Epidermolysis Bullosa and Gene therapy_ New treatment modality

Nguyen Thi Ngoc Trang, MD
Neonatology 2 – Metabolism - Genetics Department

1. Overview
2. Classical treatments
3. New treatment modallities
4. Gene Therapy
5. Our patients

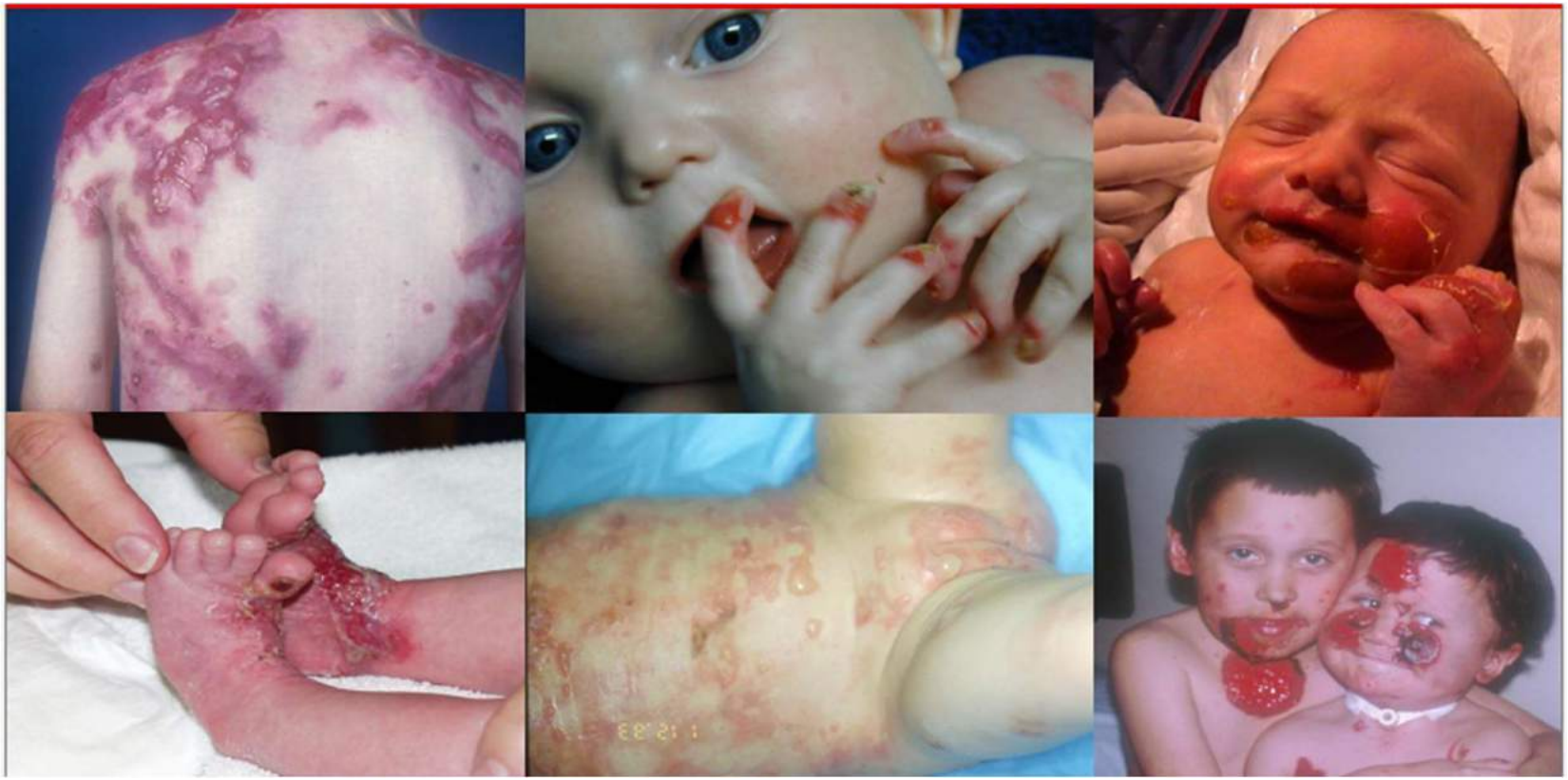
Overview

Epidermolysis Bullosa

Overview

Epidermolysis bullosa (EB) is a rare group of *inherited disorders* that manifests as *blistering or erosion* of the skin and, in some cases, the epithelial lining of other organs, in response to little or *no apparent trauma*

Overview

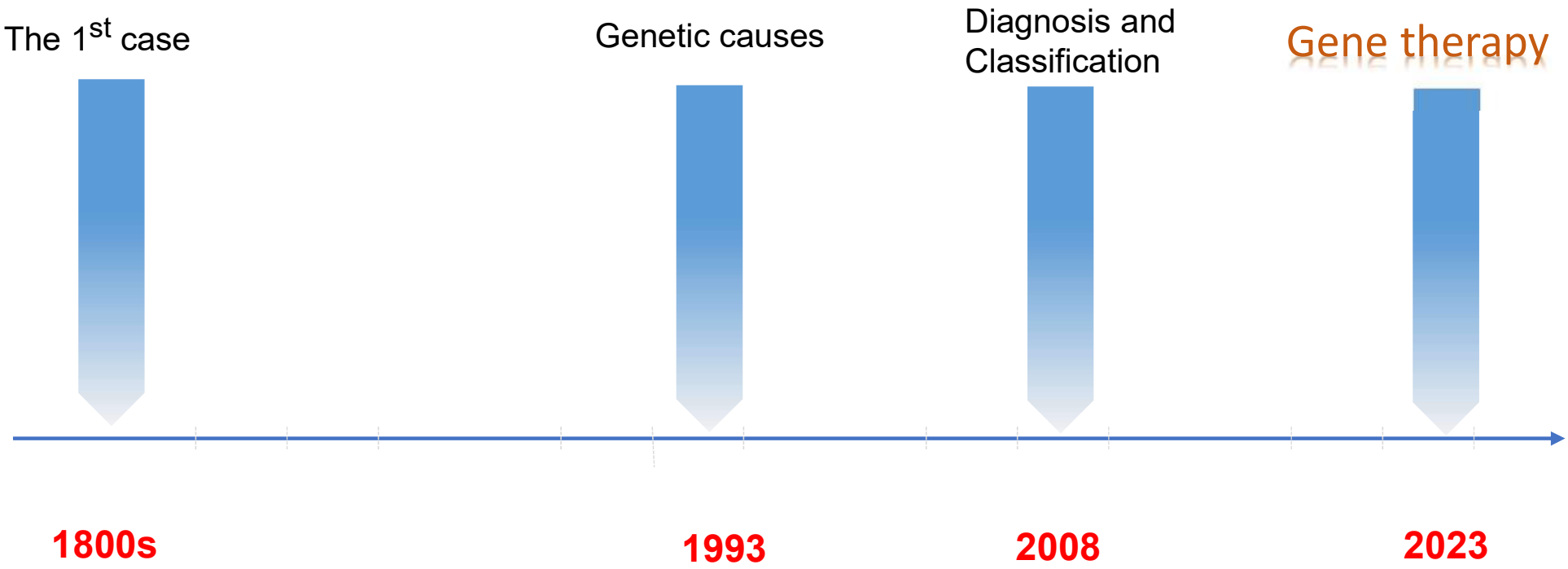


Overview

A hug, loving rub on the back, or diaper change can injure the skin, leading to blisters and open wounds

"Butterflies Children"

Overview


The 1st case
Genetic causes
Diagnosis and Classification
Gene therapy
1800s
1993
2008
2023
NO CURE
New Treatments

Epidemiology

Frequency

- United States : 11 cases / 1 million population
- Scotland : 49 cases / 1 million population
- Japan : 2 cases / 1 million population
- Australia : 10 cases / 1 million population

Sex: the incidence does not differ by sex

Age of onset: at birth or early infancy

REVIEW ARTICLE

BJD
British Journal of Dermatology

Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility*

C. Has,[1] J.W. Bauer,[2] C. Bodemer,[3] M.C. Bolling,[4] L. Bruckner-Tuderman,[1] A. Diem,[2] J.-D. Fine,[5] A. Heagerty,[6] A. Hovnanian,[7] M.P. Marinkovich,[8] A.E. Martinez,[9] J.A. McGrath,[10] C. Moss,[11] D.F. Murrell,[12] F. Palisson,[13] A. Schwieger-Briel,[14] E. Sprecher,[15] K. Tamai,[16] J. Uitto,[17] D.T. Woodley,[18] G. Zambruno[19] and J.E. Mellerio[10]

[1]Department of Dermatology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany
[2]Department of Dermatology and Allergology and EB Haus Austria University Hospital of the Paracelsus Medical University Salzburg, Austria
[3]Department of Dermatology, Necker Hospital des Enfants Malades, University Paris-Centre APHP 5, Paris, France
[4]University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[5]Vanderbilt University School of Medicine, Nashville, TN, USA; National Epidermolysis Bullosa Registry, Nashville, TN, USA
[6]Heart of England Foundation Trust, Birmingham, UK
[7]INSERM UMR1163, Imagine Institute, Department of Genetics, Necker hospital for sick children, Paris University, Paris, France
[8]Stanford University School of Medicine, Stanford, Palo Alto Veterans Affairs Medical Center CA, USA
[9]Dermatology Department, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK
[10]St John's Institute of Dermatology, King's College London and Guy's and St Thomas' NHS Foundation Trust, London, UK
[11]Birmingham Children's Hospital and University of Birmingham, UK
[12]St George Hospital and University of New South Wales, Sydney, Australia
[13]DEBRA Chile, Facultad de Medicina Clinica Alemana–Universidad del Desarrollo, Santiago, Chile
[14]Department of Pediatric Dermatology, University Children's Hospital Zürich, Zürich, Switzerland
[15]Division of Dermatology, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[16]Dermatology Department, University of Osaka, Osaka, Japan
[17]Thomas Jefferson University, Philadelphia, PA, USA
[18]University of Southern California, Los Angeles, CA, USA
[19]Dermatology Unit, Bambino Gesù Children's Hospital, Rome, Italy

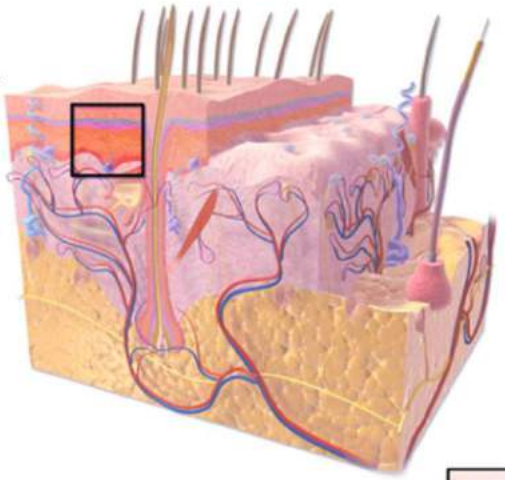
Linked Comment: Pope. *Br J Dermatol* 2020; **183**:603.

