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Foundational concepts in the biology of bacterial keratitis

Lawson Ung, MD^{1,2}, James Chodosh, MD, MPH^{1,2}

¹Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts, USA

²Infectious Disease Institute, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts, USA

Abstract

Bacterial infections of the cornea, or bacterial keratitis (BK), are notorious for causing rapidly fulminant disease and permanent vision loss, even among treated patients. In the last sixty years, dramatic upward trajectories in the frequency of BK have been observed internationally, driven in large part by the commercialization of hydrogel contact lenses in the late 1960s. Despite this worsening burden of disease, current evidence-based therapies for BK – including broad-spectrum topical antibiotics and, if indicated, topical corticosteroids – fail to salvage vision in a substantial proportion of affected patients. Amid growing concerns of rapidly diminishing antibiotic utility, there has been renewed interest in urgently needed novel treatments that may improve clinical outcomes on an individual and public health level. Bridging the translational gap in the care of BK requires the identification of new therapeutic targets and rational treatment design, but neither of these aims can be achieved without understanding the complex biological processes that determine how bacterial corneal infections arise, progress, and resolve. In this chapter, we synthesize the current wealth of human and animal experimental data that now inform our understanding of basic BK pathophysiology, in context with modern concepts in ocular immunology and microbiology. By identifying the key molecular determinants of clinical disease, we explore how novel treatments can be developed and translated into routine patient care.

Keywords

Bacterial keratitis; microbial keratitis; corneal infections; immunology; innate immunity; adaptive immunity; *Pseudomonas aeruginosa*; *Staphylococcus aureus*; *Streptococcus pneumoniae*

CORRESPONDENCE: Dr. James Chodosh, MD, MPH, Massachusetts Eye and Ear, 243 Charles Street, Boston, Massachusetts 02114, United States of America, james_chodosh@meei.harvard.edu, Tel.: 617-573-6398.

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CONFLICTS OF INTEREST

None to declare.

INTRODUCTION

Bacterial corneal infections, or bacterial keratitis (BK), are sight-threatening emergencies that can lead to rapid vision loss. In the canonical *System of Ophthalmology* (1965), Sir Duke-Elder observed that BK caused by *Pseudomonas aeruginosa* – now regarded among the most common and destructive of corneal pathogens – was “relatively rare”, with only 100 reported cases in the literature at that time (Duke-Elder, 1965). Today, BK ranks among the leading causes of global ocular morbidity (Ung et al., 2019a), with steep upward trends in disease frequency driven by the widescale adoption of hydrogel contact lenses in the late 1960s (Galentine et al., 1984; Golden et al., 1971; Stapleton et al., 2008), and a rapidly growing world population (Bourne et al., 2021). Most treatment approaches to BK involve the collection of corneal cultures followed by broad-spectrum topical antibiotics, with surgical interventions usually reserved to treat complications such as worsening infection and/or stromal thinning and perforation (Jones, 1980; Jones, 1981a; Lin et al., 2019). Though most patients treated with the current standard of care will achieve microbiologic resolution of their infection, clinical outcomes in BK leave much to be desired. In tertiary care settings, a significant proportion (~30%) of patients develop long-term moderate-to-severe monocular vision loss, defined as a best-corrected visual acuity of < 20/60 (McClintic et al., 2014; Prajna et al., 2019), and outcomes in resource-poor settings are even more grim (Arunga et al., 2019a; Burton et al., 2011). Poor vision is commonly attributed to infections that progress despite intensive treatment, and chronic sequelae such as visually-significant stromal scarring, cataract and glaucoma (Lotti and Dart, 1992). Though mostly unilateral in nature, BK is associated with profound and underappreciated human costs, including diminished quality of life (Arunga et al., 2019b; Li et al., 2014; Rose-Nussbaumer et al., 2016), reduced work productivity (O’Brien et al., 2015), and substantial economic losses (Collier et al., 2014; Cope et al., 2018).

Despite a growing burden of disease, therapeutic options for treating BK remain sparse. Broad-spectrum topical antibiotics (Hanet et al., 2012; McDonald et al., 2014) and corticosteroids (Herretes et al., 2014; Srinivasan et al., 2012) are the only evidence-based treatments that have been shown to salvage vision, and antibiotics are fast losing their utility due to the emergence of antimicrobial resistance (AMR) among corneal pathogens (Asbell et al., 2015; Thomas et al., 2019). In clinical medicine, bridging translational gaps in the care of any condition hinges on the identification of new therapeutic targets and rational treatment design. In BK, neither of these aims can be realized without a comprehensive understanding of disease pathophysiology, which can be distilled into three main pillars: (a) mechanisms of natural resistance against disease; (b) the processes by which pathogens breach host defenses to establish infection; and (c) host-pathogen dynamics responsible for the acute and chronic manifestations of disease. Though increasingly sophisticated experimental models of BK incorporating “omics” research have shed unprecedented light on the pathogenesis of these infections, most paradigms of understanding converge on a pathway typical of classic innate immunity (Chidambaram et al., 2017; Karthikeyan et al., 2013). BK invariably begins with altered ocular surface homeostasis – most commonly seen in contact lens wear, trauma, and ocular surface disease – that permits bacterial corneal invasion. The rapid accumulation of bacterial toxins, exoproducts, and cellular

debris provokes a florid host inflammatory response orchestrated by the corneal epithelium, stromal keratocytes, resident immune cells, and infiltrating leukocytes dominated by polymorphonuclear cells (PMNs) (Wilhelmus and Dan, 1996). Unfortunately, the activation of the local inflammasome (Martinon et al., 2002) is double-edged; indiscriminate release of reactive oxygen species, lysosomal enzymes, and autolytic proteins may result in bacterial eradication, but their collateral toxicity to the surrounding stroma may lead to permanent structural modifications that impair vision (Kessler et al., 1977b; Steuhl et al., 1987). This clinically-oriented chapter will draw on foundational concepts in ocular immunology and microbiology to dissect the cellular mechanisms that underlie the pathogenesis of BK, and in doing so explore elusive therapies that may offer hope for patients afflicted by this devastating infection.

1. THE OCULAR SURFACE IN HEALTH: INTRINSIC HOST DEFENSES

i. Anatomical protections

Under healthy conditions, the ocular surface is endowed with complex defense mechanisms that are choreographed to prevent prolonged exposure to environmental pathogens, antigens, and allergens (Gipson, 2007; Stern et al., 2004). These mechanisms are crucial in maintaining the integrity of the transparent cornea and its posterior structures, to which even the slightest damage can result in suboptimal visual function. The outermost protections of the ocular surface – including the eyelids, eyelashes, lacrimal system, lipid-secretory glands (of Meibom, Moll, and Zeis), and the conjunctival mucosa – work in concert to trap particles and neutralize foreign antigens. The initiation of the blink reflex irrigates the ocular surface with a renewed tear film as particles are washed into the lacrimal puncta, a process aided by persistent desquamation of conjunctival and corneal epithelial cells (Knop and Knop, 2007). Furthermore, the conjunctival mucosa is endowed with rich swathes of eye-associated lymphoid tissue that modulate immune responses to noxious environmental stimuli (Chodosh et al., 1998). Among many other functions, ocular surface lymphoid tissues are responsible for the production of secretory immunoglobulin A (sIgA) and priming of ocular surface immune cells, the actions of which are finely equilibrated to avoid overexuberant and potentially harmful immune responses to common environmental antigens. Intact ocular surface defenses are remarkably effective in preventing corneal infection; extreme concentrations of *P. aeruginosa* and *S. aureus* in the order of 10^{11} colony forming units (CFU/mL) do not lead to appreciable adhesion, colonization, nor penetration of intact mouse corneas, even when enucleated eyes are placed directly into the inoculum (Alarcon et al., 2011; Augustin et al., 2011; Wan et al., 2018). The importance of functioning ocular surface defenses is underscored by the observation that individual corneal epithelial cells cultured *in vitro* are highly susceptible to infection by *P. aeruginosa* (Fleiszig et al., 1995). Except for the rare pathogens that penetrate intact corneal epithelium, such as *Neisseria gonorrhoea*, *Listeria monocytogenes*, and *Shigella* spp. (O'Brien, 2005; Perez-Santonja et al., 2009; Tjia et al., 1988), BK is rare in the absence of trauma or conditions that disturb ocular surface homeostasis (Gerke and Magliocco, 1971).

ii. The trilaminar tear film

The precorneal tear film – composed of external lipid, aqueous, and innermost mucus layers – is a biologically dynamic substrate that provides lubrication, nutrition, oxygenation, and protection for the ocular surface (Figure 1A). The intrinsic antimicrobial properties of tears were first described by Scottish physician-microbiologist Alexander Fleming in 1922, who conducted a classic study describing the role of a tear enzyme (named “lysozyme”) that inhibited *in vitro* growth of Gram-positive cocci (Fleming and Allison, 1922). The study was widely derided at the time of publication because its findings challenged scientific dogma that attributed host defenses exclusively to the role of mechanical protections, including blinking, epithelial shedding, and tear washout (Fleming, 1932; Fleming and Allison, 1922). The tear film is now understood to have a broad spectrum of activity against bacteria (Fleiszig et al., 2003; Kwong et al., 2007; McNamara et al., 2005), viruses (Little et al., 1969; Selinger et al., 1979; Waarts et al., 2005), fungi (Davidson and Kuonen, 2004; Sack et al., 2001), and protozoa (Alizadeh et al., 2001; Carnt and Stapleton, 2016; Leher et al., 1998). Remarkably, modern proteomic analyses have now identified over 1500 proteins in tears (Zhou et al., 2012), which are grouped as either classical (80–90%) and non-classical proteins (10–20%) (McDermott, 2013) (Figure 1B). Classical proteins with known antimicrobial activity include lysozyme (Aho et al., 1996; Fleming, 1922; Fleming, 1932; Lee-Huang et al., 1999; Regan, 1950), lactoferrin (Broekhuysse, 1974; Flanagan and Willcox, 2009; Kijlstra, 1990; Stuchell et al., 1981), lipocalin (Dartt, 2011; Redl, 2000), secretory IgA (sIgA) (Franklin and Remus, 1984; Vinding et al., 1987; Wieczorek et al., 1988), and active complement (Sack et al., 1996; Yamamoto and Allansmith, 1979). Nonclassical proteins include secretory phospholipase A (sPLA₂) (Buckland et al., 2000; Qu and Lehrer, 1998; Turner et al., 2007), secretory leukocyte protease inhibitor (SLPI) (Doumas et al., 2005; Hiemstra et al., 1996; Tomee et al., 1997), glycocalyx-forming precorneal mucins (Gipson and Argüeso, 2003; Gipson et al., 2014; Hori, 2018), surfactant (Brauer et al., 2007; Ni et al., 2005), antimicrobial peptides (Garreis et al., 2011; Kalmodia et al., 2019; You et al., 2010), and lacritin (McKown et al., 2014). In addition to direct antimicrobial effects, tears also likely increase cellular resistance to bacterial invasion by upregulating host innate defenses at the transcriptional level (Mun et al., 2013; Mun et al., 2011).

Moreover, the composition of classical and nonclassical proteins in tears is subject to diurnal changes that are not well-understood (McNamara et al., 2005; Sack et al., 2005). Open-eye environments are rich with lacrimal gland-derived lysozyme, lactoferrin, and lipocalin. In contrast, tears in closed-eye environments are typically concentrated with pro-inflammatory cytokines, reactive oxygen species (ROS), proteases, and complement derived from local PMNS, which are possibly signatures of subclinical inflammatory responses mounted against entrapped organisms during sleep (Sack et al., 1992; Tan et al., 1993; Willcox et al., 1997). Harnessing the naturally-occurring and non-toxic components of tears may therefore present an important innovation in expanding current treatment strategies in BK.

iii. Corneal epithelium

The corneal epithelium boasts an impressive suite of physical protections, including desmosome-dependent tight junctions (Sugrue and Zieske, 1997), membrane-bound mucins (Argüeso et al., 2006; Gipson, 2004; Govindarajan and Gipson, 2010), continuous epithelial

sloughing and replacement (Fleiszig, 2006), and the barrier effect of the epithelial basal lamina (Figure 1A and 1C) (Abrams et al., 2000; Alarcon et al., 2009; Forte et al., 2010; Torricelli et al., 2013b). However, the corneal epithelium is also a sentinel participant in initiating host innate immune defenses against foreign antigens. For example, corneal epithelial cells have been shown to secrete local antimicrobial peptides, including human α - and β -defensins, cathelicidin (LL-37), keratin 6A antimicrobial peptides (KAMPs), and surfactant protein-D (Gordon et al., 2005; Hazlett and Wu, 2011; Huang et al., 2007; Kumar et al., 2007; Lee et al., 2016; Mohammed et al., 2017; Ni et al., 2008; Tam et al., 2012). Corneal epithelial cells also have the ability to “phagocytose” or vacuolize invading pathogens (Angus et al., 2008; Fleiszig et al., 1995; Niederkorn et al., 1989).

Corneal epithelial cells also contain a host of recently discovered pattern recognition receptors (PRRs) that are evolutionarily conserved to induce innate immune responses against microbial ligands known as pathogen-associated molecular patterns (PAMPs) (Li et al., 2008; Pearlman et al., 2008; Willcox, 2007) (Figure 2). Well-recognized bacterial PAMPs include virulence mechanisms and/or cellular signatures of invading pathogens, including bacterial DNA, cell wall products (e.g., lipoteichoic acid or LTA, and lipopolysaccharide or LPS, in Gram-positive and negative bacteria, respectively), cell appendages (e.g., pili and flagella), and toxins (Li et al., 2008; Medzhitov, 2001). The most well-studied PRRs within ocular tissues are membrane-bound surface PRRs known as toll-like receptors (TLR) (Deguine and Barton, 2014), which are considered part of the human TLR/IL-1R (TIR) family responsible for upregulating pro-inflammatory pathways following detection of infectious stimuli (Martin and Wesche, 2002) (Table 1). TLRs 1 through 10, with the exception of TLR8, are found in abundance on corneal epithelial cells (Jin et al., 2007; Ueta, 2008; Wu et al., 2007) and resident dendritic cells (Kaisho and Akira, 2001). Though less studied in ocular surface cells, a family of intracytoplasmic PRRs comprised of the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) NOD1 and NOD2, are now also considered important detectors of microbial ligands such as peptidoglycans and LPS (Clarke et al., 2010; Inohara et al., 2001; Strober et al., 2006), and have recently been found on corneal epithelial cells (Oh et al., 2017; Scurrill et al., 2009). PRRs confer a level of specificity once thought to be absent from the innate immune system, and may play a crucial role in the host’s discrimination of self- from non-self-antigens (Chang et al., 2006).

