VOLUME - 13, ISSUE - 11, NOVEMBER - 2024 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper | Medical Science

UNDERSTANDING EPIDERMOLYSIS BULLOSA: CHALLENGES AND FUTURE DIRECTIONS

Camila Andrea Ávila Romero MD. Universidad Militar Nueva Granada.

ABSTRACT Epidermolysis bullosa (EB) is a rare genetic disorder characterized by significant skin fragility, leading to recurrent blistering and chronic wounds. This narrative review examines the epidemiology, pathogenesis, clinical features, diagnostic approaches, and management strategies, including supportive and experimental therapies. Although no definitive cure exists, advances in gene therapy and novel wound treatments offer promising avenues. A multidisciplinary approach remains crucial for optimizing patient quality of life and long-term prognosis.

KEYWORDS : Epidermolysis bullosa, genetic disorder, skin fragility, multidisciplinary care, experimental therapies

INTRODUCTION

Epidermolysis bullosa (EB) is a group of rare genetic disorders characterized by extreme skin fragility, leading to blistering and wounds from minor trauma. EB is classified into four main types—simplex, junctional, dystrophic, and Kindler—each differing in severity, affected tissue layers, and genetic mutations. Patients with EB face complex challenges, including severe pain, risk of infections, nutritional deficits, and extracutaneous complications. Despite advancements in wound care and supportive therapies, there is currently no definitive cure. This review outlines current management practices, supportive care, and emerging therapeutic approaches aimed at improving the quality of life for individuals affected by EB (1).

Methods

A narrative review was conducted using four primary databases: PubMed, Scopus, Web of Science, and Embase. Keywords included "epidermolysis bullosa," "wound care," "genetic therapy," "pain management," and "nutritional support." Inclusion criteria focused on articles discussing the management, supportive care, and therapeutic advancements in epidermolysis bullosa. Studies from the past five years were prioritized to ensure the inclusion of the latest evidence. Data were screened and extracted independently to reduce bias. In total, 15 references were included in this review, providing a comprehensive overview of the current standards and innovations in EB management.

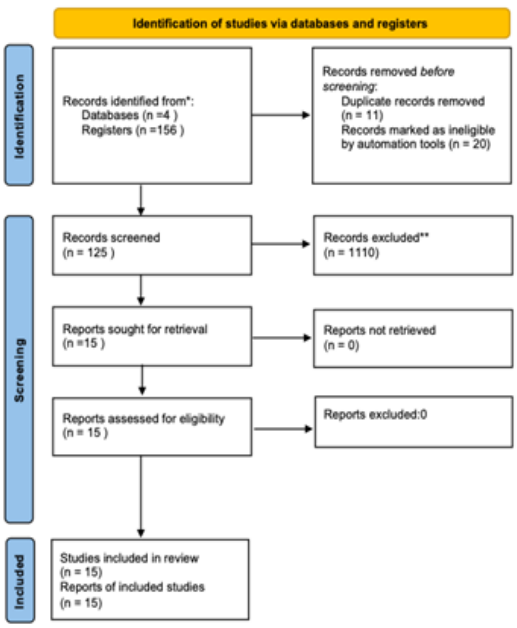

Figure 1. PRISMA.

Epidemiology

Epidermolysis bullosa (EB) is a rare group of genetic disorders characterized by skin fragility and blistering due to mutations affecting structural proteins. It affects approximately 1 in 20,000 live births globally, with prevalence varying by subtype and geographic region. EB is classified into four major types: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler syndrome. Severity ranges from mild to life-threatening, with JEB and severe DEB associated with significant morbidity and early mortality. The condition affects both sexes equally and can impact individuals of all ethnic backgrounds, although genetic counseling can help manage familial risk (1).

Pathogenesis

The pathogenesis of epidermolysis bullosa (EB) involves genetic mutations that disrupt proteins essential for skin integrity, leading to abnormal connections between skin layers. Mutations in genes responsible for proteins such as keratins, collagens, and laminins weaken the structural stability of the skin. The primary defect determines the EB subtype, with epidermolysis bullosa simplex (EBS) typically involving mutations in keratin genes, while junctional epidermolysis bullosa (JEB) is associated with abnormalities in laminin and integrin proteins, which affect the dermal-epidermal junction. Dystrophic epidermolysis bullosa (DEB) results from mutations in the COL7A1 gene, encoding type VII collagen, crucial for anchoring fibrils that secure the epidermis to the underlying dermis. In severe cases, these structural defects lead to chronic wounds, extensive scarring, and complications such as squamous cell carcinoma. Understanding the molecular mechanisms of EB is crucial for developing targeted therapies, including gene and protein replacement approaches, to potentially correct or mitigate the effects of these genetic mutations (2).

