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Review Article

Non-healing corneal ulcers: Diagnostic approaches, and emerging therapeutic strategies

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Abstract

Non-healing corneal ulcers, also referred to as refractory or persistent epithelial defects, represent a significant challenge in ophthalmic practice due to their complex etiology and resistance to conventional therapies. These ulcers arise from a multitude of infectious and non-infectious factors, including microbial infections, autoimmune diseases, neurotrophic keratitis, and iatrogenic causes, leading to prolonged inflammation, stromal degradation, and impaired epithelial regeneration. This review provides a comprehensive overview of the anatomy and physiology of the cornea, elucidating the pathophysiological mechanisms underlying non-healing ulcers. It further explores the diagnostic modalities employed to identify these ulcers and differentiates them from other corneal pathologies. Current treatment strategies, encompassing medical management, surgical interventions, and barrier therapies, are critically analyzed. Special emphasis is placed on emerging therapeutic innovations such as stem cell therapy, tissue engineering, gene therapy, nanotechnology-based drug delivery systems, and artificial corneas, which offer promising avenues for effective management of refractory cases. The review also highlights the persistent challenges in treating these ulcers, including antibiotic resistance, delayed diagnosis, and management of chronic or recurrent cases. Finally, it outlines future directions and recommendations for improving patient outcomes through multidisciplinary care, biomarker development, and continued clinical research in this evolving field.

Keywords: Corneal ulcer, non-healing ulcer, Refractory epithelial defect, Stem cell therapy, Gene therapy, Nanotechnology, Keratoprosthesis, Corneal regeneration, Biomarkers, Antibiotic resistance.

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1. Introduction

The cornea, a transparent, avascular structure, plays a pivotal role in vision by refracting light onto the retina and acting as a protective barrier against environmental pathogens. Maintaining corneal integrity is vital for preserving vision and ocular health. However, corneal injuries, infections, or underlying systemic conditions can disrupt its structure, leading to corneal ulcers. In most cases, these ulcers respond well to medical treatment, but a subset—termed non-healing or refractory corneal ulcers—pose significant clinical challenges due to their resistance to standard therapies.

Non-healing corneal ulcers are characterised by persistent epithelial defects, despite appropriate medical intervention.[1] They represent a substantial burden in ophthalmology due to their potential to cause severe complications, including corneal perforation, secondary infections, and permanent vision loss. Globally, corneal ulcers are a leading cause of blindness, with an estimated 1.5–2 million new cases annually, many of which progress to non-healing stages.[2] The increasing prevalence of predisposing factors, such as contact lens misuse, diabetes mellitus, and autoimmune diseases, underscores the need for comprehensive management strategies.

Non-healing corneal ulcers are often referred to as persistent epithelial defects (PEDs) in the absence of active infection. The terminology encompasses ulcers that fail to show clinical improvement despite two or more weeks of

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treatment.[3] This refractoriness to therapy can arise from infectious pathogens with biofilm-forming capacity or non-infectious factors like neurotrophic keratitis and severe dry eye syndrome.[4] Accurate diagnosis and classification are crucial to tailor effective therapeutic interventions.

Understanding corneal healing mechanisms is integral to deciphering why certain ulcers become non-healing. The cornea is composed of five layers: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The epithelium, the outermost layer, serves as a barrier and undergoes rapid turnover facilitated by limbal stem cells.[5] Following injury, epithelial cells migrate, proliferate, and differentiate under the influence of growth factors like epidermal growth factor (EGF) and transforming growth factor-beta (TGF-β). In non-healing ulcers, this regenerative process is disrupted, leading to chronic inflammation, stromal degradation, or poor epithelial adhesion.

The etiology of non-healing corneal ulcers can be broadly classified into infectious and non-infectious categories. Infectious causes include bacterial, fungal, viral, and protozoal pathogens that evade treatment through mechanisms like biofilm formation or resistance to antimicrobial agents.[6] Non-infectious causes involve neurotrophic keratitis, exposure keratopathy, autoimmune conditions, and iatrogenic factors such as long-term corticosteroid use. Often, a combination of these factors complicates the healing process, necessitating a multifaceted diagnostic approach.

The management of non-healing corneal ulcers is complicated by several factors. First, delayed or inadequate initial treatment can exacerbate the condition, particularly in infectious ulcers caused by resistant pathogens.[3] Second, non-infectious ulcers often require multidisciplinary care involving systemic therapy for underlying conditions like diabetes or rheumatoid arthritis. Finally, the lack of standardized diagnostic criteria and treatment protocols for refractory ulcers highlights the need for continued research and innovation.

Recent advancements in corneal therapeutics, such as amniotic membrane transplantation, autologous serum eye drops, and stem cell-based approaches, have shown promise in managing non-healing ulcers.[5] Additionally, innovations in drug delivery systems, including nanotechnology, aim to enhance the bioavailability of therapeutic agents.[6] Despite these developments, the high cost and limited accessibility of these therapies remain significant barriers in resource-limited settings.

This review aims to provide a comprehensive analysis of non-healing corneal ulcers by exploring their etiological factors, pathophysiology, diagnostic modalities, and treatment strategies. Special emphasis is placed on emerging therapies and the challenges in implementing them in clinical practice. By consolidating current knowledge, this review seeks to identify gaps in the literature and propose future research directions to improve patient outcomes.

2. Anatomy and Physiology of the Cornea

The cornea is a transparent, avascular tissue located at the anterior segment of the eye. It serves as the primary refractive surface, contributing approximately 70% of the eye's total optical power.[7] Its structural integrity, transparency, and curvature allow it to focus light onto the retina, enabling clear vision. Beyond its optical function, the cornea acts as a protective barrier against environmental insults, including microbial pathogens and physical trauma. This section discusses the detailed anatomy and physiology of the cornea, emphasizing its cellular architecture, functional mechanisms, and role in wound healing.

