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Review Article

Virulence Factors of Bacteria Related to Ocular Infections in Non Immunocompromised Patients: Review Article

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Abstract: The ocular surface is constantly exposed to pathogenic bacteria. Many Gram positive and Gram negative bacteria have been implicated in ocular infections, in non immunocompromised patients, causing severe vision impairment. These microorganisms have in their quiver a variety of arrows to cause infection. The aim of this study is to list the virulence factors of the main ocular pathogens. Data were extracted from PubMed and Google Scholar. *S. aureus* and *Streptococci, Bacillus cereus* and *Corynebacterium (non-diphtheriae)* are the main culprits as far as Gram positive bacteria are concerned. *S. aureus* causes infections of the lacrimal apparatus, cornea and eyelids, conjunctivitis, keratitis, and endophthalmitis. *Streptococcus pneumoniae, Streptococcus pyogenes, Enterococcus* and *Streptococcus viridians* are isolated from post injection endophthalmitis cases. *S. pneumoniae* is most involved in keratitis, conjunctivitis, and endophthalmitis. *Streptococcus pyogenes* is most involved in blepharitis and hospital acquired conjunctivitis in neonates in the intensive care unit. *Enterococcus faecalis* is implicated in postoperative endophthalmitis cases. *Corynebacterium (non-diphtheriae) species* are involved mainly in infections complicating cataract surgery, keratoplasty, and vitrectomy. *Bacillus species* provoke conjunctivitis, keratitis and post-traumatic endophthalmitis. *Bacillus cereus* can cause rapidly destructive endophthalmitis. Among Gram negative bacteria, *Neisseria gonorrhoeae, Pseudomonas aeruginosa, Chlamydia trachomatis*, and *Bartonella species* are major ocular pathogens, responsible for severe ocular damage. Gonococcal conjunctivitis (GC) is still a cause of blindness in some developing countries. When it occurs in neonates, it is called gonococcal ophthalmia neonatorum. *P. aeruginosa* is related to contact lens-associated keratitis. *Chlamydia trachomatis* is the culprit of trachoma and inclusion conjunctivitis. *Bartonella henselae* causes bartonellosis or cat scratch disease, or cat scratch fever. Eye infection includes optic neuropathy and neuroretinitis. When the eye is the primary site of inoculation, the patients are diagnosed with Parinaud oculo-glandular syndrome (infection of the conjunctiva, eyelid and adjacent skin with regional lymphadenopathy). Chronic *Bartonella* infection provokes blurred vision, photophobia and eye irritation. Comprehension of the mechanism of infection, caused by these pathogens, is crucial in diagnosis and treatment.

Keywords: Ocular Infection, Non Immunocompromised Patients, Virulence Factors, Gram Positive Bacteria, Gram Negative Bacteria

1. Introduction

The ocular surface is constantly exposed to the dangers of the environment, including pathogenic bacteria. Although normally we can find different types of microorganisms in the conjunctiva, eyelids and tears, bacterial infections of the human eye remain a major culprit that can cause visual impairments [1]. Many Gram positive and Gram negative

bacteria possess powerful mechanisms to evade and provoke ocular damage in non immunocompromised patients. *Staphylococcus aureus*, members of the Genus *Streptococci*, *Corynebacterium (Non-diphtheriae) Species* and *Bacillus Species* among Gram positive bacteria have evolved an arsenal that triggers inflammatory response and tissue damage [2-20]. Ocular infections due to Gram negative bacteria like *Neisseria gonorrhoeae, Pseudomonas aeruginosa, Chlamydia trachomatis*, and *Bartonella Species* are still a challenge to deal with and to avoid their devastating eyesight impairment [21-37]. The purpose of this review was to gather established and resent knowledge of the virulence factors of these bacteria, and to describe their mechanisms of ocular invasion and damage.

2. Main Body

2.1. Gram Positive Bacteria

The components of gram-positive microorganisms' cell wall that is peptioglycan, lipoteichoic acid and capsular polysaccharide are well known. Those components get involved in the pathogenesis of ocular infections by gram positive bacteria, as they trigger chemotaxis of inflammatory cells and cytokine production [2].

