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Ophthalmic Sequelae of Epidermolysis Bullosa: Pathophysiology, Clinical Implications, and Emerging Therapies

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Abstract

Epidermolysis bullosa (EB) is a rare, genetically heterogeneous group of inherited mechanobullous disorders characterized by extreme skin and mucosal fragility, affecting approximately 1 in 20,000 live births. Although dermatologic manifestations are most recognized, EB can also cause a range of ocular complications that significantly impact quality of life, including recurrent corneal erosions, conjunctival fibrosis, symblepharon, and progressive vision loss. Ocular involvement varies by EB subtype: epidermolysis bullosa simplex, junctional EB, dystrophic EB, and Kindler syndrome, each associated with distinct patterns of genetic mutations and tissue cleavage. Chronic inflammation, mechanical trauma, and fibrosis contribute to a self-perpetuating cycle of ocular surface damage in EB, indicating the need for early diagnosis and intervention. Diagnostic approaches such as slit-lamp biomicroscopy, anterior segment OCT, in vivo confocal microscopy, and genetic testing are critical for characterizing ocular involvement and guiding management. Current therapies focus on preserving the ocular surface through lubrication, scleral lenses, anti-inflammatory medications, and surgical correction of eyelid malpositions. However, emerging advances, including gene therapy, CRISPR/Cas9 gene editing, stem cell-based corneal regeneration, and nanoparticle-mediated drug delivery, offer new avenues for targeted, disease-modifying treatments. These innovations hold promise for improving long-term visual outcomes and reducing the burden of ocular morbidity in EB. A multidisciplinary, precision-medicine approach remains essential to optimizing care and advancing future therapies for this complex and debilitating disorder.

Keywords: epidermolysis bullosa, kindler syndrome, corneal erosions, conjunctival fibrosis, dry eye, regenerative medicine

I. Introduction

Epidermolysis bullosa (EB) is a rare group of inherited mechanobullous disorders that produces extreme fragility of the skin and mucous membranes. It affects approximately 1 in 20,000 live births and often presents with skin blistering, erosions, and poor wound healing following minor trauma [1]. While its dermatologic manifestations are the most common and most recognized, EB can also affect other tissues, including the eyes, where it may cause multiple complications that can lead to permanent vision loss. The four main subtypes of epidermolysis bullosa include epidermolysis bullosa simplex, junctional EB, dystrophic EB, and Kindler syndrome, each defined by the level of skin cleavage and associated genetic mutations [2]. These subtypes not only vary in their severity and systemic involvement, but also in their ocular manifestations. For instance, while EBS may involve minor eyelid blistering and dry eye symptoms, more severe subtypes like junctional EB and recessive DEB may lead to conjunctival scarring, corneal neovascularization, and vision loss [3]. Kindler syndrome, a subtype with a mixed cleavage pattern, may lead to photosensitivity and early-onset keratopathy [4]. These distinct subtypes of EB stress the importance of early recognition and subtype-specific management of ocular complications.

Ocular complications in epidermolysis bullosa (EB) can profoundly impact patients' quality of life. The combination of persistent eye discomfort, recurrent erosions, and visual disturbances makes it difficult for patients to carry out daily activities [3]. These manifestations, however, are frequently underrecognized and underdiagnosed, partly due to their variable presentation and overlap with other EB-related symptoms [3, 5]. In this review, we aim to comprehensively examine the current understanding of EB-related ocular disease by exploring the underlying pathophysiology, characterizing the clinical spectrum of ocular involvement across EB subtypes, and detailing the diagnostic strategies and current management approaches. Additionally, we will highlight promising emerging therapies, including gene and stem cell-based interventions, that offer hope for improving outcomes in patients affected by EB.

