Hereditary epidermolysis bullosa: oral manifestations and dental management

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Abstract

Epidermolysis bullosa (EB) is a diverse group of disorders that have as a common feature blister formation with tissue separation occurring at variable depths in the skin and/or mucosa depending on the specific EB type. There may be marked oral involvement, potentially creating devastating alterations in the soft and hard tissues. Oral tissue fragility and blistering is common to all EB types. However, oral debilitation as a result of soft tissue scarring is primarily limited to the recessive dystrophic EB subtypes. Generalized enamel hypoplasia appears to be limited to junctional EB, although rampant dental caries is associated with many individuals having generalized recessive dystrophic EB. While systemic treatment remains primarily palliative, it is possible to prevent destruction and subsequent loss of the dentition through appropriate interventions and dental therapy. The majority of individuals with mild EB subtypes may receive dental treatment with only minor modifications in approach. Even the most severely affected individuals with EB can retain their dentition using general anesthesia and conventional restorative techniques. With aggressive preventive interventions and management of developing malocclusions using serial extraction, it also is possible to reduce the likelihood of rampant caries, achieve an acceptable occlusion without the need for active tooth movement or appliance therapy, and allow these individuals to benefit from maintaining a natural healthy dentition. (Pediatr Dent 15:242–47, 1993)

Introduction

Fragility and skin blistering are the hallmark features of the hereditary disorders classified as epidermolysis bullosa (EB). While the specific pathogenesis of these disorders remains unknown, bullae formation has been associated with numerous basic defects including structural and/or biochemical abnormalities of keratin, hemidesmosomes, anchoring fibrils, anchoring filaments, and physicochemically altered skin collagenase.[1–6] Recent genetics studies have linked one EB type to a keratin defect, while another type has been linked previously to the type VII collagen gene.[6,7] Although tremendous progress has been made toward understanding this diverse group of disorders, they continue to present a formidable challenge to medical and dental practitioners. During the 1980s, the National Institutes of Health established four regional institutional centers that were designated as clinical sites for the National Epidermolysis Bullosa Registry (NEBR). These centers were charged with advancing our understanding of the clinical, diagnostic, and laboratory characteristics of EB. Since the NEBR became operational in 1986 approximately 1600 affected individuals have been evaluated. As a result of these and other investigations our knowledge concerning the clinical characteristics and oral manifestations of the 23 different EB subtypes has increased markedly.[8] During the past decade there also has emerged a growing body of dental literature presenting successful anesthetic and dental management for individuals having even the most severe forms of EB.[9–11] In this manuscript we will review the current classification and clinical findings of the different EB types and discuss the implications and approaches for managing the systemic and oral manifestations.

Classification

As many as 23 distinct types of EB now have been recognized, each varying in its clinical appearance, extracutaneous involvement, mode of inheritance, and level of tissue cleavage. These subtypes are classified into three main groups based on the level of tissue separation that develops following mechanical trauma to the skin (Table 1).[8,12] Blistering occurs within the epidermis, within the basement membrane, or beneath the basement membrane in simplex, junctional, and dystrophic forms of inherited EB, respectively. The ultrastructural level of separation in blistered tissue is determined using transmission electron microscopy and/or immunofluorescence antigenic mapping.[13] Characterizing morphologic features—including the hemidesmosomes, anchoring fibrils, and subbasal dense plates and the relative expression of numerous basement membrane-specific antigens, such as type VII collagen, GB3, 19 DEJ-1, and chondroitin 6-sulfate proteoglycan—also are useful diagnostic aids in further delineating EB types and subtypes.[13,14]

Mode of inheritance and clinical features, such as the severity and distribution of cutaneous and extracutaneous findings, also are considered in the final classification of each EB subtype.[15] Hereditary EB subtypes may exhibit autosomal dominant or recessive modes of transmission, with the possible exception of the Mendes Da Costa variant of EB simplex, which is reported to be X linked.[8] To

Table 1. Ultrastructural site of tissue separation and common morphologic features of the major EB types

Major EB Type	*Site of Tissue Separation*	*Common Morphologic Features of Tissue*
EB Simplex	Within or just above the stratum basalis ("epidermolytic")	Cytolysis of basilar or suprabasilar keratinocytes
Junctional EB	Within dermoepidermal junction (intralamina lucida; "lamina lucidolytic")	Absence of or rudimentary appearing hemidesmosomes; reduced or absent subbasal dense plates
Dystrophic EB	Beneath the entire dermo-epidermal junction (sublamina densa; "dermolytic")	Reduced numbers of or absent anchoring fibrils

develop an accurate prognostic prediction and treatment approach it is imperative that clinicians managing EB patients are familiar with each subtype and its particular clinical presentation.

