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Review Article

Animal Models of Bacterial Keratitis

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Bacterial keratitis is a disease of the cornea characterized by pain, redness, inflammation, and opacity. Common causes of this disease are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Animal models of keratitis have been used to elucidate both the bacterial factors and the host inflammatory response involved in the disease. Reviewed herein are animal models of bacterial keratitis and some of the key findings in the last several decades.

1. Introduction

The human eye is composed of mucosal surfaces, such as the mucosal epithelium of the cornea, as well as interior chambers, such as the vitreous humor, that are potential targets of infection (Figure 1). Bacterial infections of the eye can range from mild, self-limiting conjunctivitis to devastating panophthalmitis involving the entire orbit. Infectious diseases of the eye not only involve the effects of bacterial colonization and virulence factors but also the host responses to the pathogen. This interplay between bacterium and host often necessitates the use of live animal models for the study of ocular infections and development of efficacious treatments.

Keratitis, a disease of the cornea, can result from direct infection with viruses, bacteria, fungi, yeast, and amoebae or from immune-related complications such as the sterile keratitis associated with Lyme disease. Bacterial keratitis can occur in a variety of mammals and can be caused by multitudes of bacterial species. The most common species that have been associated with bacterial keratitis in humans in the United States in the last 50 years or so are *Pseudomonas aeruginosa* (Figure 2) and *Staphylococcus aureus* (Figure 3). Many of the epidemiological reports from India implicate *Streptococcus pneumoniae* as the most frequent cause. The differences observed in bacterial causes of keratitis in different regions and countries have sparked an interest in climate as a possible factor in the disease.

Many manuscripts published in the first half of the twentieth century were studies of trachoma, an ocular infection caused by *Chlamydia trachomatis* characterized by conjunctivitis, swollen eyelids, and sometimes corneal haze [1–4]. Other early studies of note were focused on neonatal conjunctivitis and its treatment [5–7] as well as gonococcal and tuberculous eye infections [7, 8]. The majority of reports at that time were observational studies of clinical cases and outcomes following treatment with penicillin, sulphonamides, or newer antibiotics such as tetracyclines and macrolides [1–3, 5, 9–14]. Since that time, studies of ocular bacterial infections expanded to address the mechanisms of pathogenesis and the inflammatory response in a so-called "immune-privileged" site. Basic and clinical researches leading to newer treatments and the development of newer surgical techniques have allowed for decreases in the incidence of some infections [15–17].

2. Rabbits and *Pseudomonas aeruginosa*

The most commonly used strain of rabbits for bacterial keratitis studies is the New Zealand White rabbit, although Dutch-belted rabbits have also been used. One of the earlier techniques of inducing *Pseudomonas* keratitis in the rabbit was developed by Hessburg and coworkers [19], in which a silk suture contaminated with the bacteria was passed through the rabbit corneal stroma. This technique was later used in the examination of *Pseudomonas* proteases that had been known to cause massive destruction of the cornea [20], and for antibiotic efficacy against *P. aeruginosa* [21]. Kessler et al. [22] used the intrastromal injection model, in

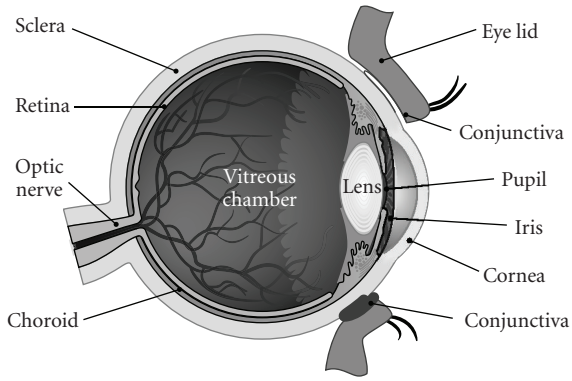

Figure 1: Diagram of the human eye (illustration by Michael K. Krider).

