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Epidermolysis Bullosa: An Update

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Abstract

Epidermolysis bullosa (EB) is caused by mutation in various components of the basement membrane zone and is characterized by increased fragility of skin and mucous membrane. There are four major types based on the level of split at the basement membrane zone – involvement of basal layer of epidermis in epidermolysis bullosa simplex (EBS), lamina lucida in junctional EB (JEB) and sublamina densa in dystrophic EB (DEB) while Kindler syndrome (KS) can exhibit multiple levels of split. More than 19 genes have been described resulting in the various subtypes of these 4 major types giving rise to diversity of phenotypic expressions. Diagnosis is based on the "onion skin approach" which includes clinical presentation, family history, antigen mapping and genetic mutation analysis. The main stay of management is supportive and wound care. The newer experimental therapies include gene therapy, fibroblast and protein therapy and mesenchymal and bone marrow transplantation.

Introduction

Epidermolysis bullosa (EB) is a heterogeneous group of genetic blistering disorders characterized by increased fragility of skin and mucous membrane resulting in blisters and erosions resolving with or without scarring. According to the National Epidemiology Epidermolysis Bullosa Registry in USA, the incidence and prevalence of epidermolysis bullosa are estimated to be 19.60 per million live births and 8.22 per million population, respectively (Fine et al., 2016). The disease results in significant morbidity in these children due to cutaneous and extracutaneous involvement as there is no specific treatment available yet and the current management strategies focuses on the prevention of trauma and wound care. In this review, we will focus on different genotypic and phenotypic expression of this diverse disease.

Classification and pathogenesis

Mutation in various components of the basement membrane zone responsible for structural support in keratinocytes and adhesion of epidermis and dermis, results in different types of epidermolysis bullosa (Figure 1). The new approach for classification in EB is termed as "onion skinning" and sequentially takes account of the level of split at the dermato-epidermal basement membrane zone, phenotypic features and genetic characteristics such as mode of inheritance, targeted protein and its relative expression in the basement membrane zone, the involved gene and the type of mutation (Fine et al., 2014).

The level of split is the basal layer of the epidermis in epidermolysis bullosa simplex (EBS) while it is at the level of lamina lucida in junctional EB (JEB) and sublamina densa in dystrophic EB (DEB). Kindler syndrome (KS) can exhibit multiple levels of split. More than 19 genes have been described resulting in the various subtypes of these 4 major types giving rise to diversity of phenotypic expressions (Tables 1-6). According to the National Epidemiology Epidermolysis Bullosa Registry in USA, 92% of the total number of patients with EB have EB simplex, 5% have dystrophic EB, 1% have junctional EB while 2% of the cases are unclassified (Fine et al., 2016).

The mode of inheritance of EB can be either autosomal dominant (AD) or autosomal recessive (AR). The majority of EBS are autosomal dominant while JEB and KS are autosomal recessive. Autosomal recessive form of EBS due to mutation in keratin (KRT) 14 has been reported and requires special attention due to difference in genetic counseling (Liu et al., 2012). Dystrophic EB can show both AD and AR inheritance. The autosomal recessive type of dystrophic EB is much more severe compared to the dominant form (Yenamandra et al., 2017).

Table 1 Differences between the clinical features of major types of Epidermolysis Bullosa

Features	EB simplex	Junctional EB	Dystrophic EB	Kindler syndrome
Skin fragility	+ (with little or no trauma)	+ (with little or no trauma)	+ (with little or no trauma)	+ (with little or no trauma)
Blisters				
Age	Birth-12-18 months*	Birth	Birth	Birth
Distribution	Hands and feet (Localized form)/generalized	Periorificial areas, fingers and toes, trunk and the upper airway mucosa	Hands, feet, knees, and elbows (mild forms)-whole body including mucosa (in severe forms)**	Acral
Characteristic Pattern	Annular or curvilinear groups or clusters	Excessive periorificial granulation tissue	Localized or generalized with scarring and milia formation	
Mucosal	+ (generalized severe forms)	+ (oral and airway mucous membrane**)	+ (severe forms)	+
Post inflammatory changes	+ hyper/hypo pigmentation (generalized forms)	+ hyper/hypo pigmentation	+ scarring	+ skin atrophy
Skin scarring	No	-/+ (generalized severe form)	+ (scarring, pseudosyndactyly, "mitten" hands and feet & contractures)	+
Nail dystrophy	-/+ (generalized severe forms)	-/+	+ and nail loss especially toenails	-/+
Milia	-/++ (generalized severe forms)	-	+	-
Others	Varying degree of palmar and plantar hyperkeratosis (generalized severe forms)	Prone to sepsis, amelogenesis imperfecta, congenital malformations of the urinary tract and bladder, aplasia cutis, non-scarring or scarring alopecia	Oral and/or esophageal scarring and strictures. Corneal erosions resulting in corneal opacity leading to loss of vision. High risk of squamous cell carcinoma	Esophageal stricture, photosensitivity, telangiectasia, colitis, urethral stenosis/strictures, and severe phimosis
Inheritance	AD/AR	AR	AD/AR	AR

