Diagnosis and Care of the Newborn with Epidermolysis Bullosa

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PRACTICE GAPS

Epidermolysis bullosa (EB) is a group of rare genetic disorders occurring in only 8.2 per million live births per year in the United States. Thus, many neonatologists have not had substantial clinical experience to feel comfortable diagnosing and caring for neonates who present with fragile skin suggestive of EB. In addition, recent updates in the classification of EB have been based more on genetic mutation analysis than solely on clinical presentation. Preferred diagnostic methods and clinical care practices are also rapidly changing.

OBJECTIVES *After reading this review, readers will be able to:*

1. Summarize how to accurately diagnose epidermolysis bullosa (EB) in an infant with fragile skin and to recognize associated complications.
2. Describe basic care of neonates with EB, including skin care, as well as treatment of associated disorders of other systems.
3. Explain how to appropriately guide the family of an infant with EB through the child's diagnosis, treatment, and prognosis.

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ABBREVIATIONS

DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
DEBRA	Dystrophic Epidermolysis Bullosa Research Association
EB	epidermolysis bullosa
EBS	epidermolysis bullosa simplex
EM	electron microscopy
IFM	immunofluorescence mapping
JEB	junctional epidermolysis bullosa
NGS	next-generation sequencing
RDEB	recessive dystrophic epidermolysis bullosa
SS	Sanger sequencing

ABSTRACT

Epidermolysis bullosa (EB) is a group of rare genetic disorders that are characterized by fragile skin. Because of its rarity, many neonatologists may not be familiar with the current diagnosis and treatment recommendations for EB. The classification of EB was updated in 2020. The diagnosis of EB is now more heavily based on genetic rather than clinical or histologic features. In this review, we summarize the basic classification of EB, the preferred methods of diagnosis including a panel of next-generation sequencing for all types of EB, as well as specific immunofluorescence and electron microscopy of skin biopsies in special circumstances. We also review the principles of skin care for the newborn with EB and discuss the possible associated comorbidities including infectious, gastrointestinal, respiratory, and genitourinary complications. Lastly, we discuss the approach to educating the family about the diagnosis, prognosis, and care of an

infant with EB and describe resources for the successful transition of the infant from the hospital to the home.

INTRODUCTION

Epidermolysis bullosa (EB) is a group of rare genetic disorders that are characterized by fragile skin. Because of its rarity, with an incidence of 8.2 per million live births in the United States, (1) many neonatologists may not be familiar with the current diagnosis and treatment recommendations for EB. The classification of EB has been updated frequently, most recently in 2020, (2) as new genes associated with fragile skin are discovered. The diagnosis of EB is now more heavily based on genetic rather than clinical features. When an infant presents with blisters and/or erosions of the skin and mucous membranes, it is imperative to consider fragile skin as part of the differential diagnosis. If EB is considered, elucidation of the molecular type is critical for diagnostic and prognostic purposes. In this review, we will summarize the basic classification of EB and the preferred methods of diagnosis including the next-generation sequencing (NGS) method of genetic screening for all types of EB, as well as specific immunofluorescence mapping (IFM) and electron microscopy (EM) of skin biopsies in special circumstances. We will also review the principles of skin care in the newborn and discuss the possible associated comorbidities including infectious, gastrointestinal, respiratory, and genitourinary complications. Lastly, we will discuss the approach of educating the family about the diagnosis, prognosis, and care of the infant and describe resources for the successful transition of the infant from the hospital to the home.

CLASSIFICATION OF EB

According to the 2020 classification of EB, there are now 16 genes associated with classical types of EB: EBS (7 genes), JEB (7 genes), DEB (1 gene) and KEB (1 gene). Other disorders associated with skin fragility, some of which were previously classified with EB, including peeling skin disorders (9 genes), erosive disorders (5 genes) and hyperkeratotic skin

Table 1. Molecular and Genetic Classification of EB

Type	Inheritance	Gene	Protein
EB simplex (Intra-epidermal)	Autosomal dominant	*KRT5*	Keratin 5
		KRT14	Keratin 14
		PLEC	Plectin
		KLHL24	Kelch-like protein 24
	Autosomal recessive	*KRT5*	Keratin 5
		KRT14	Keratin 14
		DST	BP230 (BPAG1e, dystonin)
		EXPH5 (SLAC2B)	Exophilin-5 (synaptotagmin-like protein, homolog lacking C2 domains b, Slac 2b)
		CD151 (TSPAN24)	CD151 antigen (tetraspanin 24)
Junctional EB (junctional)	Autosomal recessive	*LAMA3, LAMB3, LAMC2*	Laminin 332
		COL17A1	Type XVII collagen
		ITGA6, ITGB4	Integrin α6β4
		ITGA3	Integrin α3 subunit
Dystrophic EB (dermal)	Autosomal dominant	*COL7A1*	Type VII collagen
	Autosomal recessive	*COL7A1*	Type VII collagen
Kindler EB (mixed)	Mixed	*FERMT1 (KIND1)*	Fermitin family homolog 1 (Kindlin-1)

disorders with skin fragility (10 genes), are now considered separate from EB (Table 1):

- EB simplex (EBS): Proteins located in the epidermis (7 genes)
- Junctional EB (JEB): Proteins located in the basement membrane between the epidermis and the dermis (7 genes)
- Dystrophic EB (DEB): Recessive (RDEB) and dominant (DDEB), *COL7A1* (1 gene) located in the anchoring fibrils of the dermis.
- Kindler EB: Located in several layers of the skin, *FERMT1* (1 gene)

The other 6 genes are associated with disorders of erosive skin fragility.

