

# A Review on Treatment of Keratitis Infection

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**Abstract—** The Most Significant Challenge Faced by Modern Pharmacologists and Formulation Scientists Is Effective Ocular Drug Delivery. Among The Available Routes, Topical Eye Drops Remain the Most Convenient and Patient-Friendly Method, Particularly for Managing Diseases of The Anterior Segment. Recently, A Number of Biocompatible and Effective Technologies Have Been Developed to Treat Ocular Diseases Affecting Both the Anterior and Posterior Regions of The Eye. Infectious Keratitis Is the Fifth Most Common Cause of Blindness Worldwide. Contact Lens Wear, Ocular Injuries, And Ocular Surface Diseases Are the Primary Risk Factors. The Most Frequent Causative Organisms Are Species of Staphylococcus, Pseudomonas Aeruginosa, Fusarium, Candida, And Acanthamoeba.

Keratitis Refers to Inflammation of the Cornea, Which Is the Transparent, Dome-Shaped Front Part of The Eye. The Cornea Normally Allows Clear Visualization of the Iris and Pupil. Although Keratitis Can Be Readily Diagnosed, Identifying the Underlying Cause Is Often Challenging. Results From Direct Microscopic Examination and Culture Are Commonly Inconclusive, Requiring Clinicians to Make Treatment Decisions Based on Clinical Findings. Management Of Infectious Keratitis Depends on The Specific Causative Organism Involved. Keratitis Can Be Caused by Bacteria, Fungi, Viruses and Amoebae Infecting the Cornea. This Review Studies the Standard Therapeutic Agents for Treating Infectious Keratitis, Including Broad-Spectrum Empiric Antibiotics for Bacterial Keratitis (BK). It Also Focuses on The Systematic Study of the Anatomy of The Eye.

**Index Terms—** Eye, Ocular drug delivery system, Keratitis infection, Bacterial keratitis, Anterior segment disease, Keratitis treatment.

## I. INTRODUCTION

The eye is a highly specialized and intricate organ characterized by unique anatomical and physiological features. Structurally, it is divided into two principal segments: the anterior segment and the posterior segment. The anterior segment constitutes nearly one-

third of the total ocular volume, whereas the posterior segment forms the remaining two-thirds<sup>1</sup>. The anterior segment consists of the cornea, iris, ciliary body, pupil, and lens. The posterior segment includes the vitreous humor, sclera, choroid, and retina. Keratitis is a common disease that occurs in the anterior segment.<sup>2</sup> Dry eyes, cataracts, glaucoma, inflammatory and infectious diseases. Age-related macular degeneration (AMD), diabetic retinopathy macular edema (DME), proliferative vitreoretinopathy (PVR), and cytomegalovirus (CMV) are among the conditions that affect the posterior segment<sup>3</sup>.

Visual impairment resulting from various ocular disorders has a profound impact on quality of life. Cataract is the leading cause of blindness globally, accounting for approximately 40–60% of blindness cases worldwide.<sup>4</sup> Early onset of cataracts is associated with mutations in  $\alpha$ ,  $\beta$ , and  $\gamma$  crystallin proteins and their related genes. Glaucoma is a progressive optic neuropathy characterized by elevated intraocular pressure (IOP), which can result in irreversible blindness at advanced stages. Additionally, vision loss is often linked with aging, diabetes, and fungal infections. Other ocular disorders include age-related macular degeneration (AMD), diabetic retinopathy (DR), retinoblastoma, and fungal keratitis. Recent studies estimate that nearly 76 million individuals suffer from glaucoma, 196 million from AMD, and 92.6 million from diabetic retinopathy<sup>5</sup>.

Infectious keratitis is a corneal infection that can also be referred to as an infectious corneal ulcer or opacification<sup>6</sup>. Keratitis is a corneal inflammation characterized by edema, inflammatory cell infiltration, and ciliary congestion. It is linked to both infectious and non-infectious diseases, which can be systemic or limited to the ocular surface<sup>7</sup>. The cornea is located at the front of the eye's dome-shaped opening. The iris and pupil of a person's eye are visible through the cornea, which is typically clear. It is simple to

diagnose keratitis; however, determining the cause is not always easy. Direct microscopy and culture results are frequently unremarkable, and the patient must be selected on clinical grounds<sup>8</sup>. Infectious keratitis (IK) not only leads to visual impairment but also adversely affects the quality of life (QOL) of affected individuals. A study conducted in Uganda demonstrated that IK compromises both vision-related QOL,<sup>9</sup> primarily due to loss of vision, and health-related QOL, largely as a result of pain during the acute phase of the disease<sup>10</sup>.