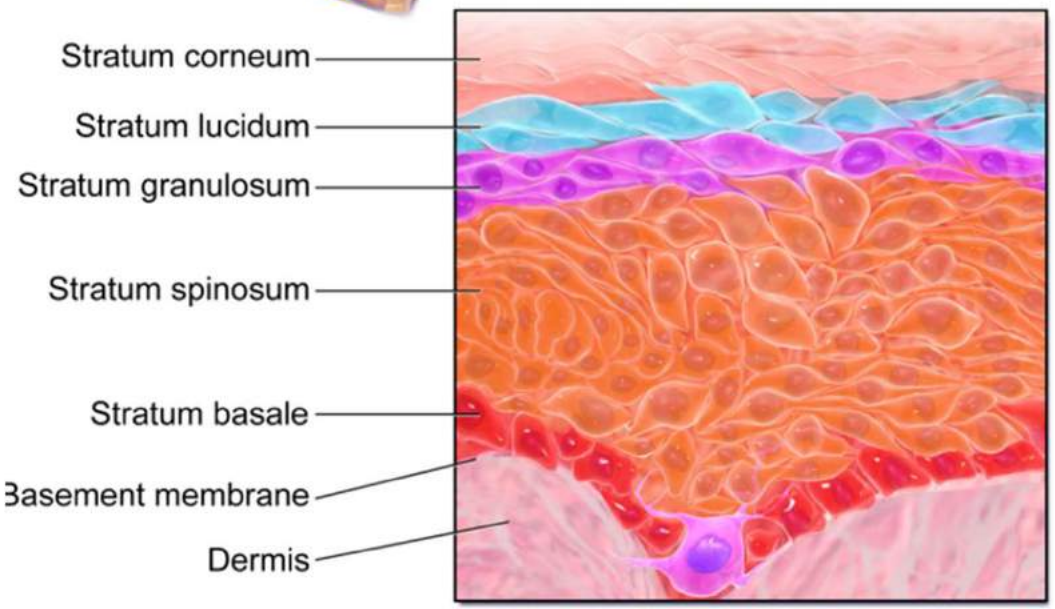
Classification

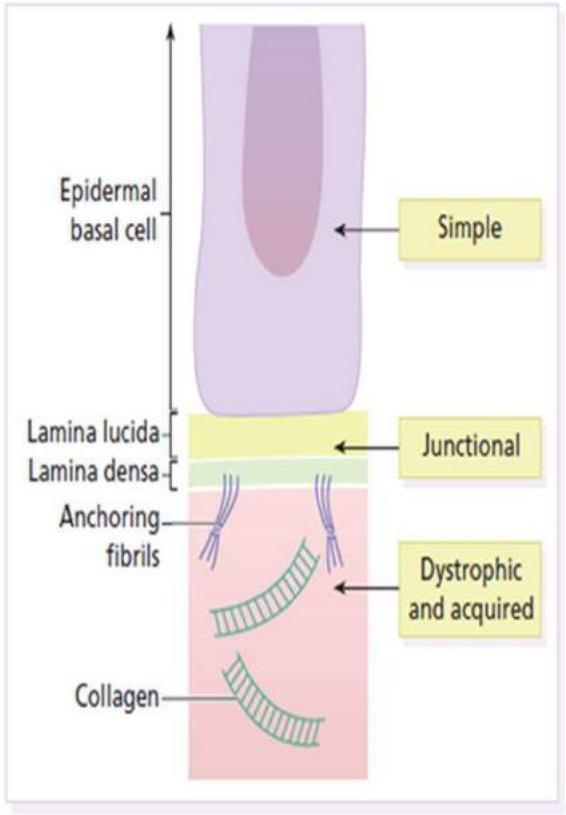
The major types of epidermolysis bullosa

- Epidermolysis bullosa simplex (EBS)
- Junctional epidermolysis bullosa (JEB)
- Dystrophic epidermolysis bullosa (DEB)
- Kindler syndrome (KS / KEB)

Classification







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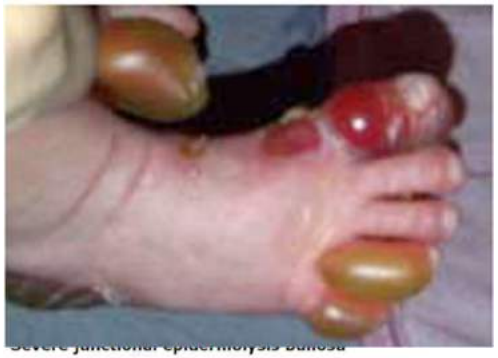
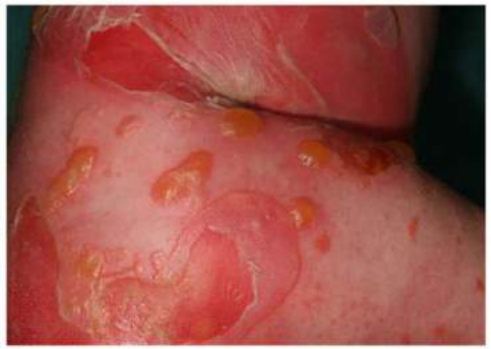
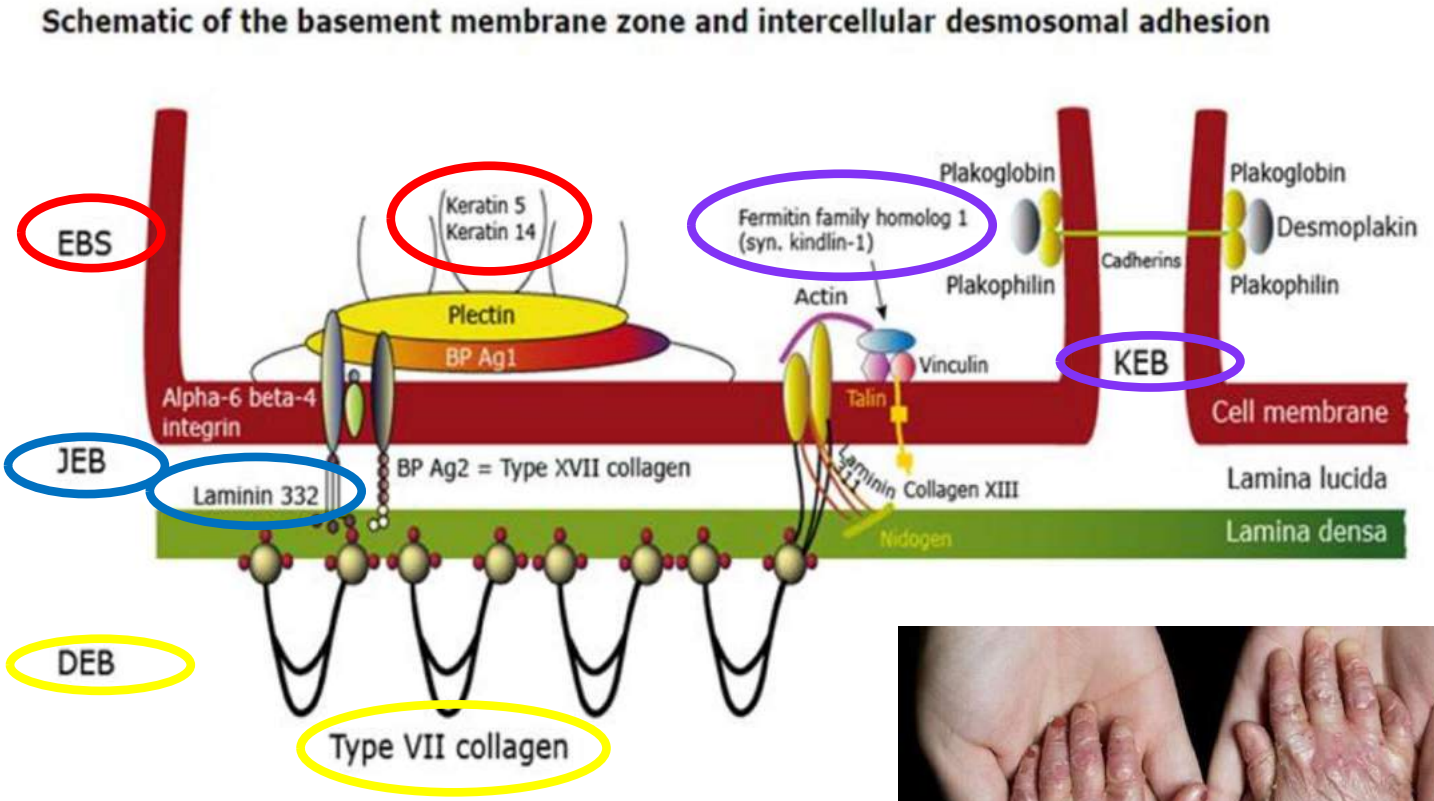
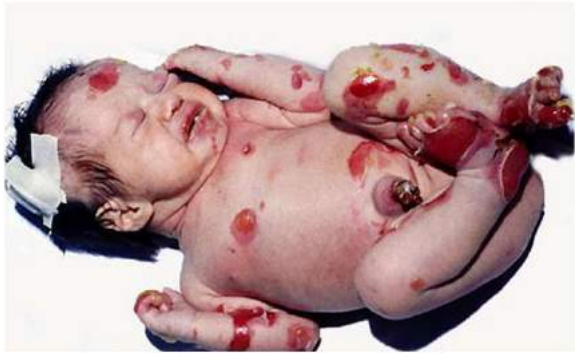




Generalized blistering, crusted erosions, and extensive areas of denudation in severe JEB.