EB is also classified into subtypes that are determined largely by the clinical manifestations and severity of each case and vary in clinical presentation and prognosis as well as location of mutations. (2)(3) Blistering of the skin in a neonate is most commonly seen in the most severe cases such as RDEB-severe, JEB-severe, and EBS-severe, as well as EB with pyloric atresia (caused by *PLEC1* and $\alpha6\beta4$ integrin mutations and classified as EBS and JEB, respectively). However, it is impossible to determine a specific diagnosis by clinical observation alone, especially in the newborn period. (4) Thus, immediate treatment is the same for all infants based on clinical needs. Unfortunately, in most cases, it is not possible to determine the prognosis of affected infants because of significant variation in disease severity, even among patients with the same genetic mutations. One exception is a diagnosis of JEB-severe that has a nearly uniformly poor prognosis with an average expected lifespan of 5 months. (5)(6) An important unmet need is to correlate the EB genotype with the phenotype and prognosis.

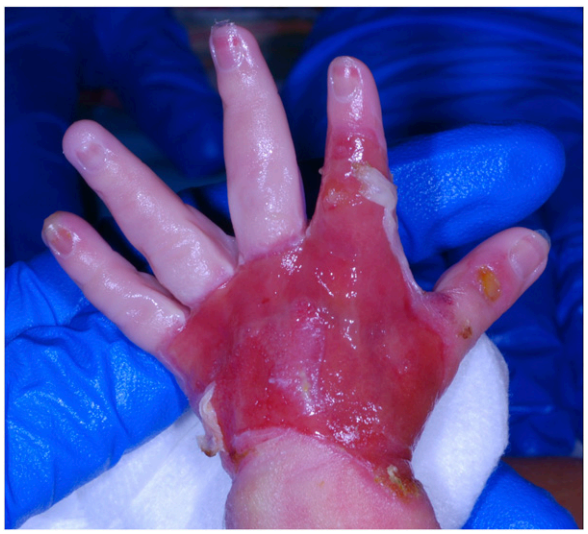

Figure 1. Aplasia cutis congenita (ACC) in a neonate with EB. ACC affects most of the dorsal surface of the hand in this neonate with recessive dystrophic EB. ACC usually occurs on the extremities and is found in all subtypes of EB.

DIAGNOSIS OF EB

Physical Findings

The subtypes of EB are usually clinically indistinguishable in the neonatal period. (7)(8) Common to all subtypes of EB are findings of skin fragility, blisters, and erosions that may develop shortly after birth as well as aplasia cutis congenita (missing skin at birth) (Fig 1). Blisters and erosions can be widespread or localized to sites of mechanical trauma. It is usually not possible to determine the EB subtype and thus, a prognosis cannot be established based solely on the affected neonate's physical examination findings.

However, several subtle clues in the newborn examination may hint at a diagnosis of the EB subtype before definitive testing results are obtained. For example, lack of lingual papillae may be seen in RDEB (9) and the presence of granulation tissue around the nails is a sign of severe JEB (Fig 2). (10) Involvement of the airway, because of granulation tissue or structural abnormalities, with some infants requiring a tracheostomy, can be found in patients with severe JEB. (11) Pyloric atresia is observed in patients with JEB who have mutations in $\alpha6\beta4$ integrin and in patients with EBS who have plectin deficiency. These patients typically also have ureter and renal abnormalities, often with a severe and lethal outcome. (12) Other extracutaneous manifestations of EB such as anemia and pseudosyndactyly present later in life.

Differential Diagnosis

The differential diagnosis of EB is based on the findings of skin fragility and blistering. Infections such as staphylococcal scalded skin syndrome, bullous impetigo, candidiasis, and herpes simplex may be ruled out with bacterial, fungal and viral cultures as well as potassium hydroxide preparations. Bullous mastocytosis and neonatal lupus can be diagnosed with a skin biopsy, including IFM. Neonatal pemphigus and pemphigoid can be present in infants born to mothers with these autoimmune conditions. Incontinentia pigmenti can present with blistering in the newborn period. Epidermolytic ichthyosis can mimic both staphylococcal scalded skin syndrome and EB and can be diagnosed with a skin biopsy and/or genetic analysis.