2.1. Anatomy of the cornea

2.1.1. Gross structure

The cornea has a diameter of approximately 11.5 mm horizontally and 10.6 mm vertically and a central thickness averaging 500–550 µm. Its shape is elliptical, with a convex outer surface and concave inner surface, ensuring efficient light refraction. The cornea is composed of five distinct layers, each with specialized structural and functional properties.

1. Epithelium: The outermost layer (10% of corneal thickness) consists of 5–7 layers of non-keratinized squamous cells: superficial (barrier and tear film retention), wing (structural), and basal cells (progenitors). Regeneration occurs every 7–10 days via limbal stem cells at the corneoscleral junction.[8]
2. Bowman's Layer: An acellular, 8–14 µm thick collagenous layer beneath the epithelium, composed of type I and V collagen, offering support and injury resistance, though it lacks regenerative ability and scars upon damage.[7]
3. Stroma: The thickest layer (90%), made of regularly arranged type I and VI collagen and proteoglycans, ensures strength and transparency.[9] Keratocytes maintain its extracellular matrix.[10] While fibril spacing minimizes light scattering
4. Descemet's membrane: A 10–12 µm thick basement membrane of the endothelium, composed mainly of type IV collagen and laminin, elastic and resistant to enzymatic breakdown; it thickens with age.[7]
5. Endothelium: A monolayer of hexagonal, non-mitotic cells regulating stromal hydration via Na^+/K^+-ATPase pumps. Damage impairs fluid control, leading to corneal edema.

2.2. Physiology of the cornea

2.2.1. Transparency

The cornea's transparency is fundamental for light transmission and is maintained by:

1. Avascularity: The absence of blood vessels prevents light scattering.
2. Collagen arrangement: Regular spacing of fibrils in the stroma prevents light scattering and maintains corneal transparency by enabling destructive interference of diffracted light waves.
3. Hydration control: Endothelial pumps and evaporation maintain a 78% water content, ensuring corneal clarity
4. Anti-reflective surface: Smooth epithelium and tear film reduce optical irregularities.

2.2.2. Refractive function

The cornea's curved surface bends light rays to achieve focused images. With a refractive index of 1.376, it provides the majority of the eye's focusing power, complemented by the crystalline lens, which fine-tunes focus for near and distant objects through accommodation

2.2.3. Barrier and defense mechanisms

The cornea acts as the first line of defense against pathogens and external insults through:

1. Tight junctions: Prevent microbial invasion.
2. Tear film and mucins: Provide lubrication and antimicrobial proteins like lysozyme and lactoferrin
3. Immune surveillance: Langerhans cells in the epithelium and cytokine release mediate immune responses.[11]

2.2.4. Wound healing mechanism

Corneal healing involves three stages:

1. Epithelial migration: Cells migrate to cover defects, driven by integrins and growth factors
2. Proliferation and differentiation: Limbal stem cells replenish lost epithelial cells
3. Matrix remodelling: Keratocytes secrete collagen during stromal repair, often resulting in scar formation if damage is severe

2.2.5. Sensory innervation

The cornea is richly innervated by branches of the ophthalmic nerve (trigeminal nerve, CN V1), providing pain sensitivity and reflexes like blinking and tearing.[12] This innervation also promotes epithelial repair by releasing neuropeptides.[13]

The cornea's anatomical complexity and physiological mechanisms make it a vital component of vision and ocular defense. Its ability to heal rapidly under normal conditions is often disrupted in non-healing ulcers due to structural damage, microbial invasion, or impaired homeostasis. Understanding the cornea's layered architecture and functional attributes provides the foundation for diagnosing and treating disorders such as non-healing corneal ulcers.