II. Pathophysiology of ocular involvement in EB

Genetic mutations that affect structural proteins necessary for the adhesion of epithelial tissues are the basis of ocular manifestations in epidermolysis bullosa (EB). In epidermolysis bullosa simplex (EBS), mutations in both the KRT5 and KRT14 genes that encode keratins 5 and 14 result in a cytoskeletal network disruption in basal keratinocytes [6]. These mutations result in intraepidermal cleavage and fragility of the cells that also involve ocular epithelial structures, rendering them susceptible to trauma-induced erosions [6]. Additionally, defects in LAMA3, LAMB3, and LAMC2 cause junctional EB (JEB) via mutations that disrupt hemidesmosomes and

anchoring filaments, which play a core role in stabilizing the basal epithelium and conjunctival surfaces [7]. Such impairment leads to disruption of dermal-epidermal integrity and ocular surface adhesion, which may cause chronically persisting erosions in conjunctival and corneal tissue [7]. Mutations in COL7A1, a gene that encodes type VII collagen, affect dystrophic EB (DEB) [3]. Loss of these fibrils leads to reduced adhesion of the basement membrane to the underlying stroma, predisposing them to development of corneal blistering and scarring with minimal trauma [8]. In Kindler syndrome, caused by *FERMT1* mutations, the pathology is more complex due to multi-level cleavage affecting both epithelial and subepithelial layers [9, 10]. The result is fragility across multiple ocular structures, including the conjunctiva, eyelids, and lacrimal apparatus [9, 10].

Chronic inflammation plays a key role in ocular complications of EB, most prominently in severe variants of the disease such as recessive DEB and Kindler syndrome [9, 10]. Impacts of a structural protein defect lead to repeated epithelial injury and an ongoing inflammatory response, catalyzing elevated levels of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [10]. These cytokines have a dual role, attracting immune cells to the area of injury but also activating downstream fibrotic pathways, which mediate tissue remodelling and scar formation [10]. In the conjunctiva, chronic inflammation causes enhanced release of fibrogenic growth factors, such as transforming growth factor-beta (TGF-β), that stimulates fibroblast activation and collagen deposition [9]. This cascade results in conjunctival fibrosis, which may lead to symblepharon formation as the palpebral and bulbar conjunctiva fuse [9]. In addition, chronic inflammation around the eyelid margins leads to cicatricial ectropion, trichiasis, and loss of lashes resulting in accelerated corneal abrasion and breaking down ocular surface homeostasis [9]. Over time, these inflammatory changes become self-perpetuating, establishing a feedforward effect in which inflammation leads to fibrosis and fibrosis in turn promotes inflammation mediated by impaired barrier function and mechanical stress [10]. This long-term inflammatory and fibrotic environment poses a markedly increased risk for sight-threatening sequelae and serves to highlight the imperative for early anti-inflammatory therapies [9, 10].

Lacrimal dysfunction in EB arises not only from anatomical deformities but also from fibrosis-driven glandular damage [9]. Chronic inflammation involving the lacrimal gland ducts, meibomian glands, and accessory tear-producing structures can result in severe aqueous and lipid layer deficiencies [9]. More specifically, the fibrosis of lacrimal excretory ducts decreases normal secretion of tears, whereas meibomian gland dropout decreases lipid secretion, resulting in an unstable tear film deposit and increased tear evaporation [9, 10]. Moreover, loss of conjunctival goblet cells due to scarring and keratinization reduces the production of mucins, which are integral to the attachment of tears to the ocular surface [9]. The result is keratoconjunctivitis sicca, or dry eye disease, a condition that not only causes discomfort and photophobia but also predisposes the eye to epithelial erosions and secondary infections [9]. Dry eye is known to be very severe, especially in conjunction with blinking anomalies resulting from eyelid malpositioning, which cause persistent corneal epithelial defects and compromised wound healing [9]. Corneal neovascularization and opacification may also occur, exacerbating visual decline [9]. This dry, inflamed ocular surface is particularly susceptible in Kindler syndrome, where there may additionally be limbal stem cell deficiency, exacerbating regenerative failure [9].

