Review Article

Persistent corneal epithelial defects: an updated review of literature

Kimia Kazemzadeh [1]

[1] *IVORC Academic Foundation (International Virtual Ophthalmic Research Center), Texas, United States*

ABSTRACT

Background: Persistent corneal epithelial defects (PCEDs) represent a significant clinical challenge characterized by the failure of the corneal epithelium to heal within the normal period, leading to potential sight-threatening complications. These defects arise from a variety of underlying etiologies, including limbal stem cell deficiency, neurotrophic keratopathy, dry eye syndrome, and systemic diseases such as diabetes mellitus. Despite advances in ophthalmic care, PCEDs remain difficult to treat due to diverse pathophysiological mechanisms and variable response to conventional therapies. Recent developments in growth factor therapies, biological treatments, surgical techniques, and regenerative medicine have expanded therapeutic options but necessitate comprehensive review to guide clinical practice.

Methods: A comprehensive narrative review was conducted through a structured search of major electronic databases including PubMed/MEDLINE, Embase, Scopus, and Google Scholar. The search incorporated Medical Subject Headings (MeSH), where available, and free-text keywords related to "persistent corneal epithelial defects," "corneal epithelial healing," "ocular surface disorders," "limbal stem cell deficiency," "neurotrophic keratopathy," "amniotic membrane transplantation," "therapeutic contact lenses," "growth factors," "autologous serum," and "emerging therapies in ophthalmology." Peer-reviewed original studies, clinical trials, reviews, and meta-analyses published primarily between 1 January 2000 and 31 March 2025 were included; earlier seminal studies and directly relevant publications identified during manuscript finalization were also considered. Articles were critically appraised and selected according to their relevance, methodological quality, and contribution to understanding PCED pathophysiology, diagnosis, and treatment advancements.

Results: The review delineates the anatomy and physiological roles of the corneal epithelium, highlighting mechanisms that lead to epithelial defect persistence, including impaired basement membrane integrity, stem cell deficiency, inflammation, and neurotrophic factors. Clinical presentation and diagnostic modalities such as fluorescein staining and advanced imaging techniques are discussed. Standard management with lubricants, therapeutic contact lenses, infection control, and autologous serum eye drops is described, alongside medical therapies targeting epithelial regeneration, including recombinant human nerve growth factor and platelet-rich plasma. Surgical interventions like amniotic membrane transplantation are used in refractory cases, while regenerative approaches involving stem cell therapy and corneal neurotization remain emerging options. Molecular therapies and bioengineered drug delivery systems also warrant further clinical evaluation in PCED treatment.

Conclusion: PCEDs pose complex therapeutic challenges necessitating a multifaceted treatment approach. Advances in molecular, cellular, and surgical therapies have substantially expanded management options and improved healing outcomes. However, continued research into personalized therapies, optimization of delivery methods, and long-term safety is essential. This review provides a comprehensive synthesis of current knowledge and emerging trends to inform clinicians and researchers in the effective management of PCEDs, ultimately aiming to preserve vision and enhance quality of life. Future research should focus on minimally invasive sustained-release therapies, biomarker-guided personalized interventions, and combination approaches targeting epithelium, inflammation, and nerves.

KEYWORDS

corneal epithelium, persistent corneal epithelial defects, neurotrophic keratopathy, limbal stem cell, limbal stem cell deficiency, corneal disease, wound healings, amniotic membrane, stem cell transplantations.

Correspondences: Kimia Kazemzadeh, IVORC Academic Foundation (International Virtual Ophthalmic Research Center), Texas, United States. Email: kimia_kazemzadeh@yahoo.com. ORCID iD: https://orcid.org/0000-0002-6948-4838.

How to cite this article: Kazemzadeh K. Persistent corneal epithelial defects: an updated review of literature. Med Hypothesis Discov Innov Optom. 2025 Fall; 6(3): 121-128. DOI: https://doi.org/10.51329/mehdioptometry231.

Received: 01 September 2025; Accepted: 03 November 2025

INTRODUCTION

Persistent corneal epithelial defects (PCEDs), also known as persistent epithelial defects (PEDs), represent a clinical condition characterized by failure of the corneal epithelium to undergo rapid and complete re-epithelialization within the normal healing window of 7 to 14 days following injury or surgery despite standard supportive treatment [1–3]. The corneal epithelium serves as a crucial protective barrier that maintains corneal transparency and prevents microbial invasion. Disruption that impairs timely epithelial closure exposes the underlying stroma to environmental insults, increasing the risk of infection, stromal ulceration, scarring, melting, or perforation, with potentially severe visual consequences [1–3].

The etiology of PCEDs is multifactorial, involving diverse ocular and systemic diseases that perturb epithelial cell migration, adhesion, proliferation, and differentiation. Common predisposing factors include neurotrophic keratopathy, limbal stem cell deficiency (LSCD), dry eye syndromes, infections such as herpes simplex keratitis, postoperative complications from procedures such as penetrating keratoplasty and vitrectomy, and systemic conditions including diabetes mellitus and autoimmune diseases. These conditions can disrupt the epithelial basement membrane, impair corneal innervation, or destabilize the tear film, culminating in chronic non-healing defects [2, 4–6].

