; Thompson et al., 1993). Frequent causes of endogenous endophthalmitis (EE) include *S. aureus*, streptococcal species, *B. cereus*, and Gram-negative bacteria including *Klebsiella pneumoniae*, *Escherichia coli*, and fungal agents such as *Candida albicans* (Greenwald et al., 1986; Jackson et al., 2003; Okada et al., 1994; Romero et al., 1999; Shammas, 1977; Shrader et al., 1990).

The clinical hallmarks of endophthalmitis are acute vision loss, severe ocular pain, periorbital swelling, hypopyon, proptosis, and the presence of white cells and flare in the anterior chamber and vitreous (Lemley and Han, 2007). The visual prognosis can vary widely depending on the infectious agent, ranging from mild inflammation and full resolution to devastating blindness and loss of the eye. Therapy for endophthalmitis caused by avirulent skin microbiota typically results in complete resolution and full vision recovery. However, posttraumatic or endogenous endophthalmitis caused by virulent pathogens may not respond to therapeutic intervention and result in partial to complete vision loss, and in some instances, evisceration or enucleation of the infected eye.

This chapter will present a summation of the latest findings of epidemiological studies and discuss current therapeutic modalities. Moreover, the bacteriology and the current state of knowledge regarding the pathogenesis and host/pathogen interactions will be explored.

Given that a number of detailed and authoritative reviews of endophthalmitis in general have been published in the last ten years, and given the paucity of reviews on endogenous bacterial endophthalmitis, this chapter will primarily focus on this route of endophthalmitis.

2. Endogenous endophthalmitis

2.1 Historical perspective

Endogenous or metastatic endophthalmitis results from microorganisms seeding the bloodstream from a distant focus of infection and invading the posterior segment of the eye via a compromised blood retinal barrier (BRB) (Arevalo et al., 2010; Greenwald et al., 1986; Jackson et al., 2003; Okada et al., 1994; Romero et al., 1999; Shammas, 1977; Shrader et al., 1990). While this form of endophthalmitis is rare, the potential for blindness in one or both eyes is high. To date, almost nothing is known about the pathogenesis of endogenous endophthalmitis (EE), even though this disease ranks as one of the most devastating infections of the eye. In the pre-antibiotic era, the majority of cases of endophthalmitis resulted in poor visual outcome. From 1944 to 1966, approximately 73% of endophthalmitis cases resulted in a final visual acuity of hand motion vision or worse. The clinical outcome of endophthalmitis improved somewhat upon the introduction of intravitreal antibiotics and vitrectomy (Neveu and Elliot, 1959; Peyman et al., 1978). Even after the introduction of intravitreal antibiotic therapy and vitrectomy, the visual outcome of EE has not improved significantly in over 50 years (Jackson et al., 2003). Morever, there is a paucity of information on the pathogenic mechanisms of this disease from both the causative agent and host perspectives. The majority of patients have an underlying condition and are immunocompromised (Jackson et al., 2003). The leading predisposing condition of EE is diabetes mellitus type 2, but intravenous drug abuse, immunosuppressive agents, malignancies, and AIDS are also underlying conditions (Arevalo et al., 2010). Symptoms of EE typically include ocular pain, blurring or loss of vision, purulent discharge, and photophobia. EE may present as focal white nodules on the lens capsule, iris, retina, or choroid, or as a ubiquitous inflammation of multiple ocular tissues resulting in purulent exudate throughout the globe. In addition, inflammation can spread to involve the orbital soft tissue (Arevalo et al., 2010).

EE was first identified and described by the German pathologist Rudolf Ludwig Karl Virchow in 1856 (Virchow, 1856). While the causative agent was not identified, it may have been bacterial. In 1894, German ophthalmologist Theodor Axenfeld reported in a treatise on endogenous endophthalmitis that the majority of cases involved only one eye and were a result of the deposition of septic emboli in the uvea (Axenfeld, 1894). However, in one-third of cases, both eyes were affected and infection was selectively localized to the retina. Axenfeld postulated that although bacteria were found in all branches of the carotid and ophthalmic arteries, the predilection for the retina was probably due to the smaller size of the retinal capillaries and „the presence of areas of disease in the capillary walls favoring the lodgment there of micro-organisms" (Tooker, 1938). Collins and Mayou (1925) further speculated that „the retina becomes infiltrated with polymorphonuclear leukocyes, which make their way inward, collecting in large numbers between the retina and the hyaloid membrane and in the neighboring vitreous". Axenfeld noted in his writings that approximately one-third of patients with EE also had endocarditis, and that the vegetations were the likely source of bacteria infecting the eye. In 1916, a case of unilateral EE in a 19 year-old soldier with cerebrospinal meningitis was described (Weakley, 1916). Gram-negative diplococci, presumably *Neisseria*

meningitidis, was cultured from both the cerebrospinal fluid and from the anterior chamber of the left eye. The patient was treated with repeated injections of antimeningococcus serum into the spinal column, which resulted in complete resolution of the meningitis. Interestingly, infection and inflammation of the affected eye was also resolved, leading the case author to speculate that the antiserum therapy may have contributed to the rapid clearance of the infection. Regardless of whether the antiserum had any effect on clearing the infection, the patient retained only perception of light visual acuity (Weakley, 1916). In 1938, Tooker described a case of unilateral EE in a patient that was readmitted to the hospital after having undergone ear surgery (Tooker, 1938). The left eye was severely inflammed and visual acuity was perception of light only. Blood cultures were positive for staphylococci and the patient expired from septicemia three days following readmission. An autopsy revealed bronchial pneumonia, vegetative endocarditis, and abscesses in the kidneys, spleen, and liver. Examination of the left eyeball revealed two primary foci in the retina and ciliary body. Tooker concluded that staphylococcal emboli lodged in the retinal and ciliary capillaries, entered the vitreous chamber, and induced a robust inflammatory response. Tooker reported that the patient had been in excellent condition prior to the ear surgery, blood glucose levels were normal, and no other underlying condition was present. It is therefore possible that a systemic inflammatory response induced a breakdown in the blood retinal barrier allowing staphylococci to invade the vitreous humor.

