Evaluation and treatment of the newborn with epidermolysis bullosa

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ABSTRACT

Epidermolysis bullosa (EB) is a heterogeneous group of inherited skin diseases characterized by increased skin fragility and variable degrees of extracutaneous involvement. The clinical spectrum ranges from localized skin disease to a life-threatening and disabling disease with extensive extracutaneous involvement. All four major types of EB, namely EB simplex, Junctional EB, Dystrophic EB and Kindler syndrome, can present with blistering and erosions at birth and cannot be distinguished clinically in the newborn period. The extensive differential diagnosis of blistering and erosions in the neonate must be considered and common etiologies ruled out. The diagnosis of EB can be confirmed via a skin biopsy for immunofluorescence mapping. This review discusses the four major subtypes of EB and their associated extracutaneous features. The evaluation of a newborn suspected of having EB, including diagnosis and management, is also reviewed.

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Introduction

Epidermolysis bullosa (EB) is an inherited mechanobullous disorder characterized by skin fragility and blister formation, following minor trauma or traction on the skin. EB encompasses many clinically distinctive phenotypes, all of which have skin blistering as a major feature, but variable risks of extracutaneous manifestations and premature death. To date, over 1000 different mutations involving 14 structural genes within the skin have been documented to lead to the clinical phenotype of EB. Mutations result in either abnormal, absent or significantly reduced levels of a specific protein that is important in epidermis to dermis adhesion, and the result is shearing of the skin, or blistering, with ultrastructurally uniform cleavage planes. In general, the precise protein affected, and the degree to which it is altered (abnormal, slightly reduced, or absent) determines the disease severity, with complete absence of a protein resulting in a more severe phenotype with involvement of extracutaneous tissues.

In 2008, EB was re-classified into four major types, based on the level in the skin where the missing or abnormal structural skin protein is located and the corresponding ultrastructural level of cleavage. In the epidermolytic type, or EB simplex (EBS), cleavage and blister formation occurs within the epidermis. This group has been further subdivided into basilar (cleavage within the basal layer keratinocytes) and suprabasilar (cleavage within the keratinocytes above the basal layer). In the junctional or “lucidolytic” type, called junctional EB (JEB), blister formation occurs within the lamina lucida, an electron-lucent region that contains anchoring filaments that connect the basal keratinocytes to the underlying lamina densa. In the dermolytic type, or dystrophic EB (DEB), blistering occurs in the dermis (or sublamina densa). The junctional and dermolytic groups of EB are further subdivided into major and minor types. Lastly,

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### Table 1 – The Four Major EB Types, with Corresponding Level of Skin Cleavage, Affected Proteins, Major and Rare Subtypes, and Mode of Inheritance.*

<table>
<thead>
<tr>
<th>EB Type</th>
<th>Junctional EB (Loricrytic)</th>
<th>Dystrophic EB (Dermolytic)</th>
<th>Mixed type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of skin cleavage</strong></td>
<td>Within the epidermis</td>
<td>Within the lamina lucida</td>
<td>Within the dermis</td>
</tr>
<tr>
<td><strong>Affected proteins</strong></td>
<td>Keratins 5 &amp; 14, plectin, dystonin, plakophilin-1, desmoplakin</td>
<td>Laminin-332, collagen XVII, n694 integrin</td>
<td>Collagen VII</td>
</tr>
<tr>
<td><strong>Major Subtypes</strong></td>
<td>JEB, other</td>
<td>JEB, non-Herlitz,</td>
<td>RDEB, severe generalized other</td>
</tr>
<tr>
<td></td>
<td>EBS-Generalized</td>
<td>EBS-Dowling-Meara</td>
<td>EBS with muscular dystrophy (MD)</td>
</tr>
<tr>
<td></td>
<td>EBS with pyloric atresia (PA)*</td>
<td>EBS with pyloric atresia</td>
<td>EBS with mitotically active atresia</td>
</tr>
<tr>
<td></td>
<td>EBS with sebaceous atresia</td>
<td>EBS with pyloric atresia</td>
<td>EBS with pyloric atresia</td>
</tr>
<tr>
<td></td>
<td>EBS Suprabasal</td>
<td>EBS late onset*</td>
<td>EBS late onset*</td>
</tr>
<tr>
<td></td>
<td>EBS Superficialis*</td>
<td>EBS laryngeal</td>
<td>EBS laryngeal</td>
</tr>
<tr>
<td></td>
<td>EBS Plakophilin deficiency*</td>
<td>onycho-cutaneous (LOC) syndrome*</td>
<td>onycho-cutaneous (LOC) syndrome*</td>
</tr>
<tr>
<td></td>
<td>Lethal acantholytic EBS*</td>
<td>JEB, inversa*</td>
<td>JEB, inversa*</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Most are AD, except for suprabasal types &amp; EBS w MD and EBS w PA</td>
<td>AR</td>
<td>RDEB-AR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: JEB, Junctional EB; RDEB, recessive dystrophic EB; DDEB, dominant dystrophic EB; AD, autosomal dominant; AR, autosomal recessive.