The clinical burden of PCEDs is substantial due to associated ocular discomfort, increased healthcare utilization, and the potential for irreversible visual impairment. Despite the availability of treatments ranging from basic lubrication to advanced surgical interventions, management remains challenging because of heterogeneity in pathophysiologic mechanisms and variability in therapeutic response. Early identification and prompt intervention are essential to prevent secondary complications that worsen prognosis [3]. Conventional treatments such as preservative-free artificial tears, bandage contact lenses (BCLs), and autologous serum eye drops aim to protect the ocular surface and create a favorable environment for healing. Recent advances targeting molecular pathways involved in epithelial regeneration, including recombinant human nerve growth factor, matrix-regenerating agents, and peptide-based therapies, have shown promise in refractory cases. Surgical innovations such as amniotic membrane transplantation (AMT) and stem cell therapies further expand the armamentarium for managing complex PCEDs [7–9].

Given the evolving landscape of PCED understanding and management, this article provides a narrative review of the anatomy and physiology of the corneal epithelium, pathophysiology, clinical presentation, diagnosis, current and emerging treatment strategies, challenges encountered, and future directions in the field of PCEDs.

METHODS

A literature search was conducted for this narrative review across major electronic databases, including PubMed/MEDLINE, Embase, Scopus, and Google Scholar. The search incorporated Medical Subject Headings (MeSH), where available, and free-text keywords related to “persistent corneal epithelial defects,” “corneal epithelial healing,” “ocular surface disorders,” “limbal stem cell deficiency,” “neurotrophic keratopathy,” “amniotic membrane transplantation,” “therapeutic contact lenses,” “growth factors,” “autologous serum,” and “emerging therapies in ophthalmology.” The principal search focused on articles published between 1 January 2000 and 31 March 2025 to emphasize contemporary understanding and recent advancements in the management of PCEDs; earlier seminal studies and directly relevant publications identified during manuscript finalization were also considered.

Inclusion criteria encompassed peer-reviewed original research articles, randomized controlled trials, observational studies, systematic reviews, meta-analyses, and relevant narrative reviews addressing the pathophysiology, clinical features, diagnosis, and both conventional and emerging treatment modalities of PCEDs. Human clinical evidence was prioritized; relevant animal studies, *in vitro* studies, and selected case reports describing emerging interventions were considered when higher-level clinical evidence was limited. Only articles published in English were included to ensure precision and clarity of scientific communication. Exclusion criteria comprised case reports without direct relevance to the review objectives, conference abstracts without full-text availability, non-peer-reviewed publications, and articles not directly relevant to corneal epithelial pathology.

Selected studies were appraised for methodological quality based on study design, sample size, study population or experimental model, validation methods, and clinical applicability to PCEDs. Particular consideration was given to literature examining novel therapeutic approaches, including cellular and molecular interventions, surgical techniques, and supportive care innovations. Emphasis was placed on synthesizing findings that elucidate heterogeneous etiologies such as neurotrophic keratopathy and LSCD while highlighting current challenges and future research needs.

Data extraction and synthesis involved iterative analysis and cross-referencing of eligible studies to ensure comprehensive coverage and accurate interpretation. This narrative review provides an interpretative and critical summary of the current state of knowledge, aimed at guiding clinicians and researchers in the effective and innovative management of PCEDs.

RESULTS and DISCUSSION

Anatomy and Physiology of the Corneal Epithelium

The corneal epithelium forms the outermost layer of the cornea and plays a critical role in protecting the eye, maintaining optical clarity, and contributing to corneal homeostasis. This layer is composed of nonkeratinized stratified squamous epithelial cells that provide a smooth refractive surface necessary for clear vision [10].

The corneal epithelium is approximately 40 to 50 micrometers thick and consists of 4 to 6 cell layers, which are organized into three main types of cells: basal, wing, and superficial cells [11]. Basal cells form a single layer of cuboidal to columnar cells attached to the underlying basement membrane by hemidesmosomes. These cells are mitotically active and serve as progenitors for the upper layers. The basement membrane itself is composed primarily of type IV collagen and laminin, providing structural support and anchorage [11, 12]. Wing cells lie above the basal layer and are named for their characteristic wing-like shape. They act as intermediate cells transitioning basal cells to superficial cells and express specific keratins essential for epithelial integrity [10, 11]. Superficial cells form the outermost 2 to 3 layers and comprise flat polygonal cells with microvilli on their apical surface. The microvilli increase the epithelial surface area, supporting tear film adherence and preventing desiccation. Tight junctions between these cells create a barrier to prevent ingress of tears, toxins, and microbes [11].

The corneal epithelium acts as a dynamic physical barrier against environmental insults, including microbial pathogens and mechanical trauma. Its cells have a rapid turnover with an average lifespan of 7 to 10 days, undergoing continuous renewal through mitosis in the basal layer. This renewal process is vital for maintaining corneal transparency and smoothness essential for vision [10, 11]. Moreover, the epithelium has a symbiotic relationship with the tear film: the mucin layer of the tear film, produced by conjunctival goblet cells, interacts with the epithelial glycocalyx to ensure proper hydration and distribution of the tear film across the corneal surface after each blink [11]. The epithelial barrier contributes to the regulation of corneal hydration by maintaining controlled trans-epithelial water permeability, mediated in part by membrane-associated proteins such as aquaporin-5, which helps preserve stromal hydration and prevents excessive swelling [13]. The basement membrane under the epithelium is an active participant in wound healing, serving as a scaffold for epithelial cell migration and contributing biochemical signals that regulate cellular differentiation during repair processes [11, 12].