In corneal epithelial cells, downstream signaling following PRR activation occurs through myeloid differentiation primary response protein 88 (MyD88)-dependent (Deguine and Barton, 2014; Sun et al., 2006; Sun et al., 2010) and MyD88-independent pathways (Takeda et al., 2003) (Figure 2). MyD88 is regarded as the master adaptor protein for most TLRs, with the exception of TLR3, and its activation triggers a potent pro-inflammatory cascade involving transcription factors such as nuclear factor- κ B (NF- κ B) and the mitogen-associated protein kinases (MAPKs) (Janssens and Beyaert, 2002). During infection, MyD88 activation leads to the massive release of pro-inflammatory chemokines, rapid recruitment of phagocytes into the cornea (Huang et al., 2006; Yu and Hazlett, 2006), increased local antimicrobial peptide production (Gao et al., 2013), and increased corneal epithelial resistance to bacterial adhesion and traversal (Tam et al., 2011). Non-MyD88 pathways involve a host of adaptor proteins including TIR-domain-containing adaptor

molecule 1 (TICAM-1, also known as TIR-domain-containing adaptor inducing IFN- β or TRIF, responsible for TLR3/TL4 signaling), and TIR-domain containing adaptor molecule 2 (TICAM-2 or TRAM, responsible for TL4-signaling). Non-MyD88 adaptor proteins have been implicated in the phosphorylation of transcription factors such as interferon regulatory factor 3 (IRF3), leading to the production of the Type I interferons IFN- α and IFN- β (Kumar and Yu, 2006). Beyond the formidable protections provided by the precorneal tear film, the corneal epithelium harbors a vast array of immune protections designed to shield the underlying stroma from harmful environmental insults.

iv. Corneal stroma

The clinical manifestations of most corneal infections arise from acute and chronic inflammatory changes that occur in the stroma, which can lead to long-term structural alterations that cause vision loss. However, it is still commonly believed that the corneal stroma is an immunologically inert tissue, with native cell populations that are unable to mount immune responses to antigenic challenge. Mannis and Smolin, for instance, boldly declared that “immune mechanisms available in the avascular cornea are limited” (Mannis and Smolin, 1996). This misconception may have been in part due to the historical evolution in our understanding of corneal immune privilege, where scientific consensus once viewed the stroma largely as an immunologic bystander, devoid of effector cells including resident leukocyte populations such as antigen presenting cells (APCs) (Streilein, 1987; Streilein et al., 1979). Even when the first discoveries of resident corneal Langerhans cells (LCs) were made in the early 1980s, such populations appeared confined to the peripheral corneal epithelium (Gillette et al., 1982; Rodrigues et al., 1981). This observation lent support to the idea that the activation of immune effector mechanisms in the cornea was the remit of cells that did not necessarily reside within the stroma, even when the stroma was the focus of inflammation. Other persistent sources of confusion include flawed models of corneal infection that, despite the absence of experimental validation, have gained wide acceptance and are still widely taught. For instance, the distinguished ophthalmologist Barrie Jones often referred to the stroma as a passive “immunological blotter”, suggesting that stromal keratocytes did not contribute significantly to the pathogenesis of viral keratitis (Jones, 1958). This hypothesis is now wholly inconsistent with our current body of evidence in infectious ocular diseases (Jonas et al., 2020; Rajaiya et al., 2015).

Efforts to characterize innate and adaptive immune responses in the corneal stroma now reveal a vastly different picture. Stromal keratocytes are nestled in a densely-packed, collagen-laden extracellular matrix (ECM) co-inhabited by bone marrow-derived APCs, macrophages, and monocytes, with occasional transit of other white cells (Brissette-Storkus et al., 2002; Hamrah et al., 2003c; Liu et al., 2002). These cell populations have essential and dynamic roles in normal immune function of the cornea and the preservation of normal vision. Current paradigms in ocular immunology advance the notion that ocular tissues are engaged in a perpetual state of what preeminent ocular immunopathologist Streilein described as a “dangerous compromise” (Streilein, 1987). Streilein proposed that immunoregulatory activities in the eye, particularly ocular surface structures that interface with the external environment, must delicately balance two opposing immunologic needs in order to maintain vision. The first included the need to clear infectious agents, principally

via mechanisms that allow for appropriate discrimination of self- and non-self-antigens. The second was the requirement for the intensity of inflammatory responses to be commensurate to the threat posed by the noxious stimulant, in order to minimize the likelihood of those very same responses inflicting blinding structural damage on the host (Streilein, 2003). Indeed, there is now an abundance of experimental data to support the role of the stroma in effecting host immune responses that, under conditions of severe stress, override the competing need to preserve immune privilege. This is the basis on which many inflammatory eye diseases are now understood.

BK (Figure 3) is a classic example of a disease where immune equipoise is tilted dramatically towards an overzealous and protracted inflammatory response launched by the corneal epithelium as described above, resident keratocytes (Cendra et al., 2017; Ebihara et al., 2007; Kumagai et al., 2005; Marino et al., 2015; Nishida, 2010; Wilson, 2020a), and bone-marrow derived resident LCs and macrophages (Matsumoto et al., 2005) (Figure 4). This will be discussed in greater detail in subsequent sections, but in brief the initial activation of PRRs in response to bacterial PAMPs activates inflammatory pathways that lead to the rapid infiltration of PMNs to the site of infection (Girgis et al., 2003; Hume et al., 2001). This is followed by a procession of migratory LCs (Hazlett et al., 2002a; Hazlett et al., 1986), natural killer cells (Lighvani et al., 2005), and CD4⁺ and CD8⁺ T-lymphocytes (Hazlett et al., 2000; Kwon and Hazlett, 1997) that enter the cornea. The pro-inflammatory storm responsible for leucocyte recruitment includes a host of cytokines, chemokines, and adhesion molecules with overlapping autocrine-paracrine functions. Pro-inflammatory cytokines that inundate the cornea include tumor necrosis factor- α (TNF- α) (Kernacki et al., 1998a), interleukin-1 (IL-1) (Fukuda et al., 2017; Rudner et al., 2000; Thakur et al., 2004), IL-8 (Jimenez-Martinez et al., 2013; Kernacki et al., 2000; Kumagai et al., 2005; Xue et al., 2003a), IL-12 (Hazlett et al., 2002b), IL-18 (Huang et al., 2002), interferons IFN- β and IFN- γ (Hazlett et al., 2002b; Huang and Hazlett, 2003), and macrophage migration inhibitory factor (MIF) (Thakur et al., 2001). Chemokines include chemokine ligand 1 (CXCL-1, also known as GRO1 or KC) (Gadjeva et al., 2010; Lin et al., 2007), CXCL-2 (Bryant-Hudson and Carr, 2012), CXCL-5 (Bryant-Hudson and Carr, 2012), CCL-2 or monocyte chemoattractant protein 1 (MCP-1) (Kimura et al., 2012; Tran et al., 1996), CCL-3 or macrophage inflammatory protein (MIP-1 α) (Kernacki et al., 1998b), and CCL-5, also known as the Regulated upon activation, normal T cell expressed and presumably secreted (RANTES) (Kimura et al., 2012). Prominent adhesion molecules include intracellular adhesion molecule-1 (ICAM-1) (Hobden et al., 1999; Kumagai et al., 2005) and platelet endothelial cell adhesion molecule (PECAM-1) (Khatri et al., 2002). Together, these pro-inflammatory mediators quickly overwhelm anti-inflammatory mediators such as IL-4 (Cole et al., 2007), IL-6 (Hume et al., 2006), and IL-10 (Cole et al., 2003). Furthermore, APC populations in the cornea are now thought to play a critical role in both innate and adaptive arms of the immune response (Hamrah and Dana, 2007). In addition to expressing TLRs so critical in provoking acute inflammatory responses, LCs serve as a bridge to adaptive immune responses by stimulating CD4⁺ helper T-cell responses that arbitrate the persistence of local PMNs in the cornea during the subacute phase of infection, a finding that has been associated with severe BK phenotypes (e.g., perforation) (Hazlett, 2002). In sum, the wealth of experimental data should lay to rest any lingering doubt as to whether the

corneal stroma actively participates in host immune responses. Indeed, understanding how distortions of stromal immunoregulation occur in inflammatory ocular diseases may be the key to understanding the clinical manifestations of conditions such as BK, and help inform therapeutic strategies to prevent chronic stromal remodeling and vision loss.

v. Corneal endothelium

The corneal endothelium is a monolayered sheet of flat squamous epithelial cells that reside on Descemet's membrane. While most research has focused on the highly specialized role of the corneal endothelium in maintaining stromal hydration and optical transparency through the action of multiple ion pumps (e.g., basolateral Na^+/K^+ -ATPase and $\text{Na}^+/\text{HCO}_3^-$ transporters), there is emerging evidence that suggests that endothelial cells also play a role in inducing host immune responses to foreign antigens. This should not be surprising, given the range of immune-mediated disorders that affect the endothelium, including endothelial "disciform") herpetic keratitis, endothelial allograft rejection, and some forms of anterior uveitis. When provoked by antigenic challenge such as viral infection, human corneal endothelial cells are quite capable of releasing pro-inflammatory cytokines including IL-1 α , IL-1 β , CCL-2 (MCP-1) and CXCL-8 (IL-8) (Miyazaki et al., 2017; Wilson et al., 1994; Yamagami et al., 2003). Not surprisingly, TLRs 2, 3 and 9 that respond to an array of infectious antigens, including LPS, LTA, and CpG motifs on bacterial DNA, have been found on the surface of human corneal endothelial cells (Inoue, 2014; Kot et al., 2019; Takeda et al., 2011). Furthermore, there is now evidence from animal models that injury to Descemet's membrane (e.g., in corneal perforation) may be associated with fibrosis of the posterior corneal stroma, with the differentiation of keratocytes into fibroblasts and myofibroblasts possibly mediated in part by mediators secreted by the endothelium (Marino et al., 2017; Medeiros et al., 2019). Therefore, although the corneal endothelium has not been widely studied in the setting of BK, it would seem inconsistent with our understanding of corneal immunology for these cells to remain completely submissive to infectious processes. Taken together, the ocular surface and entire cornea harbor a remarkable immune apparatus with many protections that have evolved to conserve vision. The complications of infection, including perforation and chronic stromal modeling, seem to occur when residual inflammation abrogates corneal immune privilege over a protracted period, which under healthy conditions requires tight regulation of corneal homeostasis.

2. THE OCULAR SURFACE IN DISEASE

i. Contact lenses and altered ocular surface homeostasis

In the economically developed world, contact lens wear is the single most important modifiable risk factor in the pathogenesis of BK. Conservative and outdated estimates now suggest that there are at least 140 million contact lens wearers globally (Nichols et al., 2013; Stapleton et al., 2007) with over 45 million in the United States alone (Cope et al., 2016; Konne et al., 2019). Population-based cohort studies estimate that the annual incidence of BK among wearers of daily hydrogel and silicone hydrogel contact lenses ranges from 1.9 to 6.9 and 4.9 to 11.9 cases per 10,000 persons, respectively, with far higher estimates of 9.3 to 96.4 and 18.0 to 25.4 cases per 10,000 persons, respectively, for extended wear lenses (Cheng et al., 1999; Jeng et al., 2010; Morgan et al., 2005; Nilsson and Montan, 1994;

Poggio et al., 1989; Schein et al., 1989; Seal et al., 1999; Stapleton et al., 2008). This translates to nearly 1 million annual physician encounters, and 250,000 hours of clinical care due to some form of keratitis in the US, with the majority of these cases likely due to BK (Collier et al., 2014). This scale of contact lens infections is perhaps not surprising, given nearly all wearers (>99%) have been shown in large population surveys to have at least one contact lens risk behavior that predisposes to infection (Cope et al., 2015).

Despite decades of research, the exact mechanisms by which contact lenses predispose to infection are not entirely clear. It is true that the most likely sources of pathogens in BK include bacterial contamination of contact lens cases (Willcox et al., 2010; Wu et al., 2010) and poor hygiene practices such as inadequate disinfection, sharing of contact lenses, topping off storage solutions, and inappropriate overnight wear (Dart et al., 1991; Zimmerman et al., 2017). However, as shown earlier, the finding that large microbial boluses do not cause infection when applied to intact corneas suggests that other factors are necessary to precipitate disease. For this reason, contact lens-related BK has been aptly described as a multifactorial condition, with underlying pathophysiological processes most likely related to changes within the ocular surface microenvironment (Fleiszig et al., 2020; Liesegang, 1997; Robertson and Cavanagh, 2008). Key factors that have been identified include: (a) reduced tear exchange and volume (McNamara et al., 1999; Paugh et al., 2001; Wei et al., 2014); (b) adsorption of tear proteins onto the surface of lenses, thereby limiting their availability and/or activation (Baines et al., 1990; Willcox et al., 2001); (c) decreased shedding of the ocular surface epithelium (Cavanagh et al., 2002; Ladage et al., 2001); (d) promotion of bacterial biofilms, particularly on the posterior lens interface with the apical corneal epithelium (Elder et al., 1995; Slusher et al., 1987; Stapleton and Dart, 1995; Tam et al., 2010); (e) reduced production of important ocular surface antimicrobial peptides in corneal epithelial cells, including human β -defensin 2 and LL-37 (Maltseva et al., 2007); (f) enhanced pathogen adherence to corneal epithelium (Fleiszig et al., 1992); (g) lipid-raft formations within epithelial cells that internalize bacterial pathogens (Yamamoto et al., 2006a; Yamamoto et al., 2005; Yamamoto et al., 2006b); (h) induction of ocular surface dysbiosis (Sankaridurg et al., 2000; Stapleton et al., 1995b); and (i) low grade ocular surface inflammation (Alghamdi et al., 2020; Gad et al., 2019; Metruccio et al., 2019). Alterations of ocular surface immunity are particularly fascinating; for instance, extended contact lens wear has been associated with centripetal migration of LCs into the cornea, which in susceptible C57BL/6 mice has been shown to be involved in activating Th1 CD4⁺-dependent pathways that are associated with severe stromal thinning and perforation (Hazlett et al., 1999; Kwon and Hazlett, 1997). In short, contact lens wearers are susceptible to infection due to ocular surface changes that result in an unstable tear film, reduced ocular surface turnover, increased opportunity for bacterial adaptation to corneal epithelium, and dysregulation of ocular surface immunity. These factors may help explain the explosive emergence of *P. aeruginosa*, an opportunistic pathogen that does not otherwise infect the intact ocular surface, as the dominant cause of BK following the introduction of contact lenses over 50 years ago (Mondino et al., 1986; Ormerod and Smith, 1986).