Major EB types and the molecular causes

Classical types of EB Level of skin cleavage	EB type	Inheritance	Mutated gene(s)	Targeted protein(s)
Intraepidermal	EB simplex	Autosomal dominant	KRT5, KRT14	Keratin 5, keratin 14
			PLEC	Plectin
			KLHL24	Kelch-like member 24
		Autosomal recessive	KRT5, KRT14	Keratin 5, keratin 14
			DST	Bullous pemphigoid antigen 230 (BP230) (syn. BPAG1e, dystonin)
			EXPH5 (syn. SLAC2B)	Exophilin-5 (syn. synaptotagmin-like protein homolog lacking C2 domains b, Slac2-b)
			PLEC	Plectin
			CD151 (syn. TSPAN24)	CD151 antigen (syn. tetraspanin 24)
Junctional	Junctional EB	Autosomal recessive	LAMA3, LAMB3, LAMC2	Laminin 332
			COL17A1	Type XVII collagen
			ITGA6, ITGB4	Integrin $\alpha 6\beta 4$
			ITGA3	Integrin $\alpha 3$ subunit
Dermal	Dystrophic EB	Autosomal dominant	COL7A1	Type VII collagen
		Autosomal recessive	COL7A1	Type VII collagen
Mixed	Kindler EB	Autosomal recessive	FERMT1 (syn. KIND1)	Fermitin family homolog 1 (syn. kindlin-1)

Epidermolysis bullosa Simplex

Classical types of EB

Level of skin cleavage	EB type	Inheritance	Mutated gene(s)	Targeted protein(s)
Intraepidermal	EB simplex	Autosomal dominant	KRT5, KRT14	Keratin 5, keratin 14
			PLEC	Plectin
			KLHL24	Kelch-like member 24
		Autosomal recessive	KRT5, KRT14	Keratin 5, keratin 14
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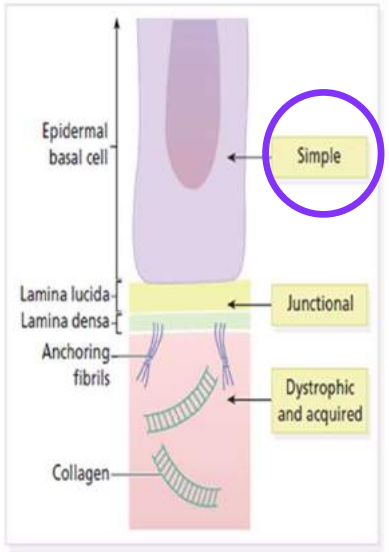
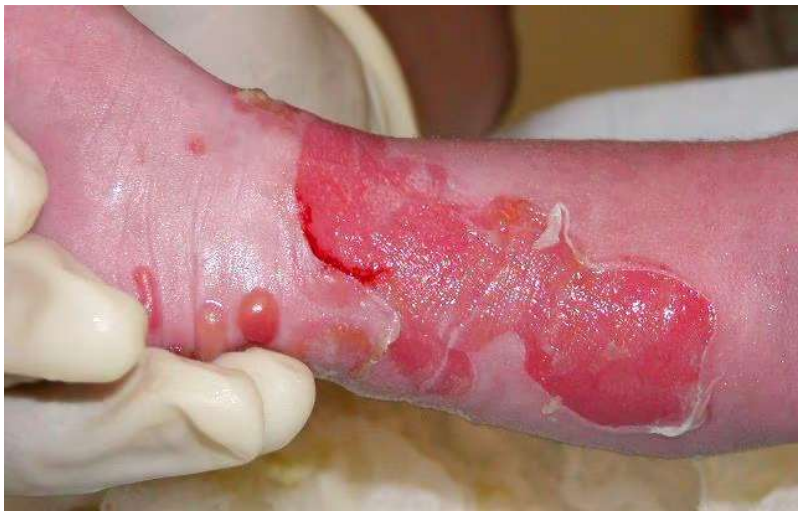
Epidermolysis bullosa Simplex





- The age of onset is at birth or early infancy
- Skin blistering due to cleavage within the basal layer of ***keratinocytes***
- Mild subtype causes local blistering of only the palms and soles
- Severe subtype causes blistering of the trunk, arms, and neck, and the oral mucosa may be involved
- Bullosa usually ***heal without scarring***

Junctional epidermolysis bullosa

Classical types of EB

Level of skin cleavage	EB type	Inheritance	Mutated gene(s)	Targeted protein(s)
Intraepidermal	EB simplex	Autosomal dominant	KRT5, KRT14	Keratin 5, keratin 14
			PLEC	Plectin
			KLHL24	Kelch-like member 24
		Autosomal recessive	KRT5, KRT14	Keratin 5, keratin 14
			DST	Bullous pemphigoid antigen 230 (BP230) (syn. BPAG1e, dystonin)
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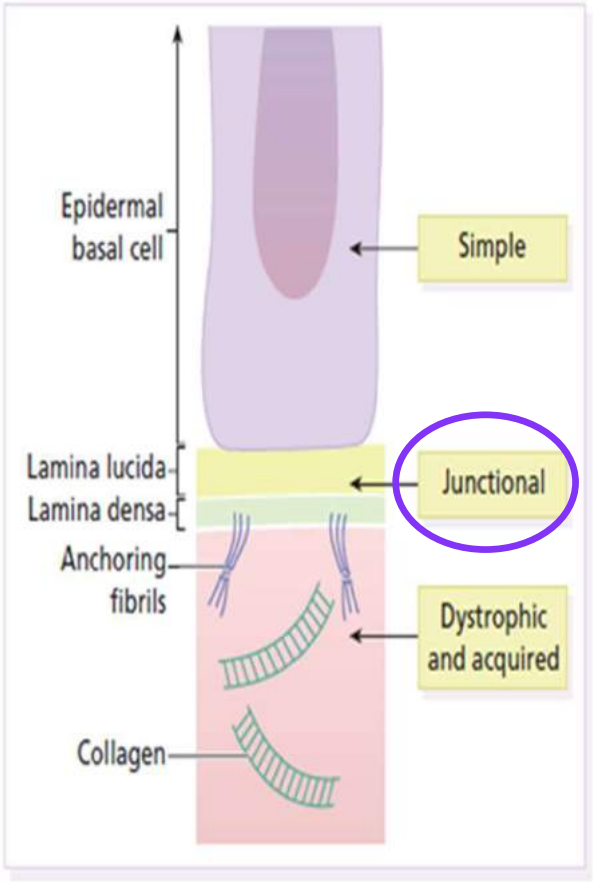
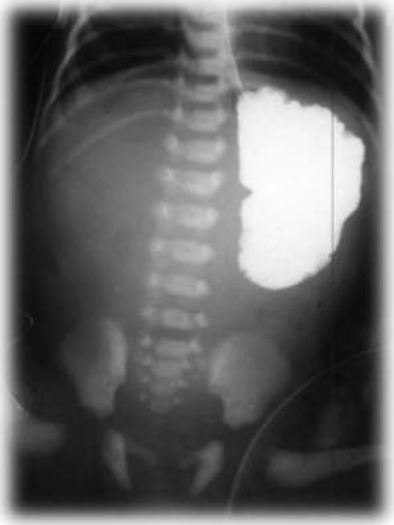
Junctional epidermolysis bullosa

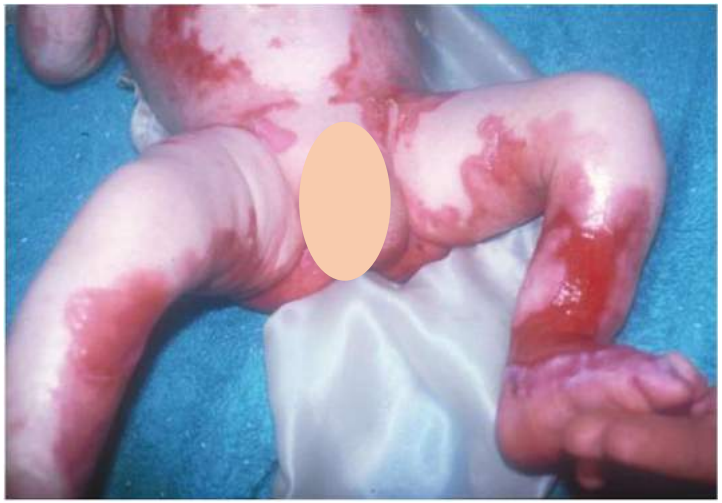


The two major subtypes of JEB

1. **Herlitz** (mutations in LAMA3, LAMB3, or LAMC2): death in early infancy within the first 2 years of life
2. **Non - Herlitz** (mutations in COL17A1 or LAMB3)**:** a near normal life-span

Junctional epidermolysis bullosa





- JEB is characterized by skin blistering with a plane of cleavage through the ***lamina lucida*** of the cutaneous basement membrane zone (BMZ)
- The age of onset is at birth
- **Herlitz:** may involve large areas of skin and the conjunctiva, mouth, and gastrointestinal, respiratory, and genitourinary tracts
- **Non-Herlitz:** affects only the elbows, hands, knees, and feet (typical friction sites) and often abates after infancy

Dystrophic epidermolysis bullosa

Classical types of EB

Level of skin cleavage	EB type	Inheritance	Mutated gene(s)	Targeted protein(s)
Intraepidermal	EB simplex	Autosomal dominant	KRT5, KRT14	Keratin 5, keratin 14
			PLEC	Plectin
			KLHL24	Kelch-like member 24
		Autosomal recessive	KRT5, KRT14	Keratin 5, keratin 14
			DST	Bullous pemphigoid antigen 230 (BP230) (syn. BPAG1e, dystonin)
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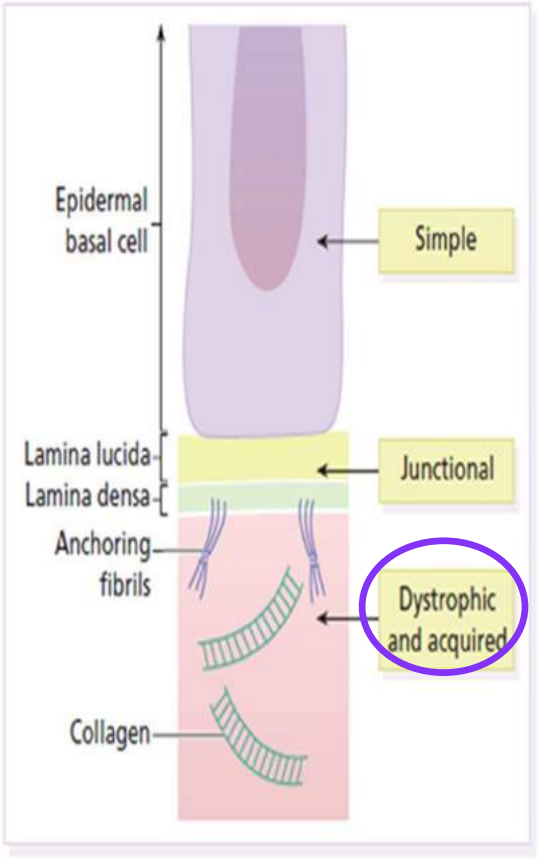
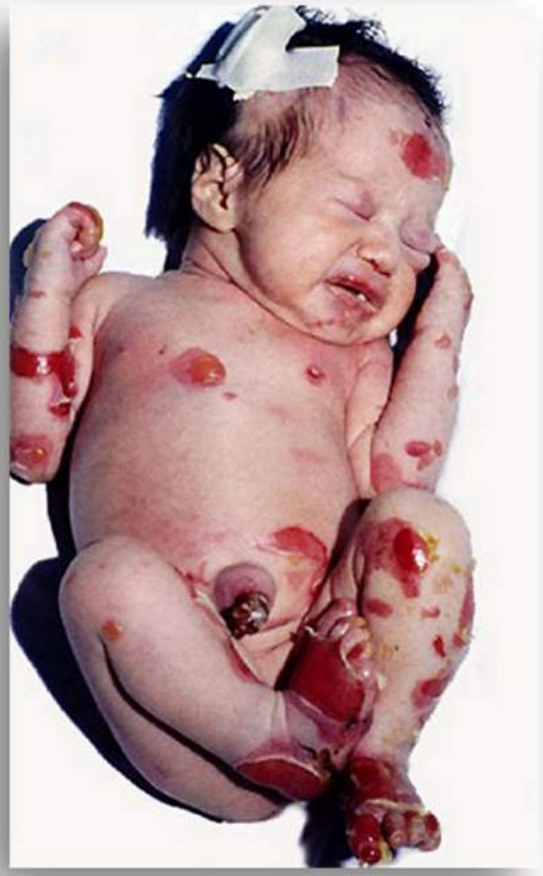
Dystrophic epidermolysis bullosa