EB patients have mechanical fragility of the ocular epithelium that renders the cornea and conjunctiva extremely vulnerable to trauma, even that occurring from normal blinking, eye rubbing, or the use of contact lenses [8]. These subtle traumas lead to recurrent corneal erosions, which are not only painful but also serve as portals of entry for pathogens [11]. Repetitive injuries breach the epithelial barrier and disrupt its protective capacity against microbial colonization [6]. Chronic erosions may be colonized by bacterial flora, most frequently by Staphylococcus aureus and Pseudomonas aeruginosa, and may result in microbial keratitis [11]. If left untreated, this can lead to corneal ulceration, stromal melting, and ultimately perforation, resulting in irreversible vision loss [11]. In addition, a compromised epithelial barrier complicates the use of contact lenses or surgical options that may be beneficial [8]. The inflammatory response to infection further activates fibrotic pathways, adding to the cycle of scarring and visual impairment [12]. In advanced cases, patients may develop corneal pannus, opacification, and neovascularization, which significantly reduce the clarity of the visual axis [6, 8]. Because of this progressive pattern, preventing trauma, treating early infections aggressively, and maintaining epithelial health through lubrication and anti-inflammatory therapies are critical for preserving ocular function in EB patients [8, 11].

III. Clinical spectrum of ocular manifestations across EB subtypes

While epidermolysis bullosa (EB) is primarily known for its cutaneous manifestations, its impact on ocular health varies significantly by subtype. The frequency and severity of ocular involvement tend to correlate with the depth of tissue and overall disease severity. Epidermolysis bullosa simplex (EBS), the most common and typically mildest form of EB, primarily presents with intraepidermal blistering of the skin in response to minor mechanical trauma. Ocular involvement is generally less frequent and severe compared to the junctional and recessive dystrophic subtypes, with studies showing minimal structural changes and a lower incidence of symptoms in EBS patients [4, 13]. However, large registry data and case series have reported that a subset of patients, particularly those with more severe forms of EBS, may still experience vision loss and complications including recurrent erosions, corneal scarring, pannus formation, and eyelid blistering [8, 14]. EBS patients also remain at risk for meibomian gland dysfunction, which is a known contributor to evaporative dry eye disease and blepharitis [15, 16]. Although typically milder, ocular manifestations in EBS should not be overlooked, especially in more severe phenotypes.

Junctional epidermolysis bullosa (JEB) is a more severe form of epidermolysis bullosa (EB) that presents with extensive blistering at the level of the lamina lucida in the skin. Correspondingly, ocular involvement is more common and often more severe than in epidermolysis bullosa simplex, with frequent reports of corneal blistering and erosions [3, 14]. These recurrent epithelial injuries increase the risk of progressive scarring and vision loss over time. As corneal erosions persist, complications such as conjunctival fibrosis and symblepharon can develop, restricting eye movement and impacting quality of

life [17]. Additional findings in JEB include corneal opacification and neovascularization, which contribute to chronic inflammation, scarring, and a cycle of worsening visual impairment [18]. Without timely management, this ongoing damage can lead to significant and potentially irreversible vision loss.

Recessive dystrophic epidermolysis bullosa (RDEB) is the most severe subtype of epidermolysis bullosa (EB), marked by deep dermal blistering and significant systemic involvement, including a high burden of ocular complications. Compared to epidermolysis bullosa simplex and junctional EB, RDEB is associated with a greater prevalence and earlier onset of eye-related symptoms, including recurrent corneal erosions, eyelid blistering, photophobia, and ocular pain [8, 14]. As the disease advances, fibrosis and corneal scarring become prominent, often leading to reduced visual acuity and progressive ocular service damage [19]. Recurrent erosions can result in eyelid cicatrization, which may lead to malpositions such as ectropion or entropion, which are conditions that disturb the tear film and expose the cornea to chronic irritation and mechanical trauma [3, 20]. This cycle of inflammation, scarring, and exposure increases the risk of keratitis, corneal ulceration, and eventual vision loss [8, 21, 22]. RDEB poses the greatest threat to long-term visual function among the EB subtypes and requires early, proactive ophthalmic management.