Although significant advances have been made in our understanding of contact lens-related infections, several uncertainties remain. For example, it has been traditionally taught that lens-induced hypoxia is a risk factor for BK (Liesegang, 1997). Early studies of ocular

surface physiology, including the landmark Gothenburg study conducted by Holden and colleagues (1985), showed that extended wear conventional hydrogels resulted in thinning of the corneal epithelium and stroma, suppressed aerobic metabolism, and increased bacterial adherence to corneal epithelium (Holden et al., 1985; Ladage et al., 2001). Several animal models have since corroborated these data by showing that lens-induced hypoxia may be associated with impaired corneal epithelial wound healing (Madigan et al., 1987), loss of tight junctions within corneal epithelium (Mauger and Hill, 1992), and attenuated TLR-dependent innate immunity (Hara et al., 2009), which together contribute to the increased likelihood of infection among contact lens wearers (Imayasu et al., 1994; Zaidi et al., 2004; Zhang et al., 2008). However, epidemiologic data suggest that the population-level consequences of contact lens-induced hypoxia may be overstated. Despite high hopes, the introduction of high oxygen-permeable silicone hydrogel contact lenses in the late 1990s has *not* reduced the incidence of contact lens-related infections (Robertson, 2013; Stapleton et al., 2013), suggesting there are mechanisms by which contact lenses alter ocular homeostasis that are independent of hypoxia-driven pathways. Addressing these persistent uncertainties in the relationship between contact lens and BK will be critical in designing innovations that may reduce risk of infection, including contact lenses that promote tear exchange, reduce biofilm formation, elute antimicrobial compounds, or even have inbuilt means of auto-decontamination (Seggio et al., 2019; Xiao et al., 2018).

ii. Ocular surface disease

A vast range of conditions render the ocular surface susceptible to bacterial infection. The mechanisms by which this occurs include: (a) mechanical and chemical trauma that expose the corneal stroma, e.g., foreign bodies, corneal abrasions, chemical and thermal burns, corneal transplantation and photorefractive procedures (Vajpayee et al., 2007); (b) anatomical abnormalities e.g., lid defects including ectropion, entropion, floppy eyelid syndrome, eyelash misdirection and trichiasis, and exposure keratopathy (Ezra et al., 2005); (c) altered function, activation, volume and/or composition of the tear film, e.g., severe dry eye disease (Baudouin et al., 2016); (d) loss of ocular surface integrity, e.g., conditions confined to the cornea, including bullous keratopathy (Luchs et al., 1997) and neurotrophic ulceration, or conditions involving the entire ocular surface, including atopic keratoconjunctivitis, ocular cicatricial pemphigoid (OCP) and Stevens-Johnson syndrome (SJS); (e) impaired immune function of the cornea, e.g., diabetes mellitus, immunodeficiencies including HIV infection (Jeng et al., 2010), malignancy treated with chemotherapy (Hazlett et al., 1977), bone marrow transplantation (Balaram et al., 2005), graft-versus-host disease (Franklin et al., 1983), severe malnutrition (Keenan and McLeod, 2013), and/or among critically-ill patients (Parkin et al., 1997); (f) medication toxicity, e.g., misuse of topical corticosteroids and anesthetic agents; and (g) microbiome-associated changes, as described in more detail below (Cavuoto et al., 2019; Zilliox et al., 2020).

The mechanisms listed above offer only a simple categorization of how altered ocular surface homeostasis may predispose to infection, and many conditions do not fit neatly into any one grouping. For example, corneal allograft transplantation is associated with surgical incision(s), surgical instrumentation, application of easily-contaminated sutures, and the use of topical corticosteroids that alter ocular surface immunity in the post-surgical

period. Complex multifactorial diseases such as OCP and SJS are characterized by chronic cicatricial changes associated with severe anatomical abnormalities (e.g., fornix shortening, symblepharon formation, and chronic ocular surface exposure), tear film instability owing to destruction of lacrimal gland ducts, conjunctival goblet cell loss, and Meibomian gland atrophy, and altered corneal epithelial cell integrity due to persistent corneal epithelial defects, limbal stem cell deficiency, and ocular surface keratinization (Miserocchi et al., 2014; Sotozono et al., 2007). Critically-ill patients who develop exposure keratopathy owing to impaired blink reflexes and common lid abnormalities are prone to corneal epithelial breakdown and subsequent ulceration. Therefore, any patient who is treated for BK requires careful management of the risk factors that predisposed the patient to infection in the first instance.

iii. The ocular surface microbiome

The increasing availability and decreasing cost of next-generation sequencing (NGS) now provide unprecedented opportunities to explore host-microbiome interactions in a multitude of body sites, including the ocular surface (Ung et al., 2020b; Zegans and Van Gelder, 2014). Most studies of the ocular surface to date have sampled the conjunctiva (e.g., with swabbing or with washings), which is now widely regarded as paucimicrobial when compared to microbiome-rich sites such as the gastrointestinal tract (Doan et al., 2016; Ozkan et al., 2018). Although studying the corneal microbiome has been historically more challenging, recent murine models have shown that commensal populations on the corneal surface are small to negligible, and far less diverse than the conjunctiva (Wan et al., 2018). The overall low diversity and volume of the conjunctival and corneal microbiomes may be due to the antimicrobial properties of the tear fluid, as well as MyD88/IL-1R-dependent mechanisms that serve housekeeping immune functions along a healthy ocular surface. Indeed, the ocular surfaces of MyD88/IL-1R knockout mice appear to permit essentially normal growth of commensal organisms. Taken together, these findings have led some researchers to postulate that there is no “core” corneal microbiome under healthy conditions (Fleiszig et al., 2020). While this may be true, however, these observations in themselves do not exclude the possibility of microbial populations – however small and transitory – having some role in the pathogenesis of a broad spectrum of ocular surface diseases, including BK (Dong et al., 2011; Okonkwo et al., 2020).

The challenge for human microbiome studies is to establish functional and clinicopathologic correlations with taxa observed within sequenced samples. In the gastrointestinal tract, for example, reduced commensal abundance and diversity increase susceptibility to disease caused by opportunistic pathogens such as *Clostridium difficile* (Ng et al., 2013), which can be treated upon reconstitution of the gut microflora (e.g., with fecal transplantation) (Cammarota et al., 2014). While there is no current parallel in ocular surface immunology, there is emerging evidence that suggests that the presence of ocular surface microbiota may be vital to prime innate defense mechanisms against infection. For example, in one model of *P. aeruginosa* keratitis, germ-free Swiss Webster mice were far more susceptible to infection than mice that had been mono-colonized with coagulase negative staphylococci, and differences in susceptibility were reportedly due to elevations found in the key pro-inflammatory cytokine IL-1 β (Kugadas et al., 2016). Similarly, one murine model of *S.*

aureus keratitis showed that the application of an antibody directed against the β -1-6-linked poly-N-acetylglucosamine (PNAG) surface polysaccharide of *S. aureus* was only effective in treating keratitis among conventional mice with an intact microbiome; germfree C57BL/6 mice could not mount an effective immune response because neutrophils could not be recruited to the site of infection (Zaidi et al., 2014). These studies suggest that the ocular surface microbiota may be an important source of foreign antigens that are involved in conditioning mucosal immunity, and that neutrophil maturation may depend on the presence of inflammatory mediators such as IFN (Kugadas and Gadjeva, 2016) and IL-6 (Kugadas and Gadjeva, 2015). On the other hand, it is not known whether observed changes in microbiome composition among contact lens wearers may predispose to infection simply due to higher densities of contaminating bacteria, or whether altered microbial composition promotes immune dysregulation. Previous studies have observed a shift towards higher proportions of *Pseudomonas* spp. and *Acinetobacter* spp. among contact lens wearers, with a concurrent reduction in flora more typical of healthy ocular surfaces, including *Staphylococci* spp. and *Corynebacterium* spp. (Shin et al., 2016). The significance of such findings is yet to be determined.

3. CLINICAL EPIDEMIOLOGY OF BACTERIAL KERATITIS

i. Clinicopathologic features of bacterial keratitis

The hallmark features of BK include corneal stromal infiltration(s) with overlying epithelial defect(s), anterior chamber inflammation, and conjunctival injection and chemosis (Figure 3). The patient will often complain of severe pain, decreased vision, and photophobia. These signs and symptoms are the physical manifestations of acute inflammation within anterior segment structures, which is characterized by leucocyte migration, increased vascular dilatation and permeability, and edema. Extravasation of centripetally recruited leucocytes, predominantly PMNs, from the perilimbal and conjunctival vascular beds to the cornea occurs within four hours of the inoculation event, and eventually manifests clinically as stromal infiltration (Hyndiuk, 1981). Exudation of serum proteins and leucocytes into the anterior chamber from engorged and leaky iris vascular tufts is observed as flare and cells, respectively, and with cellular settling due to gravity sometimes forming a hypopyon. Reduced or distorted vision in the acute phase can be attributed to stromal infiltration and surrounding corneal edema, which disturbs the collagenous lamellae and causes scattering of light. Progressive ulceration, stromal thinning, and perforation are the result of progressive release of collagenases, proteinases and other autolytic enzymes from the ensuing inflammatory process. The most severe cases of tissue destruction result in liquefactive tissue necrosis, often seen in mucopurulent infections caused by *P. aeruginosa* and *S. pneumoniae* (Figure 3A and C). When assessing patients with suspected BK, it is important to be mindful that by the time stromal infiltrates become clinically visible, the infection is well-established. The incubation period is highly variable across corneal pathogens and between individuals. This means that the absence of a stromal infiltrate does not preclude the possibility of bacterial infection, for instance among contact lens wearers who might present with non-traumatic epithelial defects that often misdiagnosed as a contact lens-associated “corneal abrasion” In some cases, the first sign of BK may be granular

elevations of the corneal epithelium, which even in the absence of stromal infiltration should be treated as infected when it is observed in a contact lens wearer (Rosenfeld et al., 1990).

ii. The causes of bacterial keratitis

Virtually any bacteria can colonize and invade the cornea in the setting of ocular surface compromise. Etiological studies suggest that the bacterial pathogens involved in BK are similar worldwide, though such studies must be viewed in light of biases related to differential selection of patients who undergo culture, non-standardized approaches to culture interpretation, and poor overall sensitivity of culture-based microbiology; for a full review, see (Ung et al., 2019b). Nonetheless, dominant organisms include *Staphylococcus* spp. (particularly *S. aureus*), *Streptococcus* spp. (including *S. pneumoniae* and the viridans group), *Pseudomonas* spp. (*P. aeruginosa* is the dominant species), Enterobacteriaceae (including *Serratia* spp., *Klebsiella* spp., *Citrobacter* spp., and *Proteus* spp.), and Gram-negative cocci (including *H. influenzae* and *M. catarrhalis*) (Teweldemedhin et al., 2017). The composition of causative agents varies with geography, climate, humidity and temperature, and the underlying risk factors of the affected population. For instance, *S. pneumoniae*, *Nocardia* spp. and *P. aeruginosa* consistently rank among the top few bacteria isolated from bacterial corneal ulcers in locations such as India, where risk factors include trauma sustained in agricultural settings, use of traditional eye medicines, and over-the-counter availability of topical corticosteroids (Lalitha et al., 2017; Srinivasan et al., 2012). In well-resourced countries where contact lens use is common, *P. aeruginosa*, *S. aureus*, *Serratia* spp. are the most common organisms (Stapleton et al., 1995a; Ung et al., 2020c). Polymicrobial infections are not uncommon and have been reported to account for nearly a quarter of culture-positive cases in some academic medical centers (Jones, 1981b).

Less common etiologies are often, but not always, associated with specific patient risk factors. For example, *Bacillus* spp., coagulase negative staphylococci (e.g., *S. epidermidis*), *Corynebacterium* spp., and *Propionibacterium* spp., are in healthy persons not usually considered pathogenic. Growth of these organisms in corneal cultures should warrant suspicion for contamination, unless such growth is consistent (e.g., on at least two rows of 'c' streaks on solid agar, or if growth is recorded on at least one row of 'c' streaks and is accompanied by the appropriate morphology on stain microscopy) (Ung et al., 2020c). However, one should be mindful that even sparse growth of common contaminants can be considered important in the setting of severe immunosuppression, e.g., in cancer patients, poorly-controlled diabetics, patients with cicatrizing ocular surface disease (e.g., OCP and SJS), and in the context of chronic ocular corticosteroid use. Post-laser in-situ keratomileusis (LASIK) corneal infections are typically flap-associated and are among the most common risk factors for nontuberculous mycobacterial (e.g., *Mycobacterium chelonae complex*) infection (Freitas et al., 2003). Atypical organisms with unusual patterns of antimicrobial susceptibility, characteristic of hospital-associated infections, may be isolated from critically ill and exposure-prone patients receiving ventilatory support or care for major injuries such as burns (O'Brien, 2003). Though history and examination findings are critical to make a provisional diagnosis of BK, definitive identification of the causative agent is ultimately only achieved with the collection of corneal tissue (e.g., corneal scrapings) for microscopy and culture-based microbiology (Dahlgren et al., 2007). The advent of rapid and sensitive

molecular diagnostic strategies may in the future provide a more complete picture of the spectrum of bacteria capable of causing corneal infection.

iii. Antimicrobial resistance in bacterial keratitis

The pace at which antimicrobial resistance (AMR) is being acquired among infectious agents, predominantly bacteria, is now a cause of global concern. Though the resistance genes that encode AMR are ancient and predated the antibiotic era (D'Costa et al., 2011), bacteria are subject to accelerated selective pressures that have been widely attributed to the indiscriminate use of antibiotics in human and veterinary medicine, as well as livestock husbandry and agriculture (Bispo et al., 2020a). AMR is often thought of as a mutation-dependent process, but perhaps even more important is the role of genetic promiscuity within and between bacterial species, which offers diverse paths to obtain novel gene content such as horizontal (lateral) gene transfer, transduction via phage, and conjugation of AMR-encoding plasmids (Tenover, 2006). In ophthalmology, the growing prevalence of multi-drug resistance among important bacterial pathogens that infect the eye has cast doubt on the long-term utility of common antibiotics. It is widely believed that novel resistant strains can arise as a direct result of selective pressures that drive microbial adaptation, and/or by the process of microbial reconstitution, where resistant strains simply replace empty anatomical niches created following a course of broad-spectrum antibiotics. Ocular prostheses and contact lenses that function as a microbial reservoir (e.g., within biofilms) may also have a role in the transfer of resistance genes among ocular flora. However, quantifying the scale of AMR in ophthalmology is difficult, in part because descriptive thresholds to interpret mean inhibitory concentrations (MICs) are still widely determined on the basis of systemic antibiotic administration, rather than the unique pharmacokinetics of topical antibiotics when applied to the ocular surface (Kaye et al., 2010).

