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Recommended Strategies for Epidermolysis Bullosa Management in Romania

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ABSTRACT

Background: *There are 72 families with epidermolysis bullosa (EB) in Romania. Since 2012 a National Program for the treatment of these patients is run by the Ministry of Health.*

The objectives *of the strategies for EB patients are to optimize the management (diagnosis, treatment, monitoring) and to provide actual information on classification and patho-physiology which dictate the course of the disease.*

Methods: *An international expert panel of specialists produced by consensus the recommendations for the management of EB cases in Romania taking into account the local possibilities. Patient association proposals were included. A review of the literature was performed to up-date the information.*

Outcomes: *A strategy for diagnosis, treatment and follow-up of the patients with EB was elaborated in clear steps. Pharmacological treatments and wound care indications are provided together with a useful score for patient evaluation.*

Conclusion: *These recommended strategies are allowing dermatologists to generate an individualized care plan for patients with EB.*

Keywords: epidermolysis bullosa therapy, epidermolysis bullosa monitoring, dressings, wound care

INTRODUCTION

Epidermolysis bullosa (EB) defines a heterogeneous group of congenital disorders characterized by fragility of the skin and mucous membranes resulting in painful blisters and erosions after minor trauma; complications include secondary infections, cancer, amyloidosis, contractures, esophageal, urethral and anal stenosis, failure to thrive and psychological disturbances (1,2).

Blisters depth and severity, the distribution of skin damage, blisters formation process can vary depending on the subtype of EB and on the underlying molecular defect inherited. There are more than 30 subtypes of EB (3, 4). Although mild subtypes of EB are associated with an almost normal life and minimum mucosal and visceral involvement, the most severe recessive forms are mutilating, affecting several organs and affecting both life quality and life span (1,2).

In term of incidence, data shows the occurrence of 50 new epidermolysis bullosa cases per one million live births, of which approximately 92% are epidermolysis bullosa simplex, 5% are dystrophic epidermolysis bullosa, 1% are junctional epidermolysis bullosa, and 2% are unclassified (5); these data may vary widely between countries and ethnic groups. 72 families with different types of epidermolysis bullosa are identified in Romania.

The onset is at birth or shortly after; mild cases of epidermolysis bullosa simplex may remain undetected until adulthood or even remain undiagnosed (6). ❑

CLASSIFICATION

The many subtypes of EB were subject to various classifications and different names. The actual classification in based on the most recent laboratory data.

- *EB simplex* range from mild forms, with blisters confined to the hands and feet up to severe generalized forms, affecting the mucous membranes and nails. Transmission is mostly autosomal dominant although a high incidence of recessively inherited cases has been reported in inbred populations (7,8). Pathophysiology is related to mutations in genes encoding keratin 5, keratin 14, PLEC1, COL17A1 etc. Structural abnormalities lead to separation of the basal epidermal cells from the basal membrane when the skin is exposed to friction or heat injury (1,9) although additional, non-mechanical mechanisms may be involved (10).

- *Junctional EB* includes a spectrum of forms ranging from mild to severe. Transmission is autosomal recessive, with only one case reported of dominant inheritance (11). Phenotypic manifestations vary from localized to generalized skin blistering associated with nail, dental and often mucosal involvement. Common complications include anemia, malnutrition, failure to

thrive, renal and pulmonary problems, skin cancer. The disease is associated with increase mortality. Mutations in at least 6 distinct genes have been found to be associated with this subtype of the disease (3,9,12).

- *Dystrophic EB* range from mild autosomal dominant forms, with lesions on hands, knees and elbows to severe autosomal recessive types (recessive dystrophic EB, severe generalized form), featuring generalized blisters healing with extensive scarring and milia lesions located predominantly in acral areas. This can lead to pseudosyndactyly of hands and feet; with age can occur contractures of the extremities, nail dystrophy, impaired dentition. Mucosal involvement leads to esophageal and urethral strictures, anal stenosis, phimosis, and corneal scarring. Anemia often occurs due to lack of iron absorption and malnutrition followed by growth retardation. Recalcitrant pruritus, pain, infections also have an impact on individuals ability to heal (1,3).