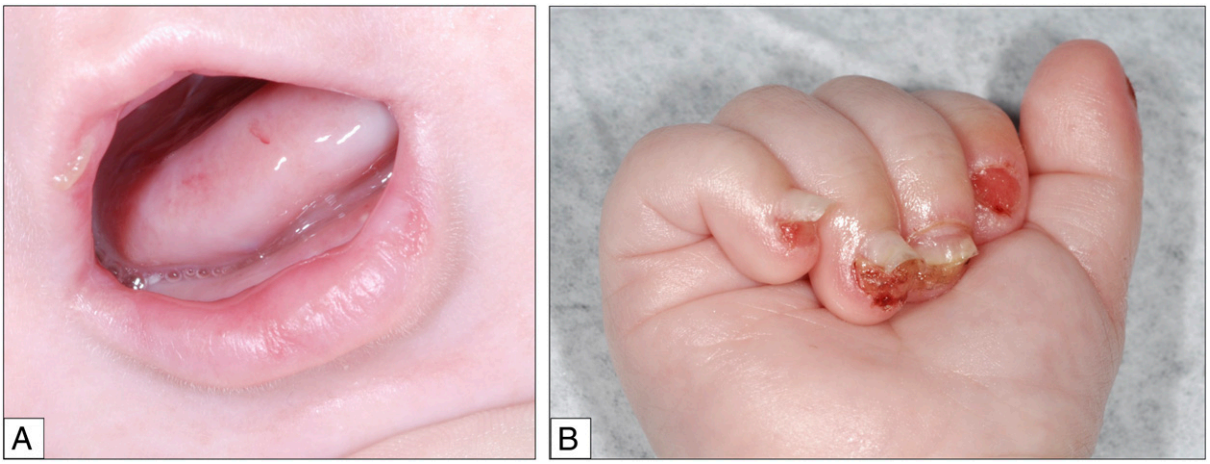

Figure 2. Physical clues to EB diagnosis. A. The absence of lingual papillae is a clue to the diagnosis of recessive dystrophic EB. B. Granulation tissue in and around the nail bed can be seen in severe junctional EB caused by mutations in laminin 332.

Sucking blisters are common on the radial forearm, wrist, hands, and fingers. (13)

Family History

The diagnosis of EB and elucidation of the EB subtype are aided by obtaining a detailed family history. It is crucial to ask about family members who carry a diagnosis of EB as well, because those individuals who tend to blister easily or have nail abnormalities may have gone undiagnosed, as these can signal mild forms of DDEB. (14) A family with a known history of a dominant condition such as EBS or DDEB will not be surprised by the same diagnosis in their newborn and will not have a steep learning curve to care for their child's skin condition. Lack of family history is also a clue to a diagnosis of either a recessive type of EB or a de novo mutation.

Diagnostic Studies

A definitive diagnosis of EB and the EB subtype is obtained via genetic mutation analysis or skin biopsy for IFM and EM. It is imperative to establish an accurate diagnosis as there are extreme differences in the care and outcomes of patients along the spectrum of EB: from severe generalized disease with a poor prognosis to mild localized disease. However, a diagnosis of the type of EB does not always predict the prognosis. It is important to set expectations with an affected family, and in severe cases, assist the family in decision-making about the extent of care to be provided. (6)(15)(16)

Current published recommendations for neonatal diagnosis are to obtain a skin biopsy for IFM and a blood sample for genetic testing to be run in parallel. (7) However, in practice, many clinicians are now first performing genetic testing, reserving biopsies only to clarify subtypes. (17) For example, 2 mutations in 1 of the laminin 332 genes is consistent with a diagnosis of JEB, and a complete absence of laminin 332 on IFM predicts a usually fatal outcome in early life. (18)

GENETIC TESTING. Genetic testing is recommended to definitively establish the diagnosis of EB and should be performed by laboratories with expertise in the identification of EB genes. (7) As noted before, genetic testing is quickly becoming the new standard for EB diagnosis. (17)(19) Samples for genetic testing may be obtained via blood, saliva, or tissue. Each of the methods described herein can be used to identify pathogenic EB mutations. Genetic counseling is recommended for all families who have a child with EB.

Sanger sequencing (SS) for mutations within specific genes was the first method used to identify pathogenic mutations that caused EB. SS uses polymerase chain reaction amplification to evaluate the coding regions and the exon/intron boundaries of a specific gene. SS may fail to detect mutations in nonexamined genes, as well as mutations causing large deletions, and mutations within introns. SS for EB diagnosis is now typically used to confirm genetic mutations identified via NGS of targeted EB panels. (7)(20)

NGS allows for parallel sequencing of multiple genes using a single sample and can be performed using targeted gene panels, (20)(21)(22) whole-exome sequencing, (23)(24)(25) or transcriptosome analysis (RNA-Seq). NGS-targeted gene panels typically have a turnaround time of 1

month, are more cost-effective than SS, and are able to assess multiple potentially causative genes at once. Specific individual mutations are subsequently confirmed via SS.

If mutations are not identified via NGS or SS, whole-exome sequencing may be performed. Whole-exome sequencing is more expensive than NGS but may identify novel genes with mutations resulting in EB. However, it may be difficult to determine which identified mutations are indeed causative versus so-called "noise." (7)

Ultra-rapid targeted genomic sequencing and whole genome sequencing are new techniques that can be used to screen for over 1,700 genes related to genetic conditions, with results available in as few as 3 days. (26) The most common genes affected in EB are included in these commercially available panels. (27)(28)

RNA-Seq is a technique that allows for quantification of the transcribed RNA and is useful for evaluating the outcomes of splice site mutations or variants of unknown significance. (7)(29)(30) This technique is currently available only in certain specialized academic centers and not currently available commercially.

Once a genetic diagnosis has been established, carrier testing in which the mutation is confirmed can be performed in the biological parents. Parental testing is useful to fully understand the inheritance pattern, particularly to elucidate de novo cases, and to assess risks for future pregnancies. Carrier testing is typically performed using SS.