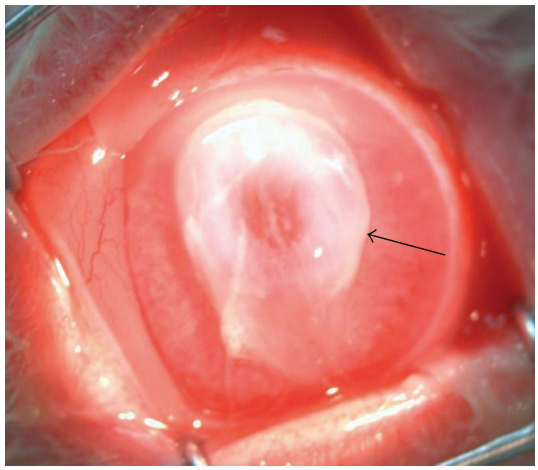

Figure 2: *Pseudomonas* keratitis in the New Zealand white rabbit 25 hours after infection. Experimental keratitis was induced by intracorneal injection of 1000 colony-forming units of a clinical urine isolate of *P. aeruginosa* according to the method of O'Callaghan's group [18]. The arrow indicates the edge of a purulent corneal ulcer.

which bacteria were injected directly within the cornea, to test the proteolytic activity of heat-killed *P. aeruginosa* in the rabbit cornea, and to examine the host response to the heat-killed bacteria. They suggested not only that the host produced a massive influx of polymorphonuclear leukocytes (PMNs) in response to the injection but also that the corneal damage could be due to host-produced proteolytic enzymes, now known to be host matrix metalloproteinases (MMPs). The influx of inflammatory cells has also been implicated as a cause of host corneal disease severity in *Pseudomonas* keratitis in the rabbit [23].

Numerous investigations using the rabbit cornea as a model for studying *Pseudomonas* virulence factors have since been published. For example, Iglewski et al. [24] injected purified exotoxin A into corneas and observed toxic effects which were neutralized by antitoxin. Thibodeaux et al. [25] transformed the genes for two *P. aeruginosa* virulence factors, elastase and alkaline protease, into a species deemed nonpathogenic in the rabbit eye, *Pseudomonas putida*. Since

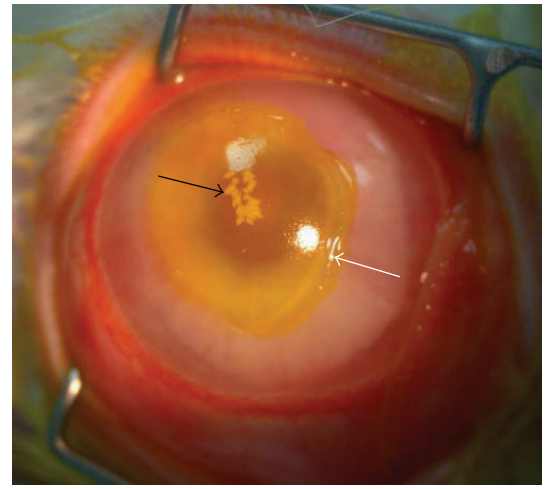

Figure 3: *Staphylococcus* keratitis in the New Zealand white rabbit 19 hours after infection. Experimental keratitis was induced by intracorneal injection of 100 colony-forming units of methicillin-resistant *S. aureus* (clinical blood specimen) according to the method of O'Callaghan's group [18]. The black arrow indicates the presence of stromal infiltration, and the white arrow indicates the edge of a large corneal epithelial erosion, which was stained with fluorescein for ease of visualization.

P. aeruginosa had been determined to increase production of other proteases when a particular protease was deleted, examining the role of a particular protease in keratitis by genetic deletion was complicated. Transformation and expression of single proteases into a nonpathogenic host such as *P. putida* allowed the investigators to determine that elastase was important for the production of corneal erosions during *P. aeruginosa* keratitis [25].

Various antibiotics and novel therapies have been tested against *Pseudomonas* in the rabbit using the intrastromal method of inoculation [18, 26–41] as well as topical inoculation [42]. Other modes of inoculation to produce keratitis by *P. aeruginosa* include topical inoculation preceded by corneal scratch [43–45], corneal abrasion [46], and mechanical removal of the corneal epithelium [42]. *Pseudomonas*-contaminated contact lenses have also been used in rabbits [47–51].

Besides antibiotic studies, rabbits have been used in a variety of immunization studies to determine whether vaccination against particular bacteria or bacterial antigens could provide protection against keratitis. Kreger et al. [52] immunized rabbits against *P. aeruginosa* lipopolysaccharide or purified proteases and then challenged their corneas with bacteria. The immunizations provided protection against the severity of *Pseudomonas* keratitis.