Worldwide, the first line of BK treatment is broad-spectrum empiric antibiotics. Unfortunately, targeted therapy is often not possible because corneal cultures are unrevealing in over half of all cases, an internationally consistent finding (Ung et al., 2019b). Without antimicrobial susceptibility testing, clinical care and antimicrobial stewardship practices are severely limited. As a result, concerning trends towards increased community multi-drug resistance among common ocular isolates has been observed in the last thirty years. For instance, the most recent results of the US national Antimicrobial Resistance Monitoring of Ocular Microorganisms (ARMOR) surveillance system found that over 30% of corneal *S. aureus* and coagulase-negative staphylococci isolates are now resistant to the 8-methoxyfluoroquinolones moxifloxacin and gatifloxacin, which were introduced as topical monotherapies for BK only recently in the early 2000s (Asbell et al., 2020). Astonishingly, the prevalence of resistance to these fourth-generation fluoroquinolones appears to have occurred over a period of little over 10 years, with the first cases reported in 2006–2007 (Jhanji et al., 2007; Moshirfar et al., 2006). Indeed, the time-scale for the emergence of AMR need not be a matter of years: a secondary analysis of the Steroids for Corneal Ulcers Trial (SCUT) showed that patients who had been treated with a fluoroquinolone prior to enrollment had moxifloxacin MICs that were up to 3.48 times higher than those who were fluoroquinolone treatment-naïve (Ray et al., 2013). Taken together, these observations explain the lower than expected commercial success of earlier-generation fluoroquinolones

such as ofloxacin and ciprofloxacin, which are no longer considered first line therapies for BK. Fortunately, overall resistance observed among *P. aeruginosa* and *S. pneumoniae* for fluoroquinolones, cephalosporins, glycopeptides (e.g., vancomycin) and aminoglycosides (e.g., tobramycin) remain low (<10%) (Asbell et al., 2020), though case reports of multi-drug resistant *P. aeruginosa* requiring last-resort topical colistin and carbapenems are clearly a worrying development (Chatterjee and Agrawal, 2016; Vazirani et al., 2015). The development of new therapies that may circumvent considerations of AMR characterizes a critical unmet need in the care of all infections, including BK.

4. A UNIFIED FRAMEWORK OF BACTERIAL KERATITIS PATHOGENESIS

i. General principles and models of bacterial keratitis pathogenesis

Fundamentally, the pathophysiology of BK comprises a sequence of host-pathogen interactions that can be summarized as follows: (a) bacterial adherence, colonization, and invasion of host corneal tissue, a process governed by the intrinsic virulence of the pathogen and its ability to evade or counteract host immune defenses (Jones, 1978; Reichert and Stern, 1984); (b) the induction of host inflammatory responses consisting of an initial burst of innate immune activity, typically within minutes to hours, followed by the adaptive immune response that ensues over a period of days, weeks, and months; and (c) the long-term visual impact of corneal remodeling, in large part contingent on the extent of visual axis involvement (O'Brien and Hazlett, 1996). There is now a wealth of experimental data from animal models that have utilized varying modes of infection to study the different components of BK pathogenesis. Traditional animal models of BK have typically used infection strategies such as direct stromal contamination after corneal abrasion ("scratch" or scarification models), intrastromal injection, and passage of contaminated sutures through the cornea (Callegan et al., 1992; Hessburg et al., 1963; Kernacki et al., 1999; O'Callaghan et al., 1999). Although such models are useful in the study of host-pathogen dynamics that occur in the stroma, they offer little insight into how the protective mechanisms of the corneal epithelium are breached in the setting of infection. For this reason, approaches that have used more superficial forms of ocular surface manipulation, including tissue blotting (Alarcon et al., 2011), scratch-and-heal (Lee et al., 2003), and the placement of contaminated lenses (Metruccio et al., 2019; Rhem et al., 2000; Szliter et al., 2002; Tam et al., 2010; Zhang et al., 2008) have been helpful in exploring how corneal defenses are compromised with respect to common disturbances of ocular surface homeostasis (e.g., contact lens wear). In this section, we offer a conceptual framework using the aforementioned principles, applying current paradigms in ocular surface immunology and microbiology to understand how corneal infections arise, progress, and resolve. The goal is not to recapitulate the depth of excellent reviews that have been published (Fleiszig et al., 2020; Hazlett, 2004; O'Callaghan, 2018), but to instead offer a parsimonious and hypothesis-generating overview that explicitly links the determinants of BK pathophysiology to its clinical manifestations. Importantly, this may aid in identifying novel therapeutics that may help achieve improved patient outcomes.

ii. *Pseudomonas aeruginosa* keratitis

P. aeruginosa, of the family Pseudomonadaceae, is an encapsulated Gram-negative rod that is by far the most well-studied of all corneal bacterial pathogens. *P. aeruginosa* is found ubiquitously in the environment, including soil, water, vegetative matter, sinks, pools, and toilet surfaces. Up to 25% of individuals are thought to be carriers (Berthelot et al., 2001). *P. aeruginosa* is most frequently described as an opportunistic pathogen because it rarely infects healthy body sites (Stover et al., 2000). Instead, *P. aeruginosa* is most frequently associated with hospital-acquired infections that arise from contaminated medical devices (e.g., ventilators, peripheral and central vascular lines, and indwelling urinary catheters), dehisced or contaminated wounds (e.g., surgical incisions and diabetic foot ulcers), and within vulnerable immunosuppressed patient populations (e.g., the critically-ill, patients with cystic fibrosis, and those affected by severe burns) (Kerr and Snelling, 2009). Shortly after the commercialization of contact lenses in the 1960s, *P. aeruginosa* gained notoriety among ophthalmologists as a particularly virulent pathogen capable of causing perforation and blindness within 24 hours of symptom onset (Dixon et al., 1966). It should not be surprising that *P. aeruginosa* quickly found a niche among contact lens wearers, given the bacteria's expansive array of virulence factors, broad cellular tropisms, low nutritional requirements, and astonishing versatility in forming tenacious biofilms on organic and inorganic surfaces. It has been estimated that only ~50 CFUs of *P. aeruginosa* are required to infect the cornea (Kupferman and Leibowitz, 1979).

Each *P. aeruginosa* bacterium consists of a large genome (~6Mbp) (Stover et al., 2000), with a cell surface composed of lipopolysaccharide (LPS), hair-like pili (fimbriae), alginate, type III secretion systems (T3SS), and a single motile flagellum (Argueso, 2021; Fletcher et al., 1993; Gupta et al., 1994; Hauser, 2009; Lyczak et al., 2000; Zaidi and Pier, 2008). Models of *P. aeruginosa* keratitis have shown that disease does not occur without areas of denuded stroma (Ramphal et al., 1981; Stern et al., 1985); superficial fluorescein-staining epithelial injuries allow for bacterial adhesion, but such injuries are insufficient to allow for bacterial translocation through the epithelium (Alarcon et al., 2011). In the presence of a compromised ocular surface and exposed stroma, however, scratch-injury or scarification animal models demonstrate appreciable infiltration of *P. aeruginosa* into the corneal stroma within minutes (Dart and Seal, 1988; Tazawa, 1990). Given the opportunity, ocular strains of *P. aeruginosa* express highly sophisticated virulence factors to overcome the external defenses of the ocular surface. Adherence and subsequent entry into corneal epithelial cells are mediated by factors including: (a) attachment of LPS to receptors such as the cystic fibrosis transmembrane-conductance regulator (CFTR) (Zaidi et al., 1999), galectin (Gupta et al., 1997), and galactose- or mannose-containing glycoproteins (Hazlett et al., 1987); (b) pili (fimbriae), which are hairy processes that attach to a variety of receptors, including sialic acid residues (Gupta et al., 1994; Rudner et al., 1992); (c) CFTR-mediated lipid rafts (Zaidi et al., 2008), and (d) the production of a polysaccharide-rich biofilm (or glycocalyx) that shields microcolonies from the hostile tear film and local opsonophagocytosis (Hyndiuk, 1981; Saraswathi and Beuerman, 2015; Thanabalasuriar et al., 2019) (Table 2).

T3SS are considered among the most important virulence mechanisms for Gram-negative pathogens, and can be likened to a series of fine molecular needles that allow invading

bacteria to inject effector proteins and/or toxins into host cells (Czechowska et al., 2014; Kroken et al., 2018). Ocular strains of *P. aeruginosa* are now commonly identified as cytotoxic, invasive, or neither, on the basis of their T3SS (Evans et al., 2007; Fleiszig et al., 1996; Fleiszig et al., 1994; Lomholt et al., 2001). Cytotoxic isolates, which swarm around host cells but do not invade, encode the exoenzyme *ExoU*, a deployable intracellular phospholipase that induces rapid death of target corneal epithelial cells and leucocytes (Fleiszig et al., 1996; Fleiszig et al., 1997; Sato and Frank, 2004). By contrast, invasive isolates are internalized by host cells, and encode the exoenzyme *ExoS*, a dual-function N-terminal GTPase activating protein and C-terminal Ras-ADP-ribosyltransferase (ADPR). The putative role of *ExoS* is to subvert the innate immune response by inducing apoptosis in infiltrating PMNs (Karthikeyan et al., 2013), reduce the production of reactive oxygen species among those that survive (Vareechon et al., 2017), and allow bacteria to resist vacuolar acidification (Heimer et al., 2013). Two other T3SS effector proteins, *ExoT* and *ExoY*, have been less studied, but may be involved in the disruption of the actin cytoskeleton of host cells (Cowell et al., 2005; Garrity-Ryan et al., 2000) and induction of immune cell apoptosis through the action of ADPR (Sun et al., 2012). The genomic epidemiology of ocular *P. aeruginosa* suggests that multiple population structures are highly adapted to the corneal epithelium. For example, *ExoU*-containing cytotoxic isolates appear to be more common among contact lens-users (Lomholt et al., 2001; Stewart et al., 2011; Winstanley et al., 2005), while *ExoS*-containing invasive isolates predominate in lower-income settings where contact lens use is less frequent (Borkar et al., 2014; Borkar et al., 2013).

P. aeruginosa T3SS are augmented by powerful exotoxins such as exotoxin A, phospholipases, hemolysins, which have direct cytopathic effects and may also activate endogenous corneal proteases (Johnson and Allen, 1978; Twining et al., 1993). Furthermore, ocular *P. aeruginosa* strains express a wide array of proteases, including the metalloproteinases (Las A protease, las B protease, alkaline protease, and modified protease), protease IV, large exoprotease (Lep A), and *P. aeruginosa* small protease (PASP) (Heck et al., 1986; Iglewski et al., 1977; Kessler et al., 1977a; Marquart et al., 2005; O'Callaghan et al., 2019; Twining et al., 1986; Twining et al., 1993). Collectively, and perhaps synergistically, these products are involved in either digesting the components of the corneal ECM (composed of collagen, laminin, proteoglycans), and/or inactivating or degrading important host immune enzymes found within the local tear film and cornea. As such, *P. aeruginosa* has the capacity to subvert host responses by reducing the impact of important proteins and mediators, including IgA and IgG (Engel et al., 1998), pro-inflammatory interleukins (McClellan et al., 2006), complement (e.g., C1q, C2, C3) (Hong and Ghebrehiwet, 1992; Laarman et al., 2012), and IFN- γ (Horvat and Parmely, 1988). Remarkably, the expression of *P. aeruginosa* virulence factors may be dictated by the phenomenon of quorum sensing, where gene transcription is dictated by local bacterial population densities and composition (Pesci et al., 1997; Whiteley et al., 1999; Willcox et al., 2008). Quorum sensing has been hypothesized to constitute a form of immune escape, where bacteria evade host immune responses until they reach a critical population density needed to begin actively invading nearby tissues.

iii. *Staphylococcus aureus* keratitis

S. aureus, of the family Staphylococcaceae, is a ubiquitous Gram-positive coccus consistently identified as a leading cause of corneal infections. One of the most impressive, albeit concerning, features of *S. aureus* is the speed at which some ocular strains appear to acquire novel mechanisms of antimicrobial resistance, easily outpacing *P. aeruginosa* and *S. pneumoniae*. For example, approximately 30% of all corneal *S. aureus* (and coagulase negative staphylococci) isolates in the US are now resistant to *all* fluoroquinolones, including fourth-generation moxifloxacin and gatifloxacin (Asbell et al., 2020). This percentage exceeds 80% among *S. aureus* isolates that are already methicillin-resistant, an observation that forms the rationale behind the preference for fortified glycopeptides (e.g., vancomycin) to provide Gram-positive coverage in empiric treatment regimens. At our institution, MRSA accounts for roughly 5% of all culture-positive cases, most of which are considered community rather than hospital-acquired (Ung et al., 2020c), with nearly all isolates in our center are resistant to all fluoroquinolones (Bispo et al., 2020b). *S. aureus* corneal infections are commonly associated with trauma, ophthalmic surgery (including contaminated sutures and ocular prostheses), and contact lens use. Unlike *P. aeruginosa*, however, *S. aureus* also commonly colonizes structures adjacent to or in close proximity to the cornea, including the conjunctival mucosa, eyelids and surrounding skin, and in the nasal epithelium. For this reason, it is generally thought that *S. aureus* ocular infections among non-contact lens wearers arise from these endogenous sources, which also predisposes to recurrent infection (Somerville et al., 2020). Unsurprisingly, the minimum infectious dose of *S. aureus* in the cornea is in the order of only 100 CFUs, similar to figures reported for *P. aeruginosa* (Kupferman and Leibowitz, 1976).