EB – Epidermolysis bullosa; AD – Autosomal dominant; AR – Autosomal recessive
* Varies depending upon the severity, gene and the variant
** Mucosal involvement of the mouth, upper respiratory tract, esophagus, bladder, urethra, and corneas

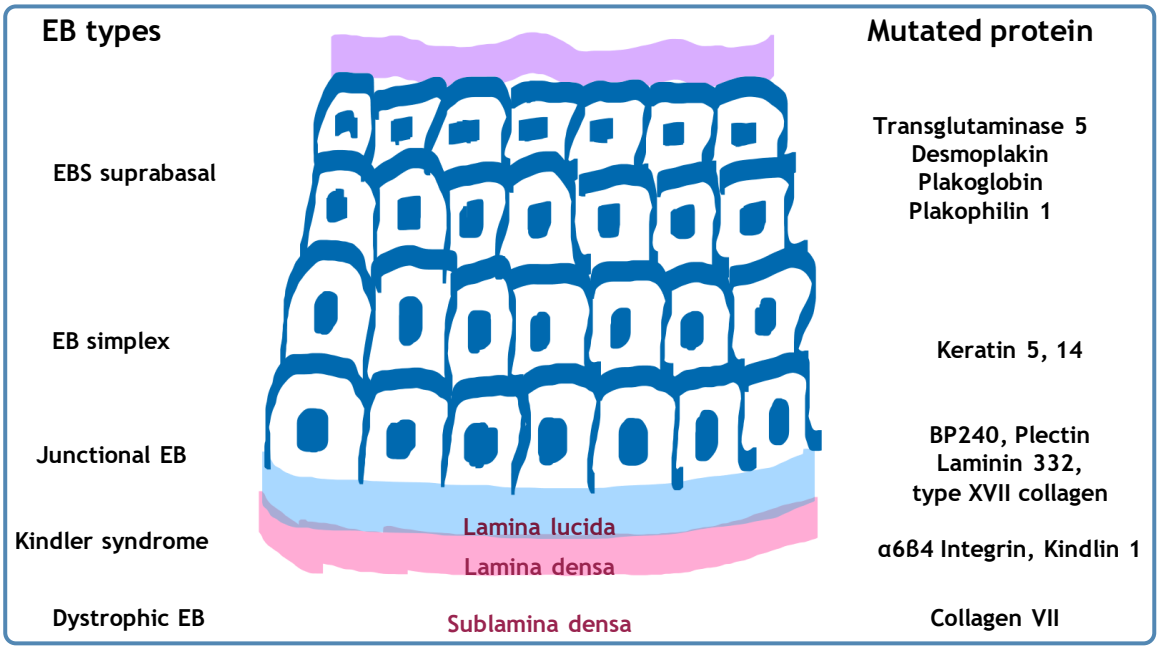


Figure 1 Structure of basement membrane zone and classification of epidermolysis bullosa based on the affected gene.

Clinical features

The onset of EB is usually at birth or immediately after the birth except a late onset in some patients with EB simplex.

Figure 2 Localized blister on palm in a patient of epidermolysis bullosa simplex localized.

The hallmark clinical characteristic of this group of disorders is skin fragility resulting in spontaneous or minor trauma-induced blistering and erosions. The blistering is superficial in EB simplex and junctional EB, thus it resolves with hyper or hypo pigmentation but without scarring. The split is deeper in dystrophic EB and thus results in milia formation and scarring, nail dystrophy and various complications such as mitten-like hand deformity, pseudosyndactyly and joint contractures (Yenamandra et al., 2017).