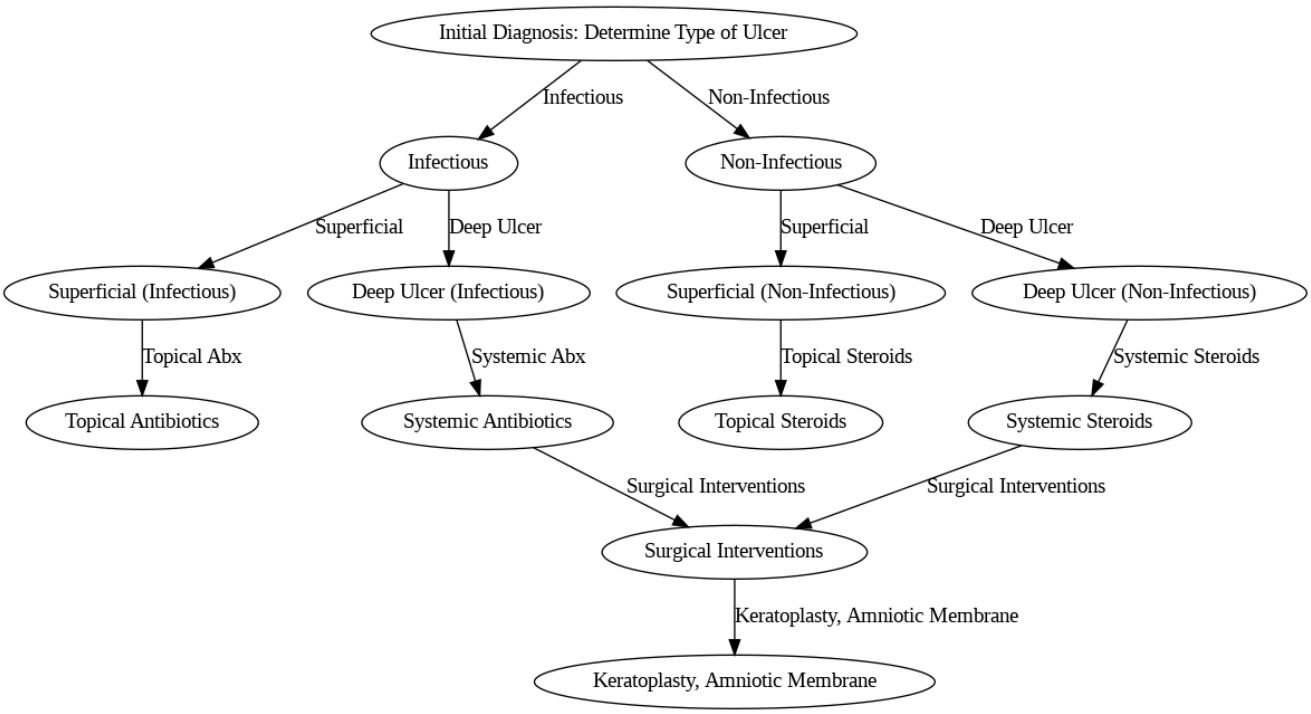

Figure 1: Diagnosis of corneal ulcers

3. Etiology and Pathophysiology of Non-Healing Corneal Ulcers

Non-healing corneal ulcers represent a major clinical challenge due to their complex etiology and intricate pathophysiological mechanisms. These ulcers fail to resolve despite standard treatment, leading to prolonged inflammation, tissue damage, and potential vision loss.[14] This section explores the etiological factors and pathophysiological processes contributing to the development and persistence of non-healing corneal ulcers.

3.1. Etiology of non-healing corneal ulcers

The causes of non-healing corneal ulcers can be broadly classified into infectious and non-infectious categories, often with overlapping factors contributing to their chronicity.

3.1.1. Infectious causes

1. Bacterial keratitis: Common in trauma or contact lens users; *Pseudomonas aeruginosa* forms biofilms and resists antibiotics. While *Staphylococcus aureus* and *Streptococcus pneumoniae* secrete stromal-degrading enzymes.[15]
2. Fungal keratitis: Commonly caused by filamentous fungi such as *Aspergillus* and *Fusarium*, typically following ocular trauma in tropical climates; characterized by deep stromal penetration and tissue necrosis.[16]
3. Viral keratitis: HSV and VZV cause recurrent ulcers via neurotrophic and immune-mediated damage, delaying healing.[17]
4. Protozoal Keratitis: *Acanthamoeba* causes chronic ulcers due to cyst formation and resistance to treatment.[18]

3.2.2. Non-infectious causes

1. Neurotrophic keratitis: Trigeminal nerve dysfunction reduces corneal sensitivity and impairs healing, often secondary to diabetes, HZO, or surgery.
2. Autoimmune disorders: Conditions like RA, SLE, and Sjögren's lead to dry eye and epithelial breakdown due to chronic inflammation.[19]
3. Chemical/thermal injuries: Alkali, acid, or heat exposure damages epithelial cells and limbal stem cells, leading to persistent defects.[20]
4. Iatrogenic factors: Prolonged corticosteroid use and preservatives delay healing; surgical complications can also contribute.[21]

3.2. Pathophysiology of non-healing corneal ulcers

The persistence of corneal ulcers arises from an imbalance between tissue degradation and repair processes (**Figure 2**). The underlying pathophysiology involves several key mechanisms.

3.2.1. Epithelial cell dysfunction

The corneal epithelium relies on limbal stem cells for regeneration. Damage to these cells, as seen in limbal stem cell deficiency, impairs epithelial migration and proliferation, leaving the stroma exposed to external insults.[22]

3.2.2. Inflammatory response

Persistent inflammation plays a central role in ulcer chronicity.

1. Cytokine dysregulation – Overexpression of pro-inflammatory cytokines like IL-1β, TNF-α, and MMP-9 leads to stromal degradation and delayed healing.[23]
2. Matrix metalloproteinase (MMP) activity – MMPs degrade extracellular matrix components, weakening corneal structure and facilitating microbial invasion.[24]
3. Neutrophilic infiltration – Chronic recruitment of neutrophils contributes to oxidative stress and tissue damage via reactive oxygen species (ROS) production.[25]

3.2.3. Stromal degradation

Infectious agents and inflammatory cells release proteolytic enzymes that digest stromal collagen and glycosaminoglycans, resulting in corneal thinning and ulcer expansion.[26] This process is exacerbated by biofilm formation, which shields pathogens from immune clearance.

3.2.4. Edema and hydration imbalance

Endothelial dysfunction impairs the Na+/K+ ATPase pump, leading to excessive stromal hydration and loss of transparency.[27] Chronic edema disrupts collagen alignment, delaying epithelial migration and wound closure.

3.3.5. Fibrosis and scarring

In severe ulcers, keratocytes differentiate into myofibroblasts, producing disorganized collagen and scar tissue.[28] This process restores structural integrity but compromises visual clarity.

Non-healing corneal ulcers are the result of complex etiological and pathophysiological interactions involving infectious pathogens, immune dysregulation, and tissue remodeling defects. Understanding these mechanisms is crucial for developing targeted therapeutic approaches to break the cycle of chronic inflammation and promote corneal repair.

3.3. Clinical presentation and diagnosis of non-healing corneal ulcers

Non-healing corneal ulcers with stromal inflammation that fail to heal despite treatment.[29] They are associated with discomfort, visual disturbances, and a high risk of complications, such as corneal perforation and scarring, requiring prompt diagnosis and intervention.