Drug delivery to the eye plays a vital role in modern medical treatment. Ophthalmic drug delivery remains one of the most complex and demanding areas for pharmaceutical scientists. Because of the eye's distinctive anatomy, physiology, and biochemical composition, it exhibits strong protective mechanisms against foreign substances. One of the main challenges in ocular drug delivery is overcoming these natural defense barriers without inducing irreversible tissue injury.<sup>11</sup> Continuous advancements in sensitive diagnostic tools and the development of innovative therapeutic agents have significantly contributed to the enhancement of ocular drug delivery systems with improved therapeutic effectiveness<sup>12</sup>.

## II. PHYSIOLOGICAL AND STRUCTURAL BARRIERS OF THE EYE:

A number of dynamic or static tissue barriers, including the cornea barrier, conjunctiva barrier, blood-aqueous barrier, and blood-retina barrier (BRB), may be encountered by the medication as it travels through the tear film and reaches its target<sup>3</sup>

- Tear Film Barrier
- Corneal Barrier
- Conjunctival Barrier
- Blood–Aqueous Barrier
- Blood–Retinal Barrier

For patients to gain maximum therapeutic effect while minimizing side effects, it is imperative that eye drops are instilled correctly. The most important steps in proper drop technique include instillation of one drop into the pocket formed by gently pulling down the lower eyelid, not touching the bottle to the eye, and eye closure and nasolacrimal occlusion after administration to reduce systemic absorption. If eye drops are instilled improperly,<sup>13</sup> it may decrease the therapeutic response, enhance systemic side effects and cause harm to the eye (i.e. bottle contamination or ocular trauma by touching the eye with the bottle tip)<sup>14</sup>.