2.1.1. S. aureus

S. aureus is a major ocular pathogen. It belongs to gram-positive cocci and has potent virulence factors in its armamentarium. It causes infections of the lacrimal apparatus, cornea and eyelids, conjunctivitis, keratitis, and endophthalmitis [3]. *S. aureus* firstly colonizes the skin and mucosa, which is performed via proteins and enzymes that promote bacterial adherence, such as fibronectin-binding protein A (FnbpA) and Fnbp B, fibrinogen binding proteins (ClfA and ClfB), iron regulated surface determinant A (IsdA), and wall teichoic acid (WTA) [4]. Keratinocytes express pattern recognition receptors such as Toll-like receptor 2 (TLR2) that recognizes lipopeptides and lipoic acids of *S. aureus*, NOD2 (nucleotide-binding oligomerization domain containing), which recognizes components of peptidoglycan (muramyl-peptide). The intracellular signal triggers the activation of NF-kB and other transcription factors that lead to the production of the pro-inflammatory cytokines IL-1a, IL-1b IL-17 [4]. These pro-inflammatory cytokines induce keratinocytes to produce antimicrobial peptides like b-defensins 2 and 3, cathelicidin, RNase 7, cytokines, chemokines, adhesion molecules, and granulopoiesis factors, that recruit neutrophils from the circulation. Neutrophils create an abscess to reduce the spread of infection and neutralize the invader [4]. *S. aureus* produces several toxins and enzymes that damage the host tissue and help the invader pathogen spread. In the same time, they attack and destroy the inflammatory cells. Of those toxins, alpha-toxin, phenol soluble modulins (PSM), and Panton-Valentine leukocidin (PVL) induce host cell lysis [5]. The PVL mechanism of action is formation of octameric transmembrane pores in lymphocytes, mononuclear cells and granulocyte lysosomes [6]. Chemotaxis inhibitory protein of *Staphylococci* (CHIPS) and extracellular adherence protein (Eap) inhibit neutrophil recruitment. Golden carotenoid pigment and superoxide dismutase enzymes inhibit reactive oxygen species [5]. *S. aureus* protein A (SpA) interferes to opsonophagocytosis and causes B-cell death in vitro with the following mechanism of action: it binds the Fc region of antibody and the Fab regions of the B-cell receptor [7]. Exfoliative toxins (ETA and ETB) and toxic shock syndrome toxin (TSST) act as superantigens. They provoke detachment of ligaments and skin detachment [5]. The leukotoxin LukAB and PSMs can lyse after phagocytosis [5]. *S. aureus* produces two coagulases (staphylocoagulase and von Willebrand factor (vWF), which trigger the conversion of fibrinogen to fibrin. The formed fibrin clots mask the surface of *S. aureus* cells, and thus inhibits phagocytosis [5].

S. aureus is related to post-traumatic and postoperative endophthalmitis with poor visual outcome. Globally regulated toxins in *S. aureus* endophthalmitis pathogenesis that are controlled by quorum-sensing systems and act in combination have been described. Those are agr (accessory gene regulator) and sar (staphylococcal accessory regulator) [2]. As *S. aureus* enters the vitreous cavity, its rapid proliferation triggers intense inflammatory response that abolishes the blood-ocular barrier and thus enhances further recruitment of inflammatory cells. In this interaction TLR2 plays a major role in the pathogenesis of *S. aureus* endophthalmitis [8].

Alpha-toxin is a virulence factor in *S. aureus* keratitis. It acts as a membrane-damaging hemolysin which attacks the corneal epithelium. *S. aureus* alpha-toxin and beta-toxin (sphingomyelinase) participate in retinal destruction [2].

2.1.2. Members of the Genus Streptococci

Streptococcus pneumoniae, Streptococcus pyogenes, Enterococcus and *Streptococcus viridians* are isolated from post injection endophthalmitis cases [9]. *S. pneumoniae* in eye infections is most involved in keratitis and conjunctivitis, endophthalmitis. The microorganism firstly colonizes the nasopharynx via the neuraminidases (Nan), NanA, NanB, and NanC. Then, due to hyaluronate lyase, which disrupts extracellular matrix components and increases tissue permeability, it invades deeper layers [10]. *S. pneumoniae* strains that do not produce capsule due to mutation or deletion, (nonencapsulated *S. pneum*oniae, NESp) are the culprit of most conjunctivitis cases [10]. The pneumococcal capsule reduces IgG and C-reactive protein binding to the microbe, and thus the complement system is not activated and the microorganism escapes phagocytosis [10].