Kindler syndrome, a rare subtype of epidermolysis bullosa, shares many ocular features with more severe forms like recessive dystrophic epidermolysis bullosa including cicatrizing conjunctivitis, ectropion, recurrent corneal erosions, symblepharon, and conjunctival scarring. However, it is uniquely characterized by marked photosensitivity, which contributes to chronic UV-induced conjunctival inflammation and keratitis, compounding the risk of ocular surface damage [9, 23]. Additional findings such as pigment deposition over the lens and the potential for early-onset cataract formation have been linked to ongoing oxidative stress and tear film instability [9, 24]. Persistent ocular irritation in Kindler syndrome can also lead to progressive corneal thinning and scarring, with severe complications documented in patients as young as 10 years old [9, 25]. Given its early onset and chronic progression, Kindler syndrome requires vigilant ocular monitoring and early intervention to minimize long-term visual impairment.

IV. Diagnostic approaches for EB-related ocular disease

Slit-lamp biomicroscopy is essential for detecting ocular surface abnormalities in patients with epidermolysis bullosa (EB). The high-resolution imaging technique allows for detailed examination of anterior segment structures and is especially useful for identifying corneal erosions, conjunctival fibrosis, and eyelid malpositions in EB [26]. Corneal erosions, often seen in the junctional and dystrophic subtypes, reflect basement membrane fragility and appear as green fluorescing patches when fluorescein dye is applied [26]. Conjunctival fibrosis, which is common in recessive dystrophic EB, can manifest as symblepharon, where the palpebral and bulbar conjunctiva fuse [27]. Eyelid issues like cicatricial ectropion or trichiasis, which are also identifiable via slit lamp, must be addressed early as they carry significant risks for corneal trauma and infection. Anterior segment optical coherence tomography (AS-OCT) complements slit-lamp findings by offering cross-sectional imaging of corneal layers. In EB, AS-OCT helps identify early epithelial basement membrane irregularities, particularly in junctional and dystrophic forms [28, 29]. Additionally, diagnostic dyes such as fluorescein and Lissamine Green are instrumental in evaluating ocular surface integrity in epidermolysis bullosa (EB). Fluorescein highlights epithelial disruptions, aiding in detection of corneal defects and helping monitor the healing progression in patients with repeated corneal injuries [30]. Lissamine Green stains devitalized conjunctival cells, providing a marker for ocular surface damage or inflammation [31]. Together, these diagnostics provide a comprehensive, non-invasive approach to identifying and monitoring the spectrum of anterior segment abnormalities seen in EB.

In vivo confocal microscopy (IVCM) offers real-time, cellular-level imaging of the cornea and is especially valuable in epidermolysis bullosa (EB) for assessing corneal nerve density, epithelial morphology, and healing capacity. EB patients often show reduced sub-basal nerve density from chronic inflammation or trauma, contributing to impaired corneal sensation and delayed epithelial repair, which are central to EB-related dry eye and post-surgical healing [32, 33, 34]. IVCM also reveals abnormal epithelial and stromal cell patterns indicative of active degeneration or scarring [35], making it a critical tool for monitoring disease progression. For definitive diagnosis and subtype classification, histopathology and immunofluorescence mapping are essential. Histologic analysis distinguishes EB subtypes by cleavage level: EBS within the epidermis, JEB at the lamina lucida, and DEB beneath the lamina densa [36, 37]. IFM further differentiates subtypes through basement membrane protein expression: loss of Laminin-332 in JEB is linked to corneal erosions and symblepharon, while type VII collagen deficiency in DEB is associated with conjunctival fibrosis [38, 39, 40]. Together, these advanced diagnostic tools offer complementary insights into the structural, cellular, and molecular features of EB-related ocular disease, enabling more accurate classification and personalized management.