Even after the introduction of antibiotic therapy, visual outcomes following EE remained poor. Walker and Fenwick (1962) reported a case of fulminate bilateral endophthalmitis following streptococcal septicemia. In spite of aggressive treatment with systemic steroids, hydrocortisone ointment, and local and systemic antibiotics, vision in the right eye was perception of light, and in the left was count fingers. More recently, Jackson et al. (2003) reviewed 267 cases of EE and found that the visual prognosis was uniformly poor. These authors offered a number of possible explanations for the poor visual outcome of EE, including misdiagnosis owing to the fact that EE may mimic other ocular conditions, the rapid progression of the disease, and the failure to recognize the overlap between ocular and systemic infection (Jackson et al., 2003). Since the earliest reports of EE, little progress has been achieved in improving the visual prognosis of this disease. This highlights the necessity for studies to characterize the factors that contribute to the pathogenesis of EE, both from the host and the bacterial perspectives.

2.2 Epidemiology and bacteriology

Current epidemiological studies indicate that EE accounts for approximately 2 to 15% of all cases of infectious endophthalmitis (Arevalo et al., 2010; Puliafito et al., 1982). The often poor visual outcome and potential for bilateral blindness make EE one of the most destructive and devastating ocular infections. In recent reviews of cases of bacterial EE, 41% of cases resulted in a final visual acuity of count fingers or better, 26% of infected eyes lost all useful vision, and 29% required enucleation or evisceration (Greenwald et al., 1986; Jackson et al., 2003; Shammas, 1977). The vast majority of infections are unilateral, with disagreement among studies as to whether there is a predilection for the right or left eye (Arevalo et al., 2010; Greenwald et al., 1986; Jackson et al., 2003; Okada et al., 1994). Bilateral infections occur in approximately 25% of patients with EE (Arevalo et al., 2010). As stated earlier, over 50% of EE patients have an underlying medical condition, with diabetes being

the most prevalent. Additional populations at risk include immunocompromised patients, patients with prolonged indwelling devices, and intravenous drug abusers. Sources of infection include suppurative liver disease, endocarditis, urinary tract infection, and meningitis (Jackson et al., 2003). Virtually any organism that can infect the bloodstream has the capability to cause EE, but frequent causes include opportunistic and environmental pathogens such as *Staphylococcus aureus*, *Streptococcus sp.*, *Clostridium septicum*, coagulase-negative *Staphylococcus*, *Bacillus cereus*, *Listeria monogocytogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Pseudomonas aeruginosa*, and *Neisseria meningitidis* (Arevalo et al., 2010). However, *S. aureus* and *K. pneumoniae* dominate as bacterial causes of Gram-positive and Gram-negative cases of EE, respectively.

S. aureus is a Gram-positive bacterium found as a member of the normal microbiota of skin and mucosa, but can cause a variety of systemic, skin, and deep tissue infections and is a leading cause of contact lens-associated corneal infections (Callegan et al., 1994; Callegan et al., 2002b). The association between *S. aureus* EE and the prolonged use of indwelling prosthetics has been reported in diabetics and patients with other underlying immunocompromise with increasing frequency (Jackson et al., 2003; Major et al., 2010; Ness and Schneider, 2009; Nixdorff et al., 2009; Okada et al., 1994). *S. aureus* causes the majority of the cases of EE in Western countries and Europe (Ho et al., 2011). The emergence of lineages resistant to methicillin in the 1960s has prompted a public health crisis due to the difficulty in treating methicillin-resistant *S. aureus* (MRSA) infections and the increasing trend of infection among individuals with fully competent immune systems. MRSA infections may be community acquired (CA) or healthcare-associated (HA), with CA-MRSA being easier to treat but considerably more virulent. Coinciding with an increase in the prevalence of MRSA strains is an increase in MRSA ocular infections (Blomquist, 2006; Major et al., 2010). Recently, Ho et al. (2011) described a series of 7 patients (8 eyes) from a single institution that were diagnosed with EE caused by MRSA. Treatment of these cases consisted of intravitreal tap and injection of vancomycin and ceftazidime, as well as intravenous vancomycin. While retinal detachment occurred in 6 of 8 eyes, most of the patients experienced improved visual acuity from initial presentation, and only one eye lost all vision and required enucleation. Previous reports found that only 23.5% of cases of MRSA EE resulted in a visual acuity better than 20/200, whereas these authors found that 37.5% of eyes showed a final visual acuity of better than 20/200 (Ho et al., 2011). The authors contend that the higher than usual retinal detachment rate observed in their study might have been due to the higher than normal time between onset of EE and presentation, generally a mean time of 3.5 to 7.1 days versus a mean time of 17 days in their study (Ho et al., 2011).

K. pneumoniae is responsible for the majority of cases of EE due to Gram-negative bacteria and is the leading cause of EE throughout East Asia (Arevalo et al., 2010). Similar to MRSA, *K. pneumoniae* represents a therapeutic challenge due to increasing rates of acquisition of antibiotic resistance determinants. Although *K. pneumoniae* is found in the environment and as a commensal member of the gastrointestinal tract microbiota, it is also a frequent cause of healthcare-associated infections such as pneumonia, bacteremia, and urinary tract infections (Chang et al., 2002; Chuang et al., 2006; Fang et al., 2004; Fung et al., 2002;). *K. pneumoniae* has become the leading cause of pyogenic liver abscess in patients in Taiwan and other countries in the Far East (Chang et al., 2000; Wang et al., 1998), and reports of *K. pneumoniae* EE resulting from septicemia following pyogenic liver abscesses in diabetics are increasing (Chang et al., 2002; Chen et al., 2004; Chuang et al., 2006; Fang et al., 2004; Fung et al., 2002;).