S. pneumoniae cells have the ability of self-lysis by secretion of autolysins. Autolysin LytA lyses noncompetent pneumococcal cells, allowing DNA exchange by the healthy cells, reduces phagocytosis, and facilitates the release of other virulence factors [10]. Pneumolysin (PLY) is the culprit of most ocular damage due to *S. pneumoniae* infection. Its mechanism of action is pore-formation and promotes host cell lysis. It also activates the classical complement pathway provoking intense immune response [10]. The pneumococcal

zinc metalloproteinases Zmp, IgA1 protease, ZmpB, and ZmpC have a distinctive role as virulence factors. IgA1 is vital for adherence to host cells and cleaves neutralizing IgA1 antibodies at the hinge region. ZmpB provokes augmentation of tumor necrosis factor-alpha, which enhances infection severity. ZmpC removes the mucins from epithelial cells and binds to P-selectin frustrating neutrophil migration [10].

S. pneumoniae pili are also considered virulence factors as they contribute in the adhesion to the host cells. These adhesive pili are encoded by the pneumococcal *rlrA* islet and trigger higher TNF response [11-13].

Streptococcus pyogenes is most involved in blepharitis and hospital acquired conjunctivitis in neonates in the intensive care unit [9]. The virulence factors of group A *Streptococci* are many secreted proteins. Proteinases facilitate or enhance bacterial spread [14]. Streptokinase (Ska) has similar activity to host urokinase-type and tissue-type plasminogen activators, which means that converts inactive plasminogen to proteolytically active plasmin. As a result, host matrix metalloproteinases are activated and fibrinolysis, degradation of extracellular matrix and basement membrane components of host tissues follows. By this mechanism, the microbe spreads through the surrounding tissues of the inoculation site [14]. The cysteine proteinase, SpeB, (streptococcal pyrogenic erythrogenic toxin B or streptococcal cysteine proteinase), degrades host proteins of the immune response like cytokines, immunoglobulins, chemokines, cathelicidin LL-37, and complement components [14]. *S. pyogenes* cell envelope protease (prtS) cleaves and inactivates neutrophil chemokines [14]. Streptococcus secreted esterase (SsE) hydrolyzes platelet-activating factor (PAF) and reduces IL-12-mediated chemotaxis of natural killer cells and neutrophils [14]. *S. pyogenes* secretes the hemolysins streptolysin O and streptolysin S. Streptolysin O (SLO) is a cytotoxin that creates pores to cholesterol-rich host membranes, disrupts them and leads the cell to apoptosis. It is also needed to transfer the streptococcal NAD-glycohydrolase into the cytoplasm of epithelial cells. Once there, it depletes the intracellular pool of NAD [14]. SLO and/or NADase are present in phagolysosome and help the survival of *S. pyogenes* in macrophages. SLO prevents acidification, whereas the NADase hydrolyzes NAD and prevents phagolysosome membrane repair [14]. Streptolysin S (SLS) accumulates proteins in the host cell membranes which form hydrophilic pores that lead to osmotic lysis. Its' activity is related to lysis of erythrocytes, leukocytes, and platelets [14]. DNases of *S. pyogenes* protect from neutrophil-mediated killing. The mechanism of action is degradation of the neutrophil extracellular traps that bind bacteria. Those traps are DNA-based and in them the bacteria are not only prevented from spreading, but they also exposed to antimicrobial agents and the bacteria's own virulence factors [14]. The hyaluronidases secreted from *S. pyogenes* promote the ability of the microbe to spread through host tissues. They include the hyaluronate lyase HylA, and the hyaluronidase HylP [14]. Streptococcal inhibitor of complement (SIC) inhibits the formation of the membrane attack complex, which leads to impairment of complement-mediated cell lysis [14]. Superoxide dismutase (SodA) is detoxifying the oxidative burst during phagocytosis, by converting superoxide anions to oxygen and hydrogen peroxide. As a result, the microorganism survives oxidative stress [14]. The immunoglobulin-degrading enzyme IdeS is a secreted cysteine proteinase that cleaves Fab-bound IgG. Thus, the *Streptococci* resist phagocytosis and through antibody-mediated cytotoxicity [14]. Endo-β-N-acetylglucosaminidase (EndoS), removes carbohydrates from immunoglobulin G. As a result, both the binding of IgG to the Fc receptors and complement activation is reduced. This mechanism promotes the microorganism's survival [14]. M protein of *S. pyogenes* helps to resist phagocytosis by polymorphonuclear leukocytes [15]. The presence of type-specific antibodies to the M protein means resistance to infection from *S. pyogenes* [16, 17].