Recessive dystrophic EB patients who survive childhood period have a high risk (50-80%) of developing very aggressive squamous cell carcinoma (SCC) in areas of chronic erosions, with early metastatic spread and death. All forms of dystrophic EB are related to mutations in COL7A1 encoding the type VII collagen, which is the major constituent of anchoring fibers (13).

- *Kindler syndrome* is a rare and difficult to diagnose subtype of EB. It is caused by mutations in the FERMT1 gene and can be easily confused with other subtypes of EB. Blisters occur in early life with variable levels of cleavage. Blistering is less prominent with time and photosensitivity and poikiloderma develop instead. Severe colitis, esophagitis and urethral strictures may complicate the disease (14).

- *Epidermolysis bullosa acquisita* is a rare acquired type of epidermolysis bullosa associated with autoantibodies against type VII collagen (6,15). It is not addressed to in this paper. ❑

CONSENSUS RECOMMANDATIONS

An international expert panel of specialists produced by consensus the recommendations for the management of EB cases in Romania taking into account the existing possibilities. Patient association proposals were also debated. In actual local conditions it is difficult to access for all patients the newest laboratory techniques. The expert panel focused on the relevant diagnostic elements that provide information on classification, treatment and, if possible, on patho-physiology.

1. Clinical diagnosis of EB relies on several aspects.

Of major importance is the history of the patient and there should be an enquiry about the ethnic origin and family history, the age of onset and cutaneous and extracutaneous manifestations. It is important to identify the traumatic nature of blisters and the seasonal variation. There is an exacerbation after physical exercise.

Physical exam is a challenge and it involves the examination of the entire body surface, quantifying the affected area.

The cutaneous findings comprise of mechanically fragile skin with the appearance of blisters, erosions, crusts which may heal with scars and milia; mitten deformities and nail dystrophy or lost of the nail are frequent. There is also scarring alopecia of the scalp and all four types of EB may show oro-pharyngeal involving either of hard or soft tissues and genital mucous lesions.

The extracutaneous findings are of different types according to the inherited form of EB. The esophagus involvement may lead to scarring, strictures or obstruction and bowel involvement to malabsorbtion, severe constipation, anal fissures, anal strictures. The genitourinary tract involvement presents with urethral strictures.

Pseudosyndactyly represents a major complication of the recessive dystrophic form of EB (RDEB) and the teeth lost or caries due to enamel hypoplasia of the jonctional EB (JEB).

Recurrent ocular involvement as painful erosions and blisters as well as photophobia blepharoconjunctivitis and ectropion arise most commonly in patient with generalized JEB and RDEB.

The most clinically significant musculo-skeletal complication is the progressive webbing and the contracture of hand and feet's; there are also subluxations of metatarsophalangeal and metacarpophalangeal joints and different other clinical manifestations of musculoskeletal involvement (16).

The dilated cardiomiopathy is an uncommon complication of RDEB and may eventually prove fatal.

The delayed puberty is common among severely affected EB children and may be associated with osteopenia and osteoporosis. There is also growth retardation which impacts patient self-esteem negatively (16).

Skin derived squamous cell carcinoma (SCC) is a very common complication of RDEB and is arising starting with the second decade of life; despite surgical excision they have a high recurrence rate and the metastatic SCC is the primary cause of death in RDEB.

Malignant melanoma may arise in children with RDEB and the risk of basal cell carcinoma is very high in adults with EB simplex (16)

2. Laboratory tests useful for monitoring the disease are of different subsets (17).

It is important to examine periodically CBC, renal function tests (BUN, creatinine, electrolytes), liver function tests, albumin, iron, inflammation markers, serum folate, B12, vitamin D metabolites, urinalysis.

According to the clinical manifestation the culture from the wounds to check for bacterial infection may be often required.

There are also recommended periodic: eye examination, urography for urethral strictures, cardiac examination, DEXA scanning for osteoporosis.

