***no patient handout*

Epidermolysis bullosa simplex

Synopsis

Epidermolysis bullosa (EB) refers to a group of genetic diseases characterized by blistering in response to minor trauma. It is divided into three major categories based on the depth of skin blistering: (1) EB simplex (intraepidermal skin separation), (2) junctional EB (skin separation within the lamina lucida), and (3) dystrophic EB (sublamina densa skin separation). A fourth major type that recently has been proposed encompasses Kindler syndrome, since that genodermatosis shares with the other three major EB types the presence of mechanically fragile skin and blisters that, in contrast to all other EB types, typically have cleavage planes within multiple levels of the basement membrane zone. Although, in general, individual EB subtypes vary in their overall clinical severity by mid-childhood or early adulthood, each may present with similar clinical features during the neonatal period. As such, accurate subclassification may not be possible until later in infancy or childhood, when characteristic phenotypic features become more apparent.

EB simplex is the most common form of EB. It is most often caused by mutations within the genes encoding for keratins-5 and -14, with the vast majority being autosomal dominantly transmitted. There are two major types of EB simplex, basilar and suprabasilar, based on the ultrastructural site within which blisters arise. Most subtypes are basilar. On the basis of collective clinical findings, in conjunction with ultrastructural and molecular data, basilar EB simplex is further divided into three main subtypes. (1) Localized EB simplex (EBS loc; formerly known as EB simplex Weber-Cockayne), the mildest EB simplex subtype, is associated with blisters primarily limited to the palms and soles. (2) EB simplex Dowling-Meara (EBS-DM; also known as EB simplex herpetiformis) is a severe subtype characterized by widespread blistering, herpetiform or arcuate grouping of blisters, possible internal organ involvement (to rarely include the upper airway), and the potential for death in the neonatal period. And (3) generalized EB simplex, other (EBS-O), is an EB simplex subtype having more widespread cutaneous involvement than EBS loc but little or no extracutaneous disease activity.

In the mildest cases of EB simplex, first signs may not develop until the child begins to walk or crawl, whereas large bullae and erosions are usually present at birth or within the first days of life in infants having a generalized EB simplex subtype. All forms of EB simplex worsen in hot, humid environments, and most improve with age. Treatment is supportive.

There are some patients with a dominant mutation that promotes ubiquitination and excessive proteolysis of *KRT14*.

For more information, see **OMIM**.

Codes

ICD10CM:
Q81.0 – Epidermolysis bullosa simplex

SNOMEDCT:
67144006 – Epidermolysis bullosa simplex

Look For

When evaluating a patient with inherited EB, it is important to realize that there may be considerable overlap in clinical findings among the subtypes, especially during infancy and early childhood. On initial evaluation, all children should have a full physical examination, with special emphasis placed on the external eyes, oral cavity (both soft and hard tissues), gastrointestinal tract (most notably the esophagus), genitourinary system (to include not only the urethra but also the ureters and kidneys), hands and feet (webbing or mitten deformities), and upper respiratory tract (with its earliest signs being persistent hoarse cry or stridor). Evaluation of more generalized EB subtypes should also include surveillance for early growth retardation and/or multifactorial anemia.

As in all patients with inherited EB, all subtypes of EB simplex are associated with vesicles and bullae that are tense and painful. The vesicle contents may be dark (hemorrhagic) or clear (serous). Unless punctured and drained, intravesicular hydrostatic pressure tends to cause these painful vesicles to gradually expand. Lesions tend to heal without scarring or atrophy, although either may be seen in more severe EB simplex subtypes. Recurrent palmar and plantar vesiculation may lead to confluent callus-like epidermal thickening and lichenification (keratoderma) in patients with EBS-DM.

EBS loc – This subtype may not be diagnosed until the child begins to walk. Tense vesicles and bullae (less than 2 cm in diameter) form primarily on the palmar and plantar surfaces of the hands and feet. It is possible, however, for blisters to arise on any skin surface in patients with EBS loc if their skin is stressed enough. Other body sites, most notably the nails and extracutaneous tissues, are almost never affected, although about 25% of patients may still develop limited blistering within the oral cavity during early childhood.

EBS-O – Large bullae and erosions initially develop at birth or shortly thereafter. In contrast to EBS loc, more widespread blistering and erosions occur, although interestingly the palms and soles are less frequently involved than in patients with EBS loc. A higher frequency of localized scarring and nail dystrophy occurs, although extracutaneous disease activity, other than oral cavity blistering, is virtually never seen.