the mixed type is called Kindler syndrome and exhibits multiple cleavage planes (Table 1).

Based on work derived from the national United States (US) EB registry, the estimated EB prevalence in the US is 8.22 per 1 million and the incidence over a 5-year period was 19.6 per 1 million live births. EB simplex is the most common type with a prevalence of 4.6 per million and an incidence of 10.8 per million. Recessive dystrophic EB (RDEB) has the lowest prevalence of 0.9 per million, and the lowest incidence of 2.0 per million live births. EB shows no geographic or racial predilection. This article reviews the clinical features of the four major EB types, and the evaluation, diagnosis and management of a newborn with EB.

### Epidermolysis bullosa simplex

In EB simplex blistering occurs within the epidermis. The localized subtype of EB simplex (EBS), EBS-localized, is the most common type of EB worldwide. EBS-localized presents with trauma-induced blisters primarily on acral surfaces in childhood. Bullae typically heal without scarring and blistering tends to improve with age, although focal keratoderma may develop. There is mild to no mucosal involvement and affected individuals have a normal lifespan. The more severe forms of EBS, EBS-generalized and EBS-Dowling-Meara (DM) can present with blistering at birth that heals with variable amounts of postinflammatory changes, although they rarely scar. In EBS-DM, blistering characteristically appears as small

![Fig. 1 – Newborn boy with JEB-Herlitz and widespread blistering localized to lower back and diaper region. Courtesy of Dr. Karen Wiss.](image)
clustered vesicles in an arcuate array ("herpetiform" appearance) and there is gradual development of diffuse palmoplantar keratoderma with variable amounts of nail dystrophy and oral involvement. This subtype of EBS is best diagnosed by electron microscopy showing clumped keratin filaments.

Most forms of EBS are inherited in an autosomal dominant manner except for the rarer subtypes, including lethal acantholytic EBS, plakophilin deficiency, autosomal recessive EBS, EBS with pyloric atresia, EBS with muscular dystrophy. Overall EBS has a good prognosis and a relatively good quality of life with adequate wound care. The less common subtypes such as EBS with muscular dystrophy, EBS with pyloric atresia and lethal acantholytic EBS have a worse prognosis and are associated with early death.

**Junctional epidermolysis bullosa**

In junctional EB (JEB) blisters form below the basal keratinocytes, at the level of the lamina lucida. All types of JEB are inherited in an autosomal recessive manner. JEB-Herlitz (JEB-H) represents the most severe form of EB and is the result of complete absence of laminin-332 expression. Patients with JEB-H will present with widespread blistering at birth and the development of excessive non-healing, granulation tissue in areas of blistering especially on the periorificial skin and upper back (Fig. 1). Blisters heal with atrophic scarring and milia, and nails are often dystrophic or absent. Airway involvement occurs in greater than 75% of patients with JEB, with a cumulative risk of 40% by 6 years of age. Involvement of the eyes, and the gastrointestinal and genitourinary systems is also common. JEB-H is associated with high mortality within the first 2 years of life, with a cumulative risk of death from all causes of 44.7% by 1 year of age, rising to 61.8% by 15 years of age. The most common causes of death in JEB-H are failure to thrive, sepsis and respiratory failure.

JEB-non-Herlitz (JEB,Other) type is associated with partial or abnormal laminin-332 or collagen XVII and presents with blistering in infancy that heals with scarring. The course and prognosis depend on how severely affected the target protein is, with some patients having a mild phenotype and a normal life span (JEB-non-Herlitz, localized) while others have a severe disease and an increased risk of death (JEB-non-Herlitz, generalized). Involvement of hair, nails and teeth is common. In fact, enamel hypoplasia is a unifying feature in all forms of JEB.