Clinical presentation: Patients typically report persistent, severe eye pain unresponsive to standard therapies. Redness and conjunctival inflammation, indicative of infection or immune response, are common foreign body sensation, photophobia, tearing, and blurred vision are also frequently experienced .Fluorescein staining reveals epithelial defects with undermined edges, indicating poor epithelial adhesion. Stromal thinning and infiltrates signal deeper tissue damage, while chronic cases may present with neovascularization, further impairing corneal clarity.[30]

3.4. Diagnostic evaluation

1. Detailed history
    a. Risk factors: contact lens use, trauma, ocular surgery, diabetes, autoimmune diseases
    b. Medication history: prolonged corticosteroid use delays healing.[31]
2. Slit-lamp examination
    a. Evaluates ulcer size, depth, and location.[32]
    b. Fluorescein staining: detects epithelial defects.[33]
    c. Infiltrates/stromal thinning suggest infection or inflammation
3. Microbiological testing
    a. Corneal scrapings for Gram stain, KOH mount, and culture.[34]
    b. PCR: detects viral DNA (e.g., HSV, VZV)[16]
4. Imaging
    a. Anterior aegment OCT (AS-OCT): assesses ulcer depth and stromal loss
5. Laboratory tests
    a. ANA, RF: screen for autoimmune conditions
    b. Blood glucose: evaluate metabolic control in diabetics

3.5. Differential diagnosis

1. Infectious keratitis
    a. Caused by bacteria, fungi, viruses, or protozoa
2. Neurotrophic keratitis
    a. Due to loss of corneal sensation (e.g., diabetes, herpes zoster)
3. Autoimmune ulcers
    a. Associated with RA, SLE, or Sjögren's syndrome.[35]
4. Exposure keratopathy
    a. Due to incomplete eyelid closure (e.g., facial nerve palsy)
5. Chemical/medication-induced toxicity
    a. From alkali burns, preservatives in drops, or steroid overuse.[36]

Non-healing corneal ulcers necessitate a thorough diagnostic approach combining clinical examination, microbiological analysis, imaging, and systemic evaluation to identify underlying causes and optimize treatment strategies. Early diagnosis and intervention are critical to prevent complications, preserve vision, and improve patient outcomes[37] diagnosis of corneal ulcer which is illustrated in **Figure 1**.

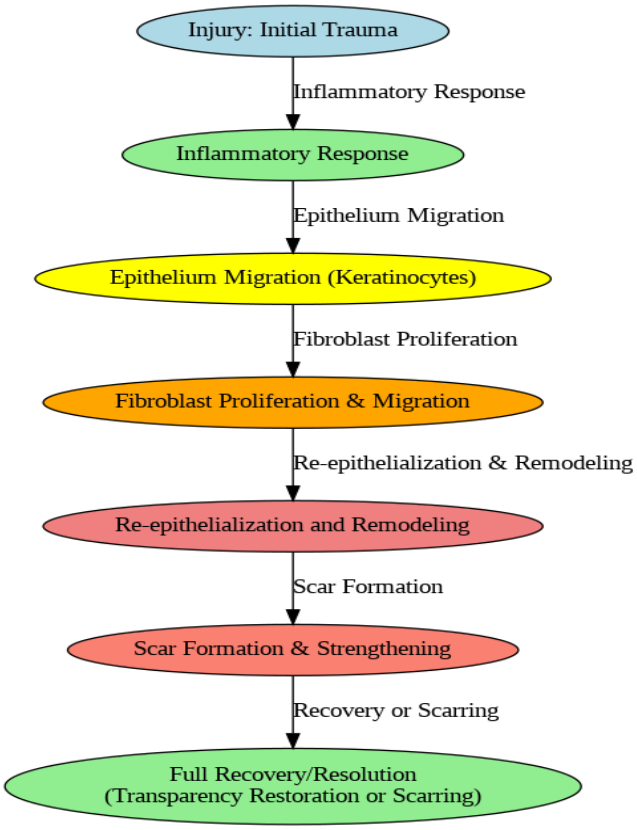

Figure 2: Pathophysiology of corneal ulcer

4. Treatment Modalities for Non-Healing Corneal Ulcers

Non-healing corneal ulcers present significant therapeutic challenges, necessitating a combination of antimicrobial therapy, anti-inflammatory agents, surgical interventions, and advanced regenerative techniques. A comprehensive treatment plan addresses both the underlying etiology and promotes corneal healing.[38]

4.1. Medical management

Prompt initiation of antimicrobial agents is essential, guided by clinical suspicion and microbiological culture results. Broad-spectrum antibiotics such as fluoroquinolones are frequently used as first-line therapy for bacterial ulcers. Fungal keratitis often requires topical antifungal agents like natamycin or voriconazole, while antiviral drugs such as

acyclovir are employed for herpes simplex infections Topical corticosteroids may be used cautiously to reduce inflammation in non-infectious ulcers, though they carry risks of delayed healing and superinfection.[39] In autoimmune-related ulcers, systemic immunosuppressive therapies like cyclosporine or methotrexate can control systemic inflammation.[40] Autologous serum eye drops, containing growth factors and vitamins, promote epithelialization and are beneficial in persistent epithelial defects.

4.2. Mechanical and barrier therapies

Bandage lenses protect the corneal surface, reduce pain, and enhance epithelial healing by providing a stable environment.[41] Amniotic membranes act as biological scaffolds with anti-inflammatory and anti-scarring properties, facilitating epithelial growth and stromal remodeling in chronic ulcers. Conjunctival flaps are used as a biological cover to reduce stromal melting and prevent perforation in cases resistant to conventional therapies

4.3. Surgical Interventions

4.3.1. Debridement

Mechanical debridement of necrotic tissues improves drug penetration and reduces microbial load, aiding in the healing process. For small perforations, cyanoacrylate adhesives provide structural stability and prevent aqueous leakage, serving as a temporary solution before definitive surgical repair Penetrating or lamellar keratoplasty is reserved for severe ulcers with extensive stromal involvement or perforation, restoring structural integrity and visual function.[42]

4.4. Adjunctive and novel therapies

Photodynamic therapy using riboflavin and ultraviolet-A light has emerged as a promising treatment for refractory corneal ulcers by eradicating pathogens and strengthening the corneal stroma.[43]

Anti-tumor necrosis factor (anti-TNF) therapies are being investigated for their role in treating autoimmune-mediated peripheral ulcerative keratitis. Optimal nutrition, including adequate protein intake and vitamins, particularly vitamin C, plays a role in promoting collagen synthesis and epithelial healing.[44] Non-healing corneal ulcers demand an individualized approach, integrating antimicrobial therapy, surgical interventions, and regenerative treatments. Advances in diagnostic techniques and emerging therapies offer improved outcomes for patients with this challenging condition.[45]

5. Emerging Therapies and Innovations in the Treatment of Non-Healing Corneal Ulcers

Advances in medical science have introduced promising new therapies for the treatment of non-healing corneal ulcers, which are notoriously difficult to manage and often lead to significant visual impairment or blindness. Emerging therapies, such as stem cell therapy, tissue engineering, gene therapy, nanotechnology-based drug delivery systems, and artificial corneas, offer novel approaches to address the limitations of conventional treatments. These cutting-edge innovations hold promise in improving the healing process, enhancing tissue regeneration, and ultimately restoring vision in patients with corneal ulcers. Emerging Therapies and Innovations for Non-Healing Corneal Ulcers is summarized in **Table 1**.

