

REPORT

The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB

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Background: Since publication in 2000 of the Second International Consensus Report on Diagnosis and Classification of Epidermolysis Bullosa, many advances have been made to our understanding of this group of diseases, both clinically and molecularly. At the same time, new epidermolysis bullosa (EB) subtypes have been described and similarities with some other diseases have been identified.

Objective: We sought to arrive at a new consensus of the classification of EB subtypes.

Results: We now present a revised classification system that takes into account the new advances, as well as encompassing other inherited diseases that should also be included within the EB spectrum, based on the presence of blistering and mechanical fragility. Current recommendations are made on the use of specific diagnostic tests, with updates on the findings known to occur within each of the major EB subtypes. Electronic links are also provided to informational and laboratory resources of particular benefit to clinicians and their patients.

Limitations: As more becomes known about this disease, future modifications may be needed. The classification system has been designed with sufficient flexibility for these modifications.

Conclusion: This revised classification system should assist clinicians in accurately diagnosing and subclassifying patients with EB. (J Am Acad Dermatol 10.1016/j.jaad.2008.02.004)

The term *epidermolysis bullosa* (EB) was first described in 1886.¹ It was not until 1962, however, when the first sophisticated

classification scheme was proposed by Pearson,² based on the application of transmission electron microscopy to the study of inherited blistering

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Abbreviations used:

DEB:	dystrophic epidermolysis bullosa
DebRA:	Dystrophic EB Research Association
EB:	epidermolysis bullosa
EBS:	epidermolysis bullosa simplex
EBSS:	epidermolysis bullosa simplex superficialis
EM:	electron microscopy
IFM:	immunofluorescence mapping
JEB:	junctional epidermolysis bullosa
LOC:	laryngo-onycho-cutaneous (syndrome)

diseases. Three major types were redefined: epidermolytic (EB simplex [EBS]), lucidolytic (junctional EB [JEB]), and dermolytic (dystrophic EB [DEB]); the types were based on differences in the ultrastructural level within which blisters develop in EB skin, either spontaneously or following minor friction or trauma. Since then, several distinctive clinical phenotypes have been described.³ In the 1980s, polyclonal and monoclonal antibodies were applied to the study of EB skin. As a result, the technique of immunofluorescence mapping was developed, enhanced by the subsequent demonstration that some EB subtypes could be distinguished by alterations in antigenic staining.⁴ Since the early 1990s, nearly every recognized EB subtype has been defined at the molecular level by demonstration of the presence of mutations within specific genes encoding for structural proteins within human skin.⁵⁻⁸

In 1988 the first consensus meeting on diagnosis and classification of EB was held in Washington, DC, in part taking advantage of early clinical, epidemiologic, and laboratory data being generated across the United States by the National EB Registry.⁹ A second meeting was convened in Chicago in 1999 to take into account newly described clinical entities and the results of mutational analyses.¹⁰ As a result of the first two meetings, several new EB subtypes were incorporated into the classification system, some previously recognized subtypes (most notably Pasini and Cockayne-Touraine variants of dominant DEB) were eliminated, and a few entities (generalized atrophic benign EB; Bart's syndrome) were either renamed or placed into more appropriate perspective. At the same time, an emphasis was placed on associating specific EB subtypes with those proteins targeted for mutation.

During the past 8 years, much has been learned about the spectrum of inherited EB, both clinically and at the molecular level. Systematic data collection and analysis have now been performed on several thousands of patients with EB worldwide, and more than 1000 mutations, encompassing more than 10 structural genes, have now been documented. At the

same time, as more has been learned about the molecular basis of EB, it is becoming increasingly clear that this group of diseases shares clinical or molecular features with several other genodermatoses, some of which are also associated with mechanical fragility of the skin. We now think that the inclusion of certain disorders, such as Kindler syndrome, within the EB group is logical on both clinical and biological bases. Inclusion will also allow patients and their families with these very rare "orphan" diseases to benefit from dedicated medical and nursing care that is already available in many centers for EB patients. As a result, it is timely that the classification system for EB be critically reviewed in this context. On May 19, 2007, 18 leading authorities on inherited EB met in Vienna, Austria, for this purpose. This report constitutes a consensus of this meeting, with recommendations given for a revised classification system which may be readily understood and employed by clinicians, medical geneticists, and investigators, and for the optimal means whereby the diagnosis of EB can be confirmed in the laboratory.

LABORATORY APPROACH TO DIAGNOSIS**Transmission electron microscopy**

Both transmission electron microscopy (EM) and immunofluorescence mapping (IFM) have been successfully employed to diagnose EB. Each technique allows determination of the diagnostic level of skin cleavage in EB skin, that is, intraepidermal, intra-lamina lucida, or sub-lamina densa. The primary advantage of EM is that it also permits visualization and semiquantitative assessment of specific structures (keratin filaments; desmosomes; hemidesmosomes; sub-basal dense plates; anchoring filaments; anchoring fibrils), which are known to be altered in number and/or appearance in selected EB subtypes¹¹⁻¹⁵ (Table I). EM is also the only nonmolecular laboratory technique that can identify patients with Dowling-Meara EBS.¹⁶ However, there are currently very few recommended reference laboratories worldwide for the performance of EM on EB skin. If EM is performed by a laboratory with little experience in the examination of EB skin, the findings may be quite misleading. It is probably safer not to have EM data at all than to rely on information provided by a laboratory without appropriate experience and expertise in processing skin biopsy specimens and interpreting the micrographs of EB skin. Given how few highly proficient EM laboratories there are now, EM is likely to play a decreasing role in the diagnosis of EB in the future, although it is likely to continue to have an important place in research.

Table I. Ultrastructural findings among major types and selected subtypes of EB

EB type or subtype	Ultrastructural site of skin findings	Other ultrastructural findings
EB simplex (EBS)		
EBS, localized	Basal layer	Split may spread to suprabasilar layer
EBS, DM	Basal layer in subnuclear cytoplasm	Dense, circumscribed clumps of keratin filaments (most commonly observed within lesional biopsy sites)
EBS-MD	Predominantly in basal layer, above level of HD attachment plaque	Reduced integration of keratin filaments with HD
EBS-AR	Basal keratinocytes	Absent or reduced keratin filaments within basal keratinocytes
EBSS	Split usually at interface between granular and cornified cell layers	—
EBS, lethal acantholytic	Suprabasal cleavage and acantholysis	Perinuclear retraction of keratin filaments
EBS, plakophilin-1 deficiency	Mid-epidermal cell-cell separation	Diminutive suprabasal desmosomes; perinuclear retraction of keratin filaments
EBS-PA	Lower basal layer, above level of HD plaque	Reduced integration of keratin filaments with HD
Junctional EB (JEB)		
JEB-H	Lamina lucida	Markedly reduced or absent HD; absent SBDP
JEB-nH	Lamina lucida	HDs may be normal or reduced in size and number
JEB-PA	Lamina lucida	Small HD plaques often with attenuated SBDP
Dominant dystrophic EB (DDEB)		
DDEB, generalized	Sub-lamina densa	Normal or decreased numbers of AFs
DDEB-BDN	Sub-lamina densa	Electron-dense stellate bodies within basal layer; reduced AFs
Recessive dystrophic EB (RDEB)		
RDEB, severe generalized	Sub-lamina densa	Absent or rudimentary AFs
RDEB, generalized other	Sub-lamina densa	Reduced or rudimentary-appearing AFs
RDEB-BDN	Sub-lamina densa	Electron-dense stellate bodies within basal layer; reduced AFs

AF, Anchoring fibril; AR, autosomal recessive; BDN, bullous dermolysis of the newborn; DM, Dowling-Meara; EBSS, EBS superficialis; H, Herlitz; HD, hemidesmosome; MD, muscular dystrophy; nH, non-Herlitz; PA, pyloric atresia; SBDP, sub-basal dense plate.