Genetic testing plays a central role in diagnosing epidermolysis bullosa (EB), allowing clinicians to predict disease courses and guide management. Gene panels have identified mutations in at least 11 genes, including *KRT5*, *KRT14*, *COL7A1*, *LAMA3*, *LAMB3*, and *FERMT1*, that correspond to the four major EB subtypes [41]. In addition to confirming the subtype, genetic testing provides insight into inheritance patterns and mutation severity. For instance, truncating mutations in COL7A1 are associated with more severe RDEB phenotypes and increased risk of ocular scarring and keratinization [42, 43]. Knowledge of the specific mutation allows clinicians to anticipate complications such as corneal erosions, conjunctival fibrosis, and lacrimal gland dysfunction, and to tailor surveillance and interventions accordingly.

V. Current management strategies for ocular complications in EB

Current management strategies for ocular complications in epidermolysis bullosa (EB) primarily focus on symptomatic and supportive care aimed at minimizing trauma and maintaining ocular surface integrity. Regular use of preservative-free artificial tears and lubricating ointments helps reduce corneal friction, which is essential in preventing epithelial breakdown [8, 14]. For patients with recurrent corneal erosions, scleral lenses and bandage contact lenses serve as protective barriers, promoting epithelial healing and reducing discomfort [44]. For

patients with severe dry eye disease, moisture chamber goggles can provide significant relief by maintaining a humid environment around the eyes and reducing tear evaporation [45]. Different pharmacologic and biologic interventions are used to manage the inflammatory and infectious aspects of EB-related ocular disease. Topical antibiotics, such as erythromycin and moxifloxacin, are frequently prescribed to prevent bacterial infections, particularly in cases of cornea erosion [3]. For patients with chronic conjunctival inflammation, corticosteroid or cyclosporine eye drops can help control immune-mediated damage and reduce discomfort [3]. Autologous serum eye drops, which are rich in growth factors and nutrients, aid in corneal epithelial healing and help stabilize the ocular surface in patients with persistent epithelial defects [3].

In more advanced cases, surgical and tissue-based interventions may be necessary to address structural complications. Eyelid malpositions such as trichiasis, entropion, and ectropion can be corrected through procedures like blepharoplasty or tarsorrhaphy, which help protect the cornea from mechanical trauma [3]. For persistent corneal defects unresponsive to medical therapy, amniotic membrane transplantation offers both anti-inflammatory and epithelial-promoting benefits, facilitating ocular surface restoration. In cases of severe corneal scarring, corneal transplantation may be considered; however, it is often approached with caution due to high risk of graft rejection and the fragile ocular surface environment in EB patients [3].

VI. Emerging therapies and future directions

Recent advances in the treatment of epidermolysis bullosa (EB) have introduced promising options like gene therapy and targeted molecular approaches that offer hope for patients with this condition. These treatments aim to address the root cause of EB by correcting such as those in the COL7A1 gene, which plays a key role in producing type VII collagen, a protein that helps anchor the epidermis to the dermis [41]. Among the most notable developments is gene replacement therapy using beremagene geperpavec (B-VEC), a topical treatment delivered via viral vector that has demonstrated promising results in treating dystrophic EB [46]. B-VEC represents a meaningful step forward in promoting wound healing in EB patients [46]. However, its current limitations include an inability to prevent new blister formation, necessitating repeated applications to maintain its effectiveness [47]. While gene therapy like B-VEC marks significant progress in EB care, ongoing research is needed to achieve more durable, preventive solutions.

Another growing area of epidermolysis bullosa (EB) research focuses on gene editing technologies like CRISPR/Cas9, which offer the potential to directly repair pathogenic mutations at the DNA level. Unlike traditional gene therapy that relies on viral vectors, CRISPR-based strategies may achieve more durable or even permanent correction of genetic defects [46, 47]. Although still in early stages, preliminary findings suggest these tools can be used safely and effectively, with relatively low risk of off-target effects [46]. Beyond gene editing, emerging therapies such as exosome-based treatments and novel biomaterials are also contributing to advances in regenerative medicine for EB [7, 46]. Another promising avenue involves restoring laminin-332 expression in junctional EB, which has been shown to rescue YAP activity, a key regulator of epidermal stem cell renewal. This strategy may not only boost skin regeneration but also help stabilize the corneal epithelium by improving adhesion at the basement membrane [48]. Gene editing approaches, particularly CRISPR/Cas9, represent a step forward in EB treatment, with the potential to correct underlying mutations at their source.