Table 1: Emerging therapies and innovations for non-healing corneal ulcers[46-51]

Therapy/Innovation	Description	Potential Benefits
Stem Cell Therapy	Use of stem cells (e.g., limbal stem cells, corneal epithelial stem cells) to regenerate damaged corneal tissue.	Promotes epithelial regeneration and repair, reduces scarring, restores vision.
Tissue Engineering	Creation of bioengineered corneal tissue using cultured cells and biomaterials for transplantation.	Enables the production of tissue for transplantation, reduces rejection risk.
Gene Therapy	Insertion or modification of genes to restore or enhance the cornea's regenerative capacity or repair genetic defects.	Corrects underlying genetic issues, accelerates healing, reduces inflammation.
Nanotechnology-Based Drug Delivery	Application of nanoparticles for delivering drugs directly to the corneal site, enhancing the efficacy of treatments.	Increases drug bioavailability, reduces systemic side effects, targeted action.
Artificial Corneas (Keratoprosthesis)	Prosthetic corneal implants used when traditional corneal transplant is not feasible due to conditions like blindness or rejection risk.	Provides vision restoration when donor tissue is unavailable, especially for high-risk patients.
Amniotic Membrane Transplantation	Use of amniotic membrane grafts to promote healing and reduce inflammation in non-healing corneal ulcers.	Accelerates epithelial healing, reduces inflammation, prevents scarring.

5.1. Stem cell therapy and tissue engineering

Stem cell therapy and tissue engineering have emerged as promising strategies for regenerating damaged corneal tissues and promoting healing in non-healing corneal ulcers. The cornea's unique regenerative capacity is often overwhelmed in cases of severe injury, infection, or disease, leading to stromal damage.[18] Corneal stem cell therapy involves the transplantation of stem cells to restore the corneal epithelium and stroma. Limbal stem cells, which reside in the limbus (the junction between the cornea and the conjunctiva), are responsible for corneal epithelial regeneration. In cases of limbal stem cell deficiency (LSCD), stem cell transplantation can provide a means of restoring the corneal surface and improving visual outcomes. The most common approach involves autologous limbal stem cell transplantation, in which stem cells are harvested from the patient's healthy eye and transplanted to the damaged eye.

In addition to limbal stem cells, other sources of stem cells, such as mesenchymal stem cells (MSCs), have also been explored for corneal regeneration. MSCs have shown the ability to modulate inflammation and promote tissue repair through the secretion of growth factors and cytokines, enhancing corneal wound healing. Tissue engineering aims to create synthetic or biological scaffolds that mimic the natural structure of the cornea.[52] These scaffolds are seeded with stem cells or growth factors to promote cell proliferation, differentiation, and tissue regeneration. One significant development in corneal tissue engineering is the creation of bioengineered corneal constructs, which can be used as a replacement for damaged corneal tissue. These constructs can be made from various materials, including biodegradable polymers, collagen, or decellularized tissues, and have shown promise in clinical trials for the treatment of corneal ulcers.

5.2. Gene therapy approaches

Gene therapy is an emerging treatment modality that offers potential benefits for corneal ulcer healing by directly modifying the genetic material of corneal cells. The application of gene therapy in corneal ulceration involves the delivery of therapeutic genes to promote healing, reduce inflammation, or enhance tissue regeneration. One of the main challenges in gene therapy for corneal ulcers is the efficient and targeted delivery of genes to the corneal tissues. Various delivery systems, such as viral vectors (adenovirus, lentivirus) and non-viral systems (liposomes, nanoparticles), have been explored for their ability to introduce therapeutic genes into the cornea.[53] These gene delivery systems can be used to express growth factors such as vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF), which have been shown to promote corneal epithelial healing and reduce scarring. Gene editing technologies like CRISPR-Cas9 have also been investigated as potential tools for treating genetic disorders that predispose individuals to corneal ulcers. For example, mutations in the collagen genes can lead to corneal dystrophies, which are often associated with persistent corneal ulcers. The use of CRISPR-Cas9 to correct such mutations could provide a revolutionary approach to treating these conditions at the genetic level.

5.3. Nanotechnology-based drug delivery systems

Nanotechnology is rapidly transforming the field of drug delivery, offering several advantages in the treatment of non-healing corneal ulcers. Nanoparticles, due to their small size and unique properties, can enhance drug bioavailability, improve drug penetration into the corneal tissues, and reduce systemic side effects.[54]

Nanoparticles, such as liposomes, dendrimers, and solid lipid nanoparticles, have been extensively studied for their ability to deliver therapeutic agents directly to the site of the corneal ulcer. These nanoparticles can be engineered to carry antimicrobial agents, anti-inflammatory drugs, or growth factors, ensuring a controlled and sustained release of the drug at the site of action.

For instance, nanoparticles loaded with antimicrobial agents like moxifloxacin have shown superior efficacy in treating bacterial keratitis compared to traditional eye drops, due to their enhanced penetration into the corneal stroma and sustained release at the infection site. Similarly, nanocarriers have been used to deliver anti-inflammatory drugs such as dexamethasone, which can reduce inflammation and promote healing in corneal ulcer. Nanostructured hydrogels represent another innovative approach for drug delivery in corneal ulcers. These hydrogels can provide a sustained release of therapeutic agents while conforming to the corneal surface, ensuring enhanced therapeutic efficacy and minimizing ocular irritation. These systems can also be designed to include bioactive molecules that promote epithelial growth, thus accelerating the healing process of corneal ulcers.