Enterococcus faecalis is implicated in postoperative endophthalmitis cases. These strains produce a cytolysin with a large lytic subunit (CylLL) and a small lytic subunit (CylLS) and are related with poor visual outcome [2].

2.1.3. Corynebacterium (Non-diphtheriae) Species

Corynebacterium (non-diphtheriae) species are normal occupants of ocular surfaces, and thus, nonpathogenic. They are opportunistic pathogens involved mainly in infections complicating cataract surgery, keratoplasty, and vitrectomy [18]. They possess pili with tissue tropism to colonize host tissues via the transpeptidase sortase. After initial attachment additional minor pilins help anchoring and provide proximity between the bacterial surface and the host cell plasma membrane [19, 20].

2.1.4. Bacillus Species

Bacillus species provoke conjunctivitis, keratitis and post-traumatic endophthalmitis. *B. cereus* can cause a rapidly destructive endophthalmitis [9, 19, 21]. Many factors result in an intense inflammatory response that leads to vision loss in a few days, from the onset of infection. The ability of the *Bacillus* for rapid replication and migration throughout the eye, as well as toxin production has been described [19].

Peptidoglycan on the surface of *B. cereus* reacts with TLR2. The combination with Toll-like receptor 4 (TLR4) and its adaptor molecules MyD88 and TRIF triggers acute intraocular inflammatory response. The flagella of the bacterium help the movement of the bacterium intraocularly. It has not been determined interaction of the flagella with TLR5 [19].

Adhesins (including pili and fimbrae) have been reported as virulence factors of *B. cereus* eye infections [19]. Strains with pili had better intraocular growth and it was more difficult to control infection [19].

In *B. cereus* endophthalmitis, the rapid vision loss is mainly due to the devastating results of the cytolysins and enzymes which the microorganism produces. Those include hemolysins, lipases, enterotoxins, and proteases. Hemolysin BL of B. cereus is a tripartite pore-forming toxin that gets involved at the early stages of inflammation [19]. Cereolysin AB, cereolysin O, and collagenase are observed to play a role in the pathogenesis of endophthalmitis. Cereolysin AB acts on cell

membrane and has cytolytic activity. Cereolysin O also provokes cell lysis in a two-step process. At first, it binds to cholesterol and then induces cell lysis. Collagenase targets the collagen which is abundant in the vitreous [19].

2.2. Gram Negative Bacteria

2.2.1. Neisseria gonorrhoeae

Gonococcal conjunctivitis (GC) is an infection that concerns all age groups. It is still a cause of blindness in some developing countries. When it occurs in neonates, it is called gonococcal ophthalmia neonatorum. The newborn is infected during delivery, where it is exposed to infectious vaginal secretions [21, 22].

The first step of *N. gonorrhoeae* infection is adherence to columnar or cuboidal mucosal epithelium. Attachment is mediated by pili. The second step of infection is epithelial invasion, followed by intense infiltration of neutrophils and formation of submucosal micro abscesses [21]. The second step is performed by the neisserial opacity (Opa) proteins which help the bacterium attach and invade human epithelial cells [23, 24]. *N. gonorrhoeae* pili not only promote adherence to host epithelial cells, but also inhibit phagocytosis [23]. The transmembrane protein CD46 (or membrane cofactor receptor) that is expressed by all nucleated cells, serves as a receptor for gonococcal pilus [25].