In a case review of 18 patients with EE in Korea, Chung et al. (2011) also reported a close association between diabetes and infection with *K. pneumoniae*, and these factors were linked to a poor visual prognosis. These findings highlight the necessity for increased scrutiny of diabetic patients that present with ocular symptoms.

2.3 Diagnosis and therapeutic modalities

Early diagnosis and the initiation of treatment are critical to controlling infection and improving the visual prognosis of EE. Diagnosis of EE is difficult to establish based on clinical presentation alone because of the nonspecific nature of the symptomology. Diagnosis is usually based on clinical presentation and additional methods such as fundoscopy, ultrasonography, optical coherence tomography, and magnetic resonance imaging (Jackson et al., 2003). When EE is suspected, cultures of blood, vitreous and aqueous humor, and Gram stains are criticial for confirmation (Arevalo et al., 2010). Symptoms of systemic disease may also be useful in diagnosis, however only 57% of patients with EE manifested systemic signs of infection (Okada et al., 1994). Moreover, EE might be missed in patients with systemic infection until ocular pain and vision loss are experienced. Therapy for diagnosed bacterial EE consists of administration of systemic antibiotics such as third generation cephalosporins, vancomycin, and aminoglycosides (Lemley and Han, 2007). Fourth generation fluoroquinolones are also used at the discretion of the physician (Lemley and Han, 2007). Therapy also consists of intravitreal injection of 1 mg vancomyin per 0.1 ml for Gram-positive and 2.25 mg ceftazidime per 0.1 ml for Gram-negative pathogens and/or the aminoglycoside amikacin (0.4 mg). Jackson et al. (2003) reported in a literature review that vitrectomy is beneficial in cases of severe EE caused by highly virulent organisms and increases the likelihood of a better visual outcome by threefold. Vitrectomy is also indicated for cases of EE complicated by retinal detachment (Arevalo et al., 2010). As stated earlier, however, the visual outcome of EE has not improved in over 50 years. The lack of clinical improvements in EE is likely due to the lack of a reproducible animal model in which to study this disease; a disease model would be beneficial in terms of therapeutic testing and analysis of pathogenesis.

2.4 Pathogenesis

EE is one of the most frequently blinding intraocular infections, however little is known about the interplay of host and bacterial factors that contribute to the development of this disease. Moreover, the pathogenic mechanisms underlying the migration of bacteria toward and into the eye, inflammation, and vision loss have not been addressed. It is also unknown as to why diabetes is a common predisposing condition, although there are a number of possible explanations. Diabetes compromises the eye both immunologically and architecturally, resulting in changes that may weaken the ability of the eye to exclude organisms during systemic infection. One of the most serious and common complications among diabetics, specifically those with type 2 diabetes, is diabetic retinopathy (Aiello et al., 1998; Engler et al., 1991). During the progression of diabetic retinopathy, the vasculature, glia, and neurons of the retina are affected. The initial changes that occur within the retinal vasculature are the death of pericytes and thickening of the basement membrane, which lead to capillary leakage and occlusion. These changes ultimately result in macular edema, formation of new vessels, and neuroretinal degeneration (Asnaghi et al., 2003; Fong et al., 2003; Martin et al., 2004; Neely and Gardner, 1998; Qaum et al., 2001; Takeda et al., 2001).

Increases in vascular endothelial growth factor (VEGF) and the cytokines interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor alpha (TNFα) in diabetic retinas contribute to angiogenesis and to breakdown in the BRB, implying an association with inflammation in the disease process (Jo et al., 2010). Intercellular adhesion molecule 1 (ICAM-1) and CD18 are upregulated and contribute to increased leukocyte adhesion to the endothelial wall. This is turn results in endothelial cell injury and death (Funatsu et al., 2005; Miyamoto et al., 1998; Miyamoto et al., 1999; Schroder et al., 1991). Elevated expression of matrix metalloproteases in the retina may also facilitate increases in vascular permeability and degradation of tight junction complexes, leading to BRB dysfunction (Giebel et al., 2005). Retinal pigment epithelia (RPE) and vascular endothelium, barrier cells of the BRB, also undergo changes in hyperglycemic environments *in vitro* and *in vivo*, including increases in VEGF that may contribute to vascular permeability (Amrite et al., 2006; Losso et al., 2010). The deterioration of the BRB during the development of diabetic retinopathy may allow pathogens to more readily invade the interior of the eye and might partially explain the link between diabetes and an increased risk of acquiring EE. Unfortunately, a clinical link between patients with diabetic retinopathy and EE has not been reported, only speculated. Retinal vascular permeability is not the only change occurring in a diabetic individual. Diabetes also compromises the innate immune response and depresses the ability to clear infections in general. Polymorphonuclear leukocytes (PMN) are of critical importance in clearing pathogens from the bloodstream and in the eye during acute bacterial endophthalmitis (Callegan et al., 1999; Ramadan et al., 2006; Ramadan et al., 2008; Wiskur et al., 2008). These important cells are impaired in diabetics. PMN defects in chemotaxis, phagocytosis, and bactericidal activity have been reported in the context of diabetes (Delamaire et al., 1997; Walrand et al., 2004) and PMN from diabetic mice and humans are incapable of phagocytizing and killing both *S. aureus* and *K. pneumoniae* (Lin et al., 2006; Park et al., 2009). These defects in the ability of PMNs to clear bacteria that are destined to cross a compromised blood retinal barrier may also contribute to the development and pathogenesis of EE, but this has not been scientifically analyzed.