5.4. Artificial corneas (Keratoprosthesis)

In cases of severe corneal damage that cannot be managed with conventional treatments or tissue regeneration techniques, artificial corneas (keratoprostheses) provide a viable option. These synthetic corneal implants are used in patients with corneal blindness resulting from conditions such as severe burns, trauma, or chronic infection.

The two most commonly used keratoprostheses are the Boston Keratoprosthesis (BKPro) and the AlphaCor device. The BKPro, which is made from polymethyl methacrylate (PMMA), has been successfully used to restore vision in patients with end-stage corneal diseases.[55] It consists of a central optic that is surgically implanted into the corneal stroma, with a surrounding collar that helps anchor the device in place.

Despite their advantages, keratoprostheses face several challenges, including the risk of infection, glaucoma, and device extrusion. However, innovations in design and

surgical techniques have improved the outcomes for patients undergoing keratoprosthesis implantation. For example, the use of tissue engineering approaches to create bioinspired materials for keratoprosthesis may help to reduce complications and improve long-term outcomes

The treatment of non-healing corneal ulcers has evolved significantly with the advent of emerging therapies, such as stem cell therapy, gene therapy, nanotechnology-based drug delivery systems, and artificial corneas. These innovations offer great potential for improving healing rates, restoring vision, and providing new therapeutic options for patients with refractory corneal ulcers. Continued research and clinical trials are essential to fully realize the benefits of these technologies and to optimize their clinical application in managing corneal diseases. **Figure 3** represents systemic drug delivery systems in ocular regions.

6. Challenges and Gaps in Current Treatments for non-Healing Corneal Ulcers

Despite significant advances in the treatment of corneal ulcers, several challenges persist, hindering optimal management and healing outcomes. These challenges primarily involve issues related to antibiotic resistance, the diagnosis of atypical pathogens, and the management of recurrent or chronic cases. Addressing these challenges is essential to improving treatment efficacy and minimizing the risk of vision loss in patients with non-healing corneal ulcers.

6.1. Antibiotic resistance

Antibiotic resistance is one of the most significant challenges in the management of corneal ulcers, particularly bacterial keratitis. The overuse and misuse of antibiotics in both clinical and agricultural settings have led to the emergence of resistant strains of common ocular pathogens, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumonia*. These resistant pathogens are harder to treat with conventional antibiotics and can result in prolonged infections, worsening symptoms, and increased risk of corneal scarring or perforation.[56] The mechanisms by which pathogens develop resistance include the acquisition of resistance genes via horizontal gene transfer, mutations in the target enzymes, and the formation of biofilms. Biofilm formation, in particular, is a critical factor in antibiotic resistance in corneal ulcers. Bacteria within biofilms are protected from both the host immune system and the effects of antibiotics, leading to chronic and difficult-to-eradicate infections. This makes the treatment of corneal ulcers caused by biofilm-forming organisms especially challenging. The increasing prevalence of antibiotic resistance necessitates the use of more potent or broad-spectrum antibiotics, which can have side effects and increased costs. In some cases, treatment failure may occur even with the use of advanced antibiotics, and surgical interventions, such as corneal transplantation, may be required. Furthermore, the prolonged use of antibiotics increases the risk of secondary fungal or viral infections, complicating the treatment regimen and prolonging recovery times. Therefore, there is a pressing need for the development of new antibiotics, alternative treatments, and more effective diagnostic tools to detect resistant organisms early.

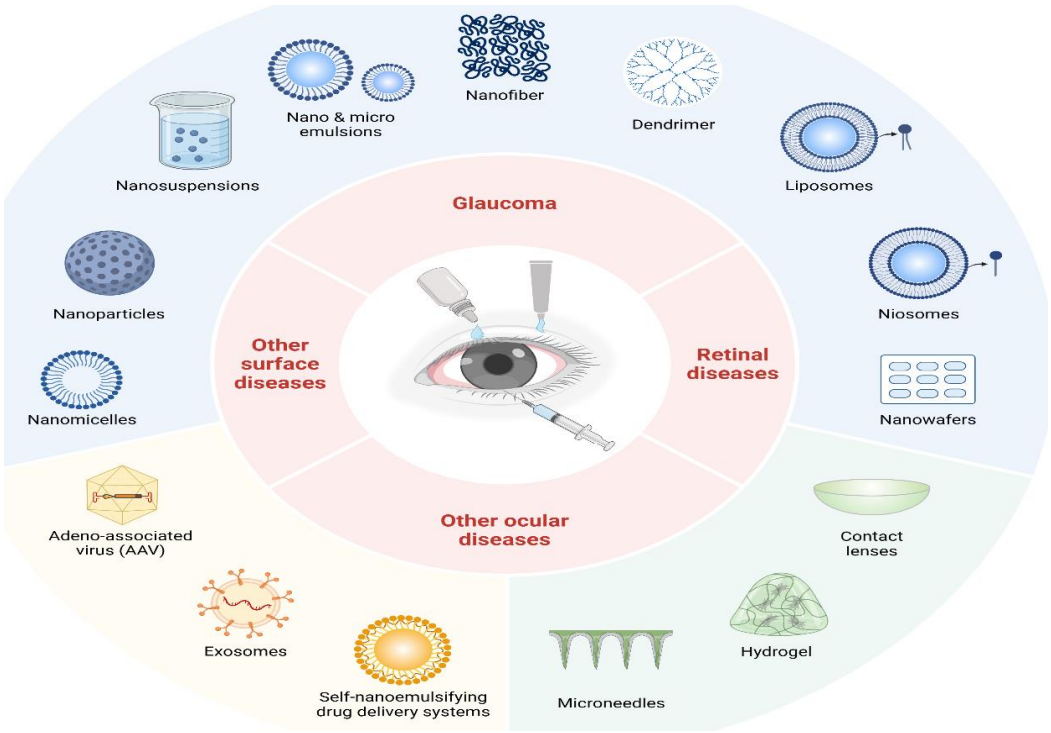

Figure 3: Systemic drug delivery systems in ocular regions

6.2. Diagnosis of atypical pathogens

The diagnosis of non-healing corneal ulcers can be particularly difficult when atypical or rare pathogens are involved. While bacterial infections are the most common cause of corneal ulcers, fungi, viruses, and parasites can also contribute to non-healing ulcers, often requiring different treatment approaches. Atypical pathogens, such as *Acanthamoeba* and *Fusarium*, can be particularly challenging to diagnose due to their distinctive characteristics and less common clinical presentation.