Classification

Epidermolysis bullosa (EB) is classified into four main types based on the location of tissue separation within the skin layers and the specific genetic mutations involved: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler syndrome. Each type presents distinct clinical manifestations and varying severities (3,4).

Epidermolysis Bullosa Simplex (EBS):

The most common and generally mildest form, EBS results from mutations in keratin genes (KRT5 and KRT14), causing blistering within the basal layer of the epidermis. Subtypes include localized EBS, generalized intermediate EBS, and generalized severe EBS. Patients may experience mild blistering, typically on hands and feet, with limited impact on daily activities (3,4).

Junctional Epidermolysis Bullosa (JEB):
JEB results from mutations in laminin and integrin genes, affecting the dermal-epidermal junction. It is typically more severe than EBS, with blistering and potential complications involving mucosal surfaces, nails, and other organs. Subtypes include JEB-Herlitz, which is often fatal in infancy, and JEB-non-Herlitz, which has a milder course(3,4).

Dystrophic Epidermolysis Bullosa (DEB):
Caused by mutations in the COL7A1 gene encoding type VII collagen, DEB affects the anchoring fibrils at the basement membrane. Subtypes include dominant DEB and recessive DEB, with the latter often presenting more severe symptoms, including scarring, mitten deformities, and risk of squamous cell carcinoma (3,4).

Kindler Syndrome:
This rare form of EB, caused by mutations in the FERMT1 gene, exhibits features overlapping other types and involves skin fragility, photosensitivity, and progressive skin atrophy (3,4).

Clinical Features
The clinical features of epidermolysis bullosa (EB) vary widely based on the type and severity of the disease. In **epidermolysis bullosa simplex (EBS)**, blistering typically occurs in response to minor trauma and is often localized to the hands and feet. Blisters form within the basal layer of the epidermis, generally heal without scarring, and are often painful, especially in warmer climates. In more severe cases, generalized blistering may affect larger body áreas (5).

Junctional epidermolysis bullosa (JEB) presents more severe symptoms, including extensive blistering at birth, involving both the skin and mucous membranes. Patients may experience oral and esophageal lesions, nail dystrophy, and dental abnormalities. Respiratory complications and feeding difficulties are common, particularly in severe subtypes such as JEB-Herlitz (6).

Dystrophic Epidermolysis Bullosa (DEB) leads to blistering below the basement membrane, resulting in significant scarring and fibrosis. In severe recessive DEB, scarring can cause mitten deformities of the hands and feet, and there is an increased risk of developing squamous cell carcinoma over time. Other features include oral lesions, esophageal strictures, and chronic anemia (6,7).

Kindler syndrome presents with photosensitivity, progressive skin atrophy, and blistering across various skin layers. Patients also have mucosal involvement and may develop gingivitis, esophageal strictures, and genitourinary complications. The severity and progression of clinical manifestations differ widely among individuals, necessitating individualized management and multidisciplinary care (7).

Diagnosis
Diagnosing epidermolysis bullosa (EB) requires a combination of clinical assessment, family history, and specialized laboratory tests. Initial diagnosis often begins with recognizing characteristic **clinical signs**, such as skin fragility, blistering, and mucosal involvement, which vary in severity based on the EB subtype. Blistering that appears spontaneously or after minor trauma, coupled with family history, often raises suspicion of EB in newborns or young children (8).

A key diagnostic tool is a **skin biopsy** with immunofluorescence antigen mapping or transmission electron microscopy. This biopsy involves taking a small sample of newly formed or induced blistered skin. Immunofluorescence antigen mapping identifies the level of skin separation by examining the presence and location of specific structural proteins. In epidermolysis bullosa simplex (EBS), for instance, the blister occurs within the basal layer of the epidermis, while in dystrophic epidermolysis bullosa (DEB), the separation is found below the basement membrane. Transmission electron microscopy allows visualization of the structural abnormalities at the ultrastructural level, confirming the location and nature of skin fragility (9).

Genetic testing is essential for accurate diagnosis, as it provides information on specific gene mutations responsible for EB. Over 20 genes are associated with EB, including mutations in **KRT5** and **KRT14** for EBS, **COL7A1** for DEB, and **LAMA3**, **LAMB3**, and **LAMC2** for junctional EB (JEB). Genetic testing, typically performed using next-generation sequencing or targeted gene panels, is critical in distinguishing among EB subtypes, understanding inheritance patterns, and facilitating genetic counseling.

Additional assessments, such as blood tests and imaging studies, may be performed to monitor **complications** associated with EB. For instance, frequent monitoring of blood counts helps assess anemia due to chronic blood loss and malnutrition, while bone density scans detect osteopenia or osteoporosis, particularly in severe forms like recessive DEB.