A corneal flap model has also been developed for *P. aeruginosa* to mimic surgical complications, such as keratitis after laser-assisted in situ keratomileusis (LASIK). Holzer et al. used Dutch-belted rabbits for several studies of diffuse lamellar keratitis following corneal flap surgery [53–56]. These studies entailed creating a corneal flap in the rabbit eye, applying *P. aeruginosa* lipopolysaccharide to the

area, and then examining the eye for inflammation both *in vivo* and by histopathology.

3. Rabbits and *Staphylococcus aureus*

S. aureus keratitis has not been reported to be achieved by topical inoculation of the rabbit cornea without additional manipulations such as the application of bacteria-soaked contact lenses; therefore, the usual method to achieve *Staphylococcus* keratitis is intracorneal injection. One of the older *S. aureus* studies was an antibiotic efficacy study with intracorneal injections of bacteria and application of topical antibiotic ointments to the eyes [57]. Kupferman and Leibowitz [58] reported the intrastromal injection model of keratitis in rabbits and showed this model to be highly reproducible. These authors later used this model to test the efficacy of topical antibiotic therapy of *S. aureus* keratitis [59] and found that *in vitro* minimal inhibitory concentration assays of the antibiotics they tested did not necessarily reflect efficacies of these drugs in the eye. Moreover, they cautioned that not all strains of *S. aureus* would necessarily have the same sensitivities as the strain used in their study. Their findings continue to be relevant to date.

The rabbit model of *S. aureus* keratitis is continually used to study antimicrobial and/or antipathological compounds [18, 30, 32–34, 36, 40, 41, 60–83] as well as host factors involved in the disease [84–87]. One of the most significant findings regarding *S. aureus* keratitis using the rabbit intracorneal model was that alpha-toxin was the major bacterial virulence factor responsible for disease severity [88–91]. Moreover, immunization against alpha-toxin was protective against *S. aureus* keratitis [92], and treatment of infected corneas with cholesterol conjugated to cyclodextrin as a means to inhibit alpha-toxin was able to significantly decrease disease severity [80].

Alternatives to the intrastromal model include soaking contact lenses in *S. aureus* prior to placement on wounded rabbit corneas [84, 93–95] and induction of a post-LASIK model of keratitis in which *S. aureus* was inoculated underneath rabbit corneal flaps that mimic LASIK surgery [96] and other corneal flap models [97–99].

4. Mice and *Pseudomonas aeruginosa*

The advantage of the rabbit as a model for bacterial keratitis is that its eyes are large like human eyes so several disease parameters can be assessed. One such scale involves the scoring of seven parameters such that a maximum disease score would be 28 [100]. Mice have smaller eyes and are often assigned disease scores up to a maximum of 4 [101] because of fewer parameters that are able to be assessed. For example, conjunctival redness and the presence of fibrin in the anterior chamber can be visualized in the rabbit. However, mice have other advantages as models for bacterial keratitis. There are numerous strains of inbred and outbred mice, a multitude of commercially available reagents with which to analyze mouse-specific factors, and the availability of genetically modified mice.

Gerke and Magliocco [102] first reported using the mouse as a model for *Pseudomonas aeruginosa* keratitis. They used different methods of corneal wounding prior to topical inoculation to achieve infection: incision (3 deep scratches that did not penetrate into the anterior chamber), a 2 mm surface scratch, and needle puncture. They also performed direct intrastromal injection of bacteria and determined that the incision and injection modes were most consistent with respect to pathology. To date, the majority of mouse corneal inoculations with *P. aeruginosa* have been by topical scratch of the cornea followed by dropping the bacteria onto the eye.

Mice have been used for immunization studies for the possible development of alternative prophylaxes and therapies of *P. aeruginosa* keratitis. In one such study, mice were immunized with whole *P. aeruginosa* cells by intraperitoneal or oral route, and their corneas were subsequently challenged [103]. Monovalent and multivalent vaccines were used, and it was found that intraperitoneal immunization with the multivalent vaccine worked the best. These authors pointed to another report that was published in 1927 that tested *Pseudomonas* keratitis *in vivo* and alluded to the potential for protection against keratitis by vaccination [104].

Immunizations of mice with *Pseudomonas aeruginosa* protease and elastase toxoids, as well as the common O-antigen, were able to protect against keratitis [105, 106]. Moreover, passive administration of rabbit antisera to mice [52, 106], or passive immunization of mice with monoclonal antibodies specific for *Pseudomonas* outer membrane proteins [107], was able to successfully treat *Pseudomonas* keratitis. Zaidi et al. [108] demonstrated protection against *Pseudomonas* keratitis by active and passive immunization of live attenuated bacteria in C3H/HeN mice.