The gold standard for diagnosing corneal ulcers is microbiological culture, which involves collecting a sample from the corneal ulcer and growing it in a laboratory to identify the causative pathogen.[57] However, culture-based methods have several limitations. For example, some pathogens, such as *Acanthamoeba* and certain fungal species, are slow-growing and may take several days to weeks to culture, delaying diagnosis and treatment. Additionally, standard cultures may fail to detect organisms that require special media or conditions for growth, leading to false-negative results.

To overcome the limitations of culture-based methods, molecular diagnostic techniques, such as polymerase chain reaction (PCR), have been increasingly used. PCR allows for the rapid identification of pathogens by detecting their genetic material, providing a faster and more accurate diagnosis than traditional culture methods. However, PCR-based diagnostics can be expensive and require specialized equipment, limiting their widespread availability in resource-limited settings.

In addition to the limitations of culture and molecular diagnostics, some atypical pathogens may require specific treatment protocols. For instance, *Acanthamoeba* keratitis requires a combination of anti-amoebic agents like chlorhexidine or polyhexamethylene biguanide (PHMB), which are not used for bacterial keratitis. Misdiagnosis or delayed identification of these pathogens can result in inappropriate treatment, leading to worsening of the ulcer and potential vision loss.

6.3. Management of recurrent or chronic cases

Another major challenge in treating non-healing corneal ulcers is the management of recurrent or chronic ulcers. Recurrent corneal ulcers are often seen in patients with underlying conditions such as dry eye disease, autoimmune disorders, and diabetes mellitus. These conditions can impair normal corneal healing, leading to persistent or recurrent ulcers that are resistant to conventional treatments. Chronic ulcers can also occur due to scarring or neovascularization from previous infections, which can interfere with normal healing processes.

The pathophysiology of chronic corneal ulcers is multifactorial and involves both intrinsic and extrinsic factors. Dry eye disease, for instance, is a common contributor to recurrent corneal ulcers. Reduced tear production and inadequate eyelid function lead to poor ocular surface maintenance, making the cornea more susceptible to infection and ulceration. Autoimmune conditions such as rheumatoid arthritis or systemic lupus erythematosus can result in inflammatory damage to the cornea, leading to delayed healing and recurrence of ulcers. Additionally, the use of corticosteroids, often employed to treat inflammation, can inhibit corneal healing and promote ulcer recurrence.[58]

The management of recurrent or chronic corneal ulcers typically involves a combination of antimicrobial therapy, anti-inflammatory agents, and supportive care, including lubricants and moisture chambers. However, these treatments often provide limited success, particularly when underlying systemic conditions or autoimmune responses are not effectively controlled. In such cases, more aggressive treatments, such as amniotic membrane transplantation, limbal stem cell transplantation, or even corneal grafting, may be necessary. However, these surgical interventions carry risks of rejection, graft failure, and complications, especially in patients with autoimmune diseases or compromised immune function. Emerging therapies, such as stem cell therapy, tissue engineering, and gene therapy, offer hope for patients with chronic or recurrent corneal ulcers. Stem cell-based therapies, for example, have been used to treat limbal stem cell deficiency and promote corneal regeneration, offering potential benefits for patients with non-healing ulcers due to stem cell depletion. Similarly, gene therapy approaches targeting specific molecular pathways involved in corneal inflammation and healing are being explored as potential treatments for chronic ulcers.

However, the widespread adoption of these therapies is still limited by challenges related to cost, availability, and long-term safety and efficacy data. Clinical trials are ongoing to evaluate the effectiveness of these advanced treatments, but more evidence is needed before they can become standard options for managing recurrent or chronic corneal ulcers. The treatment of non-healing corneal ulcers remains fraught with challenges, particularly in the context of antibiotic resistance, the diagnosis of atypical pathogens, and the management of recurrent or chronic cases. Overcoming these challenges requires a multidisciplinary approach that combines advances in microbiology, molecular diagnostics, and therapeutic innovations. Continued research into new diagnostic tools, antimicrobial agents, and regenerative treatments is essential to improve outcomes for patients suffering from this debilitating condition.

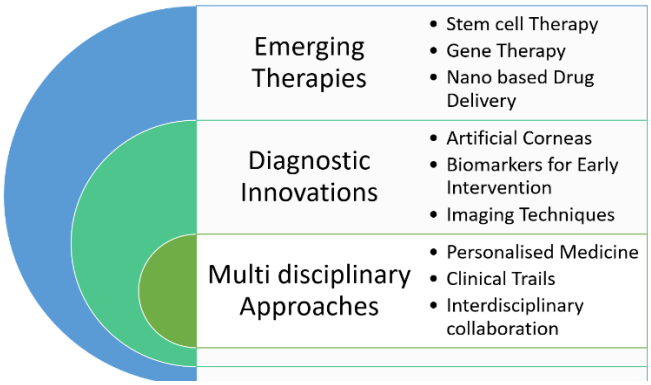

Figure 4: Novel approaches and future directions of research in corneal ulcer

7. Future Directions and Recommendations in the Treatment of Non-Healing Corneal Ulcers

Managing non-healing corneal ulcers remains a challenge due to factors like antibiotic resistance, delayed diagnosis, and comorbidities. A multidisciplinary approach, early detection using biomarkers, and ongoing clinical trials for novel therapies are crucial advancements (**Figure 4**). This section highlights recent developments (2018–2024) and future directions in improving management strategies.