Pathophysiology of Persistent Corneal Epithelial Defects

PCEDs are defined as corneal epithelial wounds that fail to heal within the normal repair period of 7 to 14 days following an injury or surgery despite standard supportive treatments [1–3, 14]. This failure originates from disruptions in the tightly regulated cellular and molecular mechanisms responsible for epithelial regeneration, leading to prolonged exposure of the corneal stroma and increased risk of secondary complications such as stromal ulceration, infection, and scarring [14].

One of the critical mechanisms underlying PCEDs is defective adhesion of basal epithelial cells to the underlying basement membrane. Normally, basal cells anchor to the basement membrane via hemidesmosomes and anchoring fibrils, which are molecular complexes crucial for epithelial stability and migration during wound healing. Disruption of this adhesion, due to basement membrane dystrophies, recurrent erosions, or toxic insults such as topical anesthetics, leads to instability of the epithelial layer and prevents effective closure of the defect [14, 15]. Overexpression of matrix metalloproteinases (MMPs) in recurrent erosions can degrade the basement membrane, further compromising epithelial attachment and wound healing [14, 15].

Limbal stem cells located at the corneal periphery play an indispensable role in regenerating the corneal epithelium after injury [11, 16, 17]. Deficiency or dysfunction of these stem cells disrupts epithelial renewal, resulting in persistent defects, stromal inflammation, neovascularization, and conjunctivalization. LSCD can arise from chemical injuries, autoimmune diseases, or iatrogenic causes, and is a well-established contributor to non-healing epithelial defects [16, 17].

Inflammation may profoundly influences the healing process. Cytokine signaling involving mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) participates in the wound-healing response, but excessive or chronic inflammation disrupts epithelial regeneration. High levels of pro-inflammatory cytokines induce overproduction of proteases such as MMPs, leading to stromal degradation and melting that delay epithelial closure. Chronic inflammatory disorders including autoimmune keratitis, Stevens-Johnson syndrome, and graft-versus-host disease are common underlying pathologies in PCEDs [14].

The cornea is one of the most densely innervated tissues, and trigeminal nerve [11, 18] input provides not only sensory feedback but also neurotrophic support essential for epithelial health. Damage to corneal nerves from diabetes mellitus, herpetic infections, surgical trauma, or chemical injuries causes neurotrophic keratopathy; a major cause of PCEDs. Loss of corneal sensation diminishes metabolic support, epithelial cell proliferation, and tear secretion, contributing collectively to impaired wound healing and persistent epithelial defects [18].

Mechanical trauma to the ocular surface such as lid abnormalities (entropion, trichiasis), exposure keratopathy due to lagophthalmos, or repetitive abrasions, deplete epithelial cells and overwhelm regenerative capacities, promoting persistent defects. Furthermore, severe ocular surface dryness, often due to mucin deficiency or lacrimal gland dysfunction in diseases like Sjogren's syndrome, destabilizes the tear film and interferes with epithelial repair [2].

Chronic PCED cases may involve keratocyte apoptosis and fibrosis within the stroma beneath the defect. The resulting disorganized extracellular matrix and stromal scarring further impair epithelial migration and adhesion, perpetuating the cycle of delayed healing [15].

Clinical Presentation and Diagnosis

Patients with PCEDs typically present with ocular symptoms such as pain, foreign body sensation, tearing, photophobia, redness, and blurred vision. However, in cases involving neurotrophic keratopathy, patients may experience reduced or absent

pain due to impaired corneal sensation, which complicates early detection [19]. On slit-lamp examination, PCEDs appear as areas of epithelial loss, often with irregular borders. Fluorescein dye instillation is the gold standard for detecting epithelial defects; the dye stains the exposed stroma where the epithelial barrier is compromised. Using a cobalt-blue light, the defect fluoresces bright green, delineating the size and shape of the lesion [14, 20, 21]. Signs that may accompany PCEDs include conjunctival injection, stromal haze, neovascularization, and epithelial edema. Secondary complications visible on exam include stromal ulceration, infiltrates, and, in advanced cases, corneal melting or perforation. Eyelid abnormalities such as entropion, trichiasis, or lagophthalmos, potentially contributing to epithelial trauma, should be carefully assessed [14].

The key diagnostic criterion distinguishing PCEDs from acute epithelial defects is the duration of non-healing. In healthy corneas, epithelial defects typically re-epithelialize within 7 to 10 days, whereas PCEDs persist beyond 14 days despite standard treatment. Persistence despite adequate lubrication, appropriate supportive treatment, and management of identifiable causative factors warrants the diagnosis. Comprehensive history-taking is essential to identify predisposing systemic and ocular conditions such as diabetes mellitus, herpetic infections, autoimmune diseases, neurotrophic keratopathy, or previous ocular surgeries that impair healing. Examination of corneal sensation using esthesiometry may aid in identifying neurotrophic components [14, 19].

Apart from fluorescein staining, other diagnostic modalities can assist evaluation [14]. Anterior segment optical coherence tomography (AS-OCT) can provide noninvasive imaging of the defect depth and underlying stromal changes [21]. Confocal microscopy may assess corneal nerve density and morphology, particularly in suspected neurotrophic keratopathy [22, 23]. Tear film assessment and ocular surface staining with lissamine green or rose bengal help evaluate ocular surface damage and areas of mucin deficiency [24].