SKIN BIOPSIES. Analysis of skin biopsies via IFM and/or EM was previously the gold standard for diagnosis of EB and EB subtypes. (7) Biopsies carry the advantage of obtaining results faster than traditional genetic testing, which may be helpful for providing guidance and prognosis to an anxious family. (31) However, skin biopsies can be tricky to perform, and the usefulness of the results depends on the biopsy technique. Furthermore, skin biopsy results are frequently equivocal. (17) Hematoxylin-eosin staining is not recommended to diagnose EB but may be used to diagnose other conditions that remain in the differential for blistering diseases of the newborn. (7)(8)

Skin biopsy specimens should be obtained from nonblistered, nonacral skin, which is rubbed with a pencil eraser just until erythema results, but not so much as to tear the skin. This can be achieved by placing the eraser against the skin with firm pressure, then rotating 180 degrees in each direction 3 to 10 or more times. This technique induces a microscopic blister, which will allow for evaluation of the level of dermal-epidermal separation. The biopsy specimen should include about half of this induced blister, with the remaining portion on uninvolved skin. Typically, a 3- to 4-mm punch biopsy specimen is obtained for IFM, and the sample is placed in Michel media. The sample should be sent for processing as soon as possible. A 2- to 3-mm punch biopsy sample may also be obtained for EM and placed in EM fixative, which contains glutaraldehyde. Samples should be sent to laboratories with expertise in the diagnosis of EB. (7)(8)(13)

IFM helps determine the level of blister formation as well as quantification of the various proteins that may be decreased or absent in EB. (31) However, samples must be sent to a pathology laboratory capable of measuring all of the EB-related proteins (Table 1). This type of mapping is only done in a few institutions and must be specified, because it is not the same as the immunofluorescence technique used routinely for autoimmune blistering diseases.

EM allows for visualization of the blister level and also the ultrastructural components of the skin. EM can be useful when IFM and/or genetic testing are inconclusive. For example, absent anchoring fibrils are characteristic of severe RDEB whereas clumped keratin within the basal layer is seen in the severe subtype of EBS. (7)(32) EM is expensive and requires expertise in both sample preparation and interpretation.

SKIN CARE OF THE INFANT WITH EB

The unexpected and presumed diagnosis of EB in a neonate presents a challenge on multiple levels for everyone involved in the initial care of the infant. Although there are published guidelines for general skin care in EB, (33)(34) none are focused solely on the newborn period. Consideration must be given to the potentially overwhelming nature of this care and the need to modify/simplify the routine. With this in mind, basic and safe recommendations should be considered when developing an individualized care plan for an infant.

Wound care in EB has 3 main components: a contact layer, a secondary layer, and securement of the dressings. As Fig 3 shows, products for each layer may overlap in their intended functions. Individualization of the dressing process is critical to success and effectiveness of the care as well as promoting confidence in the caregivers' ability to apply appropriate dressings on their child's skin.

Contact layer dressing products have direct contact with the skin and wounds. They are often silicone-based and nonadherent and can be used with or without emollient or topical antibacterial agents. Secondary layer dressing products are placed over the contact layer to absorb drainage, promote movement of drainage away from the wound, or

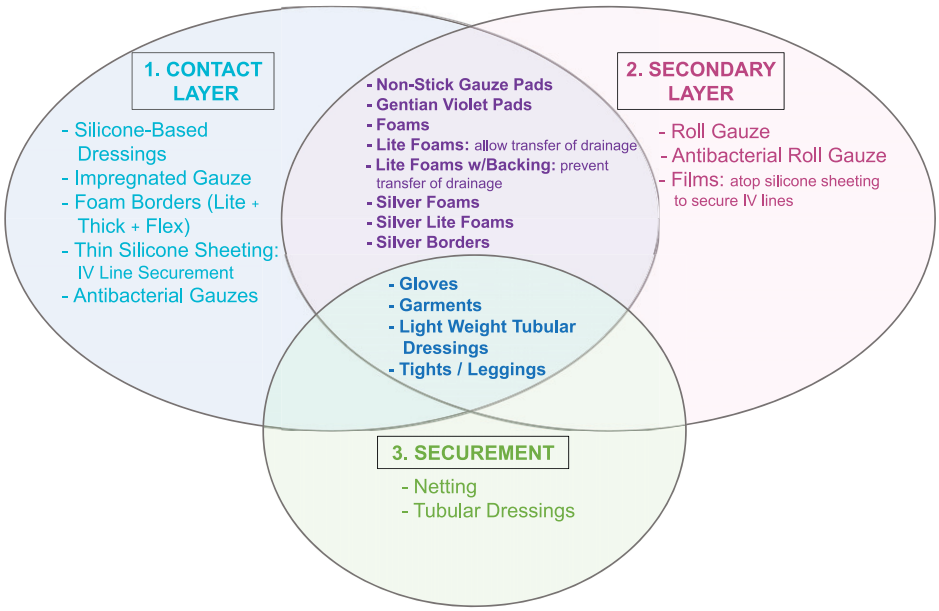

Figure 3. Venn diagram of dressings for patients with EB. Layers required for EB wound dressings are depicted. As illustrated in the image, some products have "overlap" and can be used effectively for multiple purposes.

add padding for protection. Securement dressing products are used to hold the contact and secondary layers in place.