The universal success of *S. aureus* as a pathogen is in large part due to redundancy in its broad array of virulence factors. *S. aureus* contains a heterogeneous collection of cell surface adhesins that facilitate attachment to the ocular surface epithelium and surrounding extracellular matrix, including collagen, elastin, fibronectin, fibrinogen, and laminin-binding proteins (Foster and Hook, 1998; Liesegang, 2005). These proteins are collectively known as Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMMs) (Foster and Hook, 1998; Patti et al., 1994), which are essential for biofilm formation. Colonization and subsequent invasion into the corneal epithelium are assisted by the expression of virulence factors that are mostly governed by the quorum-sensing accessory gene regulator (*agr*) (Novick, 2003; Peng et al., 1988; Traber et al., 2008). Important virulence factors include: (a) anti-phagocytic capsular polysaccharides (Que and Moreillon, 2010); (b) pore-forming cytotoxins including the α -, β -, δ -, and γ - toxins (hemolysins) (Callegan et al., 1994; Girgis et al., 2005; O'Callaghan et al., 1997; Putra et al., 2019); (c) secreted polypeptides (superantigens) such as enterotoxins A – D that may be involved in anesthetizing innate immune responses during early infection (Fraser and Proft, 2008; Salgado-Pabon et al., 2013); and (d) release of a host of extracellular enzymes, including coagulase, hyaluronidase, DNase, staphopain, and other proteases (Cheung et al., 2002; Hume et al., 2020; Jett and Gilmore, 2002a, b; Moreau et al., 1997; Novick, 2003).

The most important extracellular enzymes produced by *S. aureus* include those that neutralize host antimicrobial compounds, assist abscess formation, and degrade ECM.

For example, the enzyme catalase inhibits PMN-derived ROS; coagulase degrades fibrinogen into fibrin, allowing for abscess capsule formation; and hyaluronidase decomposes endogenous corneal glycosaminoglycans, thereby allowing *S. aureus* to establish microplanes for bacterial spread. One curious feature of the *S. aureus* virulon is that the timing of virulence factor expression is largely dependent on the phase in which the bacteria are growing (Ziebandt et al., 2004). For instance, fibronectin-binding and clumping factor proteins that assist in bacterial adhesion and possibly invasion are only expressed during the exponential phase of growth (McGavin et al., 1997), suggesting a critical CFU population size or density must be reached prior to bacterial attachment and colonization. However, such growth may also be facilitated by the formation of protective biofilms that anchor bacterial colonies on the ocular surface through MSCRAMM proteins such as protein A and fibronectin-binding protein A (Hall et al., 2003; Hou et al., 2012; Walsh et al., 2008).

iv. *Streptococcus pneumoniae* keratitis

Though considered the most common cause of BK in many low-income countries (Bharathi et al., 2002), *S. pneumoniae* (or the pneumococcus), of the family Streptococcaceae, is perhaps the most poorly understood of the major corneal bacterial pathogens. A Gram-positive facultative anaerobe visualized as single cocci, lance-shaped diplococci, or as short chains, *S. pneumoniae* colonizes the nasopharynx in over 60% of children from infancy, and remains part of the normal respiratory flora into adulthood, albeit at a lower frequency (Faden et al., 1997; Ung et al., 2020a; Weiser et al., 2018). There are now over 100 serotypes of *S. pneumoniae* that have been identified, grouped according to surface proteins found on the famed anionic polysaccharide capsule. The pneumococcal polysaccharide capsule is the most well-studied of all its virulence factors, and is thought to camouflage the bacterium from complement-mediated opsonophagocytosis, electrostatically repel leukocytes, reduce attachment of host immunoglobulins, and facilitate extracellular proliferation (Geno et al., 2015; Hyams et al., 2010). Distinct from rogue unencapsulated *S. pneumoniae* clades that cause outbreaks of epidemic conjunctivitis (Crum et al., 2004; Valentino et al., 2014), it is believed that most strains associated with BK are encapsulated and from classically invasive pneumococcal serotypes (Bispo P., personal communication) (Norcross et al., 2010). However, the exact composition of encapsulated variants among ocular strains of *S. pneumoniae* are not known because typing is rarely pursued in a clinical setting, and therefore has not been subject to systematic study. Encapsulated and unencapsulated strains both induce florid keratitis in animal models (Guzek et al., 1998; Moore et al., 2009; Reed et al., 2005), suggesting that there are mechanisms that allow the pneumococcus to infect the cornea independent of capsular virulence factors.

The *S. pneumoniae* virulon is replete with adhesins that facilitate attachment to the corneal epithelium, including cell wall products (e.g., pneumococcal surface antigen A, PsaA), cell-surface proteins that bind to choline residues (e.g., pneumococcal surface proteins A and C, PspA and PspC, and pneumococcal choline-binding protein) and also peptides that bind to ECM with high affinity (e.g., the multidomain pneumococcal adherence and virulence factors A and B, PavA and PavB) (Crain et al., 1990; Hammerschmidt, 2006; Holmes et al., 2001; Jensch et al., 2010; Jinno et al., 2020; Paterson and Orihuela, 2010). Although *S.*

pneumoniae is regarded largely as an extracellular pathogen, it expresses several adhesins that can mediate internalization of bacterium into corneal epithelial cells. For example, the choline-binding protein PspC is thought to be involved in binding to polymeric immunoglobulin receptors on epithelial cells, allowing for subsequent endocytosis into the host cell cytoplasm (Brock et al., 2002; Zhang et al., 2000). *S. pneumoniae*, unlike *P. aeruginosa* and *S. aureus*, is not known to be a prolific toxin-producer. However, the main toxin in its repertoire, pneumolysin (formerly α -hemolysin), is highly conserved among invasive isolates (Karthikeyan et al., 2013), and exhibits direct cytotoxic effects on corneal epithelium by inducing pore formation in cholesterol-containing cell membranes (Johnson et al., 1990; Taylor et al., 2013). Pneumolysin is highly immunogenic, and causes severe inflammation by activating inflammatory pathways that are mediated by classical complement, IL-1, IL-8, and TNF- α (Lawrence et al., 2015; Marquart et al., 2007). This may explain why some pneumococcal ulcers undergo rapid liquefactive necrosis in a large proportion of cases, even among patients who are promptly treated (Figure 3C).

v. Induction of the host innate response

Evidently, bacteria have evolved many mechanisms to evade ocular surface defenses and establish infection in compromised corneas. Nonetheless, the host innate response to infection in BK is understood to be remarkably uniform (Wilhelmus and Dan, 1996). Murine models have shown that PMN-depleted mice treated with a corneal intrastromal bolus of *P. aeruginosa* succumb to sepsis within 48 hours (Hazlett et al., 1977), demonstrating that the innate host response is essential for survival. In the setting of infection, the pro-inflammatory cascade in BK is less an orderly sequence of events than a storm of concomitant cytokine production and release, inflammatory cell infiltration into the cornea and surrounding ocular surface tissues, and intersecting autocrine feedback loops that potentiate the initial host response. To synthesize the current literature, the key drivers of the innate immune system in the setting of corneal infection include:

- a. Rapid recognition of bacterial ligands (PAMPs) by PRRs, including TLRs and NLRs, which are found on or within corneal epithelial cells, resident LCs, macrophages, and stromal keratocytes (Cendra et al., 2017; Chinnery et al., 2008; Ebihara et al., 2007; Kumagai et al., 2005; Marino et al., 2015; Matsumoto et al., 2005; Nishida, 2010; Redfern et al., 2011; Wilson, 2020a) (Figure 2 and Table 1). The most important TLRs that have been implicated in Gram-positive BK include TLR1 and TLR2, which recognize cell surface proteins such as lipoteichoic acids and peptidoglycans (Kumar et al., 2004; Tullos et al., 2013), while important TLRs in Gram-negative BK include TLR4 and TLR5 for the recognition of LPS and flagellin, respectively (Hayashi et al., 2001; Kumagai et al., 2005; Zhang et al., 2003). TLR9 is involved in the recognition of bacterial CpG DNA (Ebihara et al., 2007; Johnson et al., 2005). For further details, see Table 1.
- b. TLRs 1–9, with the exception of TLR3, activate MyD88-dependent pathways (Deguine and Barton, 2014; Johnson et al., 2005; Sun et al., 2006; Sun et al., 2010). TLR3 and also TLR-4 activate MyD88-independent pathways through

alternative adaptor proteins such as TRIF (TICAM-1) and TICAM-2 (Kumar and Yu, 2006; Takeda et al., 2003) (Figure 2 and Table 1).

- c. MyD88-dependent pathways lead to the upregulation of transcription factors NF- κ B and MAPK (in particular, p42/p44, JNK and p38) (Adhikary et al., 2008; Zhang et al., 2005), which mediate the release of pro-inflammatory cytokines (e.g., TNF- α , IL-1, IL-2, IL-6, IL-8, IL-12) (Jimenez-Martinez et al., 2013; Kernacki et al., 1998a; Kumagai et al., 2005; Rudner et al., 2000; Thakur et al., 2004), pro-inflammatory chemokines (CCL-3, CCL-4, CCL-5, CXCL-1, IL-18 and MCP-1) (Gadjeva et al., 2010; Kernacki et al., 1998b; Kimura et al., 2012; Lin et al., 2007), adhesion molecules (ICAM-1, MAC-1, PECAM-1, VCAM-1, E-selectin and P-selectin) (Goldberg et al., 1994; Hazlett, 2007; Hobden et al., 1995; Khatri et al., 2002; Philipp and Gottinger, 1993), immune peptides (h β D-2, LL-37, KAMPs) (Chan et al., 2017; Maltseva et al., 2007; McDermott et al., 2003), and MMPs (e.g., MMP-1, MMP-2, MMP-3 and MMP-9) (Li et al., 2001; Sakimoto et al., 2003).
- d. Non-MyD88-dependent pathways lead to activation of the adaptor protein TRIF, which upregulates the production of Type I IFNs, first IFN- β and subsequently IFN- α (Kumar and Yu, 2006; Pearlman et al., 2008). Though IFNs have been historically associated with viral immune responses, they are now understood to play an important role in innate immune cell chemotaxis in bacterial infections (Decker et al., 2005).
- e. Activation of the corneal neuroimmune axis results in the release of inflammatory neuropeptides, including tachykinins such as Substance P, from corneal nerves and infiltrating macrophages, dendritic cells, and lymphocytes (McClellan et al., 2008; O'Connor et al., 2004). Substance P is anti-apoptotic among leukocytes (Zhou et al., 2008), and may regulate the production of IFNs that are important in effecting adaptive T-cell responses (Lighvani et al., 2005).
- f. Activation of host complement pathways, including C3-mediated activation of classic, lectin, and alternative cascades, which are essential in mobilizing PMNs into the site of infection and in enhancing the efficiency of opsonophagocytosis (Cleveland et al., 1983; Hazlett and Berk, 1984; Osthoff et al., 2014).
- g. Migration of ocular surface MHC Class II⁺ LCs from the conjunctival mucosa and corneal limbus to the site of infection (Yamagami et al., 2005), and concomitant maturation of central corneal MHC Class II⁻ LCs with exposure to microbial ligands (Chang et al., 2006; Hendricks et al., 1992; Kaisho and Akira, 2001; Kaisho et al., 2001).

Pro-inflammatory mediators that flood the ocular surface in BK lead to pronounced ocular surface vascular dilatation, increased endothelial permeability, and sequestration of immune cells, serum proteins, and pro-inflammatory cytokines in the cornea. It has long been appreciated that neutrophils are the most abundant acute-phase cellular effectors, although monocytes and macrophages also play important supporting role. In addition to releasing inflammatory cytokines, PMNs create a highly acidic corneal phagolysosome,

engulfing foreign antigens, degranulating lysosomal enzymes, and producing nitric oxides. Furthermore, PMNs undergo oxidative burst to liberate reactive oxygen species (ROS), such as superoxide anions and hypochlorous acids, that are directly toxic to bacteria (Ando et al., 1990; Hazlett, 2004). More recently, neutrophils responding to various PAMPs have also been associated with the formation of neutrophil extracellular traps (NETs), which consist of chromatin-protease-antimicrobial peptide complexes that ensnare bacteria to prevent their further spread into the cornea (Geddes-McAlister et al., 2019; Papayannopoulos et al., 2010; Thanabalasuriar et al., 2019). Although these mechanisms of first defense are critical in the clearance of invading bacteria, unfortunately PMN products are also highly toxic to the corneal stroma, digesting collagen lamellae and a corneal ground substance laden with proteoglycans, laminins, and elastin. This damage is amplified by the inappropriate upregulation and release of autodigestive proteins among host corneal cells, including MMPs such as MMP-2 (a gelatinase) and MMP-9 (a proteinase) (Li et al., 2001; Sakimoto et al., 2003). Therefore, while the PMN-predominant innate response is clearly vital in achieving bacterial eradication, it is the persistent dysregulation of innate responses – in essence a prolonged deviation of corneal “immune privilege” – that are in part responsible for the acute manifestations of BK.

vi. Induction of the adaptive immune system

While most models of BK have traditionally focused on the role of innate immunity, it has become increasingly clear that functional adaptive immune responses serve a critically important role in the pathogenesis, clinical manifestations, and outcomes of BK, particularly for severe disease phenotypes characterized by progressive stromal thinning, melt, and perforation (Hazlett, 2002). Clonal expansion of antigen-specific T and B-lymphocytes are the hallmark of the adaptive immune response, which is designed to purge residual microbes and their associated antigens following the early phase of infection. Although the cornea was once believed to be devoid of resident immune cells, it is now widely recognized that the cornea is home to diverse populations of bone-marrow derived APCs, mostly LCs, that straddle the innate and acquired arms of the immune system. LCs have a prominent role in the pathogenesis of a broad range of ocular inflammatory disorders, with a variety of characteristics and putative functions including the ability to internalize apoptotic or dead microbes and their associated antigens, the expression of TLRs that respond to PAMPs, the production of soluble pro-inflammatory cytokines including IFNs, TNF- α and IL-1 β , and the ability to migrate to and from local draining lymph nodes for antigen presentation and priming of naïve lymphocytes (Hamrah et al., 2003a; Kelsall et al., 2002; Rescigno and Borrow, 2001).