- Epidermolysis Bullosa simplex (EBS): In EB simplex localized, blisters are late in onset and are mostly localized to trauma prone areas (Figure 2). Generalized severe form of EB starts at birth resulting in extensive and grouped blistering resolving with hypo or hyperpigmentation (Figure 3). Palmoplantar keratoderma is common and begins in childhood. Nail dystrophy and milia can be seen. The blistering is less severe in the generalized intermediate form of EBS.

Various genes implicated in various subtypes of EBS are shown in Tables 2 and 3. Most cases of EBS are caused by mutations in *KRT5* and *KRT14* (keratin 5 and 14) genes (Pfendner and Bruckner, 1998). EBS patients with mutation in the *TGM5* (transglutaminase 5) gene have mild blistering of skin over the acral areas consistent with the diagnosis of acral peeling syndrome. Biallelic mutations in the *DSP* (desmoplakin) gene result in lethal acantholytic EB simplex characterized by skin fragility, universal alopecia, malformed ears, anonychia and cardiomyopathy. Mutation in the *EXPH5* (exophilin-

5) and *KRT14* genes causes mild form of EBS with an autosomal recessive inheritance. Biallelic mutations in *PLEC* (plectin) gene are known to have EBS with associated muscular dystrophy and relatively higher morbidity and systemic complications. Site-specific monoallelic missense mutation in *PLEC* gene results in EBS Ogna type (EBS-O). Patients with EBS with migratory circinate erythema and mottled pigmentation have been found to have mutation in *KRT5*. There are also reports of EBS with mottled pigmentation caused by mutation in *KRT14*. Recently, some patients of EBS have been shown to have mutation in *KLHL24* gene. Digenic inheritance with mutations in *KRT5* and *KRT14* has also been described.

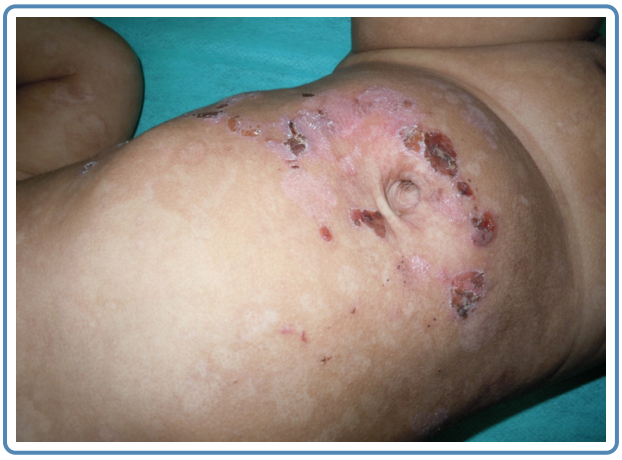


Figure 3 Generalized grouped blisters resolving with hypopigmentation in epidermolysis bullosa simplex-generalized severe form.

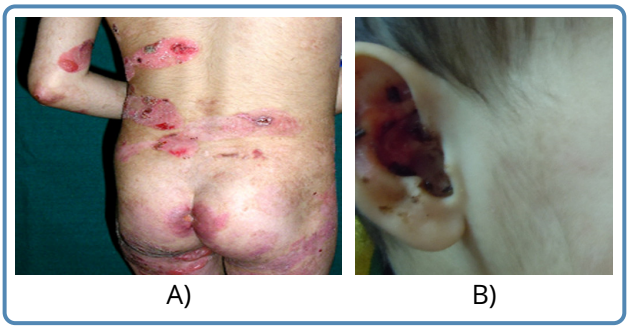
- Junctional Epidermolysis Bullosa (JEB): Generalized (Herlitz) severe junctional EB is the most devastating type of EB resulting in severe life-threatening complications in early childhood. Extensive truncal erosions at the time of birth and periorificial granulation tissue is characteristic of this form of EB (Figures 4a and b). A series of junctional EB showed that 73% of 71 children born in a five-year period died at an average age of five months (Kelly-Mancus et al., 2014). The common causes of death are sepsis, electrolyte imbalance, renal and cardiac complications. Accumulation of granulation tissue in subglottic area in these children results in weak hoarse cry. Eventually airway obstruction may result in stridor and respiratory distress and tracheostomy is required. Amelogenesis imperfecta with pitting of tooth enamel and scarring or non-scarring alopecia are common. Generalized intermediate type is a less severe clinical presentation of JEB where blistering may be localized to trauma-prone areas and systemic complications are rare.

Table 2 Various genes involved in suprabasal subtypes of epidermolysis bullosa simplex.