The skin biopsy with immunofluorescent or immunohistochemical staining from fresh (<12 hours) lesions shows cleavage planes and defective expression of EB associated proteins;

In Research Centers and for selected cases, electron microscopy of skin samples may show benefit by showing the cleavage plane, abnormal hemidesmosomes and anchoring fibrils. Genetic testing can show specific DNA defect and may be useful for family planning and prenatal diagnosis (biopsy taken from the chorion vili).

3. Therapy

Treatment for EB must be patient orientated. Individual tailoring begins with preventive measures, nutritional support and ends with wound care indications. The assessment of skin lesions and general condition of the patient are important tools not only for monitoring the patient but also for the periodic up-date of the recommended strategy.

General management principles (1,17)

Nutritional support is paramount. There is a need for monitoring nutritional status - albumin levels (less than 3g/dL), body mass index, growth curves (for pediatric patients) – and to consider nutritional consults to evaluate the caloric intake and needs. In some cases there may be need for regular oesophageal dilatations if strictures are present or for the severe forms gastrostomy.

Correcting anemia

The hemoglobin levels should be monitored and if less than 100g/L the oral iron supplementation for correction of iron deficiency is required. Blood transfusion should be considered when hemoglobin levels are consistent below 80 g/L and/or for symptomatic patients who do not respond to other measures.

Pain management

The pain evaluation (by Pain Visual Analogue Scale - VAS) is important and pain prevention is to be realized by using protective atraumatic dressings, padding of the trauma prone areas, releasing fluid from tense blisters, avoiding adhesive dressings or skin adhesive products, removing dressings in water to hydrate the surface and limit friction with removal and treatment of skin infections

Therapeutic measures to be considered for nociceptive pain are: for (a) mild-moderate pain: acetaminophen and NSAIDs, (b) severe pain: opioids and anxiolytics (c) for children under two years of age: oral sucrose 24%. For the neuropathic pain the tricyclics (amitriptyline, gabapentin, pregabalin, and other antiepileptics) might be helpful. Nonpharmacological measures encompass psychological/suggestive therapies and physical modalities (eg: cooling).

Itch management

The intensity of itch should be evaluated by Pruritus Visual Analogue Scale.

Treatment consists of nonsedating H1 antihistamine (at day time) or sedating H1 antihistamine with/without tricyclic (at night time). Topical tacrolimus/pimecrolimus for EB pruriginosa might be of some help.

Psychological evaluation

The patient and his family should be evaluated for depression.

Pharmacological treatments

Antibiotic treatment may be indicated according to the infectious status of wound and antibiogram.

The treatment with phenytoin (17) or tetracyclines (18) of the inherited forms of epidermolysis bullosa was of no benefit when compared with placebo in the systematic review of several randomized controlled trials.

Wound care comprises several steps.

1. Evaluation and monitoring by (1) IGA (Investigator's Global Assessment), (2) BSA (Body Surface Area) (3) DLQI (Dermatology Life Quality Index), cDLQI (Children's Dermatology Life Quality Index) and (4) Epidermolysis bullosa evaluation score (Annex I - Birmingham EB Severity Score Sheet (Adult); Annex II - Birmingham EB Severity Score Sheet (Child)) (19).

2. Bathing

For this there should be recommended gentle and non-toxic solutions: (a) chlorhexidine baths 0.1% , before surgical procedure and for preventing gram-positive infections; (b) salt baths - 90 g table salt in 10 L of water (c) vinegar solution: 5% white vinegar – 0.5 -1L in 10 L of water (prevents gram-negative infections: eg. pseudomonas

3. Debriding necrotic tissue

The blisters should be drained by using a needle with the maintenance the roof of blister.

For debriding there is the option of the autolytic debridement (hydrogel, calcium alginate) or of mechanical debridement.

4. Treating critical colonization/infection

It is recommended to use the antiseptic solutions and the topical antibiotics (used for shorts periods of time rotated every 2-6 weeks) and dressings containing iodine or silver. The systemic antibiotic treatment for short term according to antibiogram is mandatory when the clinical status requires and for chronic, non-healing wounds, low dose, long term antibiotics for their anti-inflammatory properties.