Current Treatment Strategies

Conservative and supportive care: Conservative and supportive care forms the cornerstone of initial management for PCEDs, aiming to create an optimal environment for epithelial cell migration, proliferation, and regeneration. The goals are to protect the denuded corneal stroma, prevent secondary infection, maintain ocular surface hydration, and reduce mechanical trauma [25, 26].

Aggressive use of preservative-free artificial tears and ocular ointments is fundamental to maintaining a stable and moist ocular surface. These lubricants reduce friction from blinking, supply essential moisture, and dilute inflammatory mediators present on the ocular surface. Preservative-free formulations are preferred to avoid toxic effects of preservatives such as benzalkonium chloride, which can exacerbate epithelial toxicity and delay healing. Ocular ointments provide prolonged lubrication, especially during sleep, reducing exposure-related damage [26–28]. Punctal occlusion with silicone or collagen plugs is frequently employed as an adjunct to increase retention time of lubricants and endogenous growth factors like epidermal growth factor (EGF) in the tear film, thus enhancing epithelial healing [29]. Mechanical protection of the fragile epithelial defect is critical. BCLs are widely used to shield the cornea from eyelid-induced trauma and to maintain a hydrated microenvironment conducive to healing. These lenses reduce pain and irritation while facilitating epithelial cell migration. Close monitoring is necessary to prevent lens-related infections, which can complicate therapy [9, 30]. Alternatively, pressure patching can be applied to protect the ocular surface especially when BCLs are contraindicated, but its use requires careful daily inspection for potential complications such as hypoxia or bacterial colonization. In eyes with severe stromal thinning, impending perforation, or a small perforation, temporary cyanoacrylate glue may be employed to provide tectonic support and prevent further progression [31].

Secondary infection is a major concern in PCEDs due to the loss of the epithelial protective barrier. Prophylactic topical broad-spectrum antibiotics are commonly prescribed in conjunction with contact lens use or in cases with signs of infection risk. Careful antibiotic selection is important to avoid further epithelial toxicity. Tetracyclines, particularly oral doxycycline, are used for their anti-inflammatory and anti-collagenolytic effects, which inhibit MMPs that degrade the extracellular matrix and delay healing. They may be considered as adjunctive treatment when inflammation or excessive collagenolysis contributes to stromal degradation, but they do not replace appropriate antimicrobial treatment when infection is present [21, 30, 33]. Topical corticosteroids should be used cautiously and generally avoided while an active epithelial defect remains because they may delay epithelial healing and increase the risks of infection and stromal melting; their use should be limited to specifically indicated inflammatory conditions under close ophthalmic monitoring [14].

Medical therapies targeting epithelial healing: In addition to conservative supportive care, medical therapies that actively promote corneal epithelial healing play a vital role in managing PCEDs. These therapies aim to enhance cellular proliferation, migration, and differentiation by supplying growth factors and bioactive molecules that are deficient or dysfunctional in PCEDs [21]. Several growth factors have been investigated for their potential benefits in treating PCEDs. EGF stimulates mitogenesis and enhances epithelial cell migration, contributing effectively to re-epithelialization. Similarly, insulin-like growth factor 1 (IGF-1) supports epithelial proliferation and survival, often exerting synergistic effects with EGF [34]. Topical recombinant human nerve growth factor (rhNGF), cenegermin (marketed as Oxervate), has gained FDA approval for neurotrophic keratitis, a prominent cause of PCEDs. rhNGF promotes corneal epithelial healing and supports neurotrophic signaling. Clinical trials have demonstrated higher rates of corneal healing with rhNGF than with vehicle after 8 weeks, whereas comparative benefits for corneal sensitivity and patient-reported symptoms remain uncertain [21, 35]. Thymosin β4 is another bioactive peptide with

anti-inflammatory and wound-healing properties that enhances epithelial restoration by regulating cytokines and promoting cell migration. Early clinical data suggests beneficial effects though more studies are needed to establish standardized protocols [26].

Autologous serum eye drops (ASEDs) have become a cornerstone therapy for refractory PCEDs because of their rich content of growth factors (EGF, IGF-1, fibronectin), vitamins, and immunoglobulins, which closely mimic natural tears and create a nutritive environment that supports epithelial regeneration. Clinical studies report healing rates exceeding 50% in patients with PCEDs [36–39]. Preparation protocols for ASEDs vary, but typically involve diluting the patient's serum with sterile saline to concentrations between 20% and 100%. ASEDs offer advantages, including promotion of epithelial cell migration and enhanced lubrication, and may be beneficial in selected refractory cases when treatment with artificial tears is insufficient [40, 41].

Platelet-rich plasma (PRP) eye drops serve as another promising autologous blood-derived option, concentrated to deliver high levels of platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), which may support tissue repair and modulate inflammation. PRP has been investigated as an adjunctive treatment for refractory corneal ulcers and PCEDs, although the available clinical evidence remains limited and heterogeneous [30, 40]. Umbilical cord blood serum and platelet-rich fibrin tears are emerging modalities that may similarly promote corneal epithelial regeneration, though these require more extensive clinical validation [21, 30]. Furthermore, *in vitro* evidence suggests that platelet releasate has growth-factor–rich epitheliotrophic potential, although its clinical efficacy in PCEDs remains to be established [43].