JEB with pyloric atresia (JEB-PA) presents with blistering at birth and symptoms of pyloric atresia and/or ureteral and renal anomalies (dysplastic/multicystic kidney, hydronephrosis/hydrouretri, ureteroecele, duplicated renal collecting system, absent bladder) become apparent shortly after birth. JEB-PA is usually severe and often lethal in the neonatal period.

Larynge-oncho-cutaneous syndrome (also called Shabbi's syndrome) was added as a new variant of JEB due to its clinical and molecular similarities. It is the result of mutations in the alpha chain of laminin-332 and presents with blisters and erosions at birth that are most prominent on the face and neck. Extracutaneous involvement and early death is common.

![Fig. 2 - Right hand of a young child with RDEB-severe generalized. Note the atrophic scarring, the syndactyly and the absence of fingernails.](image)

**Dystrophic epidermolysis bullosa**

Dystrophic EB is the result of mutations in collagen VII, an anchoring fibril located below the basement membrane in the upper dermis. As a result of defective or absent anchoring fibrils, blisters form, deep, below the epidermis and thus heal with significant scarring and milia (Fig. 2). In general, children with the dominantly inherited form (dystrophic EB (DDEB) have reduced expression of collagen VII and have a milder phenotype, whereas the recessively inherited form (recessive dystrophic EB (RDEB) is associated with complete absence of collagen VII and a more severe phenotype, poor quality of life and shortened life span. In both major types of DEB, nails are dystrophic or absent and the mucous membranes are frequently involved, including those of the mouth, gastrointestinal tract and eyes.

In RDEB-severe generalized, the classic severe form of DEB, widespread blistering is present from birth. Oral mucosal involvement may lead to difficulty in feeding during the neonatal period. RDEB-severe generalized is associated with numerous extracutaneous manifestations including involvement of the eyes, gastrointestinal tract, genitourinary tract, kidneys and heart. Children with RDEB-severe generalized, are at an increased risk of glomerulonephritis, renal amyloidosis, IgA nephropathy and cardiomyopathy. Recurrent, chronic wounds and scarring on the hands and feet can lead to syndactyly of the fingers and toes that can render the hands non-functional (Fig. 2). In addition, patients have a high likelihood of developing aggressive squamous cell carcinoma which is the main cause of early death in RDEB-severe generalized. In contrast, the blistering in RDEB-generalized other, is localized to hands, feet, knees, and elbows without the severe, mutilating scarring seen in classic RDEB-severe generalized.

In DDEB, blistering is often mild and limited to hands, feet, knees, and elbows, but nonetheless, heals with scarring. Dystrophic nails, especially toenails, are common and may be the only manifestation of DDEB (DDEB-nails only). Bullous dermolysis of the newborn (BDN) is a less common variant of DEB that can be inherited in an autosomal dominant or recessive manner (DDEB, bullous dermolysis of the newborn).
or RDEB, bullous dermolysis of the newborn). BDN presents with generalized, spontaneous or trauma-induced blistering at birth that spontaneously regresses in the first year of life.

**Kindler syndrome**

Kindler syndrome (KS) is the result of mutations in the fermitin family member 1 (FERMT1) gene, which encodes for kindlin-1 (also called fermitin family homolog 1 protein, FFH1). Kindlin-1 is a part of the connection between the actin cytoskeleton of basal keratinocytes to the extracellular matrix and plays a role in cell-cell adhesion, in addition to cell signaling, morphogenesis, differentiation and cell migration. Defective kindlin-1 results in blistering at multiple cleavage planes including intraepidermal, junctional, and sublamina densa. Initially there is trauma-induced blistering at birth, or shortly thereafter, that improves with time and can disappear altogether. Blistering is most common on acral sites. Later in life, there is progressive poikiloderma on sun-exposed skin. Poikiloderma and exquisite photosensitivity distinguish KS from all other types of EB. Extracutaneous features include gingivitis, colitis (can be severe), mucosal stenoses (e.g., esophageal, urethral) and acquired syndactyly. Patients also have an increased risk of squamous cell carcinoma. KS is inherited in an autosomal recessive manner and is associated with normal lifespan.