Mice have also been used in therapy efficacy studies of antibiotics and other potential antimicrobial compounds [109, 110]. Hobden's group recently showed that nona-D-arginine amide was bactericidal to *P. aeruginosa* and exerted anti-inflammatory effects in the infected mouse cornea [111, 112]. Kumar et al. [113] applied flagellin, a bacterial flagellar protein and an agonist of toll-like receptor 5 (TLR5), to the corneas of B6 mice and found that it protected the corneas from severity of disease and bacterial loads. Human tear fluid has also been found to protect against *Pseudomonas* keratitis in C57/BL6 mice [114]. Other novel therapies of interest using this model are caspase-1 inhibitor [115], silencing RNA molecules [116, 117], interleukin-6 (IL-6) [118], Spantide 1 [119], chemokine antibodies [120], cyclodextrin [121], and topical drops of alginate antibody [122].

Other studies of note involving *Pseudomonas* in the mouse model of keratitis include findings regarding the invasive potential of *P. aeruginosa*. Fleiszig et al. [123] first demonstrated that some strains of *Pseudomonas* were able to invade mouse corneal cells *in vivo* and subsequently showed that *P. aeruginosa* multiplied within the cells [124]. Invasive strains were found to produce type III secreted exoproteins that enabled internalization of the bacteria into mouse corneal epithelial cells [125]. Fleiszig's group has also examined alternative methods of corneal infection in the mouse. One such method involved a modification of the topical scratch in which the epithelium was allowed to

partially heal after the scratch before inoculation with *P. aeruginosa* [126]. In contrast to the invasive strains, cytotoxic strains have been shown to secrete several proteases that damage corneal tissue or induce the host immune response in the mouse model [127–130].

Prior to the development and use of transgenic animal models, studies on the host involvement in keratitis were often focused on the differences between mouse strains, elderly versus young mice, or drug-induced alterations in animals. Hazlett et al. [131] showed that administration of cyclophosphamide to mice caused *Pseudomonas* corneal infection to spread and become systemic, confirming previous suspicions that immunocompromised cancer patients were at a higher risk for systemic infection following *Pseudomonas* ocular infections. This same research group also examined the differences in pathogenicity of *Pseudomonas* keratitis in a strain of mouse that was determined to be "susceptible" to corneal infection (C57BL/6J, or T helper cell type 1 responder) and a strain determined to be "resistant" to corneal infection (DBA/2J) [132]. The susceptible strain was shown to have a decreased immune response to the bacteria as measured by a reduction in inflammatory cells compared to the resistant strain. Aged outbred mice with decreased PMN response to corneal infection with *P. aeruginosa* were also suggested to be less able to have restored corneal clarity than their young counterparts due to delayed bacterial clearance [133, 134]. However, the presence of inflammatory cells has also been implicated as a cause of host corneal disease severity in *Pseudomonas* keratitis in the mouse [135–137]. These studies of general inflammatory responses to *Pseudomonas* keratitis, plus numerous others including analyses of cytokine expression, host MMP expression, and T-cell-mediated immune responses, have been followed by many studies with other species of bacteria as well as other strains of mice.

5. Mice and *Staphylococcus aureus*

O'Callaghan's group was the first to report a mouse model of *S. aureus* keratitis and showed that, similar to *Pseudomonas* keratitis, certain strains of mice were susceptible (BALB/c and A/J) to infection whereas others were resistant (C57BL/6) [138]. These investigators also showed that aged mice, like humans, were more susceptible to severe keratitis by *S. aureus* than young mice [139], and that *S. aureus* alpha-toxin was responsible for much of the damage observed in the disease [140]. Other researchers have made slight modifications to the mouse model, such as breaking up the tear film prior to inoculation [141], or using a trephine for corneal scarification and inoculating with dead bacteria to observe inflammation [142].

6. Genetically Modified Mice

The advent of genetic modification of rodents has been revolutionary in examinations of the role of the host in bacterial keratitis. Mice in which specific genes have been deleted, altered, or alternatively controlled have been used in infection models to determine the host factors involved in disease. Most of the studies to date have used mice deficient in cytokines and other immune factors, such as toll-like receptors (TLRs). TLRs are present on or in host cells such as macrophages and epithelial cells and respond to pathogen-associated molecular patterns (PAMPs), triggering a signaling cascade that ultimately results in up- or down-regulation of inflammatory molecules such as cytokines.