Subtypes of Dystrophic Epidermolysis Bullosa (DEB):

1. **Autosomal Dominant – DDEB:** glycine substitution within the triple helical domain of the pro-alpha-chain of type VII collagen
2. **Autosomal Recessive – RDEB**: defective collagen VII synthesis

Dystrophic epidermolysis bullosa

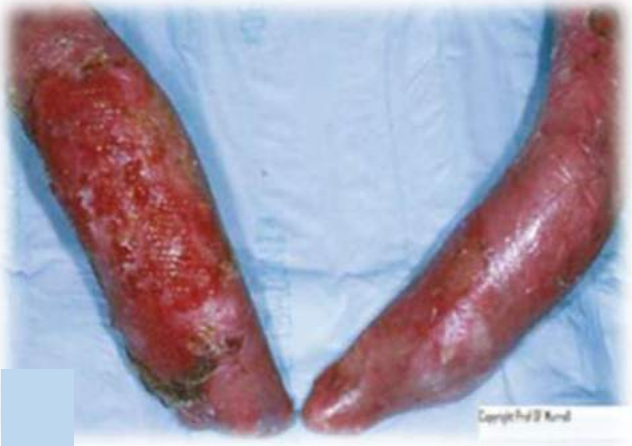


Autosomal dominant_ DDEB

- Blisters appear in *late infancy,* on *friction sites* (the knees, elbows and fingers)
- Healing occurs with scarring and milia Nails may be *deformed* or even *lost*
- The mouth is *not affected*

Dystrophic epidermolysis bullosa

Autosomal recessive_ RDEB



Pseudosyndactyly

- Blisters start in infancy.
- Blisters are sub-epidermal; filled with blood
- The hands and feet may become useless balls, having lost all fingers and toes
- The teeth, mouth and upper part of the oesophagus are all affected; oesophageal strictures may form.
- Squamous cell carcinomas of the skin are a late complication

Kindler syndrome

Classical types of EB Level of skin cleavage	EB type	Inheritance	Mutated gene(s)	Targeted protein(s)
Intraepidermal	EB simplex	Autosomal dominant	KRT5, KRT14	Keratin 5, keratin 14
			PLEC	Plectin
			KLHL24	Kelch-like member 24
		Autosomal recessive	KRT5, KRT14	Keratin 5, keratin 14
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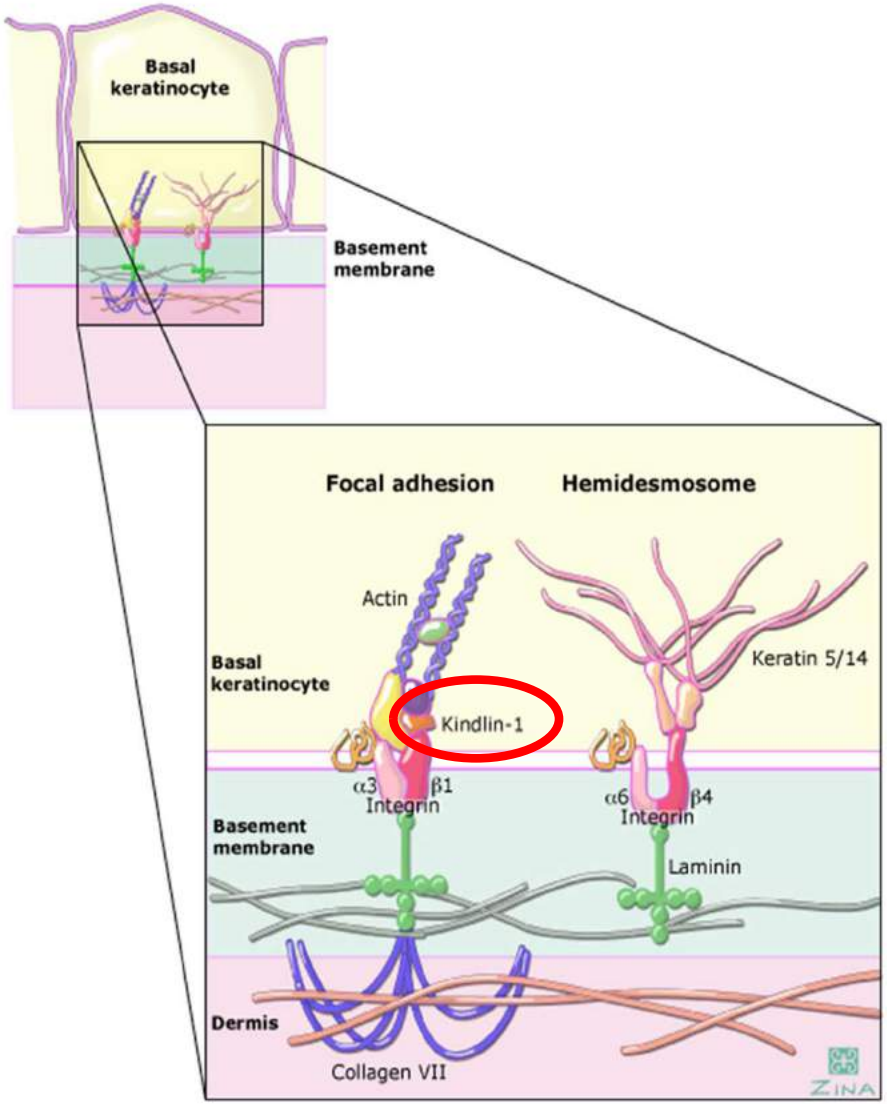
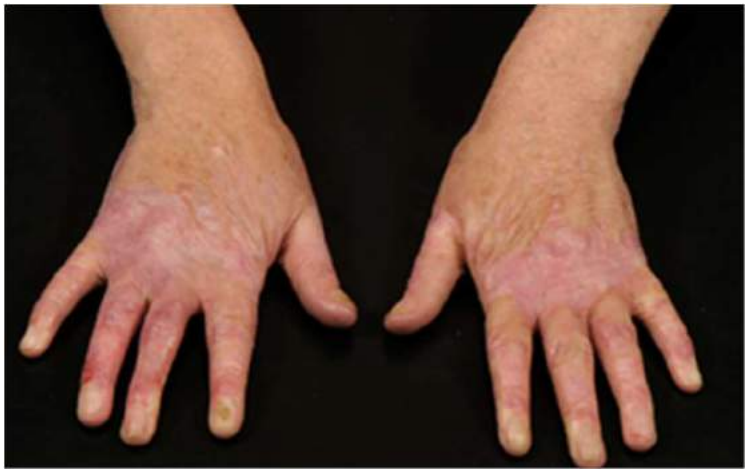
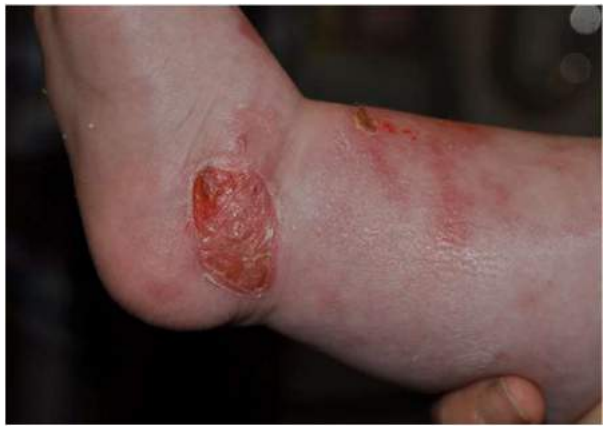
Kindler syndrome



- **1954-** Teresa Kindler
- KEB presents at birth or in early infancy

Kindler syndrome





- Blisters appear in all layers of the epidermis
- Photosensitivity
- Progressive poikiloderma (skin atrophy, telangiectasia, and dyspigmentation),
- Skin atrophy
- Nonmelanoma skin cancer

Differential Diagnoses

- Ectodermal Dysplasia
- Epidermolytic Ichthyosis
- Herpes Simplex
- Incontinentia Pigmenti
- Staphylococcal Scalded Skin Syndrome (SSSS)
- Syphilis