**The neonate with EB**

The newborn infant with EB may present with localized or widespread blistering at birth, or within the first few days of life, and it is not possible to determine EB type by clinical examination. However, EB should be one, among many other diagnostic considerations, when evaluating a newborn with blisters and/or erosions. The differential diagnosis for blisters in a neonate is extensive and includes common acquired etiologies such as sucking blisters or other birth trauma-induced blisters, infection related blisters such as herpes simplex, bullous impetigo, staphylococcal scalded skin syndrome, neonatal candidiasis, neonatal varicella; maternal autoimmune bullous conditions such as bullous pemphigoid (can also appear de novo), pemphigoid gestationis or pemphigus vulgaris; others such as bullous aplasia cutis congenita, and bullous mastocytosis; and genetic disorders including incontinentia pigmenti, ectodermal dysplasia, epidermolysis hyperkeratosis (bullous congenital ichthyosiform erythroderma), pachyonychia congenita, congenital erosive dermatosis with reticulate supple scarring and epidermolysis bullosa (all subtypes). The diagnostic possibilities range from benign and self-limited to severe and life-threatening; and thus a timely and accurate diagnosis within the first few weeks of life is essential for proper management and prognosis of the neonate. Consultation with a pediatric dermatologist can be helpful in establishing a diagnosis, as often subtle differences in the clinical appearance of blisters can help to narrow down the differential diagnosis.

In the assessment of a neonate with blisters, Nischler et al., recommend an algorithmic approach that includes a detailed medical history including a family history of inherited blistering disorders and a maternal obstetrical history, a complete physical examination, and microbial testing (bacterial, viral and fungal cultures) to rule out infectious etiologies. If infectious etiologies and exogenous causes (perinatal trauma-induced blisters) have been ruled out, a skin biopsy is warranted for histologic and ultrastructural assessment. If an immunobullous disorder is suspected, a biopsy of uninvolved skin just adjacent to a blister (peri-lesional) is optimal in order to avoid the appearance of secondary changes that may occur in established blisters. If EB is suspected, a skin biopsy should be taken from the edge of a fresh blister (1/2 blister and 1/2 uninvolved skin) that is <12h old. Ideally, a fresh blister should be induced by firmly applying a pencil eraser to an area of skin nearby the blistered skin, and rotating it laterally back and forth until mild erythema appears. It is recommended to wait at least 5 min for a blister to develop microscopically before taking the biopsy.

As described above, many different subtypes of EB, including mild and severe variants, can present with blistering at birth. In addition, the various subtypes of EB can have overlapping clinical features during the neonatal period, rendering a clinical diagnosis unreliable. For example, newborns with variants of EB simplex can present with extensive blistering and mucosal involvement at birth but then ultimately, have localized, mild disease as children. Caution must be taken not to provide the family with a presumptive diagnosis of EB prior to a full diagnostic evaluation, as this can lead to unnecessary anxiety and worry. A skin biopsy from a freshly induced blister sent in proper fixative for IFM is the first-line diagnostic test to determine the subtype of EB. This information must then be combined with a thorough family history before subtype and prognosis is discussed with the family. In cases where an initial biopsy and IFM is unable to delineate the diagnosis, a second and/or third biopsy for repeat IFM and electron microscopy should be performed. EB subtype should be determined expeditiously, given its implications for long-term prognosis including risk of extracutaneous manifestations and premature death.

**Diagnosis of EB**

Immunofluorescence mapping (IFM) (or direct immunofluorescence, DIF) on a freshly induced blister is now recommended as the primary method for the diagnosis of EB. Routine light microscopy can identify the level of the split as intraepidermal versus subepidermal but is not very helpful in delineating the specific subtype of EB, as both junctional and dys trophic subtypes will show subepidermal blistering. In IFM, antibodies conjugated with fluorochromes (i.e., rhodamine or fluorescein) are applied to skin sections and examined using ultraviolet light microscopy. IFM provides information as to the precise level of tissue separation, and the relative expression and distribution of the various protein antigens at the basement membrane zone. In the majority of patients with EB, IFM allows for subtype classification and prognosis. For example, JEB-non-Herlitz with localized blisters (JEB-non-Herlitz, localized) will show reduced collagen
XVII reactivity on IFM whereas in patients with JEB-non-Herlitz with generalized blistering collagen XVII is absent. In addition, certain subtypes of EB will have characteristic IFM findings such as the intraepidermal granules of type VII collagen seen in bullous dermolysis of the newborn. Occasionally, IFM fails to provide the exact subtype diagnosis. This most commonly occurs in the less severe DDEB subtypes where collagen VII is only slightly reduced and the IFM can appear as normal skin. In these situations, repeat biopsies for IFM and electron microscopy and genetic testing can be considered for a definitive diagnosis.