Pseudomonas keratitis studies using genetically modified mice have yielded information regarding the host response to this bacterium. Cole et al. [143] used interleukin-10 (IL-10) deficient mice to show that IL-10 was important in controlling inflammation in the cornea in response to *P. aeruginosa*. This group also used interleukin-4 (IL-4) deficient mice [144] and interleukin-6 (IL-6) deficient mice [145] to show a similar effect for IL-4 and IL-6 in *S. aureus* keratitis. Another study by Willcox and colleagues with mice lacking the gene for CXC chemokine receptor 2 showed that the host CXC chemokine receptor 2 was crucial for infiltration of PMNs into the eye and subsequent bacterial killing [146].

Genetic knockouts other than specific cytokines and chemokines have been investigated. Huang showed the importance of TLR4 in host resistance to *Pseudomonas* [147]. Likewise, mice deficient in MyD88, a TLR signaling molecule, had reduced immune cell recruitment to the eye in response to *P. aeruginosa* but had higher bacterial burden and developed systemic infections [148]. Hazlett's group used caspase-1 deficient mice to show that caspase-1 was important for the inflammation observed during keratitis [149] and matrix metalloproteinase-9 (MMP-9) deficient mice to show that MMP-9 assists *Pseudomonas* keratitis by degrading corneal collagen and upregulating proinflammatory cytokines [150]. These investigators also recently showed a role for Fas ligand in the disease [151].

Recently, Pearlman's group [152] found that corneal macrophages were the predominant cell type in the cornea that expressed three TLRs of interest. The overall finding of the study was that activation of specific TLRs in the cornea by *P. aeruginosa* resulted in transcription of chemokines responsible for neutrophil recruitment to the cornea, and that this recruitment was responsible for both the inflammatory damage observed in the eye as well as the killing of the infecting bacteria. Likewise, macrophage migration inhibitory factor (MIF), when deleted from the mouse genome, results in a severe inflammatory response to *Pseudomonas* in the cornea [153]. Peptidoglycan recognition proteins, which are similar to TLRs in that they recognize PAMPs, have also been found to be important for innate immunity to *Pseudomonas* keratitis [154]. A role for host defensins has also been addressed for *P. aeruginosa* keratitis using cathelicidin deficient mice [155].

7. Other Animals

In 1975, Davis and Chandler reported an improved method of examining and quantitating *Pseudomonas* keratitis using the guinea pig as a model [156]. One of the foci of this report

was the use of intracorneal injection of bacteria so that the inoculum would be as precise as possible. These investigators also used a scoring system for the disease severity and were able to quantitate the bacterial load from the corneas by plating dilutions of infected homogenized corneas onto bacterial growth medium. This method was determined to be highly reproducible and has since been used by numerous investigators, whether in guinea pigs or other animals such as rabbits. Davis and colleagues also used the guinea pig model for *S. aureus* keratitis [157].

Guinea pigs have also been used to study the role of antibacterial or anti-inflammatory agents in *Pseudomonas* keratitis [158–160] and contact-lens-related keratitis caused by *P. aeruginosa* [161]. Contact lenses were contaminated with the bacteria and then worn by guinea pigs for up to 48 hours to simulate extended contact lens wear by humans. The animals developed keratitis, or in some cases, a condition called contact-lens-induced acute red eye (CLARE) [161]. This research group has also used the guinea pig contact lens model to analyze the protective effect of melimine coating of contact lenses against *S. aureus* and *P. aeruginosa* [95]. A similar method to examine *P. aeruginosa* contamination of contact lenses designed for orthokeratology was reported using cats [162].

Rats have also been used in bacterial keratitis studies, and it is not apparent whether the strain of rat is important because different strains were successfully used for different reports. The method of topical corneal scratch and inoculation showed that the rat lacrimal gland responds to *Pseudomonas* corneal infection [163]. The intrastromal injection model has been used with rats to test whether amniotic membrane transplantation could aid in corneal healing following infection with *S. aureus*, and this technique was found to be useful as adjunct therapy to antibiotics [164]. Another infection model for rats has been the infection by the wearing of contaminated contact lenses [165]. A recent investigation determined that rats developed *Pseudomonas* keratitis after wearing contaminated contact lenses, and that transfer of the lenses to naïve rats caused transfer of the disease [166]. Other studies include antibiotic efficacy studies [167–169] and analysis of vitamin A deficiency and the corresponding susceptibility to *Pseudomonas* keratitis [170].