General clinical features

Cutaneous findings vary considerably and may include blisters, crusted erosions, milia, scarring, granulation tissue, pigmentation changes, cicatricial alopecia, and absence or dystrophy of nails.[8] Extracutaneous involvement may include the eyes, teeth, oral mucosa, esophagus, intestinal tract, anus, genitourinary tract, and/or musculoskeletal system.[16] In general, specific EB subtypes will have characteristic combinations of cutaneous and extracutaneous features, although there may still be considerable clinical variation in the type and severity of manifestations (Table 2).

Some clinical features are characteristic of one or a few specific EB subtypes such as the pathognomonic finding of extensive perioral granulation tissue seen in the Herlitz variant of generalized junctional EB (Fig 1 and Fig 2).[17,18] These lesions develop during infancy and may heal with atrophic scarring without specific treatment during young or mid-adulthood. In some severely affected individuals these lesions may encompass nearly the entire face, extending as far as the eyes and nasal bridge and may even lead to partial or complete obstruction of the nares. The development of digital webbing with mitten-type defor-

Table 2. Clinical features of inherited epidermolysis bullosa variants*

EB Type	*Subtype*	*Inheritance*	*Age of Onset*	*Distribution*	*Scarring*	*Mechanical Fragility*	*Growth Retardation*
Simplex	Localized (Weber-Cockayne)	AD	0–4 yr	Palms/soles	Rare	Rare	Absent
Simplex	Generalized (Koebner)	AD	0–2 yr	Extremities > elsewhere	Rare	Rare	Absent
Simplex	Herpetiformis (Dowling-Meara)	AD	Birth	Generalized	Variable	Variable	May be delayed
Simplex	Localized with Hypodontia (Kallin)	AR	3 mo – 1 yr	Hands/feet	Absent	?	Absent
Junctional	Generalized (Herlitz; Gravis)	AR	Birth	Generalized	Common	Moderate to severe	Severe
Junctional	Generalized (Mitis; Non-Herlitz)	AR	Birth	Generalized	Common but focal	Moderate	Absent or mild
Junctional	Localized (minimus)	AR	Birth	Hands, feet, pretibial	Absent	Absent	Absent
Dystrophic	Generalized (Pasini; Cockayne-Touraine)	AD	Birth	Generalized	Common	Variable	Absent
Dystrophic	Localized (Minimus)	AD	Early childhood	Acral	Absent	?	Absent
Dystrophic	Generalized (Gravis; Hallopeau-Siemens)	AR	Birth	Generalized	Common	Severe	Severe
Dystrophic	Generalized (Mitis)	AR	Birth	Generalized	Present	Moderate	Absent

* Listed are 12 of the possible 23 described EB subtypes. The reader is referred to more complete listings for a comprehensive review of the EB subtypes and their clinical features (Fine et al. 1991).

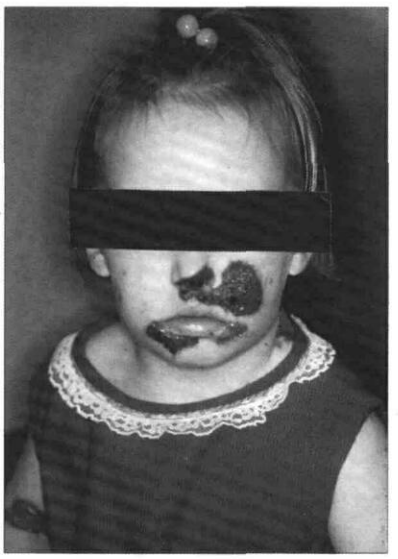

Fig 1. This 2-year-old female has the Herlitz variant of generalized functional EB demonstrating the characteristic perioral lesions unique to this specific subtype.

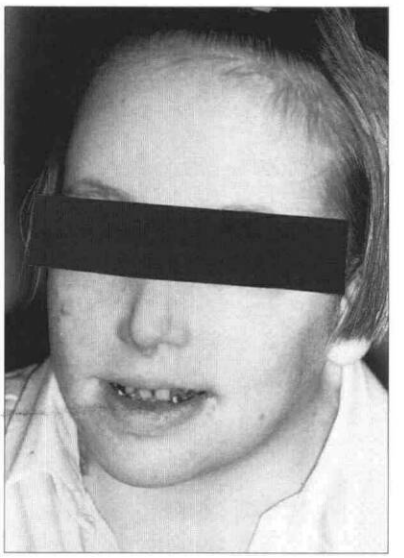

Fig 2. The same patient shows the perioral lesions have healed with no specific therapy by age 11 years, leaving the nares occluded due to scarring.