Lipooligosaccharide (LOS) of *N. gonorrhoeae* activates the alternative complement pathway and has excessive endotoxic activity [23]. LOS molecules differ from classic LPS. They lack the repeating O-antigen [25]. The consistency of the sugars of the hydrophilic part of the gonococcal LOS varies, which means that the length and the kind of sugars of the LOS carbohydrate chains may be different. This has an impact on complement activation and of the formation of the membrane attack complex (MAC) [24]. Some *N. gonorrhoeae* strains attach a host-derived sialic acid residue (terminal LOS galactose) via sialylation. LOS sialylation is mediated by gonococcus-encoded sialyltransferase. Those strains do not activate complement, as sialic acid is a host molecule [24, 25].

The outer membrane porin (PorB) of the microbe mediates apoptotic signaling, protects from both the classical and alternative complement pathways, mediates epithelial cell invasion and can affect the production of reactive oxygen species (ROS) by innate immune cells [23]. The IgA extracellular proteases of *N. gonorrhoeae* cleave the heavy chain of the human immunoglobulin IgA [23]. The Reduction modifiable protein (Rmp) together with porins form pores in the cell surface [24].

2.2.2. Pseudomonas aeruginosa

Pseudomonas aeruginosa is related to contact lens-associated keratitis. *P. aeruginosa* strains produce 10%-30% a smooth lipopolysaccharide (LPS). The rest of the LPS molecules are rough molecules [21]. Any disruption of the skin and mucosal surfaces creates the conditions of invasive *P. aeruginosa* infections [21]. Many components of the bacterium have been described as strong virulence factors.

The slime-glycolipoprotein (slime-GLP) of *P. aeruginosa*, produced during in vivo infection, leads to proinflammatory response by human monocytes. This is the result of the recognition of the bacterium by human monocytes through mannose receptor (MR) and TLR2, which act synergistically [26].

P. aeruginosa flagella are responsible for the motility of the bacterium and in biofilm formations in the dispersal and adhesion of the microbe to the surfaces. Flagella are structured by flagellin, which is recognized by Toll-like receptor 5. This triggers TNF, IL-6, and IL-8 synthesis [27].

Type IV pili of *P. aeruginosa* provide twitching motility, that is a form of surface-associated bacterial movement. The *P. aeruginosa* strains involved in the pathogenesis of corneal ulcers use twitching motility to translocate through corneal epithelial layers [28, 29].

It is well known that bacteria in biofilms communicate with each other through various communication systems (Quorum Sensing-QS). This communication enables them to adapt and modify gene expression depending on the environmental conditions. Quorum Sensing in *P. aeruginosa* biofilms leads to the regulation of various genes that leads to the production of extracellular enzymes and lysines that are responsible for the pathogenicity of infections [30]. Three primary QS systems are identified in *P. aeruginosa*, the las system, the rhl system, and the Pseudomonas Quinolone Signal (PQS). PQS acts as link between the las system and the rhl system [27].

P. aeruginosa via type III secretion system (TTSS) injects several toxins named effector proteins, directly into host cells. Those are ExoS, ExoT, ExoU and ExoY. ExoS and ExoT disrupt the host cell actin cytoskeleton, block phagocytosis, and provoke cell death. ExoU is a cytotoxin that encodes phospholipase A2 (PLA2) activity after interaction with the host cell cofactor superoxide dismutase 1 (SOD1). It localizes to the plasma membrane and causes direct dissolution of the plasma membrane. In addition, its phospholipase activity generates large amounts of arachidonic acid and consequently large amounts of prostaglandins PGE2 and PGI2. This means excessive inflammation, increased tissue damage and bacterial dissemination [27].