Immunofluorescence mapping

Immunofluorescence mapping (IFM), when coupled with the use of specific monoclonal antibodies (Table II), can provide considerable insight into not only the major type of EB present but also the structural protein most likely mutated. IFM traditionally has relied on the staining of cryopreserved EB skin specimens (harvested from fresh spontaneous or traction-induced blisters) with antibodies to bullous pemphigoid antigen, laminin-1, type IV collagen, and keratin 14, in order to determine the level (intraepidermal; intra-lamina lucida; sub-lamina densa) of blistering.⁴ Monoclonal and polyclonal antibodies to laminin-332 (formerly known as laminin-5), type VII collagen, type XVII collagen, plectin, $\alpha 6\beta 4$ integrin, and keratin 14 can also be applied to EB skin sections to determine whether there are alterations in the relative expression (ie, in

recessive EBS; JEB and recessive DEB; EB with muscular dystrophy) or distribution (ie, presence of intraepidermal granules of type VII collagen in bullous dermolysis of the newborn) of one of these antigens within affected skin.¹⁷⁻²² Such information is vital to ascertain before DNA mutational analyses can be pursued. Previous work has demonstrated that IFM is as reliable diagnostically as transmission EM,²³ at least for the diagnosis of several subtypes of EB. IFM is also a technique that readily lends itself to use as the primary laboratory means to confirm the diagnosis of EB, since virtually every dermatologist should have access to immunofluorescence transport media within the clinic, and many laboratories now exist worldwide that can properly perform this technique, using a series of “EB relevant” antibodies and well-established protocols. There are other advantages to this technique. Compared with EM,

Table II. Antigenic alterations in EB skin

Antigen	Abnormal staining in:	Usual pattern of staining
Keratin 14	EBS-AR	Absent or markedly reduced
Laminin-332 (laminin-5)	JEB-H	Absent or markedly reduced
	JEB-nH generalized*	Reduced
Type XVII collagen	JEB-nH, generalized [†]	Absent
	JEB-nH, localized	Reduced
Type VII collagen	RDEB, severe generalized	Absent or markedly reduced
	RDEB, generalized other	Reduced
	RDEB, inversa	Variable
	DEB-BDN (only during period of active blistering)	Granular staining within basal and suprabasal keratinocytes; absent or markedly reduced staining along DEJ
Plectin	EBS-MD	Absent or reduced
	EBS-PA	Absent or reduced
	EBS-Ogna	Reduced
$\alpha 6\beta 4$ Integrin	JEB-PA	Absent or reduced
	EBS-PA	Absent or reduced
	JEB-nH [‡]	Reduced
Kindlin-1	Kindler syndrome	Absent, reduced, or normal [§]

BDN, Bullous dermolysis of the newborn; DEB, dystrophic EB; DEJ, dermoepidermal junction; DM, Dowling-Meara; EBS, EB simplex; H, Herlitz; JEB, junctional EB; MD, muscular dystrophy; nH, non-Herlitz; PA, pyloric atresia; RDEB, recessive DEB.

*In the majority of JEB-nH patients.

[†]In a minority of patients with generalized JEB-nH (previously referred to as generalized atrophic benign EB); these patients lack concurrent abnormal staining by antibodies to laminin-332.

[‡]Reported in one patient.

[§]Loss-of-function mutations in both *KIND1* alleles may be associated with normal immunostaining.

Table III. Mutational analyses and inherited EB: Summary of findings by EB type and subtype

EB type	EB subtype	Target gene (protein)	Types of mutations known*
EBS	Suprabasal	<i>PKP1</i> (plakophilin-1)	Spl, Del, NS
		<i>DSP</i> (desmoplakin)	NS, Del
	Basal	<i>KRT5</i> (keratin-5)	MS, NS, Del, Spl
		<i>KRT14</i> (keratin-14)	MS, NS, Del, Ins, Spl, in-frame del/ins
		<i>PLEC1</i> (plectin)	MS, NS, Del, Ins, in-frame del/ins
	<i>ITGA6</i> , <i>ITGB4</i> ($\alpha 6\beta 4$ integrin)	MS, NS, Del, Ins, Spl	
JEB	Herlitz	<i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> (laminin-332)	NS, Del, Ins, Spl
	Other	<i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> (laminin-332)	MS, NS, Del, Ins, Spl
		<i>COL17A1</i> (type XVII collagen)	MS, NS, Del, Ins, Spl
		<i>ITGA6</i> , <i>ITGB4</i> ($\alpha 6\beta 4$ integrin)	MS, NS, Del, Ins, Spl
DEB	Dominant	<i>COL7A1</i> (type VII collagen)	MS, Spl
	Recessive	<i>COL7A1</i> (type VII collagen)	MS, NS, Del, Ins, Spl
Kindler syndrome		<i>KIND1</i> (kindlin-1)	NS, Del, Ins, Spl

Del, Deletion; in-frame del/ins, in-frame deletion and insertion; Ins, insertion; MS, missense mutation; NS, nonsense mutation; Spl, splice site mutation. In many cases with recessive inheritance, two different mutations are present in one individual (compound heterozygosity).

*This table depicts the common mutation constellations, but it is not exhaustive. For the sake of simplicity, some very rare mutation constellations have been excluded.

IFM is relatively inexpensive and simple to perform, and the equipment, including a cryomicrotome and fluorescence microscope, is much cheaper and easier to install. Moreover, the tissues can be processed within only a few hours. In addition, the results are not negatively influenced if the

specimens are delayed in being shipped to a reference laboratory, since the transport media preserves tissue antigenicity for at least several weeks when maintained at room temperature. However, the overall success of IFM and EB-relevant monoclonal antibody studies is critically dependent on the

Table IV. The 4 major EB types

Level of skin cleavage	Major EB type	Known targeted protein(s)
Intraepidermal ("epidermolytic")	EBS	Keratins 5 and 14; plectin; $\alpha6\beta4$ integrin; plakophilin-1; desmoplakin
Intra-lamina lucida ("lamina lucidolytic")	JEB	Laminin-332 (laminin 5); type XVII collagen; $\alpha6\beta4$ integrin
Sub-lamina densa ("dermolytic")	DEB	Type VII collagen
Mixed	Kindler syndrome	Kindlin-1

DEB, Dystrophic EB; EBS, EB simplex; JEB, junctional EB.

Table V. The major EB subtypes

Major EB type	Major EB subtypes	Targeted protein(s)
EBS	Suprabasal EBS	Plakophilin-1; desmoplakin; ? others
	Basal EBS	Keratins 5 and 14; plectin; $\alpha6\beta4$ integrin
JEB	JEB-H	Laminin-332 (laminin-5)
	JEB, other	Laminin-332; type XVII collagen; $\alpha6\beta4$ integrin
DEB	Dominant DEB	Type VII collagen
	Recessive DEB	Type VII collagen
Kindler syndrome	—	Kindlin-1

DEB, Dystrophic EB; EBS, EB simplex; JEB, junctional EB; JEB-H, junctional EB, Herlitz.