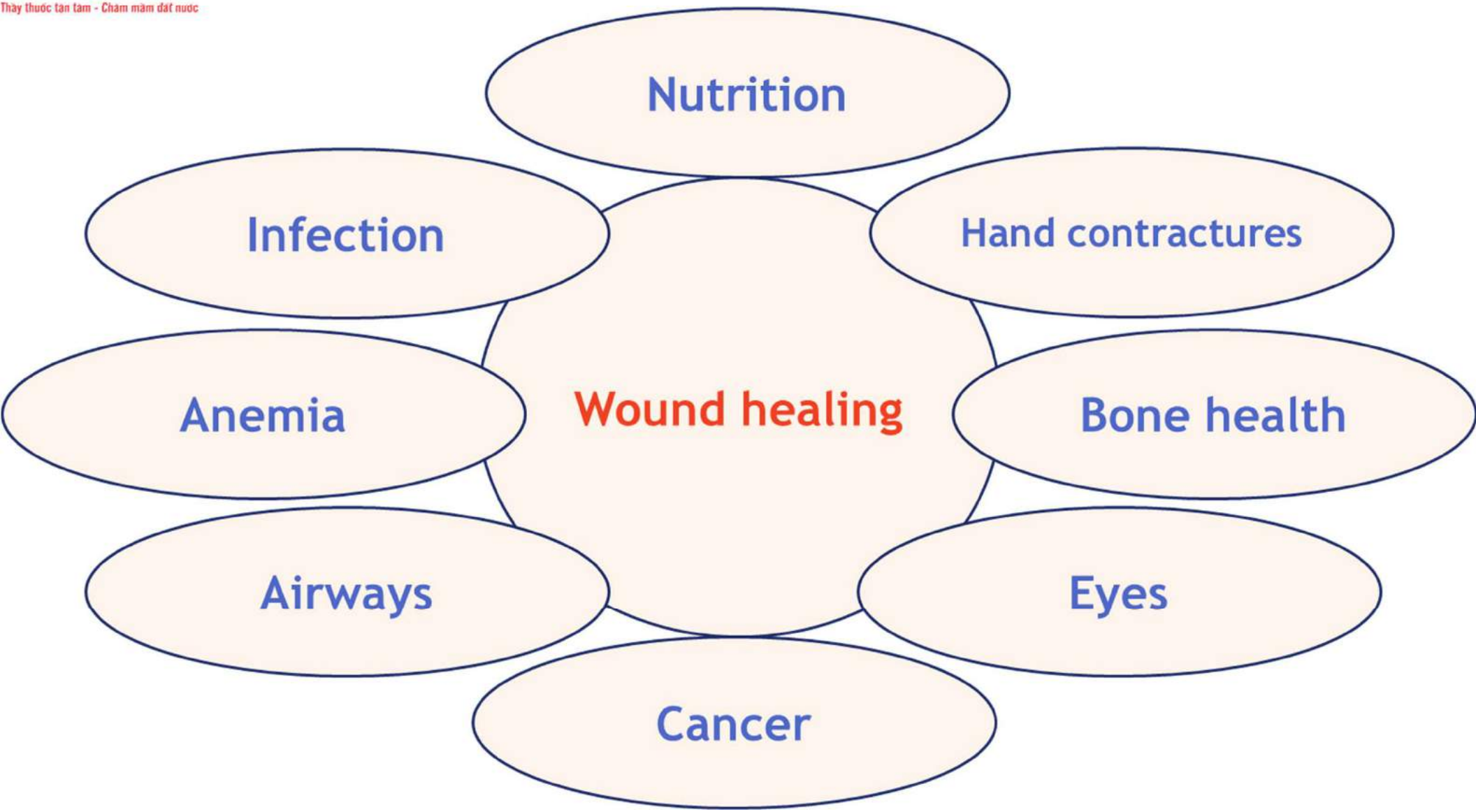
Diagnosis

- Electron microscopy (EM)
- Immunofluorescence antigen mapping (IFM)
- **Next-generation-sequencing (NGS)**

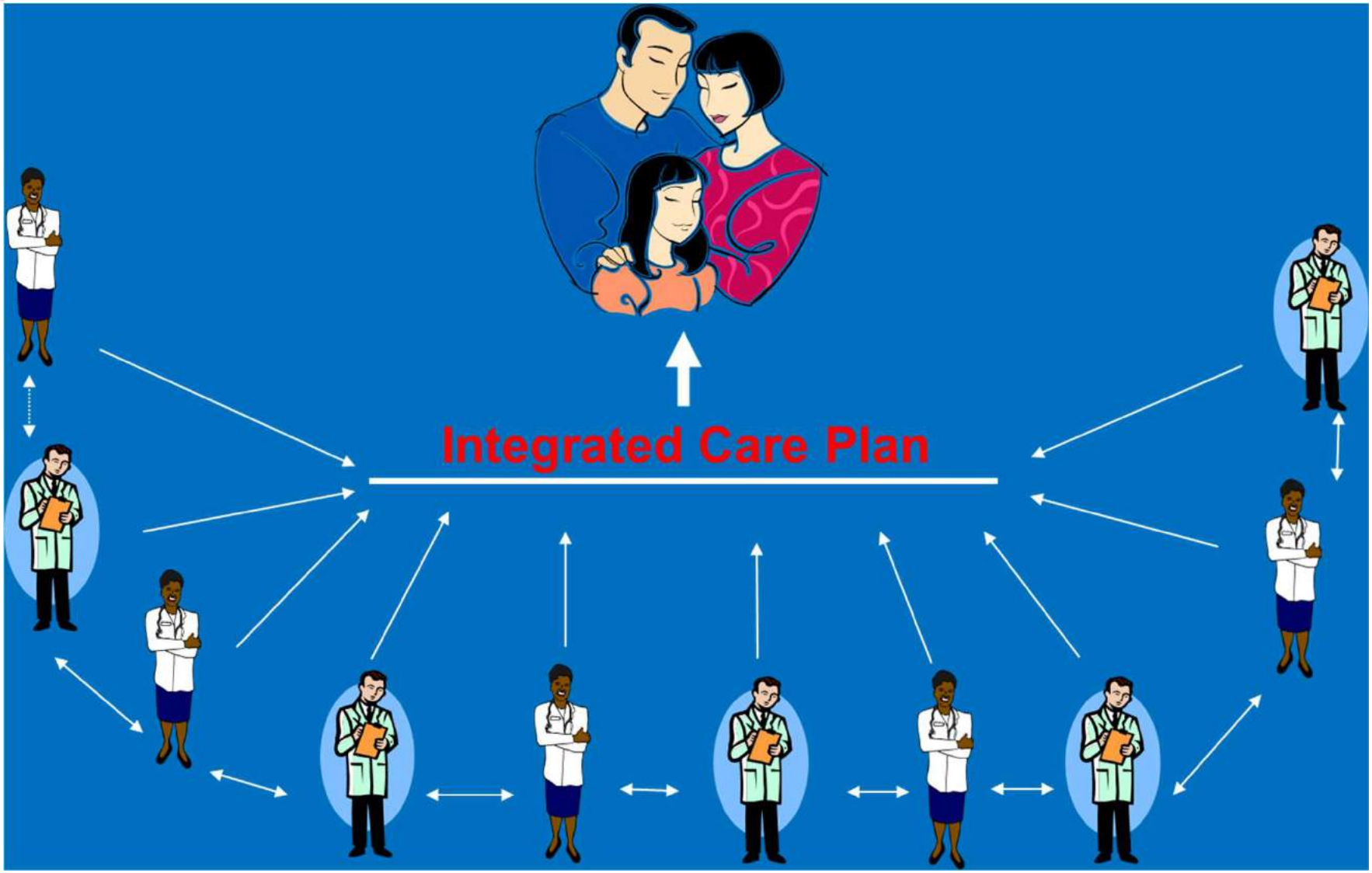
Classical Treatments

Epidermolysis Bullosa

Interdisciplinary Care



Interdisciplinary Care



Interdisciplinary Care

Dermatology and Nursing

- Wound care
- Protective bandaging, clothing, shoes
- Infection control
- Patient education and support

Nutrition and GI

- Adequate caloric intake
- Esophageal strictures and webs
- Deficiencies of Fe, Zn, et al.
- Osteopenia / osteoporosis
- Constipation

Interdisciplinary Care

Hematology

- Anemia of chronic illness
- Iron deficiency

Oncology

- Squamous cell carcinoma

Cardiology

- Cardiomyopathy
- Selenium and carnitine deficiencies

Interdisciplinary Care

Surgery (General, Plastic, Hand)

- Esophageal dilatation
- Feeding gastrostomy
- Excision and grafting of SCC
- Hand Releases

Dentistry

- Prophylactic hygiene
- Decay, crowding, oral blistering

Anesthesiology

- Anesthesia
- Pain Control

Interdisciplinary Care

Occupational and Physical Therapy

- Hand function / splints
- Aids to daily living
- Whirlpool under anesthesia

Ophthalmology

- Corneal Abrasions

Radiology

- Swallow
- Intraoperative fluoroscopy

Pathology

- Diagnosis of EB
- SCC

Interdisciplinary Care

Gynecology

- Induction of puberty
- Contraception
- Pregnancy

Psychology

- Family dynamics
- Behavior modification
- Adolescent adjustment
- Pain and depression
- Drug and alcohol addiction

Social Services

- Financial issues
- School adjustment
- Career counseling
- Family Support

New Treatments

Epidermolysis Bullosa

Table 2: Currently recruiting clinical therapy trials for EB

Therapy	Investigational Drug	EB Type	Trial identification Nr.
Therapies with curative aim			
Gene therapy	Transplantation surgery of genetically corrected cultured epidermal autograft (ATMP)	JEB with *COL17A1* mutations	ClinicalTrials.gov Identifier: NCT03490331
	Genetically corrected cultured epidermal autograft (ATMP)	RDEB*	ClinicalTrials.gov Identifier: NCT02984085
	FCX-007, Genetically modified autologous human dermal fibroblasts	RDEB*	ClinicalTrials.gov Identifier: NCT02810951
	KB103, a non-integrating, replication-incompetent herpes simplex virus vector expressing human collagen VII protein	DEB	ClinicalTrials.gov Identifier: NCT03536143
Antisense oligonucleotide	QR-313, an antisense oligonucleotide (AON)	DEB with mutations in exon 73 of *COL7A1*	ClinicalTrials.gov Identifier: NCT03605069
PTC read-through	Gentamicin, intravenous	RDEB	ClinicalTrials.gov Identifier: NCT03012191
Cell therapy	Serial mesenchymal stem cell (MSC) infusions from a related donor	All EB types	ClinicalTrials.gov Identifier: NCT02582775
	Allogeneic stem cell transplantation and "off-the-shelf" mesenchymal stem cells	All EB types	ClinicalTrials.gov Identifier: NCT01033552
Symptom-relief therapies			
Anti-fibrotic	Losartan, systemic	RDEB*	EudraCT Number: 2015-003670-32
Anti-inflammatory	Diacerein, topical	EBS	ClinicalTrials.gov Identifier: NCT03154333
	Pharmacokinetics, safety of diacerein after maximum use	EBS	ClinicalTrials.gov Identifier: NCT03472287
	Oleogel, topical	All EB types	ClinicalTrials.gov Identifier: NCT03068780
	BPM31510 3.0% Cream, topical	All EB types	ClinicalTrials.gov Identifier: NCT02793960
	Sirolimus, topical	EBS	ClinicalTrials.gov Identifier: NCT03016715

*RDEB=Recessive DEB

Bruckner-Tuderman L. ***Newer Treatment Modalities in Epidermolysis Bullosa***. Indian dermatology online journal. May-Jun 2019

Gene Therapy

Epidermolysis Bullosa

Gene Therapy

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FDA NEWS RELEASE

FDA Approves First Topical Gene Therapy for Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa

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For Immediate Release: May 19, 2023

Content current as of:

Gene Therapy

Now Approved in the US

Vyjuvek™
beremagene geperpavec-svdt
5x10⁹ PFU/mL single-use vial

Dystrophic Epidermolysis Bullosa

$24,250 per vial

$631,000 per patient per year

Gene Therapy

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VYJUVEK

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Vaccines, Blood & Biologics

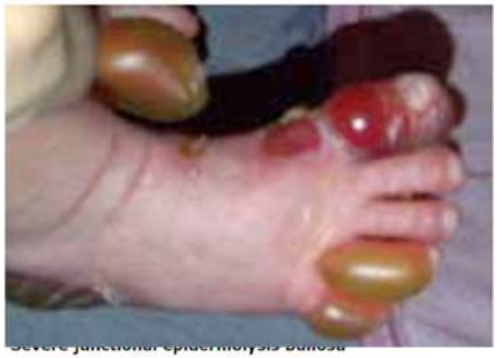
Infectious Disease Tests

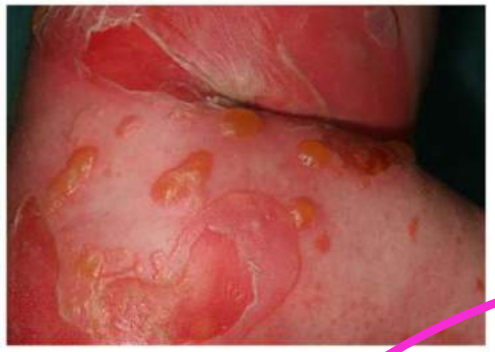
Fecal Microbiota Products

STN: 125774
Proper Name: beremagene geperpavec
Tradename: VYJUVEK
Manufacturer: Krystal Biotech, Inc.
Indication:

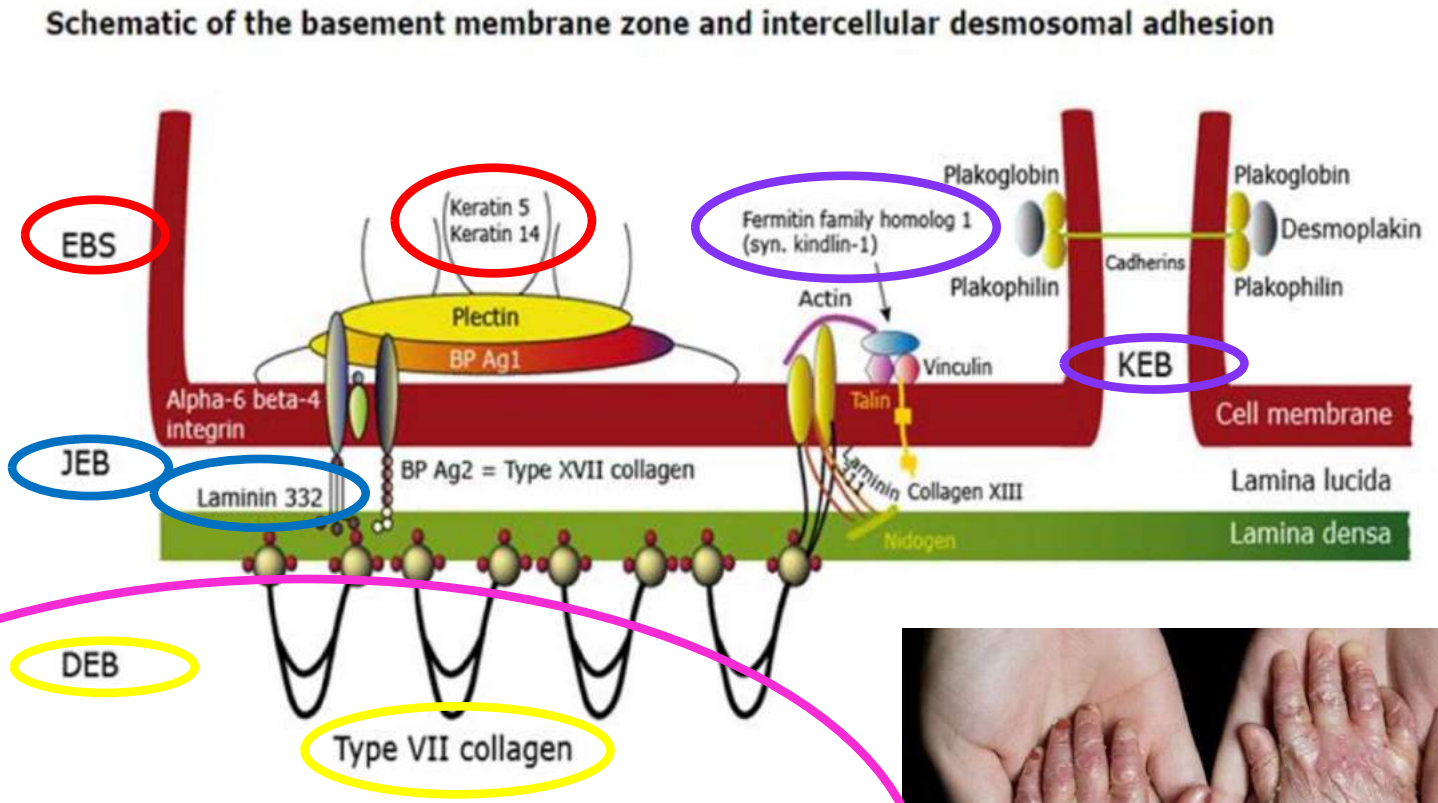
- For the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1) gene*.

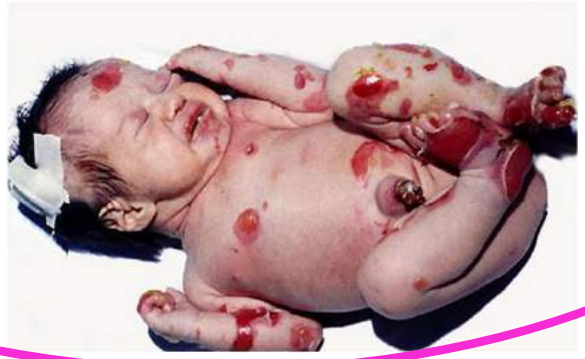
Classification





Generalized blistering, crusted erosions, and extensive area[illegible] denudation in severe JEB.

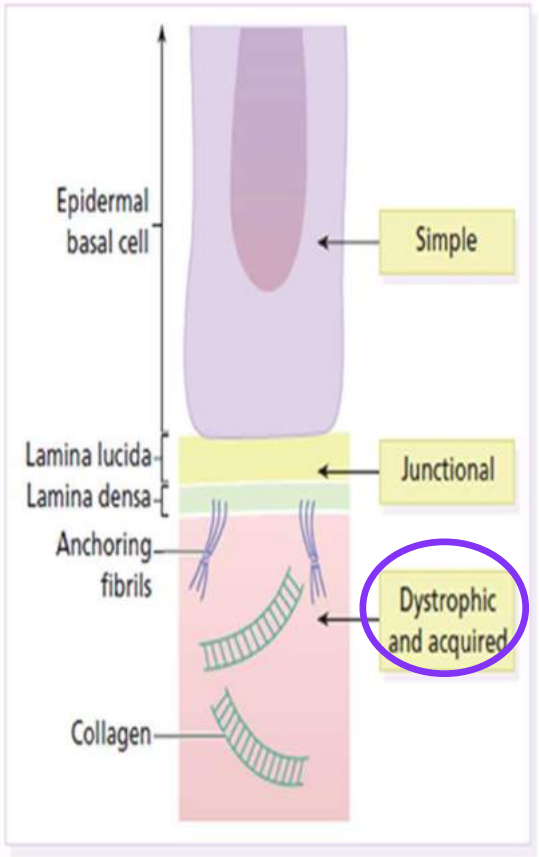




Gene Therapy

COL7A1 Gene

COL7A1 gene provides to make type VII collagen subunits. Type VII collagen is the main component of anchoring fibrils that help the stabilizion and the strengthening of the dermis.



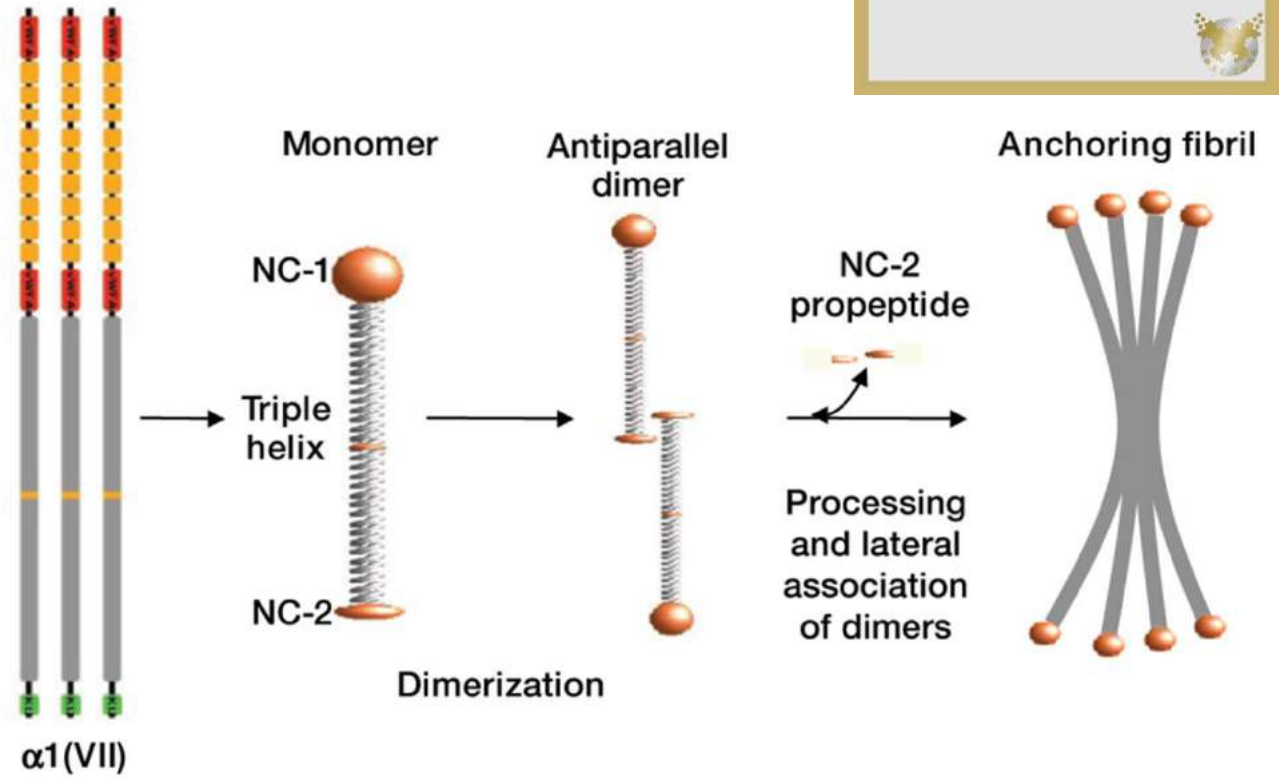


Figure 1 Schematic representation of the polymerization of anchoring fibrils. The type VII procollagen monomer consists of three α1(VII) polypeptide chains folded into a triple helix. Two monomers form an antiparallel dimer, from which the NC-2 propeptides are removed proteolytically. Finally, the mature dimers laterally aggregate into anchoring fibrils. (Courtesy of Johannes Kern, University Medical Center, Freiburg, Germany.)