Virtually nothing is known about the bacterial factors that contribute to the pathogenesis of EE. *S. aureus* and *K. pneumoniae* possess a repertoire of factors with demonstrable roles in the virulence of these species in a number of animal models of infection, however it is currently unknown if they contribute to the pathogenesis of EE. *S. aureus* expresses a number of adhesins, including the fibronectin binding proteins FnbpA and FnbpB (Green et al., 1995), the fibrinogen-binding proteins ClfA and ClfB (McDevitt et al., 1994), and the collagen binding protein Cna (Patti et al., 1992) that have been shown to mediate attachment to extracellular matrix and plasma proteins, a crucial first step in initiating infections. *S. aureus* synthesizes alpha-toxin, a cytolysin shown to be important in corneal infections (Callegan et al., 1994) and endophthalmitis (Booth et al., 1998; Callegan et al., 2002b). *S. aureus* also secretes a host of other secreted cytolytic toxins including the beta-, gamma- and delta-toxins, and Panton-Valentine leukocidin (Plata et al., 2009) that may contribute to structural damage within the eye, or in the case of Panton-Valentine leukocidin (PVL) have either anti- or pro-inflammatory effects. PVL lyses neutrophils at higher concentrations but is a potent stimulator of the release of proinflammatory cytokines such as IL-8 at lower concentrations (Otto, 2010). Some strains of *S. aureus* are also encapsulated, rendering them resistant to phagocytosis and more virulent in animal models of sepsis (Luong and Lee, 2002; Thakker et al., 1998). Most clinical isolates of *S. aureus* produce either Type 5 or Type 8 capsular polysaccharide (Roghmann et al., 2005). The capsule of *S. aureus* may afford a survival

advantage and prevent clearance from the bloodstream as well as the vitreous humor, especially in diabetics with impaired clearance mechanisms.

K. pneumoniae produces at least five major virulence factors that contribute to the pathogenesis of infection and include capsular serotype, hypermucoviscosity phenotype (HMV), lipopolysaccharide (LPS), siderophores, and pili. However, nothing is known about their potential contribution to EE pathogenesis. There are 77 capsular serotypes, however serotype K1 predominates among bacteremia, liver abscess, and EE isolates in Taiwan (Fung et al., 2002). Capsule production is likely to impede clearance of *K. pneumoniae* from the bloodstream and from the eye. The HMV phenotype is enriched among highly virulent, invasive strains of *K. pneumoniae*, especially those causing EE (Fang et al., 2004; Fang et al., 2007; Fung et al., 2002; Karama et al., 2008; Keynan and Rubinstein, 2008; Lee et al., 2006). Strains that express this phenotype possess a thick, viscous capsule-associated mucopolysaccharide web (Wiskur et al., 2008). Two commonly studied genes are associated with HMV: *magA* (mucoviscosity-associated gene A), which encodes a 43 kd outer membrane protein that has not been characterized (Fang et al., 2004), and *rmpA* (regulator of the mucoid phenotype A), a regulatory gene that controls the synthesis of the extracapsular mucopolysaccharide (Nassif et al., 1989). It has been shown that HMV confers resistance to serum killing and phagocytosis, and contributes to virulence in mice (Fang et al., 2004). *magA-* transposon mutants, which lost the HMV phenotype displayed serum sensitivity, became phagocytosis susceptible, and were avirulent in a mouse model (Fang et al., 2004). *magA* was located within a 35-kb locus containing 24 open reading frames (ORFs) with homologies to genes involved in exopolysaccharide biosynthesis or export and glycosylation (Chuang et al., 2006). This locus may represent a novel pathogenicity island responsible for the hypervirulence seen with certain *K. pneumoniae* pathogenic strains (Chuang et al., 2006). HMV+ *K. pneumoniae* are the most common cause of EE in Southeast Asia, with cases of EE caused by HMV+ *K. pneumoniae* on the rise in Western countries (Keynan and Rubinstein, 2008; Lederman and Crum, 2005). Our laboratory has previously shown that the HMV phenotype contributes to the pathogenesis of experimental *K. pneumoniae* endophthalmitis. In this model, an HMV+ strain caused significantly greater inflammation and greater loss of visual function than an HMV- strain following direct injection of bacteria into the vitreous (Wiskur et al., 2008). Further, the HMV+ strain was not readily cleared from the eye in this model (Wiskur et al., 2008). More recently, the *magA* gene was directly linked to the pathogenesis of EE in experimental *K. pneumoniae* endophthalmitis. Hunt et al. compared a wildtype HMV+ *K. pneumoniae* strain with an isogenic mutant defective in the *magA* gene, and found that mice infected with the *magA-* strain showed a significantly improved visual outcome relative to mice infected with the wildtype strain (Hunt et al., 2011). These results clearly demonstrate a role for the HMV phenotype in *K. pneumoniae* endophthalmitis. As this direct injection model circumvents systemic infection, it remains to be seen whether the HMV phenotype is important for crossing the BRB and establishing EBE.

The lipopolysaccharide O side chain has been shown to confer serum resistance to *K. pneumoniae* by preventing the deposition of complement components on the bacterial cell membrane and the ensuing complement-mediated cell lysis (Tomas et al., 1986). It is therefore possible that *K. pneumoniae* LPS from cells migrating near the BRB might elicit increases in permeability in the retinal vasculature that result in leakiness, facilitating entry into the eye. Metrickin et al. (1995), demonstrated that *E. coli* LPS induced a dose-dependent breakdown of the BRB. The siderophores enterobactin and aerobactin could also potentially be involved. While enterobactin is synthesized by nearly all isolates of *K. pneumoniae*,

aerobactin is less frequently detected (Podschun et al., 1993). However, only *K. pneumoniae* isolates with capsular serotype K1 or K2 that produced aerobactin were more virulent (LD_{50} <10^3 cfu), and transfer of the genes necessary for synthesis of aerobactin into an avirulent strain increased the virulence by 100-fold (Nassif and Sansonetti, 1986). *K. pneumoniae* produce two types of pili or fimbriae, type 1 and type 3, that mediate attachment to epithelial cells. The type 1 fimbrial adhesion gene *fimH* was shown to be enriched among blood isolates (Yu et al., 2006), and the type 3 fimbrial adhesion protein MrkD has been demonstrated to contribute to virulence by binding to epithelial cells of the urogenital, repiratory, and gastrointestinal tracts (Sebghati et al., 1998), and the type 3 fimbrial shaft protein MrkA is required for biofilm formation on intravenous and urinary catheters and human extracellular matrix (Jagnow and Clegg, 2003; Langstraat et al., 2001). It is conceivable that these pili mediate adherence to structures in the eye and aid in the establishment of EE. However, as for all of the above discussed factors, no studies have been conducted evaluating the importance of these virulence traits to EE pathogenesis due to the lack of a well-characterized animal model of this disease.