A contact layer of 1 × 36" strips of petrolatum-impregnated gauze cut into shorter strips with added petrolatum or Aquaphor® is applied to the affected areas, wrapping from the distal to proximal skin. If the petrolatum-impregnated gauze starts to fray at the edges or consistently adheres to wounds, a thin foam silicone dressing can be substituted as the contact layer. This foam dressing should be cut into long strips and applied as a roll gauze. Other appropriate dressing products are also promoted as contact layer choices, though some lack the necessary flexibility for an infant's small frame.

The secondary layer consists of a 1" soft roll gauze for extremities and a 2" soft roll gauze for the torso and scalp, which is placed over the contact layer. The contact layer should be left slightly visible at the ends of the dressing, because roll gauze in direct contact with the skin may cause blisters or wounds. It is desirable for the roll gauze to be soft, conforming, and free from strings, which is a common characteristic in burn care products.

Securement is the third essential dressing layer. Securement of the contact and secondary layers prevents these dressings from sliding and shearing the skin, subsequently causing more blisters and wounds. Choice of securement layer product includes soft fabric or elasticized mesh tubular dressings.

When caring for an infant, the response to the dressings must be evaluated during each dressing change and modifications to the dressing regimen should be made as indicated. Potential responses that should prompt a revision to the routine could include increased blistering at the edges of the dressing, wound maceration, increased blistering in general, worsening exudate, infection, or poor healing. In addition, some infants respond poorly to any dressing or excessive application of emollients, often seen in EBS, which would lead to care modifications and changes in wound management.

Emollients used in routine dressing changes may include Aquaphor, petrolatum, coconut oil, or other nonmedicated lubricants. These products should be smeared in a thin layer onto the contact layer, rather than directly onto the wound. This technique prevents shearing of the surface of the skin/wound. At each dressing change, it is important to assess both the efficacy of the amount used and frequency of application. Many caregivers have a tendency to overlubricate, which can lead to maceration, increased blistering, and movement of the dressings. Nonprescription strength ointments are used as medically necessary and may include topical antibiotics (eg, Polysporin® bacitracin), and medical-grade honey. Prescription strength topical antibiotics such as gentamicin, silver products, mupirocin, or retapamulin may be considered for infections.

Blisters of at least pencil eraser size (5 mm) should be lanced and drained as they develop. A needle or lancet may be used, puncturing the blister and gently decompressing it with gauze. The roof of the blister should not be removed. (35)

Typically, dressing changes are recommended every other day, though daily changes may be necessary initially. All anticipated dressing products should be precut, lubricated, and arranged on a work surface before old dressings are removed from the infant's skin. The dressing change is best completed 1 limb at a time, because of the tendency for movement and the potential for self-damage. Initially, an affected infant can have a sponge bath, rinsing gently using a syringe. Eventually, the infant can be safely immersed in a bath (before a dressing change) with proper care to prevent self-damage from moving arms and legs.

Diapers may lead to blistering and wounds or the infant may have an innately severely affected diaper area. Aquaphor or petrolatum should be applied to the diaper edges. Alternatively, a thin foam product may be cut to shape and used as a liner. This liner should be well-lubricated with an emollient. Often the diaper elastic around the legs is cut out from the diaper. Cloth diapers have not been found to be more beneficial. (36) Commercial wipes should not be used. Rather, it is recommended to gently cleanse the skin of the diaper area with soft gauze or cotton balls, moistened with water or mineral oil.

The occipital scalp may require special care, as the infant's natural movement can create extensive wounds. Additional lubrication and placement of a foam dressing product on the bedding for the head to rest on, may be necessary for wound protection of this area.

Affected newborns require modification of their bedding to provide them with cushioning and decrease pressure on their fragile skin. This varies institutionally and products such as "Z-Flo mattresses," sheepskin, and air mattresses can be used. Areas of skin in contact with the bedding surface may require emollient application to reduce friction and decrease potential damage. Temperature regulation is driven by medical need with the consideration that heat may increase blistering. Modification of dressings and emollient may be needed. Infants in isolettes or under therapeutic lights need special monitoring to assess for worsening skin findings. These infants can, and should, be held by their caregivers if deemed medically appropriate.

Families should be encouraged to dress newborns with EB. Clothing should be made of soft material and may be turned inside out so that seams do not rub against the skin. Some specialized clothing with seams on the outside is available. The infant's tolerance for clothing should be observed, and changes should be implemented as appropriate.

Parents are an integral part of the care team. As wound care routines change, sometimes daily, they must be assessed for understanding, comfort, and confidence.

NUTRITION

Adequate nutrition in the newborn period is essential. Infants with EB not only have baseline nutritional needs of a newborn, but also require extra calories for adequate wound healing. However, there are several barriers to adequate nutrition. First, mucosal fragility leads to oral blisters and erosions. If these are painful, infants will refuse to suck and may not learn to suck appropriately if they are unable to feed for prolonged periods. Second, many infants with EB develop gastrointestinal reflux disease, which can cause painful damage to the epiglottis and posterior pharyngeal mucosa. Third, as a result of pain as well as anemia from chronic blistering, some infants become too weak to sustain adequate oral nutrition. Solutions include coating of the oral mucosa with sucralfate, which can be soothing, and more rapid-flow, soft nipples (such as the Haberman nipple).