Table VI. EBS subtypes

Major EBS types	EBS subtypes*	Targeted proteins
Suprabasal	<i>Lethal acantholytic EB</i>	Desmoplakin
	<i>Plakophilin deficiency</i>	Plakophilin-1
Basal	<i>EBS superficialis (EBSS)</i>	?
	EBS, localized (EBS-loc) [†]	K5, K14
	EBS, Dowling-Meara (EBS-DM)	K5, K14
	EBS, other generalized (EBS, gen-nonDM; EBS, gen-nDM) [‡]	K5, K14
	<i>EBS-with mottled pigmentation (EBS-MP)</i>	K5
	EBS with muscular dystrophy (EBS-MD)	Plectin
	<i>EBS with pyloric atresia (EBS-PA)</i>	Plectin; $\alpha6\beta4$ integrin
	<i>EBS, autosomal recessive (EBS-AR)</i>	K14
	<i>EBS, Ogna (EBS-Og)</i>	Plectin
	<i>EBS, migratory circinate (EBS-migr)</i>	K5

EBS, EB simplex.

*Rare variants shown in italics.

[†]Previously called EBS, Weber-Cockayne.

[‡]Includes patients previously classified as having EBS-Koebner.

experience of those who perform and interpret them, since false-negative staining may result from inadequate binding by the secondary antibody, apparent loss of antigenic staining due to the use of outdated antibody preparations, or batch-related differences in the intensity of antibody binding to tissue. One should also be reminded that this technique is semiquantitative at best, so that it may be impossible with high sensitivity and specificity to accurately distinguish among all of EB subtypes

solely by the degree of antibody staining within a given tissue.²³

For reasons previously stated, we recommend that IFM be used as the primary laboratory means for the diagnosis in patients suspected of having inherited EB.

To assist laboratories in performing IFM, we will maintain an updated list of recommended antibodies and their suppliers via the Web site of the Dystrophic EB Research Association (DeBRA)-International (www.debra-international.org).

Table VII. Junctional EB subtypes

Major JEB subtype	Subtypes*	Targeted proteins
JEB, Herlitz (JEB-H)	—	Laminin-332
JEB, other (JEB-O)	JEB, non-Herlitz, generalized (JEB-nH gen) [†]	Laminin-332; type XVII collagen
	JEB, non-Herlitz, localized (JEB-nH loc)	Type XVII collagen
	JEB with pyloric atresia (JEB-PA)	$\alpha 6\beta 4$ Integrin
	<i>JEB, inversa (JEB-I)</i>	Laminin-332
	<i>JEB, late onset (JEB-lo)[‡]</i>	?
	<i>LOC syndrome</i>	Laminin-332 $\alpha 3$ chain

*Rare variants shown in italic type.

[†]Formerly known as generalized atrophic benign EB (GABEB).

[‡]Formerly known as EB progressiva.

Table VIII. Dystrophic EB subtypes

	All subtypes*	Targeted protein
DDEB	DDEB, generalized (DDEB-gen) <i>DDEB, acral (DDEB-ac)</i> <i>DDEB, pretibial (DDEB-Pt)</i> <i>DDEB, pruriginosa (DDEB-Pr)</i> <i>DDEB, nails only (DDEB-na)</i> <i>DDEB, bullous dermolysis of the newborn (DDEB-BDN)</i>	Type VII collagen
RDEB	RDEB, severe generalized (RDEB-sev gen) [†] RDEB, generalized other (RDEB-O) <i>RDEB, inversa (RDEB-I)</i> <i>RDEB, pretibial (RDEB-Pt)</i> <i>RDEB, pruriginosa (RDEB-Pr)</i> <i>RDEB, centripetalis (RDEB-Ce)</i> <i>RDEB, bullous dermolysis of the newborn (RDEB-BDN)</i>	Type VII collagen

DDEB, Dominant dystrophic EB; RDEB, recessive dystrophic EB.

*Rare variants in italic type.

[†]Previously called RDEB, Hallopeau-Siemens.

Mutational analysis

Mutational analysis is the ultimate means of determining the mode of inheritance and the precise site(s) and type(s) of molecular mutation present in a patient with EB. Table III summarizes the findings in each of the established EB subtypes. At the present time, mutational analysis remains a superb research tool. In addition, the eventual application of gene therapy to EB patients will be dependent on the determination of the specific mutations present.²⁴ It is also the recommended technique whereby

Table IX. Kindler syndrome: Clinical summary

Mode of transmission (usual)	AR
Onset	Birth
Skin distribution (predominant)	Generalized
Skin findings (frequency*)	
Blisters	3+, childhood; 1+, adults
Milia	Rare to 1+
Atrophic scarring	2+
Dystrophic or absent nails	1+
Granulation tissue	1+
Keratoderma	Present
Other	Poikiloderma; photosensitivity; mental retardation (rare); bone abnormalities (rare)
Relative inducibility of blisters	Variable
Extracutaneous involvement*	
Anemia	Occasional
Growth retardation	Absent
Oral cavity	
Soft tissue abnormalities	Gingival hyperplasia
Enamel hypoplasia	Absent
Caries	? Normal frequency
Gastrointestinal tract	Colitis (may be severe); esophagitis
Genitourinary tract	1+ (urethral strictures)
Ocular findings	Ectropion (rare)
Pseudosyndactyly	1+ [†]
Respiratory tract	Absent
Risk by 30 years of age of:	
Squamous cell carcinoma	Infrequent
Malignant melanoma	None
Basal cell carcinoma	None
Death related to Kindler syndrome	Uncommon

AR, Autosomal recessive.

*Scale: absent or none; rare; 1+, 2+, 3+, 4+.

[†]Digital tapering may also be seen.

prenatal and preimplantation diagnosis can be performed.^{25,26} At the present time, however, it is not considered to be a first-line diagnostic test for EB.

There are several reasons why we do not recommend its performance for this purpose. Currently only a few research or commercial laboratories are equipped to perform mutational analysis on the genes targeted in EB. The technique itself is very labor intensive and expensive to perform. Not every EB type or subtype is associated with mutational hot spots, often necessitating the need to sequence an entire gene to identify the causative mutation. Some phenotypically identical EB subtypes, most notably

Table X. EB simplex subtypes: Clinical summary (EBS superficialis, lethal acantholytic EBS, plakophilin deficiency)

	EBS superficialis (N = 23)*	Lethal acantholytic EBS (N = 2)*	Plakophilin deficiency (N = 9)*
Mode of transmission (usual)	AD	AR	AR
Onset (usual)	Birth or early infancy	Birth	Birth
Skin distribution (predominant)	Generalized or acral	Generalized	Generalized
Skin findings (frequency [†])			
Blisters	Superficial erosions, not blisters	Oozing erosions, not blisters	Superficial erosions; blisters less common
Milia	3+	Absent	Absent
Atrophic scarring	4+	Absent	Absent
Dystrophic or absent nails	4+	4+	4+
Granulation tissue	Absent	Absent	Absent
Scalp abnormalities	Absent	Alopecia	Hypotrichosis
Keratoderma	Absent	Absent	Focal, with fissuring
Other	None	Neonatal teeth	Perioral fissuring; circinate scaly erosions
Relative inducibility of blisters	Variable	Sheet-like removal	Variable
Extracutaneous involvement [†]			
Anemia	Rare	Absent	Absent
Growth retardation	Absent	Absent	2+
Oral cavity			
Soft tissue abnormalities	None	Erosions	Tongue fissuring
Enamel hypoplasia	None	None	Absent
Caries	Normal frequency	None	Normal frequency
Gastrointestinal tract	Rare	Present	Constipation; esophageal stricture in one patient
Genitourinary tract	Absent	Present	Absent
Ocular findings	Absent	Absent	Blepharitis; absent or sparse eyelashes
Pseudosyndactyly	Absent	Absent	Absent
Respiratory tract	Absent	Present	Absent
Risk [†] by 30 years of age of:			
Squamous cell carcinoma	None	None	None
Malignant melanoma	None	None	None
Basal cell carcinoma	None	None	None
Death (all causes)	None	Present	???