Gene Therapy

DEB is caused by mutation(s) in the COL7A1 gene, which results in reduced or absent levels of biologically active COL7.

- Autosomal dominant (DDEB) : *lower than normal functional anchoring fibrils*
- Autosomal recessive (RDEB) : *no functional anchoring fibrils*

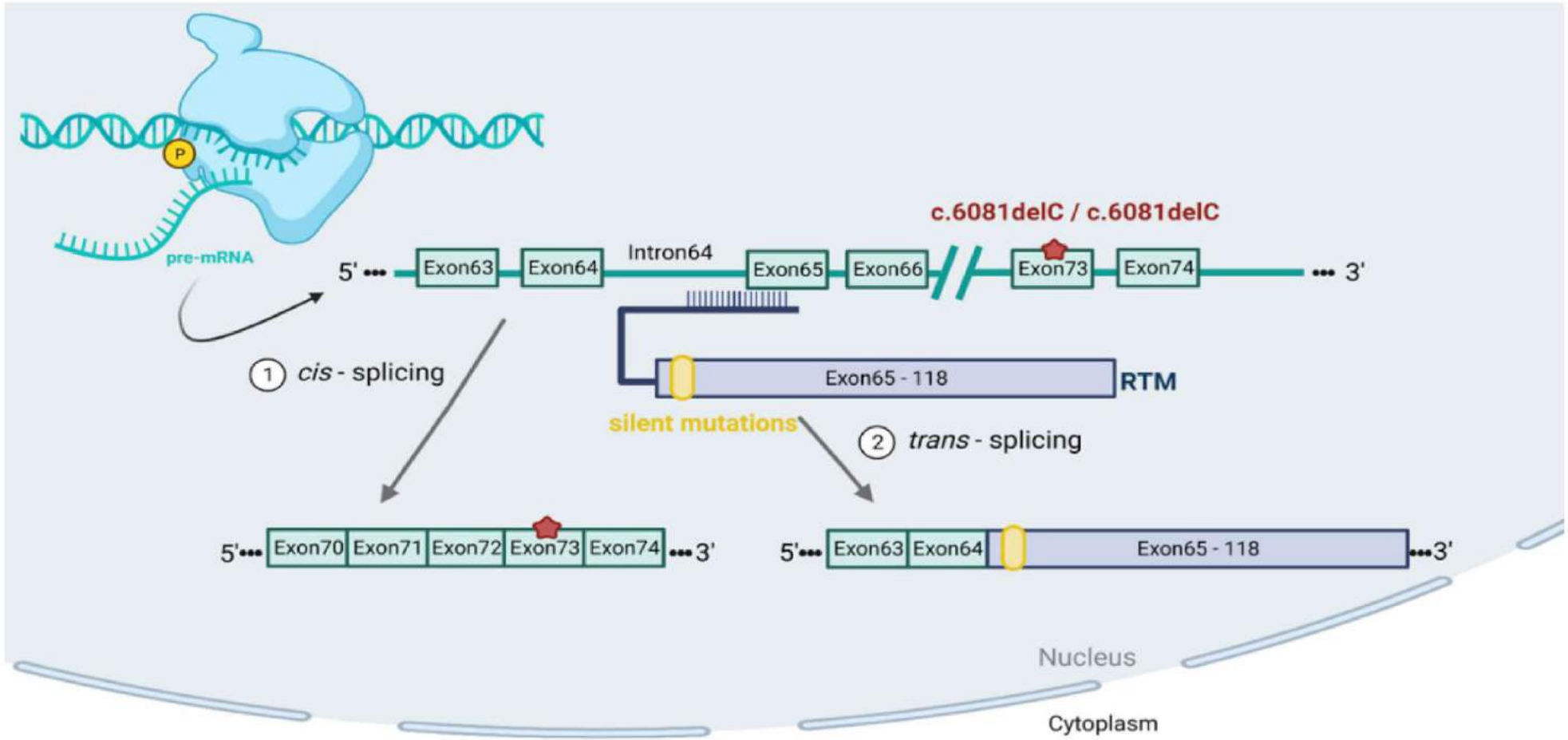
Gene Therapy

Vyjuvek (Beremagene geperpavec) can transduce both keratinocytes and fibroblasts.

It is deposited in the nucleus and transcription of the encoded human COL7A1 is initiated

⇨ **production and secretion of COL7** by the cell in its mature form.

Gene Therapy



Liemberger B, Bischof J, Ablinger M, et al. **COL7A1 Editing via RNA Trans-Splicing in RDEB-Derived Skin Equivalents**. *International Journal of Molecular Sciences*. 2023

Gene Therapy

DOSAGE AND ADMINISTRATION

For topical application only.

Age Range	Maximum Weekly Dose (plaque forming units; PFU)	Maximum Weekly Volume (milliliter; mL)*
6 months to <3 years old	1.6×10^9	0.8
≥ 3 years old	3.2×10^9	1.6

*Maximum weekly volume is the volume after mixing VYJUVEK biological suspension with excipient gel.

Apply VYJUVEK gel to the selected wound(s) in droplets spaced evenly within the wound, approximately 1cm-by-1cm apart. (2.3)

The table below provides a reference on dose per approximate size of the wound.

Wound Area (cm^2)*	Dose (PFU)	Volume (mL)
<20	4×10^8	0.2
20 to <40	8×10^8	0.4
40 to 60	1.2×10^9	0.6

*For wound area over 60 cm^2, recommend calculating the total dose based on this table until the maximum weekly dose is reached.

Our patients

CHILDREN'S HOSPITAL 1

NEONATOLOGY DEPARTMENT

3 - 4 cases per year

- 1 - 2 severe cases per year

  (EBS, JEB – Herlizt)

Our patients

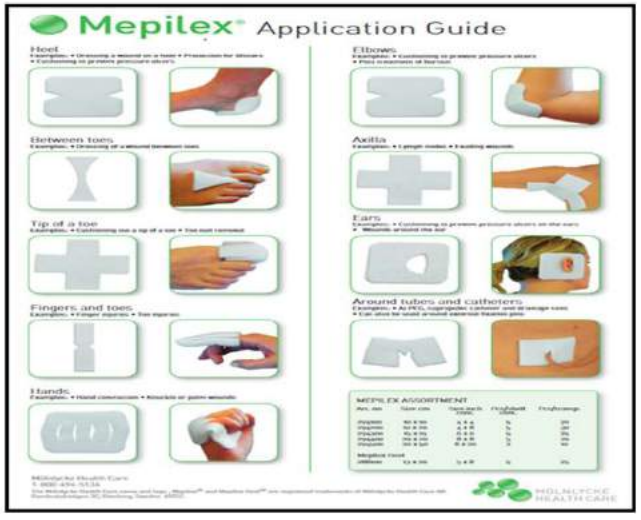
EPIDERMOLYSIS BULLOSA (EB) SUPPORT PROJECT
MEMORANDUM OF UNDERSTANDING
BY AND BETWEEN
HCMC CHILDREN HOSPITAL 1
AND
HELPING ORPHANS WORLDWIDE INC.

Epidermolysis Bullosa ("EB") is a serious inherited skin disease affecting children in every country throughout the world..

Helping Orphans Worldwide (**HOW**) and HCMC Children Hospital 1 (The **Hospital**) in the meeting in July 2014 expressed a mutual desire to facilitate treatment and quality of care for patients afflicted by EB for implementation during the period from August 20, 2014 until August 20, 2016 (the "**Period**")

Hướng dẫn thực hành xử trí trẻ sơ sinh với Ly Thượng Bì Bóng Nước nghiêm trọng Epidermolysis Bullosa (EB)

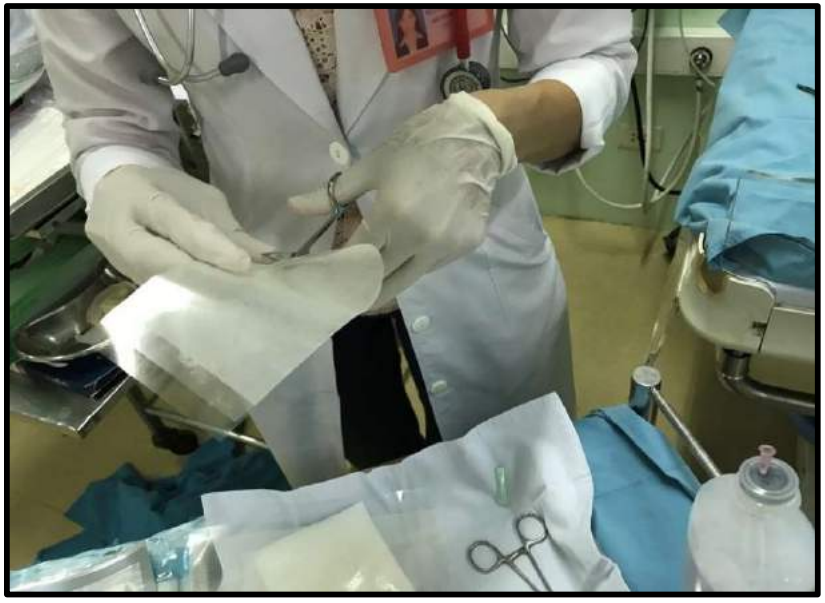
Jacqueline Denyer, Clinical Nurse Specialist (paediatric) Great Ormond Street Hospital, London and DEBRA UK, Jackie.denyer@gosh.nhs.uk
Đồng tác giả: Lesley Foster & Juliette Turner, Clinical Nurse Specialists (paediatric) Great Ormond Street Hospital, London and DEBRA UK