If oral feeding becomes inadequate, other nutritional options include total parenteral nutrition using peripherally inserted central catheters, or in young neonates, umbilical catheters for a temporary period. Such catheters must be placed and secured carefully using a special fragile skin secure dressing. It is imperative to refrain from applying adhesive materials, which can tear the fragile skin when removed, causing further cutaneous injury (Fig 4). The basic dressing should have a nonadherent thin pad (such as a silicone-based product like Mepiform®) applied directly on the skin to which the line can be securely taped. Use of a silicone-based tape such as Mepitac® is helpful. If possible, orogastric and nasogastric tubes should be avoided; these tubes may cause further oral and pharyngeal erosions and esophageal trauma, which can accelerate the development of esophageal strictures later in life in dystrophic forms of EB. (37)(38) Feeding tubes are also difficult to secure because of skin fragility. Gastrostomy placement is another solution that can be lifesaving, but it is associated with risks inherent to surgery under anesthesia at a young age and difficulty maintaining intact skin around the stoma site.

INFECTION

Any areas of denuded skin will inevitably become colonized with bacteria. It is impossible to "sterilize" such erosions, and as long as they are asymptomatic, treatment is not necessary. Overuse of topical antibiotics may result in selection of resistant organisms. (39) Thus, bland emollients such as white petrolatum, or ointments such as Aquaphor or Dermaphor®, and antimicrobials such as or silver-impregnated dressings or topical applications of medications (eg, medical-grade silver gels or honey), are preferred. When wounds become

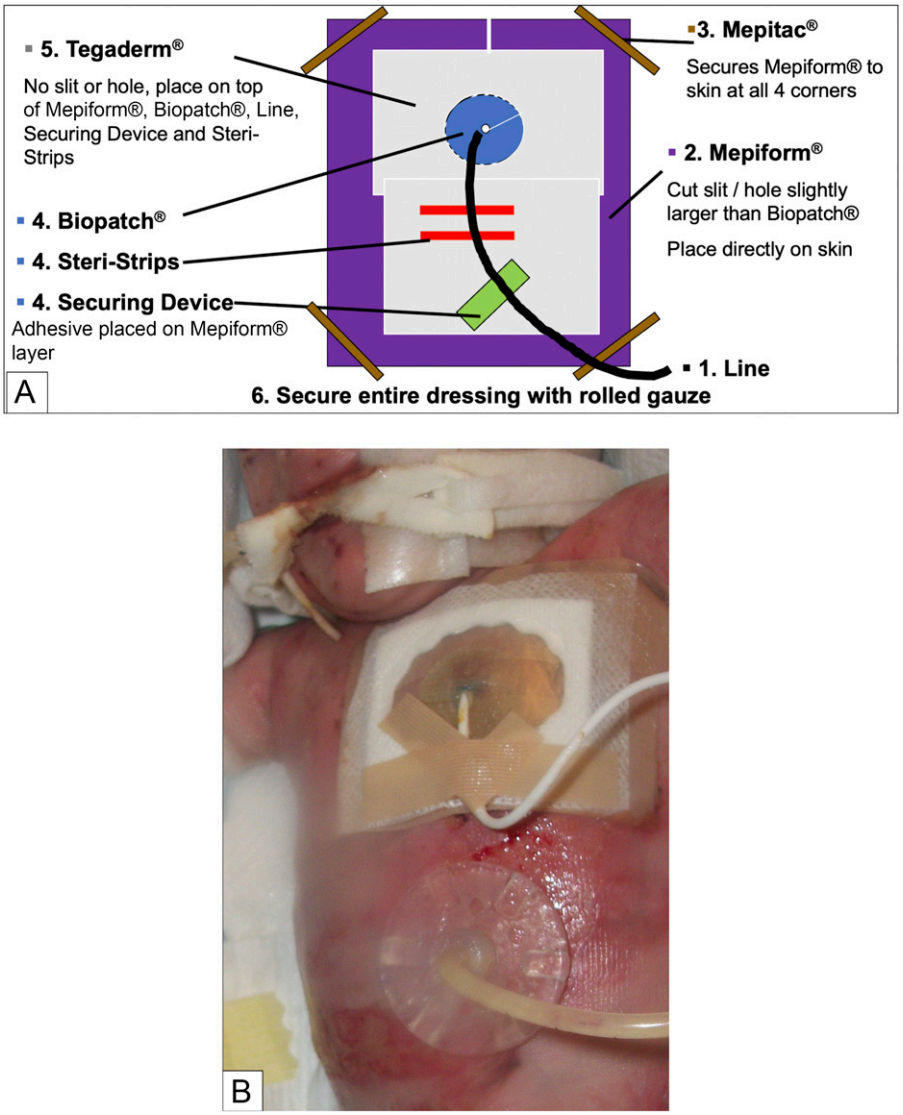

Figure 4. Securing lines in patients with EB. A. Diagram shows an appropriate method to secure lines in patients with fragile skin using silicone-based dressings instead of adhesives. B. This photograph shows a secured central venous catheter on the chest of a neonate with severe junctional EB. This very sick infant required gastrostomy and tracheostomy tubes and, unfortunately, did not survive.

erythematous and tender or have increased exudate, especially if accompanied by fever in the newborn, treatment with appropriate topical or systemic antibiotics is warranted. In older children with EB, the most common colonizing organisms are *Staphylococcus aureus* (both methicillin resistant and methicillin sensitive), *Streptococcus pyogenes,* and *Pseudomonas aeruginosa*. (39) There has not been a microbiome study to date in neonates with EB. During hospitalization, we highly recommend surveillance cultures with sensitivities in affected infants every few days so that if and when signs/symptoms of infection appear, treatment choice can be optimized.