Subtype	Gene
Acral peeling skin syndrome (APSS)	*TGM5* (Transglutaminase 5)
Epidermolysis bullosa simplex superficialis (EBSS)	-
Acantholytic Epidermolysis bullosa simplex (EBS-acanth)	*DSP* (Desmoplakin)
Skin fragility syndromes:	
• Desmoplakin deficiency: skin fragility-woolly hair syndrome	*DSP* (Desmoplakin)
• Plakoglobin deficiency: (Naxos disease)	*PKGB* (Plakoglobin)
• Plakophilin deficiency: skin fragility-ectodermal dysplasia syndrome	*PKP1* (Plakophilin 1)

Table 3 Various genes involved in basal subtypes of epidermolysis bullosa simplex.

Subtype	Gene
Major subtypes:	
• EB simplex localized	*KRT5* and *KRT14* (Keratins 5 and 14)
• EB simplex generalized severe	*KRT5* and *KRT14*
• EB simplex generalized intermediate	*KRT5* and *KRT14*
Others:	
• EB simplex Ogna	*PLEC* (Plectin)
• EB simplex with mottled pigmentation	*KRT5*
• EB simplex – migratory circinate	*KRT5*
• EB simplex – autosomal recessive	*EXPH5* (Exophilin-5), *DST* (Dystonin/BP240), *KRT14*
• EB simplex – muscular dystrophy	*PLEC*



A) B)

Figure 4 A) Extensive truncal erosions in generalized severe junctional epidermolysis bullosa. B) Periorificial granulation tissue in generalized severe junctional epidermolysis bullosa.

Table 4 shows various genes involved in JEB. Junction EB is most commonly caused by mutations in genes coding for alpha-3, beta-3, and gamma-2 subunits of laminin protein of lamina lucida of the basement membrane zone. The lethal Herlitz type of junctional EB is known to be caused by premature termination or missense biallelic mutations in *LAMB3* (laminin B3) gene while junction EB intermediate is caused by biallelic mutations in the *COL17A1* gene (Yenamandra et al., 2017). Laryngo-onycho-cutaneous syndrome (LOCS) characterized by granulating wounds, dental hypoplasia and ocular granulation tissue is known to be caused by biallelic mutations in the *LAMA3* gene. Junctional EB with pyloric atresia (EB-PA) is caused by biallelic mutations in *ITGA6* or *ITGB4* genes that code for $\alpha 6\beta 4$ integrin in the basement membrane zone (Kayki et al., 2017).

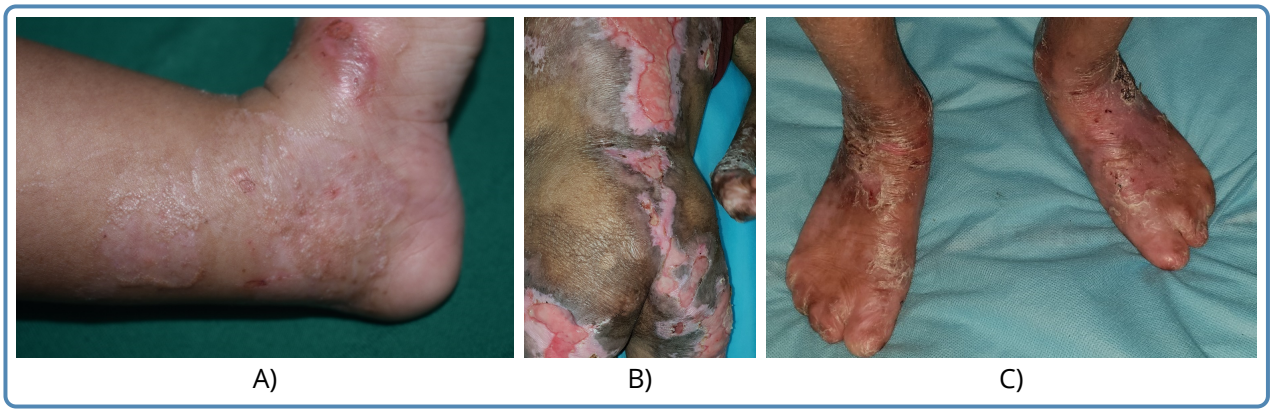
- Dystrophic epidermolysis bullosa (DEB): Generalized recessive dystrophic EB (RDEB) results in extensive blistering and erosions at birth resolving with milia and scaring while dominant dystrophic EB (DDEB) is a milder form of the disease where the disease is mostly limited to trauma-prone areas associated with nail dystrophy (Figures 5a, b and c). Presence of syndactyly, mitten like deformity, systemic complications, dental lesions, remission-less course, and oral lesions are strongly indicative of RDEB (Yenamandra et al., 2017). Esophageal erosions and stricture formation can lead to severe dysphagia and resultant malnutrition in these patients. Corneal erosions can lead to corneal opacity and loss of vision. The non-healing wounds of dystrophic EB may be complicated by aggressive squamous cell carcinoma.