3. Postoperative endophthalmitis

Postoperative endophthalmitis is the most common type of endophthalmitis and most frequently occurs following cataract surgery, with 90% of cases occuring following this procedure (Lemley and Han, 2007). The rates of postoperative endophthalmitis have been increasing over the past several years, owing to increases in the number of cataract surgeries and other types of intraocular surgeries performed. This raises concerns due to the ever-growing population of the elderly that require cataract surgery. Millions of cataract surgeries are performed each year. Fortunately, the rate of occurrence of post-cataract endophthalmitis remains low, ranging between 0.06% and 0.25% (O'Brien et al., 2007; West et al., 2005). Among the types of cataract surgeries performed, phacoemulsification accounted for approximately 48% of the postoperative endophthalmitis cases, while 38.5% and 6.6% of cases followed extracapsular or intracapsular extraction, respectively (Ng et al., 2005). Postoperative endophthalmitis can occur after other types of surgery such as secondary intraocular lens placement, pars plana vitrectomy, penetrating keratoplasty, and even after corneal suture removal (Lemley and Han, 2007).

Fig. 1. Acute endophthalmitis caused by *Staphylococcus aureus* in a 43-year-old patient 3 days following a triple surgical procedure (penetrating keratoplasty, cataract extraction, and posterior chamber intraocular lens). Note the hypopion in the anterior chamber. The vitreous was also involved. Reproduced with kind permission from Dr. Rumelt
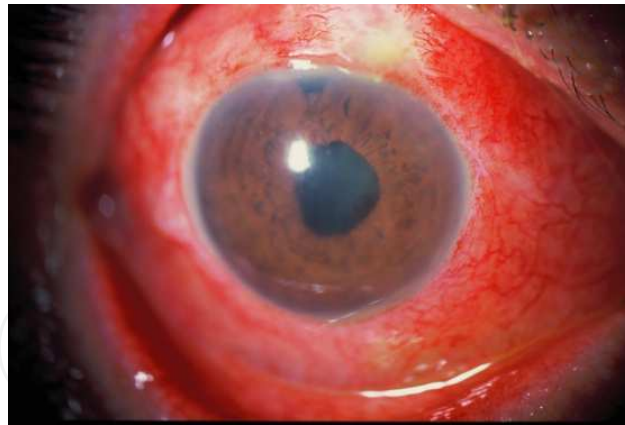
Fig. 2. Bleb-associated endophthalmitis due to *Streptococcus pneumoniae* in the right eye of a 63-year-old patient, 2 weeks after trabeculectomy. Note the whitening of the filtering bleb due to inflammatory infiltrate. There was also inflammation of the anterior and posterior segment. The earliest sign of endophthalmitis is infiltration of the bleb by inflammatory cells, and when the anterior and posterior segments are still normal, this is defined as "blebitis". Reproduced with kind permission from Dr. Rumelt

Preventative measures consist of prophylactic intracameral antibiotics or prophylactic subconjunctival antibiotic injection following cataract surgery (Kelkar et al., 2008). Patients with acute postoperative endophthalmitis generally present between 1 to 2 weeks following surgery. Endophthalmitis has also been reported to occur after intravitreal injection of anti-VEGF agents for the treatment of age-related macular degeneration (AMD). While the rate of endophthalmitis following intravitreal injection of these agents is equivalent to that of postoperative endophthalmitis following cataract surgery, approximately 0.16%, the increasing number of elderly patients requiring this type of therapy is a significant cause for alarm (Gragoudas et al., 2004).

Endophthalmitis must be distinguished from sterile inflammation following surgery. Diagnosis is established by visual acuity measurements, fundoscopy, and ERG, followed by microbiological evaluation of aqueous and vitreous samples (Lemley and Han, 2007). Gram-positive bacteria are the leading cause of postoperative endophthalmitis cases, with coagulase-negative staphylococcal (CNS) isolates being the most common, causing 47–70% of all postoperative endophthalmitis cases (Han et al., 1996). *S. aureus* account for approximately 10%, *Streptococcus* species for 9%, *Enterococcus* species for 2.2%, and Gram-negative bacteria for approximately 6% (Han et al., 1996). Fortunately, postoperative endophthalmitis caused by CNS is relatively mild and is more easily resolved with antibiotic and anti-inflammatory therapy (Josephberg, 2006). The visual prognosis is generally favorable, with 84% of cases resulting in at least 20/100 visual acuity, and 50% of these cases resulted in 20/40 visual acuity (Josephberg, 2006). Less virulent bacteria such as *Propionibacterium acnes* and CNS, and the fungal organism *Candida parapsilosis* are the most common causative agents of chronic endophthalmitis (Lemley and Han, 2007). Patients with this form of endophthalmitis typically present several months following surgery (Lemley and Han, 2007). Postoperative endophthalmitis caused by *S. aureus*, species of streptococci, enterococci, *Bacillus,* and Gram-negative bacteria can cause a more explosive and fulminant infection. The visual outcome of severe infections is uniformly poor, with only 30% of eyes attaining 20/100 visual acuity (Josephberg, 2006). The primary treatment is typically a single

intravitreal injection of antibiotics consisting of 1.0 mg vancomycin per 0.1 ml, and 2.25 mg ceftazidime per 0.1 ml or 400 μg amikacin per 0.1 ml. Fourth generation fluoroquinolones can also be employed because of their broad spectrum of activity and usefulness against Gram-negative bacteria. Vitrectomy and corticosteriod therapy are are often advocated as adjunct treatment modalities (Lemley and Han, 2007), however corticosteriod treatment is still considered controversial.