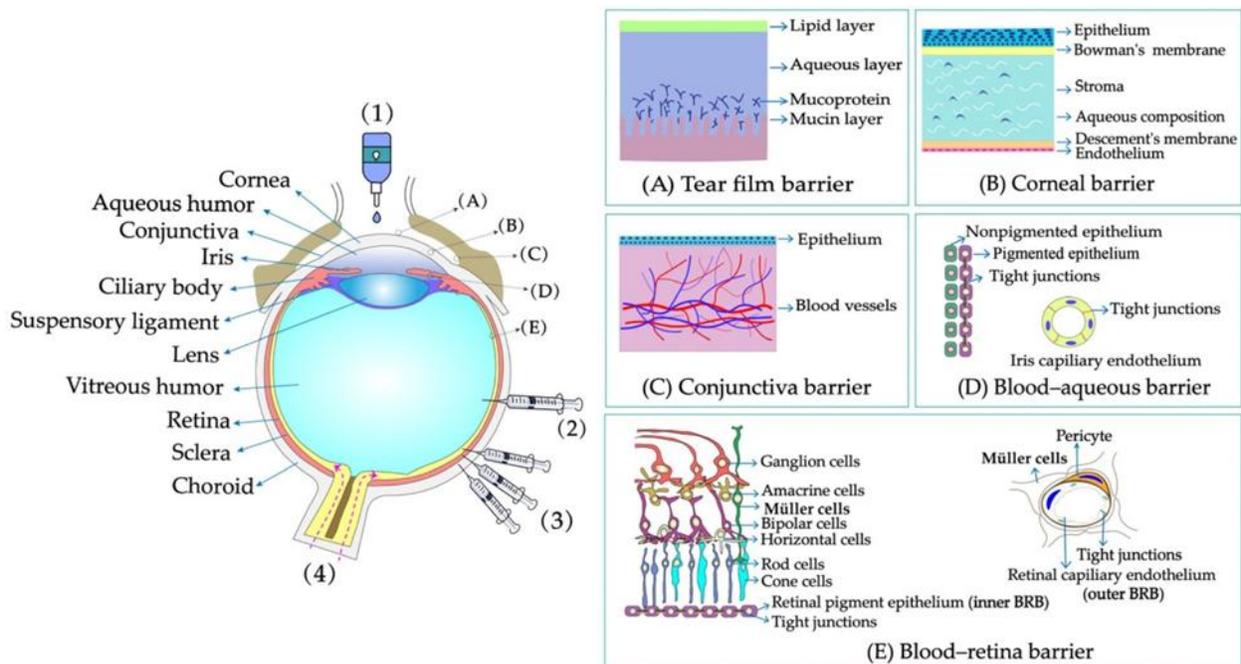


Figure 1

Figure 1 illustrates the anatomical structures of the eye, various routes of ocular drug delivery, and the main barriers affecting drug transport. From the outermost to the innermost layers, the ocular structures include the conjunctiva, cornea, aqueous humor, iris, ciliary body, lens, suspensory ligament, vitreous humor, sclera, choroid, and retina. The routes of ocular administration comprise 1) topical application, 2) intravitreal injection, 3) periocular injection, and 4) systemic administration. The principal ocular barriers include:<sup>15</sup>

(A) the tear film barrier, consisting of lipid, aqueous, and mucin layers, which protects against the entry of foreign substances;

(B) the corneal barrier, composed of the epithelium, hydrophilic stroma, and a single endothelial layer, which restricts drug penetration into the anterior chamber;

(C) the conjunctival barrier, a vascularized mucous membrane that facilitates systemic drug absorption through capillaries;

(D) the blood–aqueous barrier (BAB), formed by tight junctions in the iris and ciliary body, preventing drug passage from the systemic circulation into the aqueous humor; and

(E) the blood–retinal barrier (BRB), which consists of tight junctions in the retinal pigment epithelium and retinal blood vessels, limiting systemic drug entry into the retina and vitreous humor<sup>3</sup>.

### III. THE ANATOMY OF THE EYE

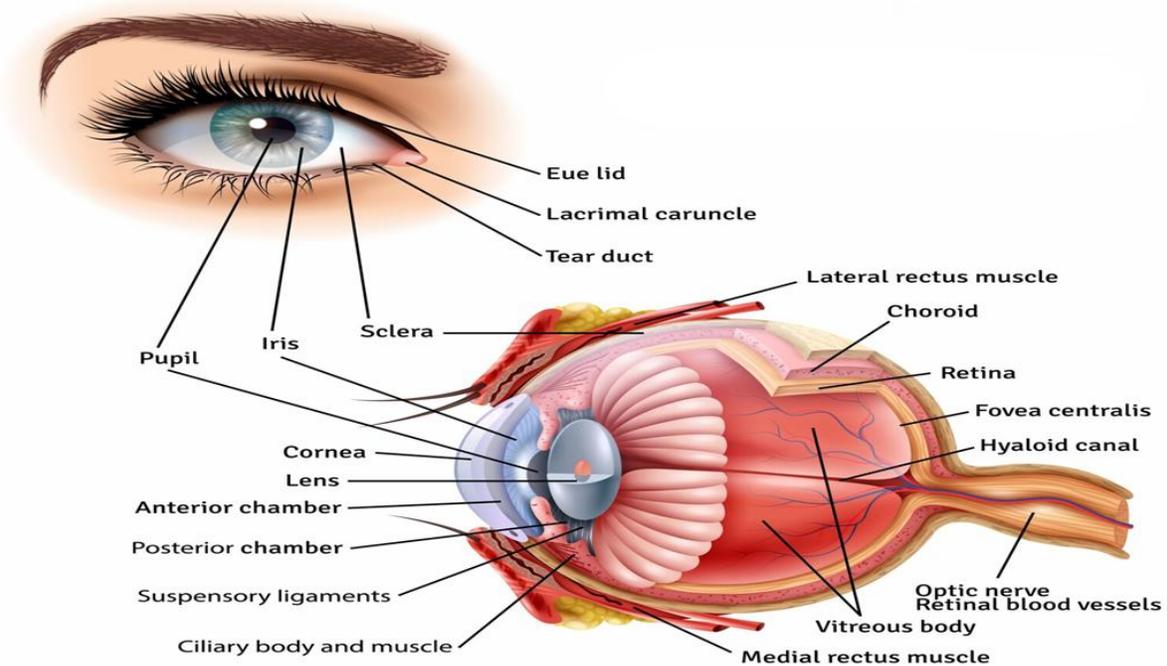


Figure 2

The human eye, remarkable in its structure and precision, serves as the primary organ of vision.<sup>16</sup> The eyeball is nearly spherical and measures about one inch in diameter. It contains several specialized parts that function together to enable sight. The eye is made up of multiple layers and internal components, each performing specific roles. A detailed explanation of each part is provided below:

#### A. Sclera

The sclera, commonly known as the white part of the eye, is a strong, protective outer layer that forms the outer covering of the eyeball. It is a dense, fibrous tissue that helps preserve the rounded shape of the eye. The sclera is thicker at the posterior region and becomes thinner toward the anterior region.<sup>17</sup>

#### B. Conjunctiva

The conjunctiva is a thin, clear mucous membrane that lines the inner surface of the eyelids and covers the front one-third of the eyeball. These two regions are known as the palpebral and bulbar conjunctiva. It consists of an outer epithelial layer and an underlying connective tissue layer called the stroma. Along with the cornea, the conjunctiva forms the exposed surface of the eye and is covered by the tear film. It plays a role in tear production by secreting fluids, electrolytes, and mucins.<sup>18</sup>

#### C. Cornea

The cornea is a tough, transparent, dome-shaped structure located at the front of the eye. In adults, its surface has a curvature radius of approximately 8 mm. It plays a major optical role by bending incoming light, which then passes through the pupil and lens to reach the retina. The cornea does not contain blood vessels and receives nutrients from capillaries surrounding its edges. It is richly supplied with sensory nerves from the ciliary nerves, making it extremely sensitive.<sup>19</sup>

#### D. Aqueous Humour

The aqueous humour is a clear, watery fluid found in the front chamber of the eye. It occupies the space between the cornea and the lens, referred to as the anterior chamber. This slightly alkaline salt solution contains small amounts of sodium and chloride ions. It is continuously produced by the ciliary processes and flows from the posterior chamber through the pupil into the anterior chamber. It exits through the trabecular meshwork and uveoscleral pathways. Schlemm's canal is a circular drainage channel located at the junction of the cornea and sclera that carries aqueous humour into the bloodstream. In humans, the aqueous humour turnover rate is about 1–1.5% per minute, with a production rate of roughly 2.5  $\mu\text{L}/\text{min}$ . Outflow occurs through pressure-dependent (trabecular) and pressure-independent (uveoscleral) routes.<sup>20</sup>

#### E. Pupil

The pupil appears as the dark central opening of the eye and is the circular space within the iris that allows light to enter. The size of the pupil changes in response to light intensity through the pupillary or light reflex.

#### F. Iris

The iris is a thin, circular, muscular structure located between the cornea and the lens. It functions as a

movable diaphragm that controls pupil size and regulates the amount of light entering the eye. The iris determines eye color, which may vary from blue and green to brown, hazel, or grey.

#### G. Ciliary Muscle

The ciliary muscle is a circular band of smooth muscle found in the middle layer of the eye. It controls the focusing ability of the eye for near and distant objects and also helps regulate the flow of aqueous humor into Schlemm's canal. It receives both parasympathetic and sympathetic nerve supply. When the ciliary muscle contracts or relaxes, it changes the curvature of the lens. Relaxation allows focusing on distant objects, while contraction enables near vision.

#### H. Lens

The lens is a clear, flexible structure enclosed within a thin capsule and is positioned behind the pupil. It is surrounded by the ciliary muscles and plays a critical role in bending light after it passes through the cornea. The lens focuses light onto the retina by changing its shape through a process known as accommodation, which is controlled by the contraction and relaxation of the ciliary muscles.

#### I. Vitreous Humor

The vitreous humor, or vitreous body, occupies the large chamber behind the lens and makes up about 80% of the eye's volume. It is a transparent, gel-like substance enclosed in the delicate hyaloid membrane and helps maintain the shape of the eyeball.