In order to ensure proper antigen preservation for successful IFM, the skin biopsy must be transported in normal saline (if it will be delivered for processing within 24 h) or in a specialized Michel’s media that can preserve target antigens for 24 h to 6 weeks until testing. Although, IFM for the diagnosis of EBM requires specialized expertise for interpretation, the technique is readily available through most dermatopathology laboratories and is the preferred initial diagnostic test for EBM. For IFM laboratories inexperienced in testing for EB, an updated list of antibodies and their suppliers is available through the Dystrophic Epidermolysis Bullosa Research Association (Debra) website (http://www.debra-international.org).

Electron microscopy (EM) uses beams of electrons focused by magnetic lenses to create a two-dimensional image with a resolution and magnification 1000 times greater than a light microscope. EM is an additional diagnostic technique that can be utilized for the diagnosis of EB. The advantages of EM are that it allows for direct visualization and provides morphologic and semiquantitative information about skin structures at the dermal-epidermal junction. It is the only technique that can identify patients with EB-Dowling-Meara by visualizing the clumped keratin filaments within the basal keratinocytes. EM requires expensive equipment, and specialized expertise for specimen processing and interpretation, and is only available in a few labs worldwide, making it impractical for use in routine clinical diagnosis.

Nonetheless, EM continues to be important in EB research and for cases where IFM has failed to establish a diagnosis. In a comparative study, IFM was shown to be more sensitive and specific than EM in the diagnosis of EB. For proper preparation, tissue for EM needs to be fixed in paraformaldehyde or glutaraldehyde.

Genetic testing can determine the precise site and type of mutation present, and provide a definitive diagnosis of EB subtype and mode of inheritance. Currently, the cost and lack of widespread availability precludes it from being a first line diagnostic test for EB. In the United States, few insurers will pay for genetic testing. Nonetheless, a list of laboratories that provide testing for EB can be found at http://www.ncbi.nlm.nih.gov/sites/GeneTests. It is important that IFM be performed prior to pursuing mutational analysis in order to focus the testing on a specific gene.

Prenatal and preimplantation diagnosis

In families with EB or those at risk for having a child with EB, prenatal and now preimplantation diagnosis is possible in order to appropriately guide and prepare the parents. In the early 1990s, prenatal diagnosis was accomplished via electron microscopy and/or IFM of a fetal skin biopsy performed after the 17th week of gestation. The major downsides to this technique were the possibility of sampling error, the risk of miscarriage and the emotional distress associated with terminations of affected fetuses at an older gestational age.

More recently, numerous groups have demonstrated the successful prenatal diagnosis of EB using DNA isolated from chorionic villus samples taken at 10–12 weeks, or amniotic fluid samples taken at 12–15 weeks gestation in at-risk pregnancies. In one report of 144 at-risk pregnancies, including families with EBS, JEB, JEB with pyloric atresia, and DDEB, prenatal genetic testing on DNA from chorionic villi or amniotic fluid predicted postnatal EB diagnosis with greater than 98% accuracy.

Prenatal diagnosis of EB via the assessment of fetal DNA in the maternal circulation is an area of active investigation. Although fetal cells in the maternal circulation have been detected as early as 4 weeks, their isolation is very difficult because of their low density. Successful implementation of this technique would allow for prenatal diagnosis of EB from a maternal blood sample as early as 6–7 weeks.

Preimplantation genetic diagnosis is a newer option for families at high risk for EB that avoids the need to consider termination of an established pregnancy. This method involves in vitro fertilization and involves testing of DNA extracted from the preimplanted embryo for mutations in the candidate gene. If testing reveals a normal or a carrier genotype, the embryo is implanted. At present, the clinical pregnancy rate after this procedure is 25% per embryo transfer. Advances in molecular genetics, which have shortened the time for mutation detection, have improved success rates and several successful unaffected pregnancies have been reported after preimplantation genetic diagnosis for JEB. Preimplantation genetic testing is a highly specialized procedure that is currently available in relatively few centers worldwide, however, continued technologic progress will widen its availability and accessibility.