4. Posttraumatic endophthalmitis

Posttraumatic endophthalmitis is a complication of a penetrating injury to the eye and is not as frequent as postoperative endophthalmitis. However, the rate of infection is higher and the visual prognosis is poorer following penetrating injury to the globe than following surgical procedures. The infection rates following traumatic injury to the globe range from 3% to 17% (Meredith, 1999; O'Brien and Choi, 1995; Thompson et al., 1993). The rates increase substantially when a foreign body remains in the globe and range from 11 to 30% (Boldt et al., 1989; Brinton et al., 1984; Thompson et al., 1993). Other risk factors include age greater than 50 and a more than 24 hour delay prior to presentation (Thompson et al., 1993). Those patients who presented for intraocular foreign body removal greater than 24 hours following injury were approximately 4-fold more likely to acquire endophthalmitis (Thompson et al, 1993), highlighting the necessity of seeking immediate medical attention following penetrating injury. Staphylocci and *B. cereus* rank as the number one and two causes, respectively, and together account for 95% of cases (Das et al., 2005; Lemley and Han, 2007).
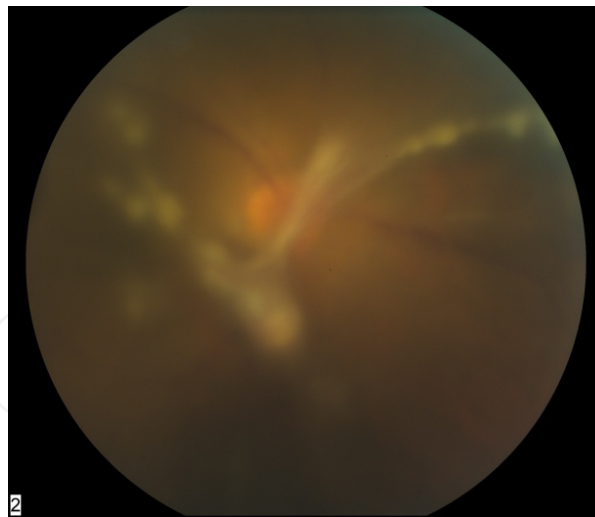

Fig. 3. Fundoscopic exam of a patient with *Staphylococcus aureus* endophthalmitis after a penetrating ocular injury. The findings of endophthalmitis in the vitreous may include not only flare and cells, but also fibrin in various degrees of organization. Organization to fibrotic bands may results in traction retinal detachment due to contraction of such bands. Reproduced with kind permission from Dr. Rumelt

B. cereus is ten times more likely to be the causative agent of posttraumatic than postoperative endophthalmitis, especially in cases involving organic or soil-contaminated

intraocular foreign bodies (Das et al., 2005). Other causative agents include CNS, streptococcal species, clostridial species, fungi, and protozoa such as acanthamoeba (Lemley and Han, 2007; Rumelt et al., 2001).
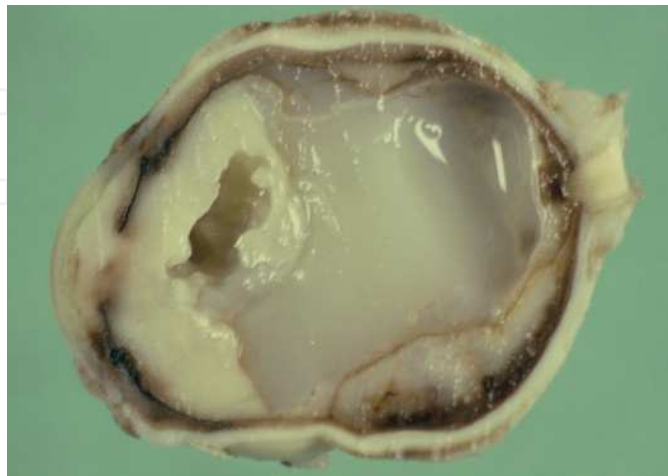

Fig. 4. Gross pathologic specimen of the globe affected by *Pseudomonas aeruginosa* endophthalmitis. The patient lost his vision in the eye and it became a blind, painful eye that underwent enucleation. Note the massive necrosis of the ocular tissues. Reproduced with kind permission from Dr. Rumelt

Fig. 5A. Endophthalmitis caused by the gas-forming bacterium *Clostridium bifermentans*. The endophthalmitis was caused following ocular penetrating injury be a soiled-contaminated foreign body. Note the brownish discoloration of the conjunctiva and a subconjunctival gas bubble. The patient was treated with intravenous and intravitreal panicillin and clyndamycin, but lost his vision despite the treatment. Reproduced with kind permission from Elsevier, Inc., in Rehany U, Dorenboim Y, Lefler E, Schirer E. Ophthalmology. 1994;101:839-42.

Fig. 5B. The same patient as in 5A a few days later. Note that the conjunctiva has become necrotic, the color became purple, and the gas bubble ruptured. Reproduced with kind permission from Elsevier, Inc., in Rehany U, Dorenboim Y, Lefler E, Schirer E. Ophthalmology. 1994;101:839-42.