Corneal LCs are characterized by differential expression of a number of important cell surface markers associated with varying stages of cell maturation, including major histocompatibility complex (MHC) and the B7 family of co-stimulatory molecules. For example, the corneal limbus is inhabited by mature or “professional” LCs that constitutively express MHC Class II⁺ (Gillette et al., 1982; Hazlett et al., 1999; Niederkorn et al., 1989), while central regions of the cornea are home to universally immature MHC Class II⁻ LCs that do not express canonical costimulatory molecules such as CD80, and CD86 (Dana, 2004; Hamrah et al., 2003b; Hamrah et al., 2003c). It is well established that inflammatory

stimuli prompt centripetal migration of peripheral MHC Class II⁺ LCs into the central corneal epithelium, thereby initiating T-cell-mediated inflammation that predominates in the subacute phase of infection (Dana et al., 1998; Dekaris et al., 1999; Hamrah et al., 2002; Hazlett et al., 2002a; Jager et al., 1995; Yamagami et al., 2005). For example, MHC Class II⁺ LCs migrate into the central cornea within 24 hours following challenge with heat-killed *S. aureus*, and somewhat astonishingly, persist within the cornea for up to 6 weeks (Niederhorn et al., 1989). On the other hand, the maturation of MHC Class II⁻ LCs in the central cornea is thought to occur upon exposure to a broad range of stimuli, including ligation of TLRs with a range of exogenous (e.g., PAMPs such as LPS and LTA) (Hertz et al., 2001; Kaisho and Akira, 2001; Lopez et al., 2004), and endogenous products (e.g., antimicrobial peptides such as β -defensin-2) (Biragyn et al., 2002).

The spatial distribution of main effector cells of the acquired immune system remain far from clear in the setting of BK. However, Hazlett and colleagues have shown in C57BL/6 (perforation-susceptible) and BALB/c (perforation-resistant) inbred mouse models of *P. aeruginosa* keratitis that Th1 CD4⁺ T-lymphocytes, possibly sourced from the conjunctiva and local draining lymph nodes, infiltrate the cornea at 5 days post-infection (Kernacki et al., 2001). Th1 CD4⁺ chemotaxis to the cornea is possibly regulated by lymphocyte chemoattractant MIP-1 α (Kernacki et al., 2001) and downstream TLR signals (Biragyn et al., 2002). Once present, Th1 CD4⁺ cells mediate the persistence of local PMNs within the corneal stroma (Kwon and Hazlett, 1997). The continued recruitment of PMNs to the cornea in BK – even if the pathogen has been eradicated – is hypothesized to lead to progressive stromal lysis in the acute setting, and contribute to corneal scarring over the longer term. Indeed, continued PMN recruitment in C57BL/6 mice appears to be dependent on LC–Th1 CD4⁺ interactions that are stimulated with B7/CD28 ligation, and are sustained by upregulated pro-inflammatory mediators such as IL-12 and IFN- γ (Hazlett, 2004; Hazlett et al., 2001). On the other hand, infection in IL-18 dependent and Th2-responsive BALB/c has been associated with a dampening of the inflammatory response, more efficient clearance of PMNs, and therefore decreased severity of infection (Hazlett et al., 2000). Remarkably, BALB/c mice can be rendered susceptible (i.e., prone to perforation) in response to *P. aeruginosa* challenge if B7.1-expressing LCs are induced into the central cornea prior to the infectious challenge. Although the exact mechanisms by which LCs stimulate T-cell recruitment have not been fully elucidated, this is thought to involve the constitutive expression of important chemokines among LCs, including MIP-1 α , RANTES, and CCR-5 (Haelens et al., 1996; Yamagami et al., 2005). Immune modulators, including antagonists of the CCR5 system, have therefore been proposed as a potential target to halt stromal thinning in inflammatory processes such as BK.

vii. Corneal wound healing

The cornea is an organ that can be described as having poor functional reserve. This is because even the slightest disturbances in its precise architecture – usually precipitated by trauma, inflammation, and or infection – can have a profound impact on corneal transparency, topography, refractive power, tensile strength, and avascularity. Under healthy conditions, keratocytes are responsible for maintaining the structural integrity and optical transparency of the stroma, laying down collagen fibrils (mostly collagen types I, V, VI, and

XII) in carefully arranged lamellae, producing a ground substance rich with proteoglycans such as sulfate-containing proteins keratan, dermatan, and chondroitin, and also secreting local collagenases to decompose aged matrices that require renewal (Bron, 2001; Pei et al., 2004; Wilson et al., 2012). This highly-regulated system is subverted in the injured cornea, leading to the formation of corneal opacities that cause vision loss by obstructing the visual axis, and/or inducing irregular astigmatism upon focal stromal thinning. Although corneal scarring is the most common cause of vision loss in BK, much of our understanding of post-infectious repair pathways have been drawn from animal models of corneal wounding that have typically used mechanical or chemical injuries, for instance abrasions, photorefractive procedures, and chemical burns (Linna and Tervo, 1997; Lorenzo-Martin et al., 2019). Nonetheless, it is thought that cellular and biochemical responses are generalizable across a broad range of corneal injuries, though this may be subject to revision as new data from alternative models emerge.

Corneal repair pathways are activated upon injury and infection of corneal epithelial cells, which lead to the constitutive production of soluble mediators that are both pro-inflammatory (e.g., IL-1 α and IL-1 β) and pro-fibrogenic (e.g., platelet derived growth factor or PDGF, insulin-like growth factor or ILGF, and transforming growth factors- β 1 and β 2, henceforth TGF- β) (Wilson, 2020b). If the epithelial basement membrane is breached, these mediators soak freely into the underlying stroma, where they mix with the onslaught of bone marrow-derived inflammatory cells that infiltrate the cornea from the perilimbal vasculature and tear film. Under these conditions, some keratocytes undergo apoptosis, while others transition from their quiescent to active repair phenotypes. Keratocytes that transform into corneal fibroblasts gain motility, secrete IL-1 α , release MMPs, and produce collagenous ECM (West-Mays and Dwivedi, 2006; Yu et al., 2010), a process vital in providing makeshift structural support to the stroma in an attempt to prevent descemetocele formation and frank perforation. While advantageous in the early phases of infection, the persistence of pro-fibrogenic mediators eventually favors the terminal differentiation of fibroblasts into contractile myofibroblasts which coalesce around corneal wounds, express α -smooth muscle actin α -SMA (Jester et al., 1996), vimentin, and desmin (Chaurasia et al., 2009), secrete ECM proteins such as fibronectin (Wilson, 2012), and lay down highly disorganized and opaque matrix (Santhanam et al., 2017). A separate lineage of myofibroblast progenitors, bone-marrow derived fibrocytes, have also been shown to be involved in disordered collagen deposition and angiogenesis (de Oliveira and Wilson, 2020; Lassance et al., 2018).

The regeneration of the epithelial basement membrane is critical in halting the flow of fibrogenic mediators into the stroma (Marino et al., 2017), and also the reciprocal flow of fibroblast-derived cross-talk molecules such as keratocyte-derived hepatocyte and keratinocyte growth factors (HGF and KGF, respectively) (Wilson et al., 1999). Without TGF- β , PDGF, and other stimulatory molecules, myofibroblasts undergo apoptosis and the scarring process gradually diminishes, although many months may elapse before the scar reaches full maturity (Torricelli et al., 2013a). This process highlights the clinical importance of achieving early re-epithelialization in affected patients, and also suggests that there are key rate-dependent steps in the genesis of post-infectious opacities that may serve as potential therapeutic targets (Jester et al., 1997; Singh et al., 2014). Clearly, as with the pendular nature of most inflammatory cascades involved in BK, the need to

activate mechanisms that lead to fibrosis in the short term (to prevent potentially catastrophic stromal thinning) must be tempered by mechanisms that promote a prompt return to stromal homeostasis after the pathogen has been cleared (e.g., by reducing myofibroblast activity when it is unneeded). Further details of corneal wound healing are found in several excellent reviews (Ljubimov and Saghizadeh, 2015; Wilson, 2020b).

5. NOVEL THERAPEUTICS FOR BACTERIAL KERATITIS

i. Current standards of care

As mentioned earlier, the only evidence-based treatments for BK are broad spectrum topical antibiotics, and in select cases, topical corticosteroids and surgical intervention. Common antimicrobial regimens include either topical monotherapy with a fourth-generation fluoroquinolone, or a combination of fortified antibiotics with appropriate broad-spectrum coverage. Fortified antibiotics typically include a cephalosporin or vancomycin for Gram-positive organisms, combined an aminoglycoside such as tobramycin or gentamicin for Gram-negative organisms (Lin et al., 2019). While the necessity of antimicrobial therapy has never come under serious question, the role of corticosteroids has in the past courted significant controversy among ophthalmologists. Heated debates that raged from the mid-1950s – when corticosteroids first became available in topical formulations – hinged on whether immunosuppressive therapy could exacerbate disease by dampening essential host inflammatory responses during acute infection, or whether a therapeutic benefit could be achieved by suppressing the destructive stromal lysis that seemed to accompany leucocyte infiltration into the cornea (Gordon, 2000; Laibson, 1973; Thygeson et al., 1960; Wilhelmus, 2002).

The ocular steroid dilemma in BK was not adequately addressed until the conduct and publication of the National Institutes of Health (NIH)-sponsored Steroids for Corneal Ulcers Trial (SCUT), a moderately-sized ($n = 500$), double-blinded randomized controlled trial that evaluated the therapeutic benefit of a relatively lightly-dosed course of topical 1% prednisolone sodium phosphate, compared to placebo, among culture-proven cases treated at baseline with standard topical 0.5% moxifloxacin (Srinivasan et al., 2012). Although no difference was found between treatment and placebo groups for the primary endpoint of best spectacle-corrected visual acuity (BSCVA) at three months, primary and secondary analyses demonstrated that corticosteroid-treated patients with central, deep and severe ulcers not caused by *Nocardia* achieved a 3- and 12-month BSCVA of at least 1-line better than compared to the placebo arm within these subgroups (Ray et al., 2014; Srinivasan et al., 2014). Though SCUT did not have the required power to detect differences in visual outcome by bacterial etiology, its conclusions provide the clinical rationale for the cautious application of topical corticosteroids in severe, culture-proven non-*Nocardia* BK after at least 48-hours of improvement while on antimicrobial treatment.

The indications for surgical intervention in BK vary in large part according to the phase of infection. In the acute setting, severe lesions that undergo progressive stromal thinning, descemetocoele formation, and local perforation may require the application of a corneal tissue adhesive to provide globe closure and tectonic support for a short period. However, commonly-used adhesives such as cyanoacrylate are limited by their direct toxic

effects on corneal cells, propensity to worsen corneal inflammation, and induction of pro-angiogenic pathways that lead to corneal neovascularization (Yin et al., 2019). A less common alternative is amniotic membrane transplantation (AMT), which has purported anti-inflammatory properties that may lead to accelerated ocular surface healing (Kim et al., 2001), though data on effectiveness remain mixed. In unsalvageable, rapidly progressing lesions and in large corneal perforations, the only prospect for visual recovery (and globe preservation) is to replace the diseased corneal tissue with a penetrating therapeutic corneal graft. While successful in many cases, corneal grafts that are performed in an infected eye are associated with an increased likelihood of disease recurrence, high-grade post-operative inflammation, and/or early graft failure, when compared to grafts performed in non-inflamed eyes (Tan et al., 2008). For long-term blinding corneal opacities, the only effective treatment is usually the placement of a corneal graft or keratoprosthesis; both require life-long ophthalmic care and cannot guarantee a return to the patient's pre-infection vision. Furthermore, because the health and socioeconomic burdens of BK are heavily skewed towards low-income countries, optical rehabilitation through surgery is simply not an option for the many patients, estimated to number in the millions, who experience blindness from infectious corneal ulcers each year (Ung et al., 2019a; Whitcher and Srinivasan, 1997).

ii. A new paradigm in BK treatment

The controversies that once surrounded topical corticosteroids illustrate the lack of therapeutic precision offered by historical and current standards of evidence-based care in BK. For example, because topical corticosteroids are agnostic to inflammatory pathways, their use as blanket immunosuppressants must be timed and titrated carefully to achieve their desired effect. Similarly, the use of broad-spectrum empiric antimicrobials, commonly through the entire duration of a patient's infection, represents an unnuanced "scorched earth" approach to achieve pathogen eradication (O'Brien, 2003). The future of BK care will require treatments that target the many dimensions of BK pathophysiology, specifically those that are most strongly associated with severity of disease and clinical outcomes. Novel treatments must be safe, minimally toxic, made widely available, and ideally would have multimodal mechanisms of action. This could include: (a) enhancing natural ocular surface defenses through the application of naturally-occurring and potentially non-toxic antimicrobial tear products; (b) optimizing the health of compromised ocular surfaces, including among contact-lens wearers; (c) preventing the adhesion, colonization, and invasion of bacterial pathogens on the corneal epithelium; (d) amplifying the antibacterial effects of the host innate response, while attenuating the persistent and destructive nature of residual inflammation within the cornea; (e) reducing the impact of disordered corneal remodeling in the post-infectious phase. As shown earlier, the pathogenesis of BK – while complex and incompletely understood – is replete with opportunities for therapeutic interventions that may improve patient care.

iii. New treatments on the horizon

Rich evidence from animal models of BK suggests there are many candidate therapies that merit further investigation. Precise molecular treatments are often applied in experimental studies to delineate the functional significance of varying inflammatory mediators or pathogen virulence factors in disease pathways. The need to interrogate new potential

treatments is urgent: only one class of treatments – comprising the fourth-generation fluoroquinolones moxifloxacin, besifloxacin, and gatifloxacin – has been approved for use in bacterial ocular surface infections in the last 20 years (Food and Drug Administration, 2003, 2010; Haas et al., 2011). Novel antimicrobial compounds that may not be subject to the same concerns surrounding AMR include antimicrobial peptides and other bacteriostatic compounds in tear fluid (Fleiszig et al., 2003; Kwong et al., 2007; Mannis and Smolin, 1996), as well as synthetic host defense peptides (Clemens et al., 2017). Monoclonal antibodies directed against important cell wall constituents on bacteria may also reduce the virulence of invading bacteria. Those that have been tested in ocular models of *P. aeruginosa* keratitis include alginate (Zaidi and Pier, 2008), H2 and F (porin) proteins (Moon et al., 1988), LPS (Welsh et al., 1984), and T3SS (Le et al., 2019). Exotoxin-inhibitors that target *ExoU* (Foulkes et al., 2021; Phillips et al., 2003) and *ExoS* (Aiello et al., 2010; Sharma et al., 2020; Uusitalo et al., 2017) have also shown promise as antimicrobial compounds. Furthermore, bacterial adhesion and internalization may be reduced by competitive binding of host receptors such as gangliosylceramide (asialo GM1) and pilus-binding protein (Hazlett et al., 1993; Hobden et al., 1996), and as well as the inhibition of lipid raft-dependent endocytosis (Zaidi et al., 2008).