Stem cell-based therapies are also attracting growing interest for their potential to address the ocular complications associated with epidermolysis bullosa (EB). One promising strategy under investigation is cultured limbal epithelial stem cell transplantation (CLET), which aims to regenerate the corneal surface by replenishing the cells damaged and depleted by recurrent corneal erosions, a frequent complication of EB that can progress to vision loss and eventual blindness [49]. CLET has already demonstrated success in treating various other ocular surface disorders and is now being explored as a potential option for EB-related eye damage [49]. Another innovative approach involves exosome-based therapies, which deliver regenerative molecules directly to injured tissues and have shown early promise in promoting wound healing and reducing inflammation in other ocular diseases [50]. Building on this, mesenchymal stem cells are also being studied for their ability to migrate to sites of injury and facilitate tissue repair. MSCs and their secreted exosomes may offer a less invasive and potentially safer therapeutic option for patients with both ocular and cutaneous EB manifestations [51]. Although these therapies are still in the early stages of research and clinical testing, they provide hope for the development of more targeted and effective treatments for EB.

Finally, lab-engineered corneal grafts are being investigated as a potential treatment option for severe ocular complications associated with epidermolysis bullosa (EB). These grafts are designed from specialized biomaterials that support corneal surface healing and regeneration. Recent research has demonstrated that these grafts can be created using a patient's own genetically modified cells, offering a more personalized therapeutic approach. In addition to promoting corneal repair, these grafts can help restore essential structural proteins, such as type VII collagen, which are critical for maintaining the integrity of both the skin and ocular tissues [52]. Alongside these advances, nanoparticle-based drug delivery systems are also emerging as a promising strategy to improve treatment outcomes. By employing distinct types of nanoparticles, researchers can more precisely deliver gene therapies to affected cells, enhancing therapeutic efficacy while reducing the risk of adverse effects [53]. Early clinical trials using these methods have shown encouraging results, with some patients demonstrating improved wound healing and more sustained skin integrity [52]. Bioengineered corneal grafts and nanoparticle-based delivery systems represent promising new technologies that offer more targeted, personalized, and effective treatment options for patients with EB.

VII. Conclusion

Ocular complications in epidermolysis bullosa (EB) represent a particularly debilitating aspect of an already complex and multisystemic disease. These complications, ranging from recurrent corneal erosions to conjunctival scarring and vision-threatening keratopathy, can progress rapidly if not addressed early, which reinforces the critical need for timely ophthalmologic intervention and longitudinal monitoring [14, 54]. Given the variable severity across EB subtypes, individualized care is essential. A multidisciplinary approach that includes ophthalmologists, dermatologists, geneticists, and other specialists ensures that management strategies are tailored

not only to the specific ocular findings, but to the patient's broader clinical and genetic profile as well.

Fortunately, emerging innovations in the fields of genetics, regenerative medicine, and tissue engineering offer new therapeutic possibilities. Gene therapy, particularly through CRISPR/Cas9-mediated editing of mutations like COL7A1, has shown potential in preclinical models to correct the underlying defects responsible for disease progression [55]. Likewise, stem cell transplantation and the application of biomaterials such as amniotic membrane grafts have demonstrated early promise in promoting ocular surface healing and reducing chronic inflammation [56, 57]. These interventions mark a shift from purely supportive care to potentially disease-modifying therapies. However, realizing their full clinical potential will undoubtedly require continued research into targeted molecular therapies and precision medicine approaches that address the unique pathophysiology of each EB subtype. Collaborative efforts in clinical trials and translational research will be vital to improving not only visual outcomes, but also quality of life for patients with EB.

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