Prenatal diagnosis is possible in families with known EB mutations. Techniques such as chorionic villus sampling and amniocentesis allow detection of EB mutations early in pregnancy. Preimplantation genetic testing (PGT) is also an option for affected families seeking to prevent transmission of EB (10).

Treatment
The management of epidermolysis bullosa (EB) is largely supportive and aims to reduce symptoms, prevent complications, and improve quality of life, as there is no cure for EB. A multidisciplinary team, often involving dermatologists, EB-specialized nurses, nutritionists, pain specialists, and other healthcare professionals, is essential in developing a personalized care plan (11).

Wound Care is a primary focus, as blistering and skin fragility are hallmark features of EB. Non-adhesive dressings are applied to reduce trauma and promote healing, often combined with antimicrobial agents to prevent infections. Diluted bleach baths or compresses can help manage infection risk in wounds that are chronically colonized with bacteria. Novel therapies, including topical gene therapy with beremagene geperpavec (B-VEC) and oleogel-S10, are now available. B-VEC, approved for dystrophic EB, utilizes a viral vector to deliver a functional gene that promotes collagen production, aiding wound closure. Oleogel-S10, a topical gel containing birch triterpenes, has shown promise in enhancing wound healing (12).

Pain and Itch Management is critical, as EB patients often experience chronic pain due to frequent blistering and wounds. Analgesics such as acetaminophen or NSAIDs may be used for mild pain, while opioids are reserved for more severe cases. Gabapentin or pregabalin may be prescribed for chronic pain management. Topical opioids, like morphine sulfate in hydrogel, can be directly applied to wounds, providing localized pain relief without systemic side effects (13).

Nutritional Support addresses the high risk of malnutrition and micronutrient deficiencies due to difficulty in eating and chronic blood loss. Nutritional supplementation, including vitamins and minerals like iron, zinc, calcium, and vitamin D, is crucial for growth and immune function. In severe cases, gastrostomy feeding may be necessary (13,14).

Experimental Treatments are an evolving area in EB

management, including gene, protein, and cell-based therapies. Gene therapy research focuses on delivering functional genes to repair defective skin proteins, while stem cell transplantation and protein replacement therapy aim to improve skin integrity and reduce blistering (14).

Monitoring and Prevention of complications, such as squamous cell carcinoma and musculoskeletal deformities, are also integral to treatment. Regular follow-up appointments and screenings help detect complications early, enabling timely interventions (15).

REFERENCES

1. Fine JD, et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol. 2008;58:931-950.
2. Fine JD. Inherited epidermolysis bullosa. Orphanet J Rare Dis. 2010;5:12.
3. Intong LR, Murrell DF. Inherited epidermolysis bullosa: new diagnostic criteria and classification. Clin Dermatol. 2012;30(1):70-77.
4. El Hachem M, et al. Multicentre consensus recommendations for skin care in inherited epidermolysis bullosa. Orphanet J Rare Dis. 2014;9:76.
5. Wagner JE, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. N Engl J Med. 2010;363(7):629-639.
6. Titeux M,. Gene therapy for recessive dystrophic epidermolysis bullosa. Dermatol Clin. 2010;28(2):361-366.
7. Mellerio JE, et al. Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines. Br J Dermatol. 2016;174:56-67.
8. Has C, et al. Practical management of epidermolysis bullosa: consensus clinical position statement from the European Reference Network for Rare Skin Diseases. J Eur Acad Dermatol Venereol. 2021;35:2349-2364.
9. Martinez AE, Mellerio JE. Osteopenia and osteoporosis in epidermolysis bullosa. Dermatol Clin. 2010;28:353-360.
10. Denyer JE. Wound management for children with epidermolysis bullosa. Dermatol Clin. 2010;28:257-264.
11. Schwieger-Briel A, et al. Betulin-Based Oleogel to Improve Wound Healing in Dystrophic Epidermolysis Bullosa: A Prospective Controlled Proof-of-Concept Study. Dermatol Res Pract. 2017;2017:5068969.
12. Mellerio JE, et al. Medical management of epidermolysis bullosa: Proceedings of the IInd International Symposium on Epidermolysis Bullosa, Santiago, Chile, 2005. Int J Dermatol. 2007;46:795-805.
13. Grocott P, Blackwell R, Weir H, Pillay E. Living in dressings and bandages: findings from workshops with people with Epidermolysis bullosa. Int Wound J. 2013;10:274-284.
14. Saad R, et al. Neonatal epidermolysis bullosa: a clinical practice guideline. Br J Dermatol. 2024;190:636-647.
15. Pope E, et al. A consensus approach to wound care in epidermolysis bullosa. J Am Acad Dermatol. 2012;67:904-914.