Dystrophic EB results from mutation in *COL7A1* (collagen type 7) gene and more than 300 pathogenic variations have been detected in this gene causing various subtypes of dystrophic EB (Dang et al., 2008).

EB pruriginosa is a distinct variant of dystrophic EB characterized by severe pruritic lichenified plaques over bilateral lower legs associated with nail dystrophy and is caused by mutation in the *COL7A1* gene (Figure 6). Pretibial form of dystrophic EB is characterized by blistering, milia and scarring limited to the pretibial area associated with dystrophic nails. It is caused by mutation in the NC2 domain of *COL7A1*. Bullous dermolysis of newborn is a self-limiting disease caused by mutation in *COL7A1* and manifests as generalized bullae and

Table 4 Various genes involved in subtypes of junctional epidermolysis bullosa.

Junctional EB type	Junctional EB subtype	Targeted protein(s)
Generalized	• Severe • Intermediate • Late onset • With pyloric atresia • With respiratory (interstitial lung disease) and renal involvement (nephrotic syndrome)	• Laminin 332 • Laminin-332, type XVII collagen • Type XVII collagen (*COL17A1*) • $\alpha 6$ (*ITGA6)* and $\beta 4$ integrin (*ITGB4*) • $\alpha 3$ integrin subunit (*ITGA3*)
Localized	• Localized • Inversa • Laryngo-onycho-cutaneous (LOC) syndrome	• Laminin-332, type XVII collagen, $\alpha 6$ and $\beta 4$ integrin subunits • Laminin-332 • Laminin $\alpha 3$a (*LAMA3A)*



A) B) C)

Figure 5 A) Localized blisters healing with scar and milia formation in dominant dystrophic epidermolysis bullosa. B) Large non-healing erosions in recessive dystrophic epidermolysis bullosa, generalized severe type. C) Mitten deformity and pseudosyndactyly in recessive dystrophic epidermolysis bullosa, generalized severe type.

erosions in the newborn period resolving by itself by one year of age. Inversa recessive dystrophic EB (RDEB-I) is a rare form, characterized by generalized involvement in the neonatal period which improves with age and a predominant involvement of flexures is seen in adults. Severe mucosal involvement is seen in these cases. A late onset of inversa RDEB is also reported. Dominant DEB presenting only as familial nail dystrophy has been reported caused by mutation in *COL7A1*.

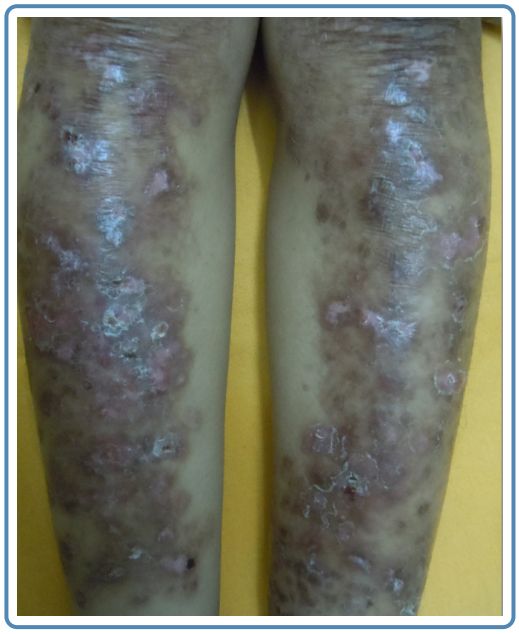


Figure 6 Lichenified papules and plaques on bilateral shin in recessive dystrophic epidermolysis bullosa, pruriginosa type.

Table 5 Various genes involved in subtypes of dystrophic epidermolysis bullosa.