A crucial prerequisite for prenatal or preimplantation mutation analysis is the identification of the candidate gene in the affected family member(s). This requires a thorough family history, detailed clinical phenotype information and knowledge of the level of skin cleavage or affected protein as determined by IFM. Prenatal testing and appropriate genetic counseling are an integral part of the management of patients with EB and families at risk of EB.

Management of the neonate with EB

At present, there is no cure for EB. Gene therapy, whereby the necessary gene is introduced into the patient’s cultured keratinocytes and then grafted back on to the patient’s own skin, protein replacement by transfection of the corrected protein into the patient’s cultured keratinocytes, and bone marrow transplantation are all being vigorously investigated as possible curative treatments. Until a safe and effective corrective treatment becomes widely available, the management of EB is based on several general principles: (1)
prevention of skin trauma to avoid new blister formation; (2) meticulous wound care with appropriate wound dressings to ensure timely healing of wounds and prevention of infection; (3) maintenance of good nutrition to maximize growth and wound healing; (4) surveillance for extracutaneous complications; and (5) ongoing psychosocial support. In the neonatal period, prevention of new blisters and wound care are the most important aspects of treatment. Psychosocial support is also especially important at this time when diagnosis and prognosis are being investigated. In the neonatal period, prevention of new blisters is attempted by gentle handling of the infant, using loose-fitting clothing, padding bony prominences, and avoiding adhesives or direct rubbing (use putting instead) of the skin. The skin should be well-lubricated with vaseline or other bland ointment, and the infant should be maintained in cool, air-conditioned environments as overheating can increase skin fragility. Babies with EB should be lifted by placing one hand beneath the child’s bottom and one hand behind the neck, rather than from under the arums, so as to minimize friction and blister development in this area. As the infant gets older, prophylactic wrapping is often used to prevent new blisters.  

In the hospitalized neonate, it is important that all individuals involved in the patient’s care are familiar with how to handle an infant with EB. No tape or adhesives should be applied directly on the skin, instead non-stick wound dressings should be placed under pulse oximeter probes, EKG leads and around IV sites. Regular gauze can then be applied over the non-stick dressings and tape can then be used to secure the lead or IV to the gauze wrap. Patients should be transferred by gentle lifting, rather than sliding. Gauze or loose-fitting clothing should be left in place under a blood pressure cuff or a tourniquet. Extra padding of beds and operating room tables can prevent accidental injury to the skin. Tubes that need to be introduced into mucosal surfaces or that come in contact with the skin should be heavily lubricated. If surgery is needed, patients with EB require special preoperative evaluation, preparation and intraoperative management, which will vary according to the EB subtype. In general, avoiding unnecessary trauma to the skin, eyes and mucosa is key. When appropriate precautions are taken, surgical procedures can be uneventful in children with EB. Perioperative guidelines for children with EB were thoroughly reviewed by Goldscheider et al. in 2010. In addition, general information about the routine and hospital care of infants with EB is available online at [http://www.debra.org/understanding](http://www.debra.org/understanding) and at [http://dermatology.stanford.edu/gsc/eb_clinic](http://dermatology.stanford.edu/gsc/eb_clinic) and printable anesthetic guidelines are available at: [http://pedanaesthesia.stanford.edu/downloads/guideline-eb.pdf](http://pedanaesthesia.stanford.edu/downloads/guideline-eb.pdf). If questions arise that are not answered online, a nurse educator is also available via telephone, weekdays 9 am to 5 pm through Debra.  

Despite careful precautions, it is impossible to prevent all blister formation in children with EB. When blisters form, proper wound care can help assure timely healing and prevention of infection. Skin should be cleansed daily and caregivers should wash hands prior to dressing changes. New blisters should be drained as soon as possible with sterile large-bore needles at two sites, in order to prevent extension. The blister roof should be left in place as it acts as a natural dressing. Vaseline or other bland healing ointment should first be applied to a non-stick dressing (e.g. Mepitel®, Mepilex®, Vaseline gauze®, or Telfa®), then the coated dressing is applied to the site. Next, a rolled gauze is wrapped around the non-adherent dressing and secured in place with a stretch netting or by cutting the tail of the rolled gauze down the middle and tying the two ends in place. If necessary, tape should only be used to secure gauze to gauze. Dressings should be changed daily after gentle skin cleansing. Topical antibiotics and antimicrobial dressings should be used judiciously in patients with EB. Bacterial colonization of wounds is inevitable and often does not interfere with healing. Due to the increased risk of bacterial resistance, topical antibiotic ointments and antimicrobial dressings should be reserved for those wounds that are colonized with bacteria and fail to heal, referred to as “critically colonized.”  