When penetrating injury occurs, the foreign body should be removed as soon as possible, especially when the material is organic or soil contaminated due to the potential for *B. cereus* contamination (Lemley and Han, 2007). In some cases, for example where the foreign body is inert glass and is located in a sensitive position such as the retina, it may not be desirable to remove the object. Even relatively minor injuries to the eye can result in severe endophthalmitis with devastating outcomes. Cases have been described following penetrating injury to the eye due to orthodontic headgear (Blum-Hareuveni et al., 2006). Diagnosis of posttraumatic endophthalmitis is established by visual acuity tests, slit-lamp examination, and ophthalmoscopy, as well as computed tomography and ultrasound (Lemley and Han, 2007). For posttraumatic endopthalmitis, treatment consists of administration of intravitreal 1 mg vancomycin per 0.1 ml, 2.25 mg ceftazidime per 0.1 ml or 400 µg amikacin per 0.1 ml (Lemley and Han, 2007). Even with early therapy, the outcomes are often poor due to the potential virulence of the infecting bacterium and the explosive inflammatory response.

5. Experimental endophthalmitis and the roles of bacterial and host factors

A rabbit model of experimental endophthalmitis has been used to assess the contribution of both bacterial and host factors to the development of endophthalmitis. This model mimics the infection course after introduction of bacteria directly into the posterior segment of the eye that would occur following a surgical procedure or penetrating injury, but does not allow for the analysis of host immunological status and bacterial factors that contribute to the development of EE. This model system allows intravitreal injection across the pars plana of low inocula that allow the bacterium under study to adapt to the intraocular environment of the eye and replicate (Booth et al., 1995; Booth et al., 1997; Callegan et al., 1999a; Jett et al., 1992; Sanders et al., 2010; Sanders et al., 2011). Depending on the infecting organisms, infection symptoms in the rabbit model develop over a period ranging from 6 hours to 3

days, and a number of infection parameters can be repeatedly monitored and quantitative data obtained. Parameters that can be monitored include ocular inflammation, fibrin deposition, electrophysiologic measurement of retinal function, and bacterial growth and distribution. Infiltration of inflammatory cells can be quantified by slit lamp biomicroscopy in which progressive inflammation is scored in different anatomical locations within the eye (Callegan et al., 1999a). Inflammation and fibrin deposition can be qualitatively assessed by analysis of thin-section histopathology. Retinal damage as a result of the production of toxin by the bacterium under study or by bystander damage due to PMN activity in the eye can be measured by electroretinography (ERG). Using the rabbit model, Callegan et al. (1999a) found that supernatants from from *B. cereus* and *S. aureus* caused retinal damage and were highly inflammogenic, suggesting that secreted toxins are of primary importance to the pathogenesis of endophthalmitis. Callegan and colleagues did not find individual roles for the *B. cereus* membrane damaging toxins hemolysin BL, phosphatidylinositol-specific phopholipase C, and phosphatidylcholine-specific phospholipase C in this model, however, other toxins controlled by the global regulator *plcR* were found to contribute to pathogenesis of experimental *B. cereus* endophthalmitis (Callegan et al., 1999b; Callegan et al., 2002a; Callegan et al., 2003). The *S. aureus* alpha- and beta-toxins, but not the gamma-toxin, were shown to make an important contribution to endophthalmitis (Booth et al., 1998; Callegan et al., 2002b). Isogenic mutants deficient in each of the toxin-encoding genes were compared in this model. Injection of rabbit eyes with the gamma-toxin deficient mutant had no impact on retinal function when compared with the wildtype strain. However, the alpha- and beta-toxin deficient mutants were attenuated when compared with the wildtype. After 2 days, rabbit eyes infected with the alpha- or beta-toxin deficient mutant showed 40% and 60% retinal function retained, respectively, as compared with 20% retained in rabbits infected with the wildtype strain. Moreover, a cumulative effect was observed as a result of inactivation of all three toxin loci on retention of retinal function (Callegan et al., 2002b). This model has also been used as a sensitive measure of the contribution of enterococcal virulence factors to pathogenesis. Jett et al. (1992) demonstrated that the course and severity of disease was significantly determined by the *E. faecalis* biocomponent cytolysin. The cytolysin destroyed the neural tissue of the retina and its architecture over a period of 24 – 72 hours. The toxicity to retinal tissue was not attenuated by either antibiotic and/or anti-inflammatory therapy when infection involved a cytolytic strain, although an isogenic, non-cytolytic infection completely resolved when both of these treatments were provided 24 h postinfection. These studies showed not only the contribution of the cytolysin to the pathogenesis of enterococcal endophthalmitis, but also the importance of inflammatory sequelae. Engelbert et al. (2004) demonstrated that the *E. faecalis* gelatinase and serine protease in concert contributed to pathogenesis in this model as double mutants in these genes were significantly attenuated when compared to the single mutants. Callegan et al. (1999a) also utilized this model to implicate the contribution of bacterial cell wall components in inciting an inflammatory response during endophthalmitis. Injection of metabolically inactive bacteria or cell wall sacculi elicited significant intraocular inflammation. The rabbit model has also been used to implicate the *Streptococcus pneumoniae* capsule in the pathogenesis of endopthalmitis (Sanders et al., 2011). Infection with an isogenic unencapsulated *S. pneumoniae* mutant strain resulted in significantly lower slit lamp examination scores, significantly greater retinal function, and significantly less neutrophil infiltration into the eye compared with the wildtype parental strain in this model. Moreover, they demonstrated the efficacy of immunizing with the *S. pneumoniae* pneumolysin in

protecting the eye from retinal damage during *S. pneumoniae* endophthalmitis (Sanders et al., 2010). In summary, the rabbit model of experimental endophthalmitis has proven invaluable in assessing the role of bacterial virulence factors and identifiying potentially new therapeutic targets.