Topical insulin, a novel agent recently studied, has shown promising epithelial wound-closure outcomes in patients with refractory PCEDs [44]. Matrix-regenerating agents such as ReGeneraTing Agents and amniotic membrane extract eye drops are also being explored for their potential to enhance extracellular matrix remodeling and provide anti-inflammatory effects [21].

Role of therapeutic contact lenses and amniotic membrane transplantation: Therapeutic contact lenses and AMT have emerged as fundamental interventions in the management of PCEDs, especially when conservative medical therapies fail to achieve complete healing. BCLs are widely utilized in PCEDs due to their ability to protect the compromised epithelium from mechanical trauma caused by blinking and eyelid movements. These lenses create a stable, hydrated microenvironment that facilitates epithelial cell migration and reduces pain and irritation. By acting as a physical barrier, BCLs reduce friction between the eyelids and the corneal surface while aiding in tear film stabilization [7, 30, 45]. Advanced contact lens designs such as gas-permeable mini-scleral lenses have recently gained attention for their therapeutic role in refractory PCEDs, especially in cases complicated by severe dry eye or neurotrophic keratopathy. These lenses vault over the cornea entirely, maintaining a fluid reservoir that continuously bathes the ocular surface in lubricating tears or autologous serum, which may support epithelial regeneration in selected refractory cases. It is important to monitor patients on therapeutic lenses closely to mitigate risks of infection, hypoxia, and lens intolerance. Concurrent prophylactic use of topical antibiotics is common to minimize infectious complications [25].

AMT offers a biologically active and surgical option for PCEDs refractory to medical and protective lens treatments. The amniotic membrane possesses anti-inflammatory, anti-fibrotic, and pro-epithelialization properties, making it an excellent substrate for promoting corneal surface healing [3, 14]. AMT can be applied as a graft or patch using sutures or fibrin glue to secure it onto the corneal surface. It facilitates epithelial migration, downregulates pro-inflammatory cytokines, suppresses protease activity, and promotes stromal remodeling. Clinical studies have demonstrated high success rates, with many patients achieving complete re-epithelialization and symptomatic relief after AMT [3]. Recent advances include the use of dehydrated and preserved amniotic membranes, which simplify storage and application while retaining biological activity. AMT is also utilized in conjunction with other therapies such as therapeutic lenses, autologous serum, and nerve growth factor treatments to optimize healing outcomes [7].

Challenges and Future Directions

Despite advancements in understanding and treating PCEDs, several challenges remain that complicate effective management. One major difficulty is the heterogeneity of etiologies underlying PCEDs, including diverse conditions such as LSCD, neurotrophic keratopathy, severe dry eye, and systemic diseases like diabetes mellitus. Tailoring treatment to address this broad spectrum requires comprehensive diagnostic precision and personalized therapeutic approaches. Another challenge is the frequent refractoriness of PCEDs to conventional therapies such as lubricants, BCLs, and ASEDs, necessitating escalation to more advanced and costly medical or surgical treatments. Accessibility and cost of novel therapies like rhNGF and limbal stem cell transplantation may limit widespread adoption, especially in resource-limited settings [14, 21].

Monitoring and compliance present additional barriers: many therapeutic regimens are complex and require frequent administration or regular clinical visits for evaluation, demanding high patient adherence and clinical expertise to optimize outcomes [14]. Emerging treatments, including advanced cell therapies, molecular agents, bioengineered scaffolds, and innovative surgical techniques such as corneal neurotization, are being investigated as potential approaches to overcoming some of these limitations. However, further large-scale clinical trials and long-term safety studies are needed to establish standardized protocols, optimal dosing, and integration into clinical practice [7].

Strengths of this review include its comprehensive synthesis of contemporary evidence across cellular, molecular, medical, and surgical domains, providing an integrated framework for understanding the multifactorial nature of PCEDs and their

evolving therapeutic landscape. The inclusion of literature spanning multiple decades allows identification of both established principles and emerging technologies with clinical relevance. However, as a narrative rather than systematic review, it is inherently subject to selection bias and may not capture all available evidence. Variability in study design, heterogeneous patient populations, and limited high-quality comparative trials constrain the generalizability of conclusions. Additionally, the rapid pace of innovation in regenerative and biologic therapies may outstrip currently published data, indicating the need for ongoing rigorous evaluation. Future research directions emphasize the development of minimally invasive, sustained-release drug delivery systems and personalized medicine approaches based on biomarker profiling for targeted intervention. Combination therapies that simultaneously address epithelial regeneration, inflammation, and nerve function may yield more durable healing responses.

CONCLUSIONS

PCEDs are a complex clinical entity marked by delayed or absent corneal re-epithelialization, with the potential for severe visual morbidity if left untreated. This narrative review highlighted the anatomy and physiological underpinnings of the corneal epithelium, and PCEDs' multifactorial pathophysiology, clinical presentation, diagnostic considerations, and current management strategies. Conservative care remains foundational, emphasizing ocular surface protection, lubrication, and infection control. Medical therapies that supply growth factors, such as ASEDs and recombinant growth factors, have expanded treatment options significantly. Therapeutic contact lenses and AMT provide important mechanical and biological scaffolds for healing. Emerging approaches involving stem cell therapy, molecular agents, neurotization surgery, and bioengineered drug delivery warrant further investigation for the management of refractory cases. Nonetheless, treatment of PCEDs remains challenging due to the diversity of causative factors and limited access to advanced therapies globally. Timely diagnosis, individualized care, and adoption of emerging therapies supported by high-quality clinical evidence will be essential in improving outcomes. Continued translational research is critical to refine treatments, enhance healing rates, prevent complications, and ultimately preserve vision in patients suffering from this sight-threatening condition.