#### J. Retina

The retina is the light-sensitive layer located at the posterior part of the eye. It acts as the surface where images are formed once light has passed through the cornea, aqueous humour, pupil, lens, and vitreous humor. In addition to receiving images, the retina converts light into electrical nerve signals. It contains rods and cones that detect light and transmit visual information to the brain via the optic nerve<sup>21,22</sup>

It has shown that histologically retina have several layers;

1. Internal limiting membrane
2. Nerve fiber layer
3. Ganglion cell layer
4. Inner plexiform layer (IPL)
5. Inner nuclear layer
6. Outer plexiform layer

7. Outer nuclear layer
8. External limiting membrane
9. Photo-receptor layer (rods and cones) &
10. Retinal pigment epithelium (RPE)<sup>23</sup>.

#### K. Macula

The macula is the central region of the retina and contains a high density of photoreceptor cells. This allows for detailed central vision, enabling tasks such as reading fine print. At the center of the macula lies the fovea, which is responsible for the sharpest visual acuity.

#### L. Choroid

The choroid is a thin, dark brown, highly vascular layer situated between the sclera and the retina. It absorbs excess light to prevent image blurring and supplies oxygen and nutrients to the outer layers of the retina. The choroid has one of the highest blood flow rates in the body and is loosely attached to the sclera by the lamina fusa.

#### M. Nerve

The optic nerve is composed of more than one million nerve fibers and carries visual signals from the retina to the brain for interpretation. The point where the optic nerve exits the eye is known as the optic disc, which is visible on the retinal surface<sup>24</sup>.

### IV. KERATITIS

Keratitis is an inflammation of the cornea. This condition's etiology could be infectious or non-infectious<sup>21</sup>. Infectious Keratitis (IK) is a serious, sight-threatening corneal disease caused by bacteria, viruses, fungi, or protozoa. It is the fifth leading cause of blindness worldwide. In the United States and other developed countries, studies of IK epidemiology estimate 2.5-27.6 per 100,000 people per year. However, in developing countries, the incidence has been reported to be as high as 113-799 per 100,000 people. Despite these large numbers, it is widely acknowledged that the true incidence of IK is likely much higher due to reporting limitations<sup>23,25</sup>.

### V. ETIOLOGY AND PATHOGENESIS.

IK is the fifth leading cause of blindness worldwide. Bacteria, fungi, viruses, and Acanthamoeba are common pathogens. While bacterial agents are the

primary cause of IK, fungal and viral infections have increased significantly in recent years.

Acanthamoeba keratitis (AK) is caused by the Acanthamoeba organism, a free-living protozoan that acts as an opportunistic parasitic pathogen. AK is a rare and frequently chronic form of IK that poses significant challenges in terms of accurate diagnosis and effective treatment<sup>14,26</sup>.

### VI. BACTERIAL KERATITIS

The eye is relatively resistant to microorganisms, and most pathogens cannot pass through the intact cornea because the eye contains a diverse collection of antimicrobial factors, particularly in the tear film, which protects the cornea from infection. However, if there is any structural damage or failure in the defense mechanisms that keep the entire surface intact, opportunistic infections can easily develop, resulting in microbial keratitis. Microbial keratitis is characterized as a defect in the corneal epithelium with stromal inflammation caused by microorganisms. Symptoms appear suddenly, causing pain and putting one's vision at risk, necessitating prompt diagnosis and treatment.

Bacterial keratitis is an ocular infection that can cause to severe visual impairment<sup>27</sup>. In the United States, bacterial keratitis is most commonly linked to contact lens wear. Severe infections may progress rapidly and can result in irreversible vision loss, sometimes necessitating corneal transplantation<sup>28,29</sup>.



Figure 3

## VII. ETIOLOGY AND PATHOGENESIS OF BACTERIAL KERATITIS.

Bacterial keratitis (BK) usually develops rapidly after exposure and may result in extensive corneal injury and possible blindness. Its severity is increased by risk factors such as contact lens use in developed countries and ocular trauma in developing regions. Worldwide, Gram-positive organisms particularly *Staphylococcus* species are the most frequent causes, whereas Gram-negative bacteria such as *Pseudomonas aeruginosa* predominate in some geographic areas<sup>24,30</sup>

## VIII. TESTS FOR DIAGNOSIS

A diagnosis of BK is made based on the patient's history and microbiology tests. Before beginning antimicrobial therapy, all corneal ulcers should be cultured to determine the etiology and antibiotic susceptibility. The American Academy of Ophthalmology (AAO), BK preferred practice pattern, suggests smears and/or cultures in the following situations.