4. Dressings

The correct use of dressings is of paramount importance and should be according to the wound characteristics; there are different types to be use: occlusive, semiocclusive, absorptive, hydrating, hemostatic etc. (Table 1);

Adhesive bandages are not recommended; retention dressings (ex. Tubifast Garments - Molnlycke Health Care, Gothenburg, Sweden) and elastic bandages (ex. Peha Crepp - Paul Hartmann AG, Heidenheim, Germany) can be safely used.

Preventive measures

The patient should avoid trauma and blister expansion by using foam dressings and soft sleeping and seating surfaces. Preventing local infestation by draining the blisters, using dressings and control local colonization might prove in itself a major challenge.

Management of squamous cell carcinoma

Clinical evaluation of suggestive lesions is mandatory and it should focus on the lesions with more than three months evolution, which are exophytic, ulcerated, or on which patient reports intense pain or that it feels different; this type of lesion undergone punch biopsy or excisional biopsy - excision (in a Dermatologic unit if the lesion is less than 3 cm in diameter; in a Surgery department/ Oncology unit – if lesion is larger than 3 cm in diameter and/or enlarged lymph nodes). If needed, the patient may have ultrasound or CT, PET-CT recommended.

Support

The EB patients need every attempt to increase their quality of life. They should be evaluated periodically (DLQI, cDLQI) and the treatment should be tailored to each patient according to his needs. A special attention should be given to the issues raised by schooling and/or employment needs. Of tremendous importance is the access to home care and specialized caring teams. There may be extensive need for psychotherapy.

The patients mat also relay on support groups (ex. DebRA). ❑

CONCLUSION

These recommended strategies are allowing dermatologists to generate an individualized care plan for patients with EB. Using the proposed monitoring instruments it will be possible to constant up-date the treatment plan for the patient and the national recommended strategy for EB management.

Conflict of interest: none declared.

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Indication	Dressing	Commercial name
Protection	foams	Mepilex*, Mepilex lite*, Mepilex border*, PolyMem**
	contact layers	Mepitel*, Mepitac*
Non-exudative	foams	Mepilex*, Mepilex lite*, Mepilex border*, PolyMem**
	modified absorbent pads	Mesorb*, ETE*
	contact layers	Mepitel*, Mepitac*
Exudative	foams	Mepilex*, Mepilex lite*, Mepilex border*, PolyMem**
	hydrofibers	Aquacel#
	hydrogels	Duoderm**
Hypergranulation	contact layers	Mepitel*, Mepitac*
	modified absorbent pads	Mesorb*, ETE*

TABLE 1. Dressing choices for different indications of wound characteristics.

*Molnlycke Health Care, Gothenburg, Sweden.
** Ferris Manufacturing, Burr Ridge, IL, USA.
# ConvaTec, Skillman, NJ, USA.

ANNEX I - BIRMINGHAM EB SEVERITY SCORE SHEET (ADULT)

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Patient's name……DOB……Type of EB……..

Scorer's name……Date……

*See overleaf for detailed instructions

Score item	Measure	Max	Actual score
*Nails	Lost nails ÷ 4 Dystrophic nails ÷ 8	5	
*Area	½ x % damaged skin: blisters, erosions, scabs, healing skin, erythema, atrophic scarring; not dyspigmentation, or well-healed scars.	50	
*Mouth	0 = no mucosal involvement 1 = occasional blisters/erosions 2 = frequent blisters 3 = persistent symptoms, early structural abnormality 4 = Moderate structural abnormality 5 = severe structural abnormality (see over for detailed scoring for each site)	5	
*Eyes		5	
*Larynx		5	
*Esophagus		5	
Scarring of hands	0 = no scarring 1 = Milia and atrophic scars 2 = Just detectable contractures or webbing 3 = obvious contractures, or proximal webbing 4 = Between 3 and 5 5 = Mitten formation with fingers all fused	5	
Skin Cancer (SCC)	Number of skin cancers +1 for local/regional/lymph node spread +2 for distant metastatic spread, up to maximum score 5	5	
Chronic wounds present for > 6/12	0 = none 1 = <1% body surface area (1% = palm size) 2 = 1-2% 3 = 2-5% 4 = 5-10% 5 = >10%	5	
Alopecia due to EB	0 = no alopecia from EB 1 = 1-19% scalp involvement 2 = 20-39% 3 = 40-59%, 4 = 60-79% 5 = 80-100%	5	
Nutritional compromise	0-5 (where 0 = normal and 5 = cachetic)	5	
TOTAL SCORE		**100**	