ETHICAL DECLARATIONS

Ethical approval: Not required.

Conflict of interests: None.

FUNDING

None.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Wilson SE, Medeiros CS, Santhiago MR. Pathophysiology of Corneal Scarring in Persistent Epithelial Defects After PRK and Other Corneal Injuries. J Refract Surg. 2018 Jan 1;34(1):59-64. doi: 10.3928/1081597X-20171128-01. PMID: 29315443; PMCID: PMC5788463.
2. Wirostko B, Rafii M, Sullivan DA, Morelli J, Ding J. Novel Therapy to Treat Corneal Epithelial Defects: A Hypothesis with Growth Hormone. Ocul Surf. 2015 Jul;13(3):204-212.e1. doi: 10.1016/j.jtos.2014.12.005. Epub 2015 Mar 28. PMID: 26045234; PMCID: PMC4498999.
3. Maqsood S, Elsawah K, Dhillon N, Soliman S, Laginaf M, Lodhia V, Lake D, Hamada S, Elalfy M. Management of Persistent Corneal Epithelial Defects with Human Amniotic Membrane-derived Dry Matrix. Clin Ophthalmol. 2021 May 28;15:2231-2238. doi: 10.2147/OPTH.S299141. PMID: 34093006; PMCID: PMC8169046.
4. Ahmad S. Concise review: limbal stem cell deficiency, dysfunction, and distress. Stem Cells Transl Med. 2012 Feb;1(2):110-5. doi: 10.5966/sctm.2011-0037. Epub 2012 Jan 26. PMID: 23197757; PMCID: PMC3659689.
5. Chen HF, Yeung L, Yang KJ, Sun CC. PERSISTENT CORNEAL EPITHELIAL DEFECT AFTER PARS PLANA VITRECTOMY. Retina. 2016 Jan;36(1):148-55. doi: 10.1097/IAE.0000000000000657. PMID: 26166798.
6. Vajpayee RB, Thomas S, Sharma N, Dada T, Tabin GC. Large-diameter lamellar keratoplasty in severe ocular alkali burns: A technique of stem cell transplantation. Ophthalmology. 2000 Sep;107(9):1765-8. doi: 10.1016/s0161-6420(00)00250-5. PMID: 10964842.
7. Thia ZZ, Ho YT, Shih KC, Tong L. New developments in the management of persistent corneal epithelial defects. Surv Ophthalmol. 2023 Nov-Dec;68(6):1093-1114. doi: 10.1016/j.survophthal.2023.06.001. Epub 2023 Jun 8. PMID: 37301520.
8. Morishige N, Uemura A, Morita Y, Nishida T. Promotion of Corneal Epithelial Wound Healing in Diabetic Rats by the Fibronectin-Derived Peptide PHSRN. Cornea. 2017 Dec;36(12):1544-1548. doi: 10.1097/ICO.0000000000001344. PMID: 28834817.
9. Feizi S, Masoudi A, Hosseini SB, Kanavi MR, Javadi MA. Microbiological Evaluation of Bandage Soft Contact Lenses Used in Management of Persistent Corneal Epithelial Defects. Cornea. 2019 Feb;38(2):146-150. doi: 10.1097/ICO.0000000000001810. PMID: 30422865.
10. Sridhar MS. Anatomy of cornea and ocular surface. Indian J Ophthalmol. 2018 Feb;66(2):190-194. doi: 10.4103/ijo.IJO_646_17. PMID: 29380756; PMCID: PMC5819093.
11. DelMonte DW, Kim T. Anatomy and physiology of the cornea. J Cataract Refract Surg. 2011 Mar;37(3):588-98. doi: 10.1016/j.jcrs.2010.12.037. PMID: 21333881.