- Large & central corneal infiltrate and/or substantial stromal involvement or melting
- Persistent infection that does not improve with broad-spectrum antibiotic treatment
- Corneal surgery history
- Unusual clinical signs of mycobacterial, amoebic, or fungal keratitis
- Several corneal infiltrates<sup>23</sup>.

## IX. TREATMENT

### Antibiotics

In order to prevent major complications like vision impairment or even eye loss, adequate treatment for BK is essential. Since culture results can take more than 48 hours and the infection can spread quickly without treatment, the initial course of treatment is typically empirical<sup>6,11</sup>

Topical antibiotics remain the primary treatment for bacterial keratitis. When selecting an antibiotic regimen, clinicians consider a variety of factors such as broad-spectrum coverage, toxicity, availability and cost, as well as pathogen epidemiology and resistance patterns by region. Indeed, a recent international survey of cornea specialists discovered that concerns

about several of these factors were associated with antibiotic selection. A recent Cochrane-style review of high-quality, randomized, controlled clinical trials on the use of topical antibiotics to treat bacterial keratitis found 16 trials that compared two or more topical antibiotics for at least 7 days. The authors found no significant difference in the relative risk of treatment success, defined as complete corneal re-epithelialization, or cure time. While aminoglycoside-cephalosporins were associated with a higher risk of minor adverse events such as ocular discomfort or chemical conjunctivitis than fluoroquinolones, there was no difference in serious complications.

Although bacterial ulcers are typically treatable with available topical antibiotic drops, an increase in antibiotic-resistant infections such as methicillin-resistant *Staphylococcus aureus* (MRSA) in North America has raised concerns. Every year, the United States Center for Disease Control (CDC) estimates that 2 million people become infected with drug-resistant microbes. Approximately 80% of ocular MRSA isolates in the United States have been found to be resistant to fluoroquinolones, the most commonly prescribed antibiotic class. In the Steroids for Corneal Ulcer Trial (SCUT), in vitro susceptibility was linked to clinical outcomes. Therefore, corneal culture and sensitivity testing is recommended for all corneal ulcers. Assessing treatment response is critical, and if the patient appears to be worsening, switching to fortified broad-spectrum antibiotics if fluoroquinolone monotherapy was used initially. On the other hand, if the initial therapy was with a broad-spectrum fortified antibiotic, toxicity from the drops can become the most important factor affecting healing, and reducing therapy is frequently recommended.

Even when bacterial ulcer pathogens are susceptible to topical antibiotics, the clinical outcome can be poor due to irregular astigmatism and corneal opacity. Investigating factors that reduce the inflammatory response to infection that causes corneal melting and subsequent scarring may have the greatest impact on clinical outcomes in bacterial keratitis<sup>12,31</sup>

## X. CONCLUSION

Infectious keratitis remains a leading cause of visual impairment and preventable blindness worldwide, posing a significant clinical and therapeutic challenge

despite advances in ophthalmology. While the eye's complex anatomy and strong protective barriers are necessary for maintaining ocular integrity, they severely limit drug penetration and therapeutic efficacy, especially with conventional topical formulations. Topical eye drops remain the most popular and patient-friendly route of administration for anterior segment diseases such as bacterial keratitis, despite their low bioavailability and rapid precorneal drug loss.

This review emphasizes the importance of understanding ocular anatomy, physiological barriers, and disease pathophysiology in managing infectious keratitis. Bacterial keratitis, in particular, necessitates early clinical diagnosis and empirical treatment to avoid rapid disease progression and irreversible vision loss. While broad-spectrum topical antibiotics remain the cornerstone of therapy and are generally effective, the increasing prevalence of antimicrobial resistance emphasizes the importance of microbiological investigation, culture, and sensitivity testing wherever possible to guide rational therapy. Overall, improving outcomes in infectious keratitis will require a combination of early diagnosis, appropriate antimicrobial selection, proper instillation techniques, and ongoing innovation in ocular drug delivery systems. The creation of advanced, biocompatible formulations capable of increasing corneal residence time and drug penetration holds the promise of more effective and targeted therapy, ultimately lowering the global burden of keratitis-related visual disability.

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