Immune modulators may attenuate the damage associated with residual host inflammatory responses. Clinically, a number of available medications are already used for this purpose. For example, anticollagenases such as the tetracycline class of antibiotics are believed to reduce stromal lysis, and are used widely by ophthalmologists even though their effect in preventing corneal perforation has not been studied in the setting of a randomized controlled trial (Golub et al., 1983; Seedor et al., 1987). In research settings, attempts to temper the host inflammatory response have involved blocking TLR-dependent pathways. This has been achieved using TLR-specific antibodies (Huang et al., 2005), and through small molecule inhibitors, e.g., glycyrrhizin, which blocks the binding of an endogenous “danger signal”, high mobility group box-1 (HMGB1), to TLRs (Ekanayaka et al., 2018; Ekanayaka et al., 2016). Monoclonal antibodies that target important inflammatory cytokines, including IL-1 β (Karicherla and Hobden, 2010; Xue et al., 2003b) and IL-17 (Zaidi et al., 2012) have also been associated with decreased severity of disease. Alternatively, vaccination with microbe-derived products is an intriguing method that may dull host inflammatory responses in the cornea. Vaccination with heat-killed *P. aeruginosa* (Masinick et al., 1997), LPS endotoxins (Kreger et al., 1986), flagellin (Kumar et al., 2008), staphylococcal α -toxin toxoid (Hume et al., 2000), and pneumococcal pneumolysin toxoid (Norcross et al., 2011) have all been demonstrated in animal models to reduce BK severity. With some imagination, ophthalmologists may one day be possible to safely administer prophylactic topical vaccinations among those with a high baseline risk of developing BK (e.g., severe ocular surface disease and/or in corneal transplants). Therapies that could conceivably reduce post-infectious corneal scarring could include anti-TGF- β and anti-PDGF agents that could augment the effect of corticosteroids that are prescribed for this indication (Chouhan et al., 2019; Esmaeili et al., 2016; Hill et al., 2018; Jester et al., 1997; Singh et al., 2014). Novel methods of drug delivery – including the use of nanoparticles, drug-eluting contact lenses, and microemulsions – could further improve drug bioavailability on the ocular surface (Dutta et al., 2016; Sharma and Taniguchi, 2017; Ustundag-Okur et al., 2015).

CONCLUSIONS

It is a sobering reality of ophthalmic care that evidence-based strategies to prevent and treat BK have remained largely stagnant in the past few decades. Amid growing concerns of diminishing antibiotic utility in treating common ocular pathogens, attention has naturally turned to the development of medical innovations that may help overcome our therapeutic stasis. A simple framework that reconstructs the complex biology and host-pathogen interactions that determine the clinical course of disease is helpful to identify precise targets for therapeutic intervention and future research. Indeed, our wealth of experimental animal and human data suggests that our current standard of care could be augmented by treatments that bolster host defenses on the ocular surface, reduce the likelihood of bacterial corneal invasion, modulate the destructive components of the host immune response, and optimize corneal wound healing in the post-infectious phase of disease. As the global burden of BK grows, the next frontier of clinical management will lie in exploring how such treatments can be developed and translated into routine patient care.

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ABBREVIATIONS

 α -SMA

α -smooth muscle actin

AMR

antimicrobial resistance

AMT

amniotic membrane transplantation

APC

antigen presenting cell

ARMOR

Antimicrobial Resistance Monitoring of Ocular Microorganisms

BSCVA

best spectacle-corrected visual acuity

BK

bacterial keratitis

C3

complement component 3

CCL
chemokine (C-C motif) ligand

CFU
colony forming unit

CTFR
cystic fibrosis transmembrane-conductance regulator

CXCL
chemokine ligand

ECM
extracellular matrix

hβD-2
human β-defensin 2

HGF
hepatocyte growth factor

HMGB-1
high mobility group box-1

HIV
human immunodeficiency virus

ICAM-1
intracellular adhesion molecule 1

IFN
interferon

IgA
immunoglobulin A

IgG
immunoglobulin G

IL
interleukin

ILGF
insulin-like growth factor

IRF3
interferon regulatory factor 3

JNK
c-Jun N-terminal kinases

KAMP

keratin-derived antimicrobial peptide

KGF

keratinocyte growth factor

LASIK

laser-assisted in-situ keratomileusis

LC

Langerhans cell

LL-37

cathelicidin

LPS

lipopolysaccharide

LTA

lipoteichoic acid

MAC1

macrophage-1 antigen

MAPK

mitogen-activated protein kinases

MHC

major histocompatibility complex

MIC

mean inhibitory concentration

MIF

macrophage migration inhibitory factor

MIP

macrophage inflammatory protein

MMP

matrix metalloproteinase

MSCRAMMs

microbial surface components recognizing adhesive matrix

MyD88

myeloid differentiation primary response protein 88

NETS

neutrophil extracellular trap

NF- κ Bnuclear factor κ B**NIH**

National Institutes of Health

NGS

next generation sequencing

NLR

nucleotide-binding oligomerization domain-like receptors

NOD

nucleotide-binding oligomerization domain

OCP

ocular cicatricial pemphigoid

PAMP

pathogen-associated molecular pattern

PavA

pneumococcal adherence and virulence factor A

PavB

pneumococcal adherence and virulence factor B

PECAM-1

platelet endothelial cell adhesion molecule

PDGF

platelet-derived growth factor

PMN

polymorphonuclear cell

PNAG

poly-N-acetylglucosamine

PRR

pathogen recognition receptors

PsaA

pneumococcal surface antigen A

PspA

pneumococcal surface protein A

PspC

pneumococcal surface protein C

P. aeruginosa*Pseudomonas aeruginosa***RANTES**

regulated upon activation, normal T-cell expressed and presumably secreted

ROS

reactive oxygen species

SCUT

Steroids for Corneal Ulcers Trial

S. aureus*Staphylococcus aureus***sIgA**

secretory immunoglobulin A

SJS

Stevens-Johnson syndrome

SLPI

secretory leukocyte protease inhibitor

sPLA₂

secretory phospholipase A

ssRNA

single stranded RNA

S. pneumoniae*Streptococcus pneumoniae***T3SS**

type III secretion systems

TGF

transforming growth factor

Th1

type 1 T-helper cell

Th2

type 2 T-helper cell

TICAM-1

toll/interleukin-1 receptor-domain containing adaptor molecule 1

TICAM-2

toll/interleukin-1 receptor-domain containing adaptor molecule 2

TIR

toll/interleukin-1 receptor

TIRAP

toll/interleukin-1 receptor-domain containing adaptor protein

TLR

toll-like receptor

TNF- α tumor necrosis factor – α **TRAM**

toll/interleukin-1 receptor-domain containing adaptor molecule 2

VCAM-1

vascular cell adhesion protein 1

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Highlights

1. Bacterial corneal infections can cause rapidly fulminant disease and permanent vision loss.
2. Topical antimicrobials and corticosteroids fail to salvage vision in many patients.
3. The pathogenesis of bacterial corneal infections involves loss of corneal immune privilege.
4. Innate immune responses are orchestrated by the corneal epithelium, stromal keratocytes, and resident immune cells.
5. Novel treatments targeting the molecular bases of infection may improve patient outcomes.

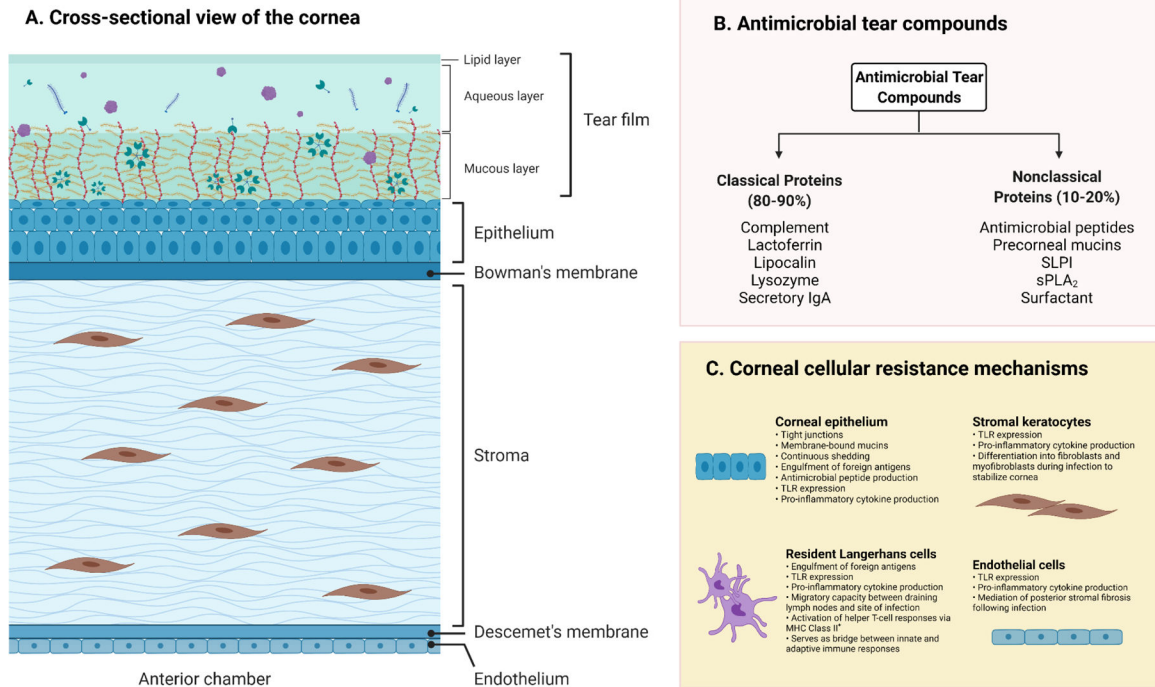


FIGURE 1. The ocular surface in health.

(A) Cross sectional view of the cornea and pre-corneal tear film. The trilaminar tear film consists of outermost lipid, middle aqueous, and innermost mucous layers that trap foreign particles and are highly concentrated with protective antimicrobial compounds. (B) Summary of antimicrobial tear compounds, divided into classical and nonclassical proteins. (C) Summary of major resistance mechanisms against infection in corneal cells. Note that Langerhans cell (LC) populations in the cornea are highly diverse; two major populations include mature LCs that express MHC Class II⁺ reside in the peripheral corneal epithelium, and another population of MHC Class II⁻ LCs that reside in the central cornea, and which require stimulation (e.g., with PAMPs) to mature. **Key** – IgA: immunoglobulin A; MHC: major histocompatibility complex; SLPI: secretory leucocyte protease inhibitor; sPLA₂: secretory phospholipase A; TLR: toll-like receptor. Created with [Biorender.com](https://www.biorender.com) under a standard academic license.

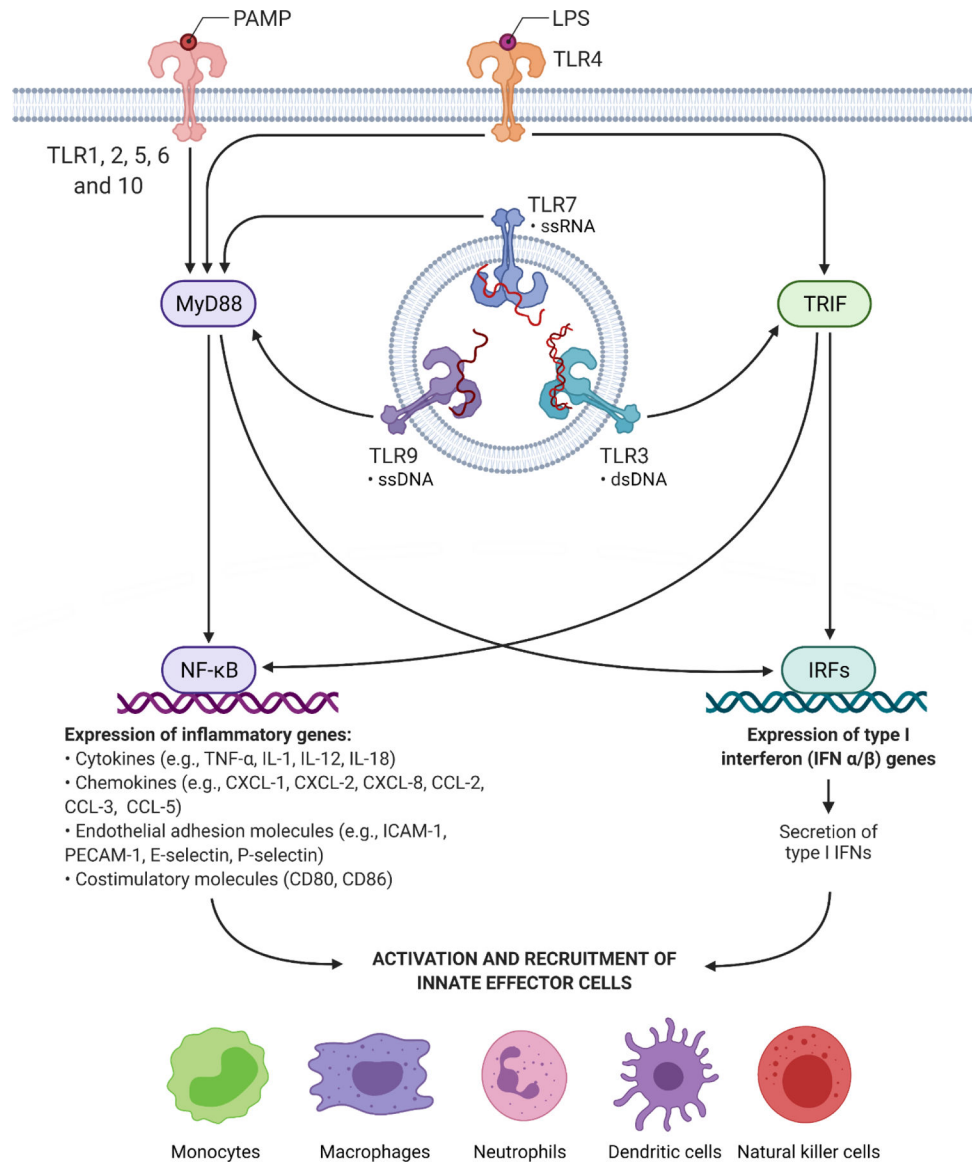


FIGURE 2: The putative role of toll-like receptors (TLRs) in the cornea.