12. Torricelli AA, Singh V, Santhiago MR, Wilson SE. The corneal epithelial basement membrane: structure, function, and disease. Invest Ophthalmol Vis Sci. 2013 Sep 27;54(9):6390-400. doi: 10.1167/iovs.13-12547. PMID: 24078382; PMCID: PMC3787659.
13. Wong HL, Poon SHL, Bu Y, Lo ACY, Jhanji V, Chan YK, Shih KC. A Systematic Review on Cornea Epithelial-Stromal Homeostasis. Ophthalmic Res. 2021;64(2):178-191. doi: 10.1159/000509030. Epub 2020 May 29. PMID: 32474566.
14. Vaidyanathan U, Hopping GC, Liu HY, Somani AN, Ronquillo YC, Hoopes PC, Moshirfar M. Persistent Corneal Epithelial Defects: A Review Article. Med Hypothesis Discov Innov Ophthalmol. 2019 Fall;8(3):163-176. PMID: 31598519; PMCID: PMC6778469.
15. Yan C, Jin L, Zhang Q, Liu X, Yu T, Zhao F, Mu Y, Xu J, Zhang L. Management of delayed corneal epithelial healing after refractive surgery: five case reports. Front Med (Lausanne). 2025 Mar 4;12:1517403. doi: 10.3389/fmed.2025.1517403. PMID: 40103788; PMCID: PMC11913852.
16. Fatima A, Iftekhar G, Sangwan VS, Vemuganti GK. Ocular surface changes in limbal stem cell deficiency caused by chemical injury: a histologic study of excised pannus from recipients of cultured corneal epithelium. Eye (Lond). 2008 Sep;22(9):1161-7. doi: 10.1038/sj.eye.6702895. Epub 2007 Jun 8. PMID: 17558385.
17. Sangwan VS. Limbal stem cells in health and disease. Biosci Rep. 2001 Aug;21(4):385-405. doi: 10.1023/a:1017935624867. PMID: 11900318.
18. Sacchetti M, Lambiase A. Neurotrophic factors and corneal nerve regeneration. Neural Regen Res. 2017 Aug;12(8):1220-1224. doi: 10.4103/1673-5374.213534. PMID: 28966630; PMCID: PMC5607810.
19. Sejpal K, Bakhtiari P, Deng SX. Presentation, diagnosis and management of limbal stem cell deficiency. Middle East Afr J Ophthalmol. 2013 Jan-Mar;20(1):5-10. doi: 10.4103/0974-9233.106381. PMID: 23580847; PMCID: PMC3617528.
20. Napoli PE, Braghiroli M, Iovino C, Demarinis G, Fossarello M. A study of refractory cases of persistent epithelial defects associated with dry eye syndrome and recurrent corneal erosions successfully treated with cyclosporine A 0.05% eye drops. Drug Des Devel Ther. 2019 Jun 19;13:2001-2008. doi: 10.2147/DDDT.S207453. PMID: 31354245; PMCID: PMC6590396.
21. Kwon JE, Kang C, Moghtader A, Shahjahan S, Bibak Bejandi Z, Alzein A, Djalilian AR. Emerging Treatments for Persistent Corneal Epithelial Defects. Vision (Basel). 2025 Apr 1;9(2):26. doi: 10.3390/vision9020026. PMID: 40265394; PMCID: PMC12015846.
22. Hamrah P, Cruzat A, Dastjerdi MH, Zheng L, Shahatit BM, Bayhan HA, Dana R, Pavan-Langston D. Corneal sensation and subbasal nerve alterations in patients with herpes simplex keratitis: an in vivo confocal microscopy study. Ophthalmology. 2010 Oct;117(10):1930-6. doi: 10.1016/j.ophtha.2010.07.010. Epub 2010 Sep 1. PMID: 20810171; PMCID: PMC2949523.
23. Vera-Duarte GR, Jimenez-Collado D, Kahuam-López N, Ramirez-Miranda A, Graue-Hernandez EO, Navas A, Rosenblatt MI. Neurotrophic keratopathy: General features and new therapies. Surv Ophthalmol. 2024 Sep-Oct;69(5):789-804. doi: 10.1016/j.survophthal.2024.04.004. Epub 2024 Apr 26. PMID: 38679146.
24. Srinivas SP, Rao SK. Ocular surface staining: Current concepts and techniques. Indian J Ophthalmol. 2023 Apr;71(4):1080-1089. doi: 10.4103/ijo.IJO_2137_22. PMID: 37026238; PMCID: PMC10276680.
25. Vilares Morgado R, Moura R, Moreira R, Falcão-Reis F, Pinheiro-Costa J. New Promising Therapeutic Approach for Refractory Corneal Epithelial Defects. Cureus. 2023 May 22;15(5):e39324. doi: 10.7759/cureus.39324. PMID: 37351246; PMCID: PMC10283014.
26. Katzman LR, Jeng BH. Management strategies for persistent epithelial defects of the cornea. Saudi J Ophthalmol. 2014 Jul;28(3):168-72. doi: 10.1016/j.sjopt.2014.06.011. Epub 2014 Jul 2. PMID: 25278792; PMCID: PMC4181455.
27. Vazirani J, Kate A, Agarwal S, Basu S, Bhalekar S, Chaudhary S, D'Souza S, Fogla R, Gour A, Goel S, Gokhale NS, Gupta N, Joshi P, Mehta P, Mittal V, Murthy SI, Pillai VS, Shanbhag SS, Singh S, Srinivasan B, Suman S, Sangwan VS. Preservative Related Ocular Surface Toxicity and the Need for Preservative Free Eye Drops in Ocular Surface Disorders - Recommendations of an Expert Group. Semin Ophthalmol. 2025 Sep 12:1-4. doi: 10.1080/08820538.2025.2555903. Epub ahead of print. PMID: 40937610.
28. Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, Dong PN, Geerling G, Hida RY, Liu Y, Seo KY, Tauber J, Wakamatsu TH, Xu J, Wolffsohn JS, Craig JP. TFOS DEWS II Management and Therapy Report. Ocul Surf. 2017 Jul;15(3):575-628. doi: 10.1016/j.jtos.2017.05.006. Epub 2017 Jul 20. PMID: 28736343.
29. Tuli SS, Schultz GS, Downer DM. Science and strategy for preventing and managing corneal ulceration. Ocul Surf. 2007 Jan;5(1):23-39. doi: 10.1016/s1542-0124(12)70050-2. PMID: 17252163.
30. Golhait P, Peseyie R. Persistent Epithelial Defect. 2023 Jul 31. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 34424633.
31. Vote BJ, Elder MJ. Cyanoacrylate glue for corneal perforations: a description of a surgical technique and a review of the literature. Clin Exp Ophthalmol. 2000 Dec;28(6):437-42. doi: 10.1046/j.1442-9071.2000.00351.x. PMID: 11202468.
32. Chan SM, Tseng CL, Huang WH, Lin CT. Therapeutic Assessment of Diverse Doxycycline-Based Formulations in Promoting Deep Corneal Wound Healing: Evidence from a Rat Model. Vet Sci. 2025 Feb 8;12(2):143. doi: 10.3390/vetsci12020143. PMID: 40005905; PMCID: PMC11860526.
33. Hossain P. The corneal melting point. Eye (Lond). 2012 Aug;26(8):1029-30. doi: 10.1038/eye.2012.136. Epub 2012 Jul 6. PMID: 22766538; PMCID: PMC3420049.
34. Yu FS, Yin J, Xu K, Huang J. Growth factors and corneal epithelial wound healing. Brain Res Bull. 2010 Feb 15;81(2-3):229-35. doi: 10.1016/j.brainresbull.2009.08.024. Epub 2009 Sep 4. PMID: 19733636; PMCID: PMC3010187.
35. Labetoulle M, Baudouin C, Calonge M, Merayo-Lloves J, Boboridis KG, Akova YA, Aragona P, Geerling G, Messmer EM, Benítez-Del-Castillo J. Role of corneal nerves in ocular surface homeostasis and disease. Acta Ophthalmol. 2019 Mar;97(2):137-145. doi: 10.1111/aos.13844. Epub 2018 Sep 17. PMID: 30225941.
36. Poon AC, Geerling G, Dart JK, Fraenkel GE, Daniels JT. Autologous serum eyedrops for dry eyes and epithelial defects: clinical and in vitro toxicity studies. Br J Ophthalmol. 2001 Oct;85(10):1188-97. doi: 10.1136/bjo.85.10.1188. PMID: 11567963; PMCID: PMC1723716.
37. Young AL, Cheng AC, Ng HK, Cheng LL, Leung GY, Lam DS. The use of autologous serum tears in persistent corneal epithelial defects. Eye (Lond). 2004 Jun;18(6):609-14. doi: 10.1038/sj.eye.6700721. PMID: 15184926.