7.1. Multidisciplinary approaches in treatment

Non-healing corneal ulcers result from complex factors like infection, inflammation, and systemic diseases. Managing such ulcers requires collaboration between ophthalmologists, microbiologists, immunologists, and infectious disease specialists. Patients with autoimmune diseases, diabetes, or chronic inflammatory conditions present with impaired corneal healing. For instance, dry eye disease and diabetes mellitus significantly hinder corneal recovery. In these cases, endocrinologists and rheumatologists play crucial roles in managing systemic conditions, while infectious disease experts help tackle antibiotic-resistant infections. When pharmacological treatments fail, surgeons specializing in corneal transplants or ocular surface reconstruction intervene. Procedures like limbal stem cell transplantation and amniotic membrane grafting are now essential. Regenerative medicine, including stem cell therapies and tissue engineering, offers promising advancements. Collaboration among ophthalmologists, stem cell researchers, and bioengineers is vital for developing effective cell-based treatments.

7.2. Biomarkers for early detection

Early detection of non-healing corneal ulcers is essential to prevent complications like perforation and vision loss. However, diagnosis can be difficult, especially with atypical infections or comorbidities. Biomarkers can significantly aid early diagnosis and monitoring. Elevated levels of matrix metalloproteinases (MMPs), particularly MMP-9, correlate with ulcer severity and delayed healing. Other inflammatory markers like IL-1β and TNF-α are also under investigation. Tear fluid analysis and biosensor technologies offer non-invasive methods to detect these markers quickly. Advances in genomics and epigenetics have revealed gene expression profiles and epigenetic modifications that influence healing outcomes. Genes linked to immune response and tissue repair, as well as DNA methylation patterns, may serve as diagnostic and prognostic tools. Transitioning biomarkers into clinical use requires standardized detection methods, validation across populations, and actionable interpretation by clinicians. Nonetheless, biomarker development holds great potential for improving the management of stubborn corneal ulcers.

7.3. Clinical trials on novel therapies

Clinical trials are vital for exploring new therapies for non-healing corneal ulcers. With antibiotic resistance rising and current treatments proving insufficient, innovative approaches are urgently needed. Stem cell therapies and gene therapies are promising. Limbal stem cell transplantation has shown success in regenerating corneal epithelium. Gene therapies targeting healing and inflammatory pathways are under investigation, offering hope for ulcers related to autoimmune and inflammatory diseases. Nanotechnology also provides new avenues. Nanocarriers improve drug delivery, increasing bioavailability and minimizing side effects. Trials with nanoparticle-based antibiotics have demonstrated effectiveness against resistant bacteria, while nanoparticle-based corticosteroids offer potential for safer long-term inflammation control. When conventional treatments fail, corneal transplantation remains a last resort, although donor shortage and graft rejection are significant hurdles. Artificial corneas, such as the Boston KPro, offer alternatives and are undergoing clinical trials to refine designs and improve outcomes. The future of managing non-healing corneal ulcers lies in multidisciplinary care, early detection through biomarkers, and the adoption of novel therapies. Continued collaboration between specialists and researchers is crucial. Advancements in diagnostics, regenerative medicine, and clinical trial outcomes offer a path toward more effective, personalized treatments. Investment in research and the creation of standardized diagnostic tools and treatment protocols will be essential for improving patient outcomes.

8. Conclusion

Non-healing corneal ulcers represent a persistent clinical challenge due to their multifactorial pathogenesis and resistance to conventional therapies. While traditional approaches such as antibiotics and surgical interventions have provided relief in some cases, treatment remains suboptimal, especially in patients with underlying systemic conditions or chronic inflammation. This review has highlighted the critical need for a multidisciplinary approach and the integration of emerging therapies that address the root causes and enhance healing potential. Innovative strategies such as stem cell therapy, gene therapy, nanotechnology-

based drug delivery, and artificial corneas are at the forefront of modern research. These advancements offer new hope by restoring tissue integrity, modulating immune responses, and improving drug targeting. Furthermore, the development of biomarkers for early diagnosis and monitoring holds promises for timely interventions and better prognostication. Despite these promising developments, significant challenges remain, particularly in translating these therapies into routine practice. Large-scale, multicentre clinical trials are needed to establish the efficacy and safety of novel treatments across diverse populations. Cost, accessibility, and healthcare infrastructure will also influence the feasibility of these interventions, especially in low-resource settings. Additionally, antibiotic resistance continues to complicate the management of corneal ulcers, necessitating ongoing research into new antimicrobial agents and personalized therapeutic approaches. Moving forward, collaborative efforts among ophthalmologists, researchers, and clinicians from related disciplines will be essential to bridge current gaps and develop more effective, accessible, and individualized treatments for non-healing corneal ulcers.

9. Figure Declaration

All clinical images included in this manuscript are original. No images have been copied or taken from other sources.

10. Highlights of the Study

1. Non-healing corneal ulcers present a major challenge due to delayed epithelial closure, recurrent infections, and risk of vision loss.
2. Clinical assessment combined with targeted microbiological and imaging tools (e.g., confocal microscopy, AS-OCT) enhances diagnostic accuracy.
3. Common causes include microbial resistance, neurotrophic keratitis, autoimmune disorders, and inadequate treatment of initial ulcers.
4. Novel therapies such as amniotic membrane transplantation, autologous serum eye drops, and recombinant growth factors show promising results.
5. Advanced drug delivery systems, including nanocarriers and sustained-release formulations, are emerging to improve therapeutic outcomes.
6. Early identification of non-responders and integration of individualized treatment plans are key to successful management.

11. Source of Funding

None.

12. Conflict of Interest

None.

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