How to fill in the BEBS score sheet

Nails: enter number in each box and add up horizontally

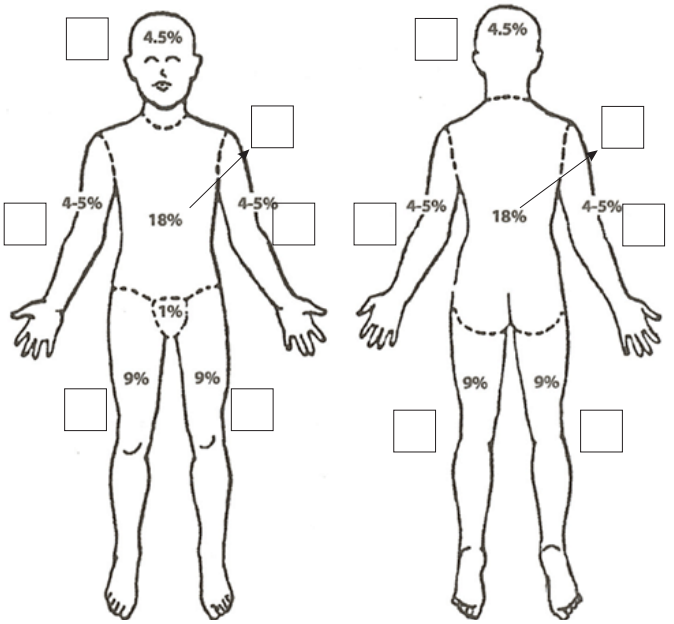
	R hand	L hand	R foot	L foot	Subtotals A	Subtotals B	Total score
lost nails	+	+	+	+	=	÷ 4 =	}=
dystrophic nails	+	+	+	+	=	÷ 8 =	
normal nails							
total	5	5	5	5			

Area:

Please shade in affected areas on the diagram, then work out percentage for each part and fill in the numbers in the adjacent boxes.

eg if half of the anterior trunk is affected, then put 9% in the box on anterior trunk.

Patient's palm size area corresponds to 1% of total body surface area



Front total = %

Back total = %

Front + back = %

Mouth, Eyes, Larynx, Esophagus: detailed scoring

	Mouth	Eyes	Larynx	Esophagus
0	No problem from EB	No problem from EB	No problem from EB	No problem from EB
1	Occasional soreness	Occasional soreness	Occasional hoarseness	Occasional dysphagia
2	Frequent soreness	Frequent soreness	Frequent hoarseness	Frequent dysphagia
3	Persistent soreness Just detectable tongue tethering	Persistent soreness early visible external eye disease	Persistent hoarseness	Persistent dysphagia
4	Between 3-5	Between 3-5	Between 3-5	Between 3-5
5	Severe tongue tethering & microstomia	Bilateral sight-threatening eye disease	Life threatening laryngeal obstruction	Difficulty swallowing solids & liquid

ANNEX II - BIRMINGHAM EB SEVERITY SCORE SHEET (CHILD)

Reproduced with permission of C. Moss

Patient's name……DOB……Type of EB……..