38. Phan TM, Foster CS, Boruchoff SA, Zagachin LM, Colvin RB. Topical fibronectin in the treatment of persistent corneal epithelial defects and trophic ulcers. Am J Ophthalmol. 1987 Nov 15;104(5):494-501. doi: 10.1016/s0002-9394(14)74107-8. PMID: 3674183.
39. Jeng BH, Dupps WJ Jr. Autologous serum 50% eyedrops in the treatment of persistent corneal epithelial defects. Cornea. 2009 Dec;28(10):1104-8. doi: 10.1097/ICO.0b013e3181a2a7f6. PMID: 19730088.
40. Shtein RM, Shen JF, Kuo AN, Hammersmith KM, Li JY, Weikert MP. Autologous Serum-Based Eye Drops for Treatment of Ocular Surface Disease: A Report by the American Academy of Ophthalmology. Ophthalmology. 2020 Jan;127(1):128-133. doi: 10.1016/j.ophtha.2019.08.018. Epub 2019 Sep 24. PMID: 31561880.
41. Vazirani J, Sridhar U, Gokhale N, Doddigarla VR, Sharma S, Basu S. Autologous serum eye drops in dry eye disease: Preferred practice pattern guidelines. Indian J Ophthalmol. 2023 Apr;71(4):1357-1363. doi: 10.4103/IJO.IJO_2756_22. PMID: 37026267; PMCID: PMC10276663.
42. Anam A, Liu C, Tong L, Liu YC. Blood-Derived Eye Drops for the Treatment of Corneal Neuropathic Pain. J Ocul Pharmacol Ther. 2024 Jun;40(5):281-292. doi: 10.1089/jop.2023.0155. Epub 2024 Apr 22. PMID: 38648544; PMCID: PMC11296151.
43. Hartwig D, Harloff S, Liu L, Schlenke P, Wedel T, Geerling G. Epitheliotrophic capacity of a growth factor preparation produced from platelet concentrates on corneal epithelial cells: a potential agent for the treatment of ocular surface defects? Transfusion. 2004 Dec;44(12):1724-31. doi: 10.1111/j.0041-1132.2004.04079.x. PMID: 15584987.
44. Abdi P, Ghaffari R, Azad N, Alshaheeb A, Latifi G, Soltani Shahgoli S, Fakhredin H. Topical insulin for refractory persistent corneal epithelial defects. Sci Rep. 2024 May 30;14(1):12459. doi: 10.1038/s41598-024-63091-y. PMID: 38816428; PMCID: PMC11139959.
45. Lim L, Lim EWL. Therapeutic Contact Lenses in the Treatment of Corneal and Ocular Surface Diseases-A Review. Asia Pac J Ophthalmol (Phila). 2020 Dec;9(6):524-532. doi: 10.1097/APO.0000000000000331. PMID: 33181548.