Dystrophic EB type	Dystrophic EB subtype	Targeted protein(s)
Dominant dystrophic epidermolysis bullosa (DDEB)	DDEB, generalized DDEB, acral DDEB, pretibial DDEB, pruriginosa DDEB, nails only DDEB, bullous dermolysis of newborn	Collagen 7
Recessive dystrophic epidermolysis bullosa (RDEB)	RDEB, generalized severe type RDEB, generalized other RDEB, inversa RDEB, pretibial RDEB, pruriginosa RDEB, centripetalis RDEB, bullous dermolysis of newborn	Collagen 7

- Kindler syndrome: Kindler syndrome is characterized by acral blisters early in life followed by poikiloderma, periodontitis and involvement of oral, oesophageal, urogenital and ocular mucosa (Figure 7) (Kantheti et al., 2017).

Table 6 Gene involved in the pathogenesis of Kindler syndrome.

Type	Targeted protein(s)	Gene
Kindler syndrome	Kindlin 1	*FERMT1*

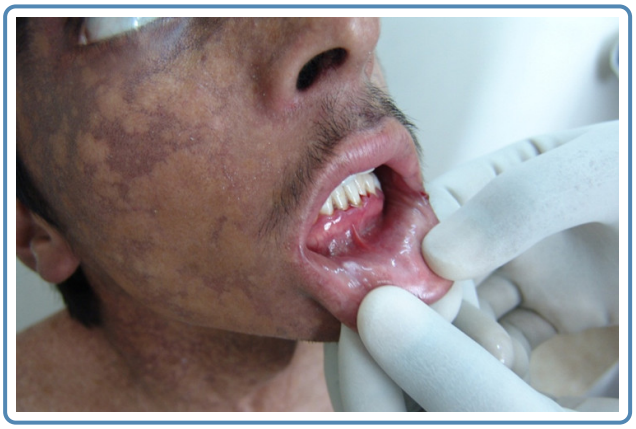


Figure 7 Poikiloderma and periodontitis in Kindler syndrome.

Laboratory diagnosis

In most patients diagnosis of EB is made clinically based on the presence of characteristic clinical findings (Yenamandra et al., 2017).

Immunohistochemistry studies: Diagnostic of specific EB type requires identification of the level of split via antigen mapping on a newly induced blister. Antigen mapping refers to the use of monoclonal antibodies in immunofluorescence or immunohistochemistry directed against components of the basement membrane zone and detecting their altered staining corresponding to the presence of a mutation in their gene (Yenamandra et al., 2017).

Molecular genetic testing: The gold standard for the diagnosis is confirmation by DNA analysis using next generation sequencing, if available and affordable, as this will permit the identification of the specific EB subtype, help in detection of newer types, and in prenatal genetic diagnosis, genetic counselling and future gene therapy. The different molecular testing approaches are single gene testing, use of a customized multi-gene panel or a whole exome analysis. Epidermolysis bullosa sequencing based diagnostic assay called EBSEQ was developed recently for simultaneous detection of 21 genes with a known role in EB (Lucky et al., 2018).

Management

The definitive treatment for EB is not available yet and mainstay of management is supportive care.

Supportive treatment: Avoidance of trauma, proper wound care to prevent secondary infection and scarring and to promote early healing, nutritional support, genetic counseling and management of complications remains the primary treatment of disease. Recently, a wound care guideline was compiled by international experts (Pope et al., 2012). These guidelines recommended adequate wound assessment and use of appropriate wound dressing according to the wound type. Bath soaks are recommended prior to removal of wound dressings to minimize the trauma. Addition of salt to bath water has shown to relieve the pain and prevent infection. The frequent use of antibiotics is discouraged to prevent development of antibiotic resistance in these patients. Adequate management of pain and pruritus is recommended to improve the quality of life. Assessment of nutritional deficiency and its correction is very important for the proper growth and development of these children. Physical therapies to improve the mobility and use of aids to improve their functionality are also essential for their well-being.

Newer therapies: Newer experimental therapies include gene therapy, fibroblast and protein therapy and mesenchymal and bone marrow transplantation (Gostyńska et al., 2018; Hirsch et al., 2017). Extensive research and long-term studies are required to evaluate the efficacy and safety of these experimental therapies.

DEBRA (Dystrophic Epidermolysis Bullosa Research Association) International (`http://www.debra-international.org/homepage.html`) is an umbrella organization for a worldwide network of national groups that work for children affected with epidermolysis bullosa. The organization provides guidelines and support for better research and care of these children.

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