AD, Autosomal dominant; AR, autosomal recessive.

*Number of subjects studied.

[†]Scale: absent or none, rare, 1+, 2+, 3+, 4+.

non-Herlitz JEB, may result from mutations in entirely different genes, further necessitating the need to sequence multiple genes. In some other types of EB, particularly EBS, mutations have not as yet been identified in every patient, suggesting the possibility that there may be other unidentified genes associated with this disease. With the exception of EBS, the strength of genotype-phenotype correlation varies considerably, making it difficult to use mutational findings to reliably distinguish among specific subtypes. Finally, at least in the United States, only a small portion of the cost of molecular testing is routinely reimbursed by private insurers or federal programs, making mutational analysis as yet unaffordable for many families. For all of the above reasons, at the present time DNA testing is pursued primarily when

prenatal diagnosis is being considered.²⁵⁻²⁷ To do so, however, the genotype of the proband (and preferably also the parents) will need to be determined. This technique is also useful in determining the mode of genetic transmission in dystrophic patients lacking an informative family history, and in selecting unaffected embryonic cells for use in preimplantation in vitro fertilization.²⁸

RECOMMENDED REVISIONS IN THE EB CLASSIFICATION SYSTEM

General scheme

There are several ways in which EB patients can be subclassified; these include our recommended system which, like its predecessors,^{9,10} relies on combinations of clinical and nonmolecular

Table XI. EBS subtypes: Clinical summary (localized EBS, Dowling-Meara EBS, EBS, other generalized [non–Dowling-Meara])

	EBS, localized	EBS, Dowling-Meara	EBS, other generalized (non–Dowling-Meara)
Mode of transmission (usual)	AD	AD	AD
Onset (usual)	Early childhood	Birth	Birth
Skin distribution (predominant)	Palms and soles	Generalized	Generalized
Skin findings (frequency*)			
Blisters	4+	4+	4+
Milia	Rare	1-2+	1+
Atrophic scarring	Rare	2+	1+
Dystrophic or absent nails	Uncommon	2+	1-2+
Granulation tissue	Absent	Absent	Absent
Scalp abnormalities	Absent	Absent	Absent
Keratoderma (palms and soles)	Focal (by adulthood in some)	Usually diffuse	Focal
Other	None	Arciform (“herpetiform”) blistering	None
Relative inducibility of blisters	Common	Common	Common
Extracutaneous involvement*†			
Anemia	Absent	Variable	Absent
Growth retardation	Absent	Common	Absent
Oral cavity			
Soft tissue abnormalities	Erosions in approx. 25%	Common	Variable
Enamel hypoplasia	Absent	Absent	Absent
Caries	Normal frequency	Normal frequency	Normal frequency
Gastrointestinal tract	Absent	2+ (constipation)	Absent
Genitourinary tract	Absent	Absent	Absent
Ocular findings	Absent	Absent	Rare
Pseudosyndactyly	Absent	Absent	Absent
Respiratory tract	Absent	Uncommon	Absent
Risk* by age 30 of:			
Squamous cell carcinoma	None	None	None
Malignant melanoma	None	None	None
Basal cell carcinoma	None	None	None
Death related to EB	None	Uncommon	None

AD, Autosomal dominant; EBS, EB simplex.

*Scale: absent or none, 1+, 2+, 3+, 4+.

†See references 42-47 for specific frequencies of major extracutaneous involvement.

laboratory findings, most notably the level within which blisters arise. We have chosen to continue this approach, since it is easily understood by clinicians as well as experts in this field. Our recommended revised scheme is summarized in [Tables IV through VIII](#). The scheme begins with the separation of EB into 4 major EB types—*intraepidermal* (EBS), *junctional*, *dermolitic* (DEB), and *mixed* (Kindler syndrome) types—based on distinguishing ultrastructural sites of blister formation. Patients are then separated by major and minor EB subtypes. It should be noted that we have further separated *intraepidermal* EB into two subgroups (*basal* and *suprabasal*) to take into account newly described entities which also fall within the realm of a mechanobullous disease.

[Tables IX through XX](#) clinically summarize each of the entities listed within our expanded classification scheme. It should be emphasized that these tables attempt to provide a description of the prototypic patient within each EB subtype. Since the literature well documents that clinical variations may occur within each subtype, the information summarized within each table should be considered as guidelines, rather than as rigid descriptions of each possible EB phenotype.

Limitations during the newborn period or early infancy

It may not be possible to precisely subtype every newborn or infant with inherited EB. It is well known, for example, that some infants having what

Table XII. EB simplex subtypes: Clinical summary (autosomal recessive EBS, EBS-Ogna, EBS-migratory circinate)

	Autosomal recessive EBS	EBS-Ogna	EBS-migratory circinate
Mode of transmission (usual)	AR	AD	AD
Onset (usual)	Birth	Birth	Birth
Skin distribution (predominant)	Generalized; anogenital	Mainly acral; may be widespread	Generalized
Skin findings (frequency*)			
Blisters	3+	3+	4+
Milia	Rare	Absent	Absent
Atrophic scarring	1+	Absent	Absent
Dystrophic or absent nails	2+	Onychogryphosis	Absent
Granulation tissue	Absent	Absent	Absent
Scalp abnormalities	Absent	Absent	Absent
Keratoderma (palms and soles)	Focal	Absent	Absent
Other	Ichthyotic plaques	Tendency to bruise	Migratory circinate erythema; brown postinflammatory hyperpigmentation
Relative inducibility of blisters	3+	2+	Variable
Extracutaneous involvement*			
Anemia	1+	Absent	Absent
Growth retardation	2+	Absent	Absent
Oral cavity			
Soft tissue abnormalities	3+	Absent	Absent
Enamel hypoplasia	Absent	Absent	Absent
Caries	1+	Normal frequency	Normal frequency
Gastrointestinal tract	2+ (constipation)	Absent	Absent
Genitourinary tract	Absent	Absent	Absent
Ocular findings	Absent	Absent	Absent
Pseudosyndactyly	Absent	Absent	Absent
Respiratory tract	Absent	Absent	Absent
Risk* by age 30 of:			
Squamous cell carcinoma	None	None	None
Malignant melanoma	None	None	None
Basal cell carcinoma	None	None	None
Death related to EB	None	None	None

AD, Autosomal dominant; AR, autosomal recessive.