Mammals other than humans, in addition to being used as models, are potential victims of bacterial keratitis. For example, infectious bovine keratoconjunctivitis, usually caused by *Moraxella bovis*, is a major health problem in cattle. *Pseudomonas*, to name one genus, is a cause of keratitis in horses and dogs. Cats can also acquire bacterial keratitis, although less frequently than dogs. Numerous other mammals can develop keratitis, underscoring the prevalence of bacteria able to cause pathogenesis in the eye.

8. Limitations of Animal Models

Animals, particularly rabbits and mice, have been demonstrated to be useful models for studying bacterial keratitis. Some disadvantages exist, however, when using species that have characteristics different from humans. One of the most obvious differences is that most of the animals used as models are inbred. The advantage of using inbred animals is experimental consistency; however, inbred animals do not represent the human population as well as outbred animals. Less obvious differences are specific anatomical features, tissue composition, and various functions of ocular components in animals and humans. Humans have a corneal size of approximately 11 mm in diameter, whereas rabbits and mice have corneal sizes of about 13 and 2.2–3.5 mm, respectively [171, 172]. Corneal thickness is greater for humans than rabbits and mice, and the blink interval for humans is approximately 2.8 seconds whereas the interval for rabbits and mice is over 30 seconds [171]. Rabbits have a nictitating membrane whereas humans and mice do not. The arrangement of corneal collagen [171] and the properties of corneal epithelial cells [173] are different between rabbits, mice, and humans, which could produce alternate reactions of the cornea to invading pathogens. Likewise, the corneal epithelial basement membrane in humans is a network of fibers resembling a bird's nest, whereas that of the rabbit's is straight and flat. The anterior, collagen-rich banded portion of Descemet's membrane, which is the basement membrane of the corneal endothelium, appears organized in a pattern in humans but disorganized in rabbits [174]. Descemet's and Bowman's membranes are also substantially thinner in rabbits and mice than in humans [175]. Mouse corneas have a higher ratio of corneal epithelial cells to stroma than humans and more cell layers in the corneal epithelium [172]. Recently, confocal microscopy has detected more differences between species, such as subcellular differences between keratocytes of rabbits and mice [176]. Corneal proteins are also differentially present; for example, mice have abundant amounts of actin in their corneal epithelial cells whereas rabbits and humans do not [173]. All of these anatomical differences, as well as the blink intervals, have an effect on bacterial adherence and possible invasion, susceptibility to bacterial enzymes and other virulence factors, and availability of host defense molecules in the tear film.

Features outside of the cornea can account for discrepancies between the way humans and animals respond to ocular bacterial infections. The lacrimal gland, which is involved in tear secretion, is different for humans, rabbits, and rodents [177]. Compounding this difference is the vast gap in blink intervals between humans, rabbits, and mice as described above [171]. Not only is the architecture of the lacrimal gland different between these species, but also is function. For example, lysozyme is a paramount protein produced by the human lacrimal gland but is not as pronounced in rabbits and mice. This difference is important to note because lysozyme is an enzyme that damages bacterial cells walls. Other differences in lacrimal gland functions are electrolyte secretion, production of lipid-binding proteins, secretory IgA and secretory component secretion, and cytokine and growth factor secretion [177]. Many ocular surface mucins in humans terminate in sialic acids whereas those from rabbits terminate in 1-2 fucose or alpha-1-3 N-acetylgalactosamine [178]. Since bacteria produce enzymes which cleave specific residues in the host, studies of the effects of bacterial

virulence in animals could yield results that necessitate cautious interpretation.

9. Conclusion

Infection of the cornea with bacterial pathogens such as *P. aeruginosa* and *S. aureus* can result in loss of vision due to the damage caused by the disease. This damage is attributed not only to bacterial factors but also to host immune factors. Therefore, models of bacterial keratitis have been developed in animals to analyze the disease from both the bacterial aspect and the host aspect. Despite the differences between human and animal characteristic that are involved in bacterial keratitis, the use of animal models has contributed to the understanding of this disease and the discovery of more effective treatments that may prevent corneal damage.

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