Scorer's name……Date……

*See overleaf for detailed instructions

Score item	Measure	Max	Actual score
*Nails	Lost nails ÷ 4 Dystrophic nails ÷ 8	5	
*Area	½ x % damaged skin: blisters, erosions, scabs, healing skin, erythema, atrophic scarring; not dyspigmentation, or well-healed scars.	50	
*Mouth	0 = no mucosal involvement 1 = occasional blisters/erosions 2 = frequent blisters 3 = persistent symptoms, early structural abnormality 4 = Moderate structural abnormality 5 = severe structural abnormality (see over for detailed scoring for each site)	5	
*Eyes		5	
*Larynx		5	
*Esophagus		5	
Scarring of hands	0 = no scarring 1 = Milia and atrophic scars 2 = Just detectable contractures or webbing 3 = obvious contractures, or proximal webbing 4 = Between 3 and 5 5 = Mitten formation with fingers all fused	5	
Skin Cancer (SCC)	Number of skin cancers +1 for local/regional/lymph node spread +2 for distant metastatic spread, up to maximum score 5	5	
Chronic wounds present for > 6/12	0 = none 1 = <1% body surface area (1% = palm size) 2 = 1-2% 3 = 2-5% 4 = 5-10% 5 = >10%	5	
Alopecia due to EB	0 = no alopecia from EB 1 = 1-19% scalp involvement 2 = 20-39% 3 = 40-59%, 4 = 60-79% 5 = 80-100%	5	
Nutritional compromise	0-5 (where 0 = normal and 5 = cachetic)	5	
TOTAL SCORE		**100**	

How to fill in the BEBS score sheet

Nails: enter number in each box and add up horizontally

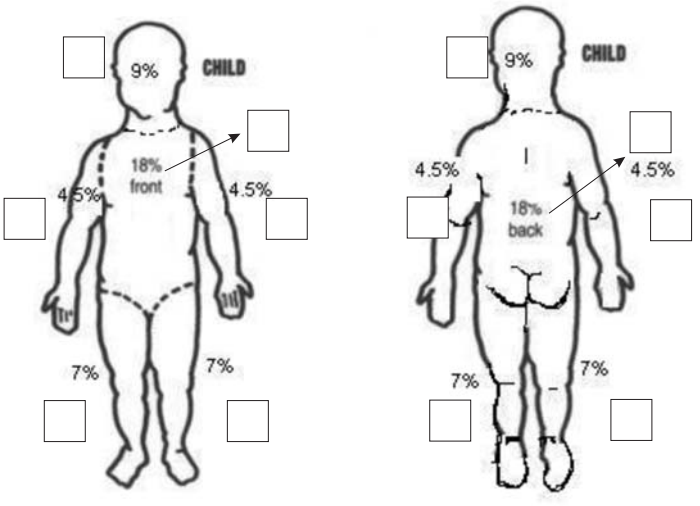
	R hand	L hand	R foot	L foot	Subtotals A	Subtotals B	Total score
lost nails	+	+	+	+	=	÷ 4 =	}=
dystrophic nails	+	+	+	+	=	÷ 8 =	
normal nails							
total	5	5	5	5			

Area:

Please shade in affected areas on the diagram, then work out percentage for each part and fill in the numbers in the adjacent boxes.

eg if half of the anterior trunk is affected, then put 9% in the box on anterior trunk.

Patient's palm size area corresponds to 1% of total body surface area.



Front total =	%
Back total =	%
Front + back =	%

Mouth, Eyes, Larynx, Esophagus: detailed scoring

	Mouth	Eyes	Larynx	Esophagus
0	No problem from EB	No problem from EB	No problem from EB	No problem from EB
1	Occasional soreness	Occasional soreness	Occasional hoarseness	Occasional dysphagia
2	Frequent soreness	Frequent soreness	Frequent hoarseness	Frequent dysphagia
3	Persistent soreness Just detectable tongue tethering	Persistent soreness early visible external eye disease	Persistent hoarseness	Persistent dysphagia
4	Between 3-5	Between 3-5	Between 3-5	Between 3-5
5	Severe tongue tethering & microstomia	Bilateral sight-threatening eye disease	Life threatening laryngeal obstruction	Difficulty swallowing solids & liquid