*Scale: absent or none, 1+, 2+, 3+, 4+.

will later become a localized subtype of EB (in particular, inverse subtypes) may instead present with generalized blistering during early life. Some neonates with generalized or severe manifestations, such as those with Bart's syndrome (the coexistence of inherited EB and congenital absence of skin) may later have a milder phenotype, such as a localized subtype of DEB. It is also well known, based on exhaustive sensitivity and specificity analyses on the study population of the American National EB Registry, using cutaneous findings as surrogate diagnostic markers, that even collections of these phenotypic features may fail to achieve fully diagnostically reliable levels (ie, >90%) simultaneously for these two statistical parameters.²³ This is a reflection not only of the frequency with which several findings (to include atrophic scarring, milia formation, and dystrophic nails) occur within each of the 4 major EB types, but also differences in the age

during which some of these findings first occur.²⁹ For example, scarring and nail changes may not always be present in infants with JEB or DEB, at times suggesting instead an incorrect diagnosis of EBS. It is for these reasons that determination of the major type of EB present must be confirmed by IFM or transmission EM in every patient before any realistic discussion of prognosis can be considered. Even after distinguishing among the 3 traditional major EB types (simplex, junctional, and dystrophic), however, it still may not be possible during the first months of life to reliably subclassify every patient in the absence of an informative family tree (ie, the presence of an affected relative with diagnostically characteristic phenotypic findings). In those situations in which the EB subtype is unclear, we recommend the use of the term "indeterminate subtype," given the psychological implications of misdiagnosis for parents and caregivers. Once the child is older,

Table XIII. EB simplex subtypes: Clinical summary (EBS with mottled pigmentation, EBS with muscular dystrophy, EBS with pyloric atresia)

	EBS with mottled pigmentation	EBS with muscular dystrophy	EBS with pyloric atresia
Mode of transmission (usual)	AD	AR	? AR
Onset (usual)	Birth	Blisters as early as birth; muscular dystrophy: infancy to adulthood	Birth
Skin distribution (predominant)	Generalized	Generalized	Generalized
Skin findings (frequency*)			
Blisters	4+	4+	4+
Milia	Rare	2+	Absent
Atrophic scarring	Absent	2-3+	2-3+
Dystrophic or absent nails	1+	2+	Absent
Granulation tissue	Absent	Absent	Absent
Scalp abnormalities	Absent	Absent	Absent
Keratoderma (palms and soles)	1+ focal	Rare focal	Absent
Other	Mottled or reticulate brown pigmentation	None	Widespread congenital absence of skin
Relative inducibility of blisters	Common	Common	Common
Extracutaneous involvement*			
Anemia	Absent	Absent	3+
Growth retardation	Absent	Absent	3+
Oral cavity			
Soft tissue abnormalities	Absent	Absent	3+
Enamel hypoplasia	Absent	Absent	Absent
Caries	Normal frequency	Normal frequency	Normal frequency
Gastrointestinal tract	Absent	Absent	4+ (pyloric atresia)
Genitourinary tract	Absent	Absent	Absent
Ocular findings	Absent	Ptosis	Absent
Pseudosyndactyly	Absent	Absent	Absent
Respiratory tract	Absent	Granulation tissue/stenosis	Absent
Other	Absent	Muscular dystrophy	Malformed pinnae and nasal alae; joint contractures; cryptorchidism
Risk* by age 30 of:			
Squamous cell carcinoma	None	None	None
Malignant melanoma	None	None	None
Basal cell carcinoma	None	None	None
Death related to EB	None	1-2+	3+

AD, Autosomal dominant; AR, autosomal recessive.

*Scale: absent or none, 1+, 2+, 3+, 4+.

then it should be possible to revisit the issue of subclassification and do so accurately. This is particularly important, now that parents and physicians rely on the Internet for medical information.

Alternative classification schemes for EB

There are certainly other ways in which an EB classification system might be constructed. In general, though, these are as yet chiefly of value only to

basic researchers. One scheme, for example, might attempt to incorporate all genodermatoses that are characterized by mutations in proteins within the same protein family. For example, since most forms of EBS are the result of mutations within keratins 5 and 14 (K5 and K14), such a scheme would also encompass others with skin fragility, or, in a wider perspective, epithelial fragility resulting from keratin gene mutations. This would make a case for

Table XIV. Junctional EB subtypes: Clinical summary (JEB, Herlitz type; JEB, non-Herlitz type, generalized; JEB, non-Herlitz type, localized)

	JEB, Herlitz type	JEB, non-Herlitz type, generalized	JEB, non-Herlitz type, localized
Mode of transmission (usual)	AR	AR	AR
Onset (usual)	Birth	Birth	Birth
Skin distribution (predominant)	Generalized	Generalized	Localized
Skin findings (frequency*)			
Blisters	4+	4+	2+
Milia	2+	2+	1+
Atrophic scarring	3+	3+	Absent
Dystrophic or absent nails	4+	4+	4+
Granulation tissue	4+	Rare	Absent
Scalp abnormalities	2+	3+	Absent
Keratoderma (palms and soles)	Absent	Focal+	Absent
Other	None	None	None
Relative inducibility of blisters	4+	4+	2+
Extracutaneous involvement*†			
Anemia	4+	2+	Absent
Growth retardation	4+	2+	Absent
Oral cavity			
Soft tissue abnormalities	4+	3+	1+
Enamel hypoplasia	4+	4+	4+
Caries	Excessive	Excessive	Excessive
Gastrointestinal tract	3+	2+	Absent
Genitourinary tract	2+	2+	Absent
Ocular findings	3+	2+	Absent
Pseudosyndactyly	1+	Absent	Absent
Respiratory tract	3+	2+	Absent
Other	Delayed puberty	None	None
Risk* by age 30 of:			
Squamous cell carcinoma	Uncommon	Uncommon	None
Malignant melanoma	None	None	None
Basal cell carcinoma	None	None	None
Death related to EB	4+	1+	None

AR, Autosomal recessive; JEB, junctional EB.

*Scale: absent or none, 1+, 2+, 3+, 4+.

†See references 42-47 for specific frequencies of major extracutaneous complications.

including disorders such as pachyonychia congenita (K6, K16, K17), epidermolytic hyperkeratosis (bulbous congenital ichthyosiform erythroderma) (K1 and K10), ichthyosis bullosa of Siemens (K2e), Dowling-Degos disease (K5), and various keratodermas (K1, K9), and even Meesmann's corneal dystrophy (K3, K12) and white sponge nevus (K4, K13).³⁰ Although conceptually interesting, blistering is not a consistent or major feature in several of these keratin disorders, making their inclusion among the group of mechanobullous diseases inappropriate.

Another scheme might incorporate all of the genodermatoses that are characterized by mechanical fragility, such as Ehlers-Danlos syndrome, even in the absence of blistering. Although each of these approaches is of interest scientifically, for now each

appears to lack direct clinical applicability. To reiterate, the purpose of the recommended classification is to provide a clinically useful framework for dermatologists and other specialists seeing children and older patients with skin fragility and blistering as a major clinical feature of their disease. The adoption of any of these other classification systems would likely add confusion instead of clarity to the clinical literature on this disease.

Recommended additions to the current classification system

The rationale for our inclusion of selected new entities as types of EB is (1) that they have friction-induced blisters and other clinical features in common with more established forms of EB; (2) that they are hereditary; and (3) that, from a practical

Table XV. Junctional EB subtypes: Clinical summary (JEB with pyloric atresia; JEB, inverse)

	JEB with pyloric atresia	JEB, inversa
Mode of transmission (usual)	AR	AR
Onset (usual)	Birth	Birth
Skin distribution (predominant)	Generalized	Intertriginous
Skin findings (frequency*)		
Blisters	4+	3+
Milia	1+	1+
Atrophic scarring	3+	3+
Dystrophic or absent nails	3+	3+
Granulation tissue	Absent	Absent
Keratoderma	Absent	Absent
Other	May be associated with large areas of aplasia cutis	None
Relative inducibility of blisters	Common	Common
Extracutaneous involvement*		
Anemia	Variable	Absent
Growth retardation	Variable	Absent
Oral cavity		
Soft tissue abnormalities	Variable	Variable
Enamel hypoplasia	Present	Present
Caries	Unknown	Increased frequency
Gastrointestinal tract	4+ (pyloric atresia)	2+
Genitourinary tract	Multiple GU malformations; acquired GU abnormalities [†]	Absent
Ocular findings	Unknown	Unknown
Pseudosyndactyly	Absent	Absent
Respiratory tract	Absent	Absent
Other	Rudimentary ears	None
Risk* by age 30 of:		
Squamous cell carcinoma	None	None
Malignant melanoma	None	None
Basal cell carcinoma	None	None
Death related to EB	4+	None

AR, Autosomal recessive; GU, genitourinary; JEB, junctional EB.

*Scale: absent or none, 1+, 2+, 3+, 4+.

[†]Polypoid bladder wall lesions; hemorrhagic cystitis; urethral strictures.

perspective, the patients, especially neonates, and their families, will potentially benefit from the growing resources already available for EB patients. We have chosen not to include at this time two major disorders, bullous congenital ichthyosiform erythroderma (epidermolytic hyperkeratosis) and pachyonychia congenita, though biologically similar, since they are considered by dermatologists and pediatricians to be different entities, and since they already have well-established, active patient advocacy (self-help) groups of their own.

Kindler syndrome, an autosomal recessive genodermatosis, may clinically mimic severe subtypes of EB, including Herlitz JEB or DEB, in the neonatal period, but in later life appears more similar to non-Herlitz JEB. It has recently been proven that this entity arises as a result of a mutation in the gene encoding for kindlin-1, which is a component of focal contacts in basal keratinocytes.^{22,31} We have

chosen to separate Kindler syndrome from the other 3 major EB types (see Table IV) because, as opposed to all other mechanobullous diseases, there are typically multiple cleavage planes (intraepidermal, junctional, or sub-lamina densa) within affected skin, preventing inclusion within any of the main types of EB. In addition, there are additional rather striking clinical findings, most notably poikiloderma and photosensitivity, which readily distinguish Kindler syndrome from all other known forms of inherited EB.

LOC syndrome (*laryngo-onycho-cutaneous syndrome*; Shabbir's syndrome)^{32,33} is now considered to be a new variant of JEB, since it has similar clinical features and is associated with mutations in the $\alpha 3$ chain of laminin-332.³⁴ Clinical findings are summarized in Table XV.

The newly described entities lethal acantholytic EB³⁵ and migratory circinate EBS³⁶ have been added

Table XVI. Junctional EB subtypes: Clinical summary (JEB, late onset; LOC syndrome)

	JEB, late onset	LOC syndrome
Previous name or eponym	EB progressiva	Shabbir's syndrome
Mode of transmission (usual)	AR	AR
Onset	Young adulthood or later	Birth
Skin distribution (predominant)	Variable	Especially face and neck
Skin findings (frequency*)		
Blisters	2+	2+, with erosions
Milia	Absent	1+
Atrophic scarring	Absent	2+
Dystrophic or absent nails	4+	4+
Granulation tissue	Absent	3+
Keratoderma	Absent	Absent
Other	Hyperhidrosis, absent dermatoglyphs	Increased incidence in Punjab
Relative inducibility of blisters*	Unknown	1+
Extracutaneous involvement*		
Anemia	Absent	1+
Growth retardation	Absent	1+
Oral cavity		
Soft tissue abnormalities	Variable	4+ larynx
Enamel hypoplasia	Present	3+
Caries	Normal frequency	2+
Gastrointestinal tract	Absent	? Absent
Genitourinary tract	Absent	? Absent
Ocular findings	Absent	4+ conjunctival
Pseudosyndactyly	Absent	Absent
Respiratory tract	Absent	4+
Risk* by age 30 of:		
Squamous cell carcinoma	None	None
Malignant melanoma	None	None
Basal cell carcinoma	None	None
Death related to EB	None	Common

AR, Autosomal recessive; JEB, junctional EB; LOC, laryngo-onycho-cutaneous.

*Scale: absent or none, 1+, 2+, 3+, 4+.

to our system, as has plakophilin deficiency. Acantholytic EB and migratory circinate EB are summarized in [Tables X and XII](#), respectively.

Distinction is now made between localized and generalized non-Herlitz JEB subtypes, as summarized in [Table XIV](#), which can be predicted from IFM in the neonatal period (see [Table II](#)).³⁷

After considerable debate, we have also chosen to retain a few entities which appear to be distinctive either clinically or ultrastructurally, even though they have been reported in only one or a few patients. For example, several cases of EBS superficialis (EBSS) were described nearly two decades ago. The proband, who had strikingly unique phenotypic features, was characterized both ultrastructurally and antigenically, whereas a large unrelated family (in which type VII collagen mutations were later detected) was characterized only at the light microscopic level, raising concerns about the validity of

their diagnosis. Until it can be proven molecularly that the original EBSS proband has a variant of DEB rather than EBS, retention of this entity seems prudent, particularly since other suprabasal subtypes of EB have now been recently identified. Similarly, although there are only rare patients who have been described with recessive DEB centripetalis, JEB of late onset, JEB inversa, and acral dominant DEB, their existence merits recognition even if these represent only exceedingly rare EB subtypes. Their elimination from an extended classification system seems scientifically inappropriate at a time when we are still trying to determine the true breadth of inherited EB.

Recommended name changes

See [Table XXI](#). For decades many EB subtypes have been linked with the names of physicians who first described them, often independently and with

Table XVII. Dystrophic EB subtypes: Clinical summary (DDEB, generalized; RDEB, severe generalized; RDEB, generalized other)

	DDEB, generalized	RDEB, severe generalized	RDEB, generalized other
Previous name or eponym	Pasini; Cockayne-Touraine	Hallopeau-Siemens	Non—Hallopeau-Siemens
Mode of transmission (usual)	AD	AR	AR
Onset (usual)	Birth	Birth	Birth
Skin distribution (predominant)	Generalized	Generalized	Generalized
Skin findings (frequency*)			
Blisters	2-3+	4+	3-4+
Milia	3+	4+	3-4+
Atrophic scarring	3-4+	4+	3-4+
Dystrophic or absent nails	4+	4+	4+
Granulation tissue	Absent	Rare	Absent
Scalp abnormalities	2+	3+	2+
Keratoderma	None	None	None
Other	“Albopapuloid lesions” (variable)	None	None
Relative inducibility of blisters	Variable	High	High
Extracutaneous involvement*†			
Anemia	1+	4+	2+
Growth retardation	Rare	4+	2+
Oral cavity			
Soft tissue abnormalities	3+	4+	3+
Enamel hypoplasia	Absent	Absent	Absent
Caries	Normal frequency	Excessive	Normal frequency
Gastrointestinal tract	2+	4+	3-4+
Genitourinary tract	Rare	Rare	Rare
Ocular findings	Absent	3+	2+
Pseudosyndactyly	Rare	4+	2+
Respiratory tract	Absent	Absent	Absent
Other	Absent	Glomerulonephritis, renal amyloidosis; IgA nephropathy; CRF; cardiomyopathy; delayed puberty; osteoporosis	Absent
Risk* by age 30 of:			
Squamous cell carcinoma	None	3+	2+
Malignant melanoma	None	1+	None
Basal cell carcinoma	None	None	None
Death related to EB	None	4+	2+

AD, Autosomal dominant; AR, autosomal recessive; CRF, chronic renal failure; DDEB, dominant DEB; DEB, dystrophic EB; RDEB, recessive DEB.

*Scale: absent or none, 1+, 2+, 3+, 4+.

†See references 42-47 for specific frequencies of major extracutaneous complications.

differing clinical findings. Although these names are of historical interest, we believe that it is timely to exchange several of these eponyms with names that are more visually descriptive. A similar debate has been recently raised in the general medical literature.^{38,39} For example, Weber-Cockayne EBS refers to a subtype of EBS which preferentially involves the palms and soles. We therefore propose renaming it “localized EBS” to more readily facilitate its recognition by clinicians. As noted by Cockayne⁴⁰ himself, it is well known that this entity may involve other sites,

such as the flexures during very hot weather, only later to revert to primarily palmoplantar involvement. Therefore the name “localized EBS” is used to denote this entity’s most common clinical presentation. In equivocal cases, the diagnosis is most easily confirmed clinically by the presence of several generations of family members having history or evidence of more typical palmoplantar blistering.

We have retained the eponym Dowling-Meara for the most severe subtype of generalized EBS, since it still has a strikingly unique clinical phenotype, that of

Table XVIII. Dystrophic EB subtypes: Clinical summary (DDEB [acral] and RDEB [acral]; DDEB [pretibial] and RDEB [pretibial]; DEB, pruriginosa)

	DDEB (acral) and RDEB (acral)	DDEB (pretibial) and RDEB (pretibial)	DEB, pruriginosa
Mode of transmission (usual)	AD or AR	AD or AR	AD or AR
Onset (usual)	Infancy	Birth or infancy	Childhood
Skin distribution (predominant)	Hands and feet	Pretibial; hands and feet; nails (fingers and toes)	Generalized or localized
Skin findings (frequency*)			
Blisters	4+	4+	4+
Milia	4+	4+	4+
Atrophic scarring	4+	4+	4+
Dystrophic or absent nails	3+	4+	4+
Granulation tissue	Absent	Absent	Absent
Scalp abnormalities	Absent	Absent	Absent
Keratoderma	Absent	Absent	Absent
Other	None	Lichen planus–like lesions	Severe pruritus
Relative inducibility of blisters	Variable	Variable	Variable
Extracutaneous involvement*†			
Anemia	Absent	Absent	Rare
Growth retardation	Absent	Absent	Rare
Oral cavity			
Soft tissue abnormalities	Absent	Absent	Absent
Enamel hypoplasia	Absent	Absent	Absent
Caries	Normal frequency	Excessive	Normal frequency
Gastrointestinal tract	Absent	Common (constipation)	Common (constipation)
Genitourinary tract	Absent	Absent	Absent
Ocular findings	Absent	Absent	Absent
Pseudosyndactyly	Absent	Absent	Absent
Respiratory tract	Absent	Absent	Absent
Risk by age 30 of:			
Squamous cell carcinoma	None	None	None [†]
Malignant melanoma	None	None	None
Basal cell carcinoma	None	None	None
Death related to EB	None	None	None

AD, Autosomal dominant; AR, autosomal recessive; DDEB, dominant DEB; DEB, dystrophic EB; RDEB, recessive DEB.

*Scale: absent or none, 1+, 2+, 3+, 4+.

†There may be an increased risk of squamous cell carcinoma after 30 years of age.

arcuate (“herpetiform”) vesiculation, a finding which is well known to all dermatologists. We have added a new name, “EBS, generalized, others,” to incorporate all generalized EBS subtypes (to include Koebner EBS) other than Dowling-Meara EBS. We have similarly changed the name Hallopeau-Siemens RDEB to “severe generalized RDEB” to allow more immediate visualization of this particular subtype of RDEB.

Recommended eliminations

See Table XXI. After lengthy discussion, a majority of our panel recommend that the term “hemidesmosomal EB” no longer be used. The term “hemidesmosomal EB” was originally created to encompass those EB subtypes in which tissue

separation occurs at the level of the hemidesmosome, thereby directing attention to those candidate genes which encode for critical polypeptide components of this structure.^{7,41} These subtypes include EBS with muscular dystrophy, EB with pyloric atresia, and some patients with non-Herlitz JEB. Although this concept is an intriguing one, since it is based on a correlation with a targeted structure, the hemidesmosome, it has its limitations. In particular, the separation of non-Herlitz JEB into two different categories (JEB vs hemidesmosomal EB), based solely on whether mutations arise within laminin-332 or type XVII collagen, respectively, in the absence of consistent clinical differences between these two groups of patients, makes this construct too artificial to allow for its application by the

Table XIX. Dystrophic EB subtypes: Clinical summary (DDEB, nails only, and DEB-BDN)

	DDEB, nails only	DEB-BDN
Mode of transmission (usual)	AD	AD or AR
Onset (usual)	Birth or infancy	Birth or infancy
Skin distribution (predominant)	Nails only	Generalized
Skin findings (frequency*)		
Blisters	Absent	2-3+
Milia	Absent	2-3+
Atrophic scarring	Absent	2-3+
Dystrophic or absent nails	4+	2+
Granulation tissue	Absent	Absent
Scalp abnormalities	Absent	Absent
Keratoderma	Absent	Absent
Other	None	None
Relative inducibility of blisters	None	Variable
Extracutaneous involvement*		
Anemia	Absent	Absent
Growth retardation	Absent	Absent
Oral cavity		
Soft tissue abnormalities	Absent	Absent
Enamel hypoplasia	Absent	Absent
Caries	Normal	Excessive frequency
Gastrointestinal tract	Absent	Absent
Genitourinary tract	Absent	Absent
Ocular findings	Absent	Absent
Pseudosyndactyly	Absent	Absent
Respiratory tract	Absent	Absent
Risk* by age 30 of:		
Squamous cell carcinoma	None	None
Malignant melanoma	None	None
Basal cell carcinoma	None	None
Death related to EB	None	None

AD, Autosomal dominant; AR, autosomal recessive; BDN, bullous dermolysis of the newborn; DDEB, dominant DEB; DEB, dystrophic EB.

*Scale: absent or none, 1+, 2+, 3+, 4+.

clinician at the bedside. The concept also potentially misleads parents into believing that only one of these two subgroups is a form of JEB when, in fact, both groups of patients appear to have the same risks over a lifetime of developing specific extracutaneous outcomes.

APPROACH TO CLASSIFICATION AND SUBCLASSIFICATION OF NEW PATIENTS WITH EB

As previously discussed, after careful consideration of the differential diagnosis for blisters arising in newborns and infants, the diagnosis of EB must first be firmly documented either immunohistochemically or ultrastructurally. Subclassification will

then be possible in most patients, by combining laboratory results, family history, and clinical findings. Algorithms for the latter were published as part of our Second Consensus Report in 2000.¹⁰ Since our last published report, several papers have been published, using data from the National EB Registry and other patient cohorts, which have more precisely defined for each major EB subtype the cumulative risks of developing specific extracutaneous outcomes, to include external eye blistering or scarring, hand and foot deformities, esophageal strictures, tracheolaryngeal stenosis or strictures, genitourinary tract complications, cancer, and cause-specific premature deaths.⁴²⁻⁴⁷ These data, in conjunction with the proposed revised classification scheme, can be used to better counsel parents and patients and to prognosticate on the likely course of disease over time.

RESOURCES FOR CLINICIANS AND FAMILIES

Lay support organizations

There are several nonprofit, lay organizations worldwide, most notably the Dystrophic EB Research Association (DeBRA), that provide information and support to EB patients, their families, and their primary care providers. Their names and Web sites are listed in Table XXII. Some of these organizations provide direct clinical services. Some, most notably DeBRA-International and the EB Medical Research Foundation, also contribute substantially to the funding of basic science and clinical research. We would encourage physicians to make EB patients and their families aware of these outstanding resources and to consider individually supporting these organizations so that they will be able to continue to provide needed support to both EB patients and investigators worldwide.

EB registries

There are now several registries of EB patients. The largest of these, based in the United States, has enrolled more than 3300 patients since its inception in 1986.⁴⁸ Smaller registries have been established throughout Europe, most notably in Italy,⁴⁹ Scotland,⁵⁰ Austria, Germany, and Australia. These registries serve not only as repositories of data and tissues for ongoing and future research but also as sources of clinical information and advice for patients and their physicians.

The coauthors gratefully acknowledge the support of many organizations for research related to EB, which include the National Institutes of Health (for the National [USA] EB Registry NO1 contracts and for several R01 and P01 grants), Dystrophic EB Research

Table XX. Dystrophic EB subtypes: Clinical summary (RDEB, inversa, and RDEB, centripetalis)

	RDEB, inversa	RDEB, centripetalis
Mode of transmission (usual)	AR	AR
Onset (usual)	Birth	Birth or infancy
Skin distribution (predominant)	Intertriginous, acral, lumbosacral, axial	Pretibial, nails (fingers and toes)
Skin findings (frequency*)		
Blisters	3+	3+
Milia	3-4+	3+
Atrophic scarring	3-4+	3+
Dystrophic or absent nails	4+	4+
Granulation tissue	Absent	Absent
Scalp abnormalities	Absent	Absent
Keratoderma	Absent	Absent
Other	None	None
Relative inducibility of blisters	Common	Common
Extracutaneous involvement*†		
Anemia	2+	Absent
Growth retardation	2+	Absent
Oral cavity		
Soft tissue abnormalities	4+	2+
Enamel hypoplasia	Absent	Absent
Caries	Increased	Normal frequency
Gastrointestinal tract	4+	Absent
Genitourinary tract	4+‡	Absent
Ocular findings	Absent	Absent
Pseudosyndactyly	1+	Absent
Respiratory tract	Absent	Absent
Other	External auditory canal stenosis	None
Cumulative risk* by age 30 of:		
Squamous cell carcinoma	None	None
Malignant melanoma	None	None
Basal cell carcinoma	None	None
Death related to EB	None	None

AR, Autosomal recessive; DEB, dystrophic EB; RDEB, recessive dystrophic EB.

*Scale: absent or none, 1+, 2+, 3+, 4+.

†See references 42-47 for specific frequencies of major extracutaneous complications.

‡Severe vulvovaginal nonhealing erosions, blisters, and strictures.

Association (DebRA)-International (and its many individual chapters worldwide), the Food and Drug Administration, the Veterans Administration, the European Commission (for the Geneskin Coordination Action and Therapeuskin STREP projects), French Ministry of Health, Association Française Contre les Myopathies (AFM), Epidermolysse Bulleuse Association d'Entraide (EBAE), INSERM—Programme National de Recherche en Dermatologie, and the Federal (German) Ministry for Education and Research (for the German Network Epidermolysis Bullosa). We also thank Dr D. Koss-Harnes for providing clinical information on EBS-Ogna.

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Table XXI. Current terms recommended for change or elimination

Name	Recommendation	Reason(s)
EBS, Weber-Cockayne	Change to "EBS, localized"	Lack of uniformity in original descriptions; new name has more immediate visual impact
EBS, Koebner	Change to "EBS, generalized other"	Inconsistency in definition even among EB experts; <i>not</i> associated with Koebner phenomenon
EB with pyloric atresia	Separate into "EBS-PA" and "JEB-PA" subtypes	Pyloric atresia may occur rarely with EBS, as well as with JEB
Hemidesmosomal EB	Eliminate this term	Includes only one of two JEB-nH subtypes having identical EM and clinical findings; distinction is based solely on targeted protein
RDEB, Hallopeau-Siemens	Change to "RDEB, severe generalized"	New term has more immediate utility for clinicians
RDEB, non—Hallopeau-Siemens	Change to "RDEB, generalized other"	Consistency in nomenclature
Transient bullous dermolysis of the newborn	Change to "bullous dermolysis of the newborn"	Not always transient; rare patients continue to blister beyond the newborn period or infancy

EB, Epidermolysis bullosa; EBS, EB simplex; JEB, junctional EB; nH, non-Herlitz (subtype); PA, pyloric atresia; RDEB, recessive dystrophic EB.

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Table XXII. Useful EB Web sites and other resources

EB organizations

DebRA Web sites

DebRA-International: www.debra-international.org

DebRA-UK: www.debra.org.uk

DebRA of America: www.debra.org

DebRA-Australia: www.debra.org.au

DebRA-Austria: www.debra-austria.org

DebRA-New Zealand: www.debra.org.nz

DebRA-Netherlands: www.debra.nl

DebRA-Italy: www.debraitaliaonline.org

DebRA-France: www.ebae.org

DebRA-Chile: www.debrachile.cl

EB Medical Research Foundation: www.ebkids.org

Diagnostic laboratories

Beutner Laboratories: www.beutnerlabs.com (for immunofluorescence mapping)

Gene Dx: www.genedx.com

EB Center Freiburg: www.netzwerk-eb.de

Laboratory for Molecular Therapy, eb house Austria, Department of Dermatology, University Hospital Salzburg, Müllner Hauptstr, 48, 5020 Salzburg

Department of Anatomy, Texas Children's Hospital (Dr J. Hicks) (for electronmicroscopy):

www.texaschildrenshospital.org/FindADoctor/displaybio.asp?person_id=380

Department of Genetics, Inserm Paris and Toulouse: www.skindiagnostic.fr

Department of Human Genetics, Radboud University Medical Center Nijmegen, Netherlands (for *COL7A1* testing):

www.dnadiagnostieknijmegen.nl/en/dd_index_en.php

Department of Genetics, University Medical Center Groningen, Netherlands (for *COL17A1*, *LAMB3*, *KRT5*, AND *KRT14* testing): www.rug.nl/umcg/faculteit/disciplinegroepen/medischegenetica/geneticcounseling/index

Laboratory of Molecular and Cell Biology, Instituto Dermopatico Dell'Immacolata, Rome, Italy (d.castiglia@idi.it)

Dermatopathology.stanford.edu/services/epiderm.html

Other useful Web sites

www.internationalebforum.org

www.schmetterlingskinder.at

www.netzwerk-eb.de (German EB Registry)

www.ebnurse.org

www.magec.eu (Maladies génétiques à expression cutanée [MAGEC])

www.lyon.inserm.fr/therapeuskin

www.geneskin.idi.it

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