In severe forms of EB, especially JEB (although any type can be affected), typical signs of sepsis such as fever, change in appetite, or lethargy should be addressed rapidly. Growing evidence suggests that thymic development is compromised in patients with JEB because of absence of laminin 332. (40) Rapid and often fatal sepsis is not uncommon.

AIRWAY

Airway compromise can be a life-threatening feature of EB, especially in patients with JEB-severe. Other subtypes of EB can also manifest with airway dysfunction with typical symptoms of stridor, a hoarse or weak cry, and ultimately hypoxemia. Causes include excess granulation tissue (in JEB), tracheomalacia, "floppy" arytenoids, or blister formation in the upper airway. (41)(42) In all types

of EB, acid from gastrointestinal reflux disease can affect the epiglottis and posterior pharynx, resulting in respiratory compromise. Evaluation of the airway requires an experienced otolaryngologist and must be performed with caution because of the inherent fragility of the mucosa. Radiographic imaging is a safe way to evaluate the airway. Monitoring for hypoxemia can be a challenge, and any adhesive material must be removed from pulse oximeters; instead, oximeters can be secured via nonadherent methods by using Velcro® or Mepitac.

PAIN MANAGEMENT

Infants can experience significant pain from eroded skin, particularly during dressing changes. Pain control often requires narcotics, but with time, infants can be weaned to nonsteroidal anti-inflammatory drugs or acetaminophen. Simple measures such as sucking on a sugar water–sweetened nipple may afford some relief. (43) It should be noted that because of oral blisters, the use of a soft nipple, such as a nipple made for premature infants or the Haberman nipple, for administration of sugar syrup is crucial.

CARE OF THE FAMILY

The immediate reaction of most families confronted with a child diagnosed with EB is usually shock and guilt. If there is no previously affected family member, most people have not heard of this diagnosis. EB is often referred to as "The Worst Disease You Have Never Heard Of." (44) Searching the internet usually confronts families with frightening photos and descriptions of the worst outcomes for children with EB. Many parents blame events that may have occurred during pregnancy and, when they are informed that this condition is genetic, bear an undeserved burden of guilt. Taking the time to listen to a family's questions and feelings about the diagnosis of EB is important so that parents can feel reassured that their child's condition is not caused by anything that they did or did not do and was not preventable.

It is important to note that although it is necessary to establish a genetic diagnosis to better predict future issues that might arise, it is usually not possible to predict the severity of each individual case. Because it may take several weeks to receive a molecular genetic diagnosis, it is imperative to reassure families that routine care during this waiting time is not dependent on diagnosis. Prenatal testing can be discussed with parents for purposes of future family planning at a later date.

In this era of social media, many supportive parent groups exist online. Families will be confronted with unsolicited advice of varying degrees of benefit and sometimes harm. Building trust with families to assure them that as an informed medical professional, you will be available to discuss what they encounter online is vital at this stage.

Table 2. Interdisciplinary Specialties Caring for the Newborn with EB

Specialty	EB Sequelae Management
Dermatology	Wound care, skin/wound infections, overall EB care coordination
Neonatology	Overall care when hospitalized
Primary care	Overall care as outpatient
Ancillary services	
Nursing	Dressings and feeding
Nutrition	Adequate calories, micronutrients, vitamins
Social services	Access to care and financial resources
Occupational therapy	Feeding education
Physical therapy	Contracture prevention
Medical specialties	
Gastroenterology	Gastroesophageal reflux disease, gastrostomy tube management
Pathology	Diagnosis of EB
Hematology	Anemia
Ophthalmology	Corneal abrasions
Infectious diseases	Wound infections, sepsis
Radiology	Diagnosis of pyloric atresia, infections, line placement
Anesthesiology	Advanced airway placement
Pain management	Pain, itch management
Palliative care	End of life care, decision-making for gastrostomy tube/tracheostomy placement
Surgical specialties	
General pediatric surgery	Tracheostomy or gastrostomy tube placement
Plastic surgery	Skin grafting for aplasia cutis
Otolaryngology	Tracheostomy/airway stenosis evaluation and management

Finally, in some cases, such as extensive aplasia cutis congenita or a diagnosis of JEB with evidence of complete absence of laminin 332, a rapidly progressive course involving respiratory failure or inability to sustain adequate nutrition, difficult discussions about the extent of life support and comfort care may be needed. Common dilemmas also include whether to place a tracheostomy and/or feeding gastrostomy. In these situations, collaboration with a palliative care team and/or hospital chaplain are invaluable.