2.2.3. Chlamydia Trachomatis

Chlamydia trachomatis is the culprit of trachoma and inclusion conjunctivitis. The causative agents of trachoma are serovars A-K. Endemic trachoma is caused by serotypes A, B, Ba, and C. The culprit for neonatal conjunctivitis and adult inclusion conjunctivitis are C. trachomatis serotype D-K [31]. The inoculation of the bacterium triggers an outburst of inflammatory response in the conjunctiva. This is due to the infiltration of neutrophils, lymphocytes, macrophages, plasma cells, eosinophils, and T cells. The result of the release of cytokines and interferon is the replacement of the loose Type I stromal collagen of the area by compact Type V collagen and leads to trachomatous scarring of conjunctiva and severe vision impairment [31].

2.2.4. Bartonella Species

Bartonellosis or cat scratch disease, or cat scratch fever, is due to the gram-negative intracellular bacterium *Bartonella henselae*. Eye infection includes optic neuropathy and neuroretinitis. When the eye is the primary site of inoculation the patients are diagnosed with Parinaud oculo-glandular syndrome (infection of the conjunctiva, eyelid, and adjacent skin with regional lymphadenopathy). Chronic *Bartonella* infection provokes blurred vision, photophobia, and eye irritation. Primary inoculation leads to local infection. After a period of a few weeks, a secondary systemic reaction follows. *Bartonella* targets and enters in the CD34+ cells, mainly erythrocytes and endothelial cells. Once inside the cell, it survives in a vacuole [32, 33].

B. henselae and *B. quintana* cause chronic intraerythrocytic bacteraemia in humans. The intracellular survival protects from host defense mechanisms [34].

B. henselae pathogenesis includes a two steps procedure. The first step is pro-inflammatory and autocrine activation and proliferation of the endothelial cell, which leads to inhibition of apoptosis. The second step is paracrine activation of macrophages and epithelial cells [35]. Once the bacterium enters human macrophages, it induces the production of secreted VEGF which has paracrine action as endothelial cell mitogen. When the bacterium binds on endothelial cells, the adhesion molecules such as E-selectin and ICAM-1 are upregulated, and chemokines are produced which attract macrophages. In addition, caspases are inhibited, thus leading to enhanced endothelial cell survival [35].

The TFSS transport systems of gram-negative bacteria exist also in *B. henselae*. They are encoded by the *virB* operon which is induced when the endothelial cell is infected. As a result, several proteins are produced that trigger proinflammatory activation and anti-apoptotic protection of endothelial cells. These proteins include the *Bartonella* effector proteins (Beps) A-G and the VirD4 TFSS coupling protein [35].

The outer membrane proteins (OMPs) of *B. henselae* are important virulence factors. They express a variety of components (lipopolysaccharide, hemin-binding protein (HbpA), immunoreactive antigens and a red blood cell invasion protein (IalB). They activate endothelial cells NFκB and are important for bacterial adhesion and entry [35].

The LPS of *B. henselae* is atypical. It is lacking an O-chain polysaccharide and it contains a penta-acylated lipid A with an acyloxyacyl residue 16:0 [3-O (28:0 (27-OH))]. It has diverse and unique properties compared to the LPS of other gram negative bacteria. It is a weak stimulus of cytokine secretion, especially IL-8 and it antagonizes TLR4. It is a less potent stimulator and it acts antagonistically to the host's innate immune response [32, 33, 36].

BadA of *B. henselae* is an outer membrane protein homologous to Yersinia adhesin A (YadA), Haemophilus surface fibrils (Hsf), Moraxella surface protein A (UspA) and Haemophilus adhesin (Hia) It is part of the trimeric autotransporter adhesion (TAA) family, and causes bacterial autoaggregation. BadA activates an important mediator of angiogenesis and mediates interaction of the microorganism with extracellular matrix proteins and prevents complement activation [35, 37].

3. Conclusions

A variety of Gram positive and Gram negative bacteria are involved in ocular infections in non immunocompromised patients. These pathogens have potent virulence factors that cause severe eye damage. They provoke direct tissue damage and interact mainly with components of the innate immunity. The outcome of the battle is abolishment of the blood-ocular barrier and enhanced recruitment of inflammatory cells. For biofilm forming bacteria like *P. aeruginosa*, comprehension of their communication, survival and attack of host tissues is always a challenge. The enlightenment of the mechanisms of infection caused by these pathogens is crucial in diagnosis and treatment as they remain major causes of vision impairment.

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