More recently, a mouse model of experimentally induced endophthalmitis has been employed to explore various aspects of disease development, course, and outcome. As with the rabbit model, infection parameters can be qualitatively and quantitatively measured including bacterial growth, ocular inflammation, and retinal function. Ocular inflammation can be qualitatively assessed via thin-section histopathology as well as quantified by slit-lamp biomicrosopy and indirect measurements of PMN influx by a myeloperoxidase ELISA (Ramadan et al., 2006). As stated earlier, Wiskur et al. (2008) implicated the HMV phenotype in the persistence of *K. pneumoniae* in the eye by comparing the bacterial growth of an HMV+ to that of an HMV- strain after intravitreal injection of 100 CFU. The HMV- strain did not grow to the same level as the HMV+ strain and were cleared with 27 hours. HMV+ infected eyes underwent phthisis within 24 hours. This study provided evidence that the HMV phenotype makes an important contribution to *K. pneumoniae* endophthalmitis pathogenesis. As discussed above, Hunt et al. (2011) confirmed these findings using a *magA*-mutant of *K. pneumoniae* in the mouse endophthalmitis model. *S. aureus* cell wall teichoic acids have also been shown to contribute to the pathogenesis of endophthalmitis and that inhibitors of cell wall teichoic acid synthesis might serve as candidates for therapy of *S. aureus* endophthalmitis in this model (Suzuki et al., 2011).

An important aspect of the murine model of experimental endophthalmitis is that factors of the host immune system can be assessed by comparison of the infection course in genetic knockout mouse strains with that in wildtype strains of the same genetic background. Ramadan and colleagues (2006) showed that as early as 4 hours post-injection with *B. cereus*, significant decline in retinal function and PMN infiltration were observed, which coincided with an increase in the proinflammatory cytokine TNF-α. In TNF-α knockout mice, *B. cereus* replicated more rapidly, retinal function declined more sharply, and fewer PMN infiltrated the eye. These findings illustrate the power of this model in allowing the repeated measurement of multiple infection parameters and showed that damage to the retina occurred earlier than was previously thought. Furthermore, the necessity of TNF-α in PMN recruitment and control of *B. cereus* replication was established. Engelbert and Gilmore (2005) used C3 and FasL knockout out mice to dissect components of the innate immune and ocular immune privilege systems in controlling *S. aureus* endophthalmitis. The infection course in C3 knockout eyes followed a similar course to their wildtype counterparts, suggesting that complement does not play a significant role in ocular defense against *S. aureus* infection. On the other hand, the membrane-bound Fas ligand (FasL), which functions to maintain the immune privilege status of the eye by inducing apoptosis in infiltrating inflammatory cells, was found to be criticial in bacterial clearance. Mice deficient in FasL were unable to control *S. aureus* infection after injection of an inoculum that is cleared in wildtype mice (Engelbert and Gilmore, 2005). The host heat shock protein alphaB-crystallin was shown to be upregulated in the retina and prevent apoptosis and retinal damage during murine *S. aureus* endopthalmitis (Whiston et al., 2008). These authors found that mice deficient in the production of this molecular chaperone displayed increased retinal apoptosis and damage, and that *S. aureus* produced a protease capable of cleaving this

protective protein. Finally, Kumar et al. (2010) suggested that the host toll-like receptor (TLR) 2 is involved in controlling infection by *S. aureus* in this model by showing that pretreatment of mice with intravitreal injections of the TLR2 ligand Pam3Cys reduced bacterial load when compared with mock-injected animals. In summary, the murine model of experimental endopthalmitis has proven to be invaluable in analyzing both host and bacterial factors that contribute to this disease. The growing number of available genetic knockouts in components of the innate and adaptive immune systems and the relative ease of use will continue to make the murine model key to understanding the complex interplay between host and bacterial factors during the initiation, course, and resolution of endophthalmitis.

6. Conclusions

Endophthalmitis remains a relatively rare infection, but the potential for vision loss and/or blindness is significant. The potential for poor prognosis, which depends on the causative organism and the immune status of the patient, remains high despite antibiotic and surgical intervention. Research on the contribution of bacterial virulence factors has implicated both secreted toxins and proteases, capsules, and the intraocular host response to bacterial cell wall components in the pathogenesis of experimental *B. cereus, S. aureus, E. faecalis, S. pneumoniae,* and *K. pneumoniae* endophthalmitis. Moreover, components of the host inflammatory response and mediators of ocular immune privilege have been shown to play critical roles in controlling experimental *B. cereus* and *S. aureus* endophthalmitis. Virtually nothing is known about the contribution of bacterial or host virulence factors to the development of EE. The fact that visual prognosis of EE and other types of bacterial endophthalmitis caused by pathogenic organisms remains uniformly poor highlights the need for continuing research on the interactions between the offending pathogen, the internal structures of the eye, underlying disease state and the immune response.

7. Acknowledgments

8. References

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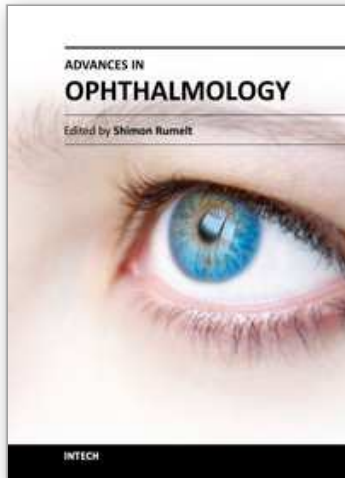
Advances in Ophthalmology

Edited by Dr Shimon Rumelt

This book focuses on the different aspects of ophthalmology - the medical science of diagnosis and treatment of eye disorders. Ophthalmology is divided into various clinical subspecialties, such as cornea, cataract, glaucoma, uveitis, retina, neuro-ophthalmology, pediatric ophthalmology, oncology, pathology, and oculoplastics. This book incorporates new developments as well as future perspectives in ophthalmology and is a balanced product between covering a wide range of diseases and expedited publication. It is intended to be the appetizer for other books to follow. Ophthalmologists, researchers, specialists, trainees, and general practitioners with an interest in ophthalmology will find this book interesting and useful.

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