ROLE OF EB CENTERS AND RESOURCES

Although in mild cases most NICUs can handle the medical needs of infants with EB, EB centers across the United States see large numbers of such patients. Transfer of affected infants to 1 of these centers may be appropriate in some cases. However, most EB centers can also provide remote advice and education to physicians and staff, as it can be quite disruptive to transfer families away from their home support systems. The EB centers usually employ specialists in all areas likely to be called upon for EB care. These specialists are familiar with how to handle the special needs of infants with EB. The specialties usually involved are listed in Table 2.

Teaching families to be comfortable with all aspects of their newborn's EB care before discharge from the hospital is essential. This work may include helping families to secure home health care, connecting families to appropriate durable medical equipment providers to obtain the financial coverage of their bandage and/or feeding supplies. (45) Securing available state (eg, Medicaid or state-supported programs for handicapped children) as well as federal financial support (eg, Social Security) can be lifesaving. Referral for ongoing visits to an EB center after discharge is an ideal solution to complement routine medical care.

In addition to EB centers, online resources are available, such as the many country-specific Dystrophic Epidermolysis Bullosa Research Association (DEBRA) groups. These include DEBRA of America (www.debra.org) and DEBRA International (www.debra-international.org). These sites contain excellent supportive material to educate families and medical professionals, help for families to navigate the resources available for home care of their infant, and reports of clinical and scientific meetings and publications. In particular, DEBRA International has sponsored a series of "Guidelines of Care" prepared by international teams. (46) These organizations sponsor national and international meetings, some of which welcome families to participate. In addition, many have robust development programs that are intended to fund EB research. With rapid advances in research on EB, clinical trials of several wound-care treatments are currently ongoing, as well as topical, parenteral, and transplant molecular and gene therapies for EB. (47)(48)(49)

Summary

EB is a group of rare genetic disorders that lead to fragile skin. Because of the skin blistering and other complications of EB, affected infants are often referred to NICUs. Familiarity with the genetic classification and characteristics of the different types of EB; understanding the basic principles of wound care; and being aware of the potentially associated complications such as poor nutrition, infection, airway obstruction, and pain are essential for the neonatologist treating these patients. Caring for all the emotional and financial consequences of EB with the family is necessary for a successful transition home. Collaboration with EB centers and other resources in the local, national, and international community can be very helpful in the care of these infants and their families.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the inheritance patterns, cutaneous and laboratory manifestations, management, and outcome of epidermolysis bullosa.
- Know the management of bullous skin lesions in the newborn infant.

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NEO QUIZ

1. A male term infant is noted to have multiple blisters and fragile skin 1 day after birth. Epidermolysis bullosa (EB) is suspected. Which of the following statements regarding classification of EB is correct?

   A. The most current classification of EB is based solely on clinical features.
   B. EB simplex is the subtype characterized by abnormal or missing proteins located in the epidermis.
   C. Junctional EB is characterized by abnormal proteins below the dermis.
   D. The main classification is based on whether the inheritance pattern is dominant (dominant EB) or recessive (recessive EB).
   E. The 5 subtypes of EB are named after each of the 5 geneticists who discovered the primary gene responsible for each subtype.

2. A newborn male term infant is noted to have blistering of the skin and also found to have emesis and feeding intolerance soon after birth. Which of the following conditions is found in EB caused by PLEC1 or $\alpha 6\beta 4$ integrin mutations?

   A. Hirschprung disease.
   B. Lactose intolerance.
   C. Annular pancreas.
   D. Necrotizing enterocolitis.
   E. Pyloric atresia.

3. A newborn female has skin fragility, blisters, and skin erosions that appear during the first few days after birth. There are signs that this may be a severe case of EB. Which of the following physical findings or signs in the newborn period would indicate a stronger likelihood of recessive dystrophic EB?

   A. Anemia and thrombocytopenia.
   B. Absence of any fingernails or toenails.
   C. Lack of lingual papillae.
   D Presence of granulation tissue around the nails.
   E. Involvement of airway leading to tracheostomy requirement.

4. A 5-day old infant who has been diagnosed with EB is being cared for in the NICU. Which of the following aspects of care would be most appropriate?

   A. The optimal wound care in EB involves air exposure with avoidance of any emollients or dressings.
   B. Contact layer dressing products are best when adherent and always have a broad-spectrum antibiotic component.
   C. When skin wound dressings are applied, securement should be avoided as dressings should be easily maneuverable without inhibition.
   D. When emollients are used, they should not be applied directly onto the wound, but rather smeared into a thin layer onto the contact layer.
   E. The main anti-infective agent to be applied for an infection is metronidazole.

5. Nutrition is a critical component of caring for newborns with EB because of their increased caloric and other nutritional needs. Which of the following statements most appropriately describes supplemental nutrition for patients with EB when oral feeding is inadequate?

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A. Parenteral nutrition is contraindicated in all cases of EB because of the potential for adverse events.

B. If catheters are placed, it is imperative to refrain from applying adhesive materials, which can tear the fragile skin when removed.

C. Because almost all patients with EB will have inadequate feeding, an orogastric tube should be placed immediately after diagnosis or suspicion of diagnosis.

D. Umbilical catheters can be kept in infants with EB for a prolonged period, up to 1 month, compared with other infants without risk of infection.

E. Infants with EB should be fed soy-based formula to minimize their risk of later developing other skin disorders such as eczema.