TLRs are evolutionarily conserved membrane-bound pattern recognition receptors (PRRs) that initiate host innate immune responses to pathogen-associated molecular patterns (PAMPs). TLRs are differentially localized within cells, either on the cell surface (TLR1, 2, 4, 5, 6, 10) or within intracellular endosomes (TLR 3, 7, and 9). TLR8 is not known to exist in the cornea. With the exception of TLR3, TLRs activate the myeloid differentiation primary response protein 88 (MyD88), a master adaptor protein that upregulates NF-κB and MAPK-dependent pathways, leading to the expression of pro-inflammatory cytokines, chemokines, adhesion molecules, and co-stimulatory molecules that are essential for the recruitment of innate effector cells. On the other hand, TLR3 (and also TLR4) stimulate alternative adaptor proteins, such as toll-interleukin receptor domain-containing adapter-inducing interferon-β TRIF), leading to the upregulation of interferon regulatory factor (IRF) pathways that lead to the production of type I interferons IFN-α and IFN-β. While IFNs have

been historically associated with viral infections, recent evidence suggests that IFNs are also potent inducers of innate immune effectors in the setting of bacterial infection (Monroe et al., 2010). For further details regarding PAMP recognition among TLRs, refer to Table 1. Created with [Biorender.com](https://biorender.com) under a standard academic license.

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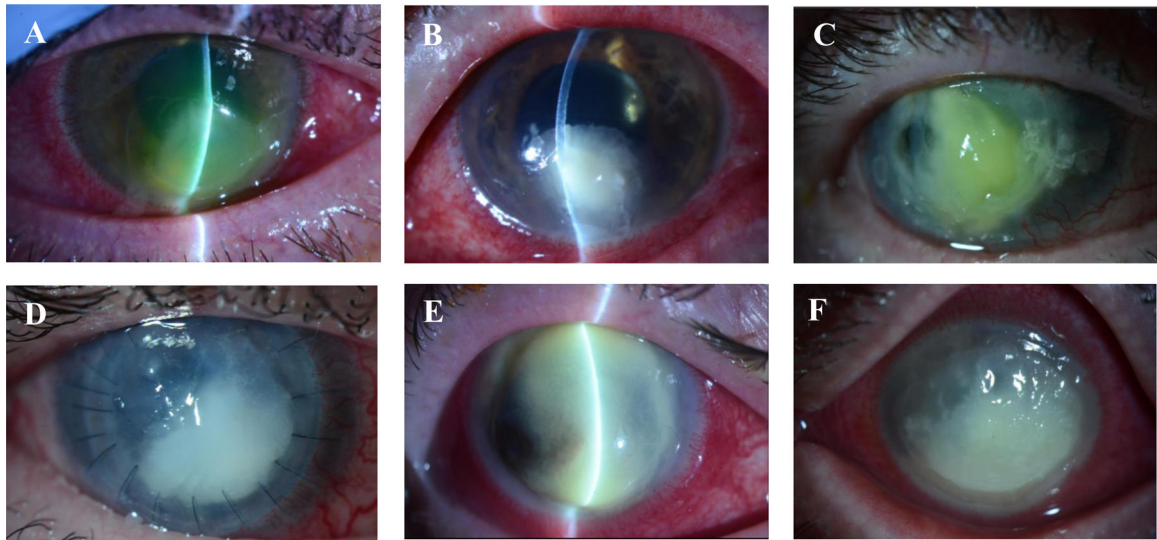


FIGURE 3. Clinical slit-lamp photography of sight-threatening bacterial keratitis caused by common pathogens.

(A) A large, inferior *P. aeruginosa* corneal ulcer in a soft contact lens user, requiring therapeutic penetrating keratoplasty following perforation; (B) severe methicillin-sensitive *S. aureus* ulcer arising in the setting of previous herpetic eye disease; (C) large, diffuse, and necrotic *S. pneumoniae* ulcer arising in an old penetrating keratoplasty, crossing the graft-host junction; (D) *M. catarrhalis* ulcer causing graft failure in a penetrating keratoplasty; (E) *S. marcescens* ulcer in a patient with possible underlying herpetic eye disease; and (F) polymicrobial infection (caused by *Streptococcus mitis* and *Enterococcus faecalis*).

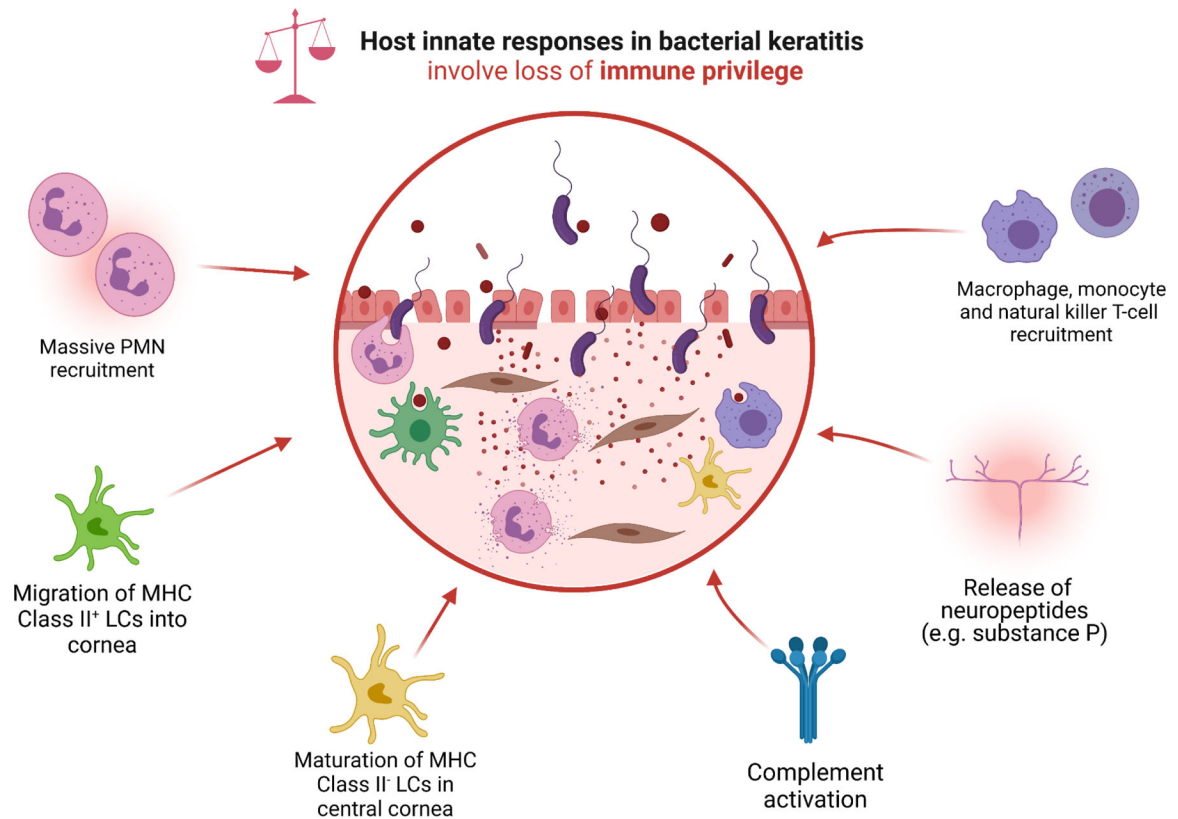


FIGURE 4: Schematic overview of host innate responses to bacterial corneal pathogens, which involve the loss of corneal immune privilege.

Pattern recognition receptors (PRRs), predominantly toll-like receptors (TLRs), ligate with pathogen-associated molecular patterns (PAMPs) including bacterial lipoteichoic acid and lipopolysaccharides. PRR-binding leads to the upregulation of pro-inflammatory transcription factors such as NF- κ B, with subsequent cellular release of pro-inflammatory cytokines (TNF- α , IL-1, IL-6, IL-8, IL12, IL-18, IFNs and MIF), chemokines (CXCL-1, CXCL-2, CXCL-5, CCL-4, CCL-5, IL-18, MCP-1), endothelial adhesion molecules (ICAM-1, MAC-1, PECAM-1, VCAM-1, E-selectin, and P-selectin). Several cell types (e.g., corneal epithelial cells) also inappropriately upregulate the production and release of digestive MMPs, including MMP-1, MMP-2, MMP-3, and MMP-9. This pro-inflammatory storm of cytokines induces massive neutrophil recruitment; migration of MHC Class II⁺ LCs from the corneal limbus, conjunctiva, and surrounding vascular beds into the stroma; maturation of resident stromal MHC Class II⁻ LCs; recruitment of macrophages and monocytes; activation of complement; and release of neuropeptides such as substance P. The activation of LCs serves as a bridge to the adaptive immune response, which is characterized by recruitment of Th1-predominant helper-T cells that preside over the persistence of PMNs, and are associated with severe disease phenotypes (e.g., corneal perforation).

TABLE 1.

Putative location and ligands of toll-like receptors in the human cornea, based on *in vivo* animal and *in vitro* human cell culture studies.

TLR ^a	Putative Location in Cornea	Mice or Human?	Putative Location in Cell	Ligands	Activation of NF-κB or TRIF (IFN-3) pathways?	References
1	Epithelium Stroma	Both	Surface	LTA and PGN (Gram-positives) LPS (Gram-negatives)	NF-κB	(Kumar et al., 2004)
2 ^δ	Epithelium Stroma Endothelium	Both	Surface	Fungal zymosan and β-glycan (fungi) LTA and PGN (Gram-positives) LPS (Gram-negatives) Phospholipomannan Envelope glycopeptides (viruses)	NF-κB	(Adhikary et al., 2008; Choi et al., 2011; Ebihara et al., 2007; Jin et al., 2009; Johnson et al., 2005; Kot et al., 2019; Kumar et al., 2004, 2006a; Tullios et al., 2013; Zhao and Wu, 2008)
3	Epithelium Stroma	Both	Endosomal	dsRNA	TRIF (IFN-3)	(Kumar et al., 2006b; Liu et al., 2008; Ueta et al., 2005)
4	Epithelium Stroma Endothelium	Both	Surface	LPS (Gram-negatives) Glycosaminositol phospholipids (protozoa) Envelope glycopeptides (viruses)	TRIF (IFN-3) and NF-κB	(Choi et al., 2011; Jin et al., 2009; Johnson et al., 2005; Kot et al., 2019; Kumagai et al., 2005; Kumar et al., 2006a; Zhao and Wu, 2008)
5	Epithelium Stroma	Both	Surface	Flagellin	NF-κB	(Hayashi et al., 2001; Zhang et al., 2003)
6	Epithelium Stroma	Both	Surface	LTA and PGN (Gram-positives) LPS (Gram-negatives)	NF-κB	(Redfern et al., 2011)
7	Epithelium Stroma	Both	Endosomal	Viral ssRNA	NF-κB	(Chang et al., 2006; Redfern et al., 2011)
8	No known corneal presence	Both	Surface	Viral ssRNA	NF-κB	(Heil et al., 2004; Redfern et al., 2011)
9	Epithelium Stroma Endothelium	Both	Endosomal	Bacterial CpG DNA motifs Viral CpG DNA motifs	NF-κB	(Ebihara et al., 2007; Inoue, 2014; Johnson et al., 2005; Takeda et al., 2011)
10	Epithelium Stroma	Human	Surface	Unknown [‡]	NF-κB	(Hasan et al., 2005; Redfern et al., 2011)

Key-dsRNA: double stranded ribonucleic acid; IFN: interferon; LPS: lipopolysaccharide; LTA: lipoteichoic acid; NF-κB: nuclear factor κB; PGN: peptidoglycans; ssRNA: single-stranded ribonucleic acid; TRIF: TIR-domain-containing adapter-inducing interferon-β

^aIn total, 13 TLRs have been discovered among mice and humans; only those found in humans are listed in this table.

[‡]TLR10 homodimerizes with TLR1 and TLR2, so it may have similar ligands (Hasan et al., 2005).

^δTLR2 dimerizes with TLR1 to recognize tri-acylated lipoproteins; TLR2 dimerizes with TLR6 to recognize di-acylated lipoproteins (Pearlman et al., 2008).

TABLE 2.

Summary of key epidemiologic and virulence factors for ocular strains of *P. aeruginosa*, *S. aureus*, and *S. pneumoniae*.

Pathogen	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>S. pneumoniae</i>
Key epidemiologic features	<ul style="list-style-type: none"> Ubiquitous; most common cause in contact-lens microbial keratitis Cytotoxic (<i>ExoU</i>⁺), invasive (<i>ExoS</i>⁺), or neither; epidemiologic composition in most locations unknown 	<ul style="list-style-type: none"> Ubiquitous; common worldwide Majority (>90%) are methicillin-sensitive, but growing proportion of MRSA isolates particularly in tertiary care centers 	<ul style="list-style-type: none"> Ubiquitous; most common in low-to-middle income countries Most corneal isolates characterized as encapsulated invasive strains
Minimum infectious dose in cornea (CFUs)	~50	~100	Unknown
Cell surface features	Lipopolysaccharide (LPS) Pili (fimbriae) Flagella Alginate Glycocalyx (biofilm)-forming peptides Type III secretion systems	Lipoprotein Lipoteichoic acid (LTA) MSCRAMMs including collagen, elastin, fibronectin, fibrinogen, and laminin-binding proteins, as well as clumping factor Peptidoglycans Protein A	Lipoteichoic acid (LTA) Peptidoglycans Polysaccharide capsule Pneumococcal adherence and virulence factors A and B (PavA and PavB) Pneumococcal choline-binding protein Pneumococcal surface antigen A (PsaA) Pneumococcal surface protein A (PspA) Pneumococcal surface protein C (PspC) Protein A
Secreted virulence factors	Exotoxin A Hemolysins Large exoprotease Leucocidin Metalloproteinases (Las A protease, Las B protease, alkaline protease, modified protease) Phospholipases Protease IV <i>P. aeruginosa</i> small protease (PASP)	α-toxin Catalase Coagulase DNase Hemolysins (α-, β-, δ-, and γ- toxins) Hyaluronidase Leucocidin Staphylokinase Superantigens (enterotoxins A – D)	Autolysin Pneumolysin Reactive oxygen species (e.g., hydrogen peroxide) Secretory IgA protease
Antimicrobial resistance in ocular strains (in the US)	Low; <10% of ocular isolates resistant to fluoroquinolones and aminoglycosides (tobramycin). However, multi-drug resistant strains requiring last-line carbapenems and colistin are becoming of increasing concern.	High and rapidly accumulating: <ul style="list-style-type: none"> >30% of all strains resistant to fourth-generation fluoroquinolones > 80% of MRSA resistant to fourth-generation fluoroquinolones ~ 10% MSSA resistant to fourth-generation fluoroquinolones No observed resistance to vancomycin 	Low; <10% of ocular isolates resistant to fluoroquinolones.