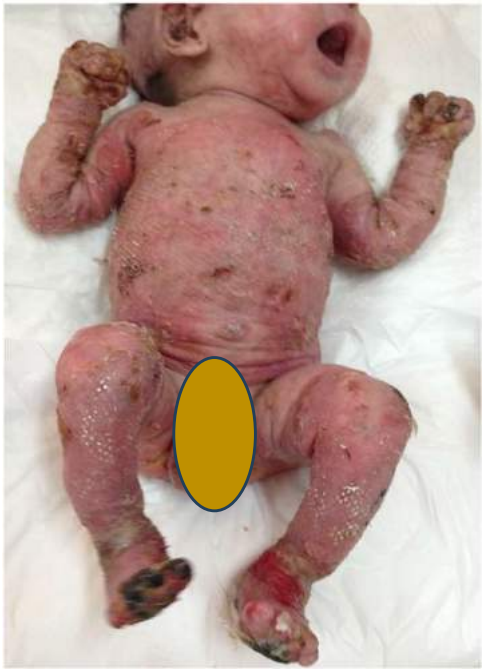
EB CARE SUPPLIES FROM **HOW**

2016, URGO FOUNDATION

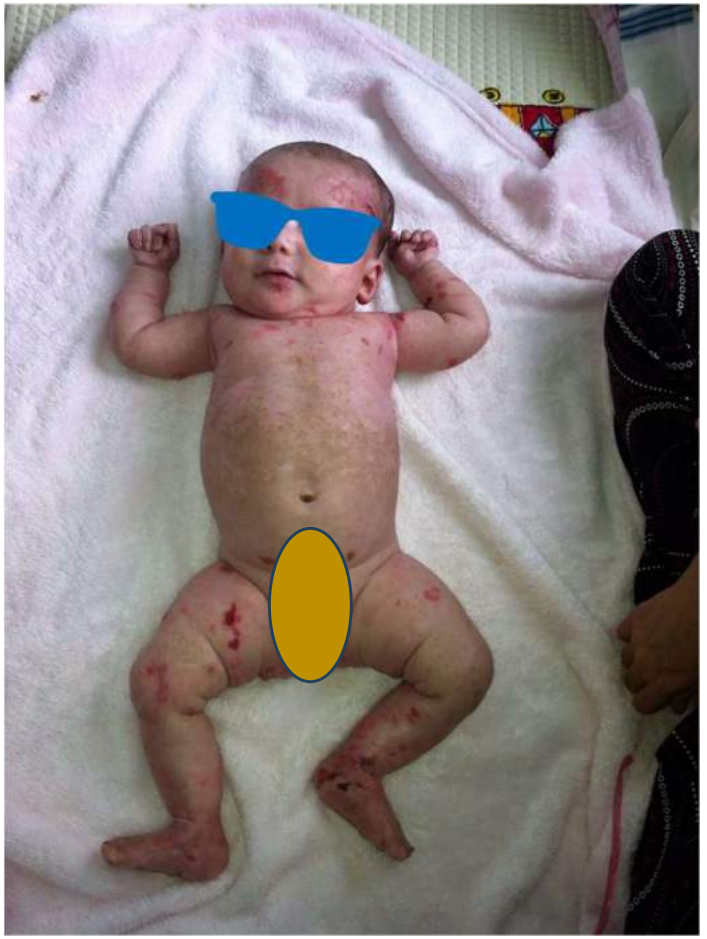
URGO
MEDICAL
Healing people®



Our patients



2014
EB type?



Our patients

Biopsie fixée et en liquide de Michel d'une bulle récente de la hanche droite.

La biopsie fixée a été colorée par l'hématéine éosine. Il existe à la jonction dermo-épidermique, une cavité bulleuse. Le toit de la bulle est constitué d'épiderme intact. La cavité bulleuse comporte de la sérosité et quelques éléments inflammatoires mononucléés ainsi que des polynucléaies éosinophiles. Le plancher de la bulle est constitué en partie par un épiderme semblant en voie de reconstitution. A l'origine du clivage de la bulle, on observe au plancher une couche de kératinocytes, suggérant un clivage possiblement intra épidermique. Le derme sous jacent comporte un infiltrat modéré inflammatoire périvasculaire constitué de lymphocytes, d'histiocytes, de polynucléaires neutrophiles et éosinophiles péricapillaires.
Une étude en immunohistochimie a été réalisée sur coupes congelées.

ANTICORPS	Marquage	Présence d'un clivage	Plancher / Toit
Cytokératine 14	+	+	Plancher et toit
Laminine (Laminine 332)	+	+	plancher
LH7-2 (collagène VII)	+		plancher

+ = présence d'un marquage comparable au témoin peau normale
- = absence de marquage
+/- = présence d'un marquage diminué par rapport à un témoin peau normale.

CONCLUSION :

1/1

(Suite) No Examen **18NA02633** Concernant le patient **DOAN BAO NGOC**

L'aspect histologique et la cartographie de la jonction dermo-épidermique évoquent une épidermolyse bulleuse dans une forme épidermolytique (=simplex).

Dicté le : 29/03/2
Validé le : 09/
Dr Stéphani

2016
EBS

Our patients

2018

EBS

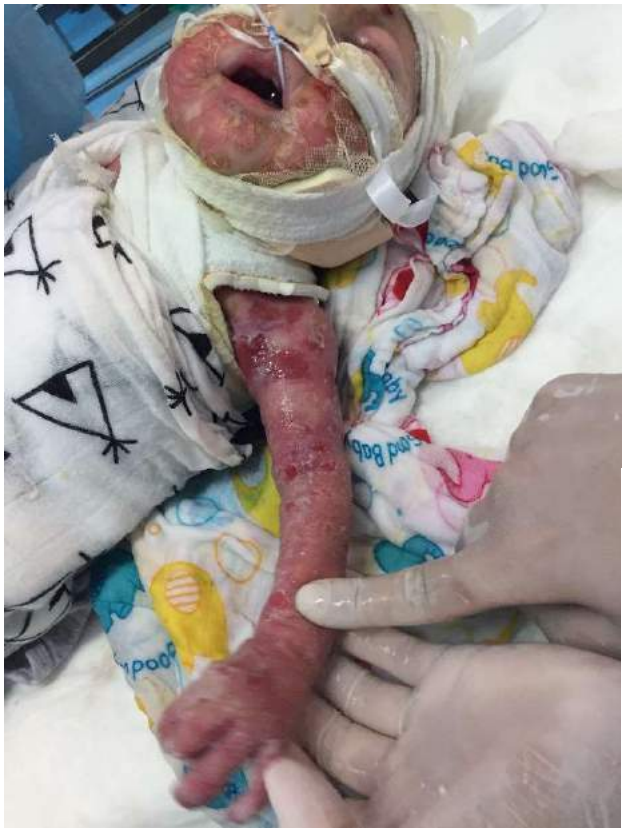
Thông tin lâm sàng: Bé sinh 36.5 tuần, 2,7 kg, sau sanh ngay ngày đầu xuất hiện trượt da vùng chi (2 chân từ đầu gối đến bàn chân, khuỷu tay), chẩn đoán BVTD: ly thượng bì bóng nước)

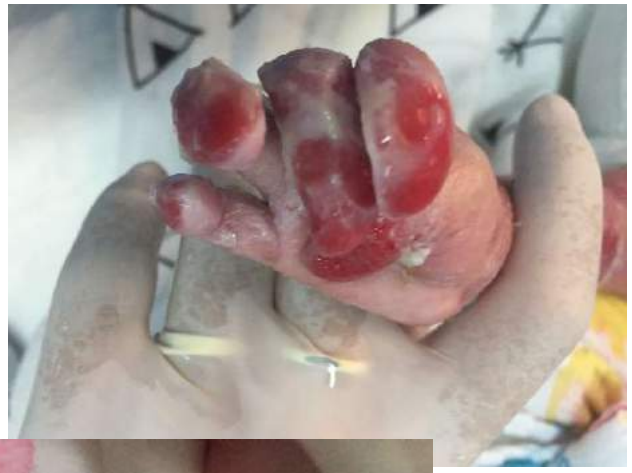
KẾT QUẢ

Gen	Dạng di truyền	Biến thể phát hiện	Đồng hợp/ dị hợp
KRT5	Trội	NM_000424.3(KRT5):c.1429G>A (p.Glu477Lys)	Dị hợp

KẾT LUẬN: Phát hiện đột biến trên gene *KRT5*

Our patients





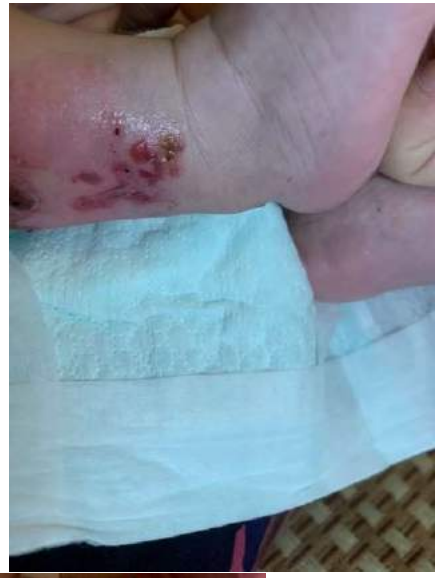
2019
JEB

KẾT QUẢ

Gen	Dạng di truyền	Đồng/ Dị hợp	Vị trí	Thay đổi Nucleotit/ Protein	Hệ quả	Kiểu hình	Phân lớp đột biến
LAMA3	Lặn	Dị hợp	chr18: 23881927	NM_000227.5:c.286-9T>A	Đột biến intron	1. Epidermolysis bullosa, junctional, Herlitz type 2. Epidermolysis bullosa, generalized atrophic benign 3. Laryngoonychocutaneous syndrome	Chưa được báo cáo trên ClinVar
LAMA3	Lặn	Dị hợp	chr18: 23931206	NM_000227.5:c.3749+5G>A	Đột biến vùng chuyển tiếp	1. Epidermolysis bullosa, junctional, Herlitz type 2. Epidermolysis bullosa, generalized atrophic benign 3. Laryngoonychocutaneous syndrome	Chưa được báo cáo trên ClinVar

DIỄN GIẢI KẾT QUẢ:

Our patients



2023

JEB

Gen	Dạng di truyền	Đồng/Dị hợp	Vị trí	Thay đổi Nucleotit/ Protein	Hệ quả	Kiểu hình	Phân lớp đột biến Clinvar
LAMC2	Lặn	Đồng hợp	chr1: 183228616	NM_005562.3: c.1711C>T (NP_005553.2: p.Arg571Ter)	Đột biến ngưng dịch mã	1. Epidermolysis bullosa, junctional, Herlitz type 2. Epidermolysis bullosa, junctional, non-Herlitz type	Gây bệnh

Take home messages

Take home messages

- Epidermolysis bullosa (EB) includes a group of ***rare inherited disorders*** characterized by marked mechanical fragility of epithelial tissues, with blistering and erosions following minor trauma
- Four major types are based upon the ultrastructural level of blister formation within the epidermal basal membrane zone
- The Interdisciplinary Care is the most important modality in medical care for EB
- Vyjuvek (beremagene geperpavec), the first topical gene therapy for treatment of wounds in patients with dystrophic epidermolysis bullosa

BỆNH VIỆN NHI ĐỒNG 1
1956
Thầy thuốc tận tâm - Chăm mầm đất nước

Thank you for your attention!