EBS-DM – Widespread bullae and erosions may develop at birth, secondary to trauma during delivery and handling in the nursery. Milia, atrophic scarring, and nail dystrophy are common with increasing age. During periods of relatively mild disease activity, it is usually possible to identify the pathognomonic grouping of vesicles ("herpetiform"), sometimes in arcuate array, arising either on normal-appearing or erythematous skin. Mucosal involvement is common, leading to interference in feeding (secondary to oral cavity pain) and, less frequently, a hoarse voice and weak cry (secondary to laryngeal involvement) and marked gastroesophageal reflux. Over time, patients with EBS-DM develop characteristic confluent thickening of the palms and soles. Some degree of growth retardation and multifactorial anemia are also common in these

patients.

For more detailed information on this subtype, see Epidermolysis bullosa simplex, Dowling-Meara (Epidermolysis bullosa simplex herpetiformis), in VisualDx.

Diagnostic Pearls

Parents, siblings, and relatives should also be questioned and examined, as most EB subtypes are autosomal dominantly inherited.

Many families with EBS loc may not consider their children to have a significant medical problem, given its presence within multiple generations of the family and the relatively localized nature of the blistering in most.

Rarely, disease activity may not present itself in some of these patients until adolescence or adulthood, when blistering interferes with strenuous activities such as contact sports and military training.

Differential Diagnosis & Pitfalls

- EB simplex may be mimicked by bullous **tinea pedis**
- **Bullous pemphigoid**
- **Dyshidrotic dermatitis**
- **Insect bites**
- **Linear IgA dermatosis**
- **Pemphigus vulgaris**
- **Epidermolysis bullosa acquisita**
- Common **friction blisters**
- Burn (see **thermal or electrical burn**; chemical burns are covered separately, by chemical agent)
- **Porphyria cutanea tarda**
- **Variegate porphyria**

Best Tests

Skin biopsies from the edge of a freshly induced blister should be sent for immunofluorescence antigenic mapping and/or electron microscopy to confirm the diagnosis and more precisely establish the subtype.

Genetic testing is available.

Management Pearls

Patients with milder forms of EB simplex (EBS loc and EBS Koebner subtype) often have long family histories of the disease, and will already be well aware of provoking factors, avoidance strategies, and blister care. The primary role of the dermatologist is to ensure that patients are properly informed in skin care, treat secondary infections, perform surveillance for possible extracutaneous involvement (especially important in EBS-DM), and serve as a resource.

The Dystrophic Epidermolysis Bullosa Research Association of America (DebRA-US), DebRA-UK, and its international counterpart DebRA-International all provide excellent Web-based resources containing extensive information, assistance, and support to patients, families, and health professionals.

Other management recommendations:

- Keep the skin dry and reduce friction by using fragrance-free absorbent powders, such as talc. Although somewhat controversial, some patients with EBS loc may benefit from application to the palms and soles of agents used to reduce sweating, such as Drysol, especially if sweating appears to exacerbate blister formation.
- Both adults and children with EB simplex, most notably EBS-DM, may experience recurrent blepharitis, bullous lesions of the conjunctivae, keratitis, scarring, visual impairment, and rarely even blindness. Any patient having ocular signs or symptoms should be immediately referred to an ophthalmologist.
- Patients with EBS-DM may have increased nutritional needs as a result of the cycle of ongoing generalized cutaneous injury and repair. Nutritional assessment and supplementation is often warranted.

Therapy

Treatment is supportive, since there is as yet no cure.

Avoidance of skin trauma is paramount. Consider padding for areas prone to friction and trauma, such as pressure points. Wounds should be covered with nonadherent dressings, such as Mepilex, Mepilex, Xeroform or hydrogels and held in place by roller gauze bandages (Kerlix, Kling) or elastic tube dressings (not adhesive tape).

For localized infection, treat with topical antibiotics (eg, mupirocin ointment, but only for a limited time, so as to prevent the overgrowth of resistant *Staphylococcus*). Different topical antibiotic preparations may need to be used on a rotating basis to avoid the emergence of resistant organisms. For generalized infection, treat with systemic antibiotics, especially ones having Gram-positive cocci coverage.

Several types of skin grafts have been used to treat the wounds of EB with some promising results, although these are rarely ever employed in EB simplex. These include split-thickness skin grafts, acellular human dermis (AlloDerm), tissue-engineered skin (Apligraf), and allogeneic composite cultured skin.

Tetracycline has been reported to help several patients with EB simplex in small trials.

Molecular, cellular, and proteins therapies may eventually provide more longstanding or even definitive treatment options for patients with EB in the future.