Frank wound infection (increased erythema, swelling, purulence, odor and pain) often requires systemic antibiotics. In some cases, topical antibiotics are used on a rotational basis in children with chronic and/or critically colonized wounds. Children with EB have increased caloric and protein needs due to the increased energy expenditure for wound healing, similar to burn patients. At the same time, involvement of the oropharyngeal, esophageal and gastrointestinal mucosa in some patients may limit intake and decrease absorption of nutrients making it difficult to satisfy the high-caloric needs. Maximizing nutrition is of vital importance in order to promote growth and development, optimize wound healing and improve quality of life.  

The risk of malnutrition is more prevalent in the severe forms of EB, most notably in RDEB-severe generalized and JEB-Herlitz, although it is also observed in children with EBS-DM, JEB-non-Herlitz and RDEB-generalized other. In infants with EB, painful blistering in the mouth can prevent adequate intake and specialized nipples and caloric supplementation of breast milk and/or formula may be required. Despite caloric, vitamin and nutrient supplements and efforts to increase intake, supplementary gastrostomy feeding is sometimes necessary. Gastrostomy feedings have been shown to improve both growth and nutrition in EB patients. Growth charts must be closely monitored. A nutritionist or dietitian who is experienced with EB can help to optimize the child’s nutritional status. 

Surveillance for subtype-specific extracutaneous manifestations is required beyond the neonatal period. The extracutaneous features associated with the different subtypes of EB and their relative frequency was reviewed by Fine et al. in 2006. In patients with JEB-Herlitz, tracheal-laryngeal structures can be life-threatening if undetected. Patients with JEB should also be monitored closely for external eye involvement, excessive dental caries and failure to thrive. Children with DEB are at an increased risk of esophageal strictures and malabsorption. Syndactyly of the fingers and toes from repeated scarring is one of the most debilitating sequelae of RDEB. Preventative wrapping of individual fingers with tension in the web space, beginning in infancy is recommended in an attempt to preserve function for as long as possible. Metastatic-squamous cell carcinomas (SCC) is the leading cause of death in patients with RDEB-severe generalized, thus surveillance for SCC with frequent complete skin
examinations is required in this population, beginning at age 10. SCC and basal cell carcinoma also occur with increased frequency in patients with JEB-Herlitz and EBS-Dowling Meara, respectively.

Lastly, ongoing psychosocial support for both the child and the family is critical as they manage this devastating disease that can isolate the child and family. This is often best accomplished via a multi-disciplinary approach where the mental health professional is part of the management team and is aware of all medical issues. The complete care of patients with EB requires a multi-disciplinary team that includes a dermatologist, EB nurse specialist, gastroenterology/nutrition specialist, pain management, physical and occupational therapist, geneticist, psychologist, and dentist. In some areas, specialized EB clinics allow for this comprehensive care in one visit. If such a clinic is not available a dermatologist or pediatrician should coordinate with the various specialists via consultation. It is important to seek specialists who are familiar with the specific needs of children with EB.

Conclusions

Epidermolysis bullosa encompasses over 30 clinically distinctive phenotypes that are all characterized by increased skin fragility. The clinical spectrum ranges from localized skin disease with a normal lifespan as in the most prevalent subtype, EBS-localized; to a debilitating disease, associated with numerous extracutaneous complications and early death, as in RDEB-severe generalized. A reliable clinical diagnosis is not possible in the neonatal period and an extensive differential diagnosis must be considered in a newborn with blistering. A skin biopsy for IFM is the first-line diagnostic test for EB. Prenatal and preimplantation diagnosis also allow at risk families to make informed decisions. No curative therapy exists for EB, and thus current treatment centers around multi-disciplinary care with an emphasis on meticulous wound care, and surveillance and treatment of extracutaneous complications. Exciting ongoing research into curative treatments, provides hope for children with EB. Information on EB, EB care centers, ongoing clinical trials and support groups is available online at http://www.Debra.org and http://www.Debra-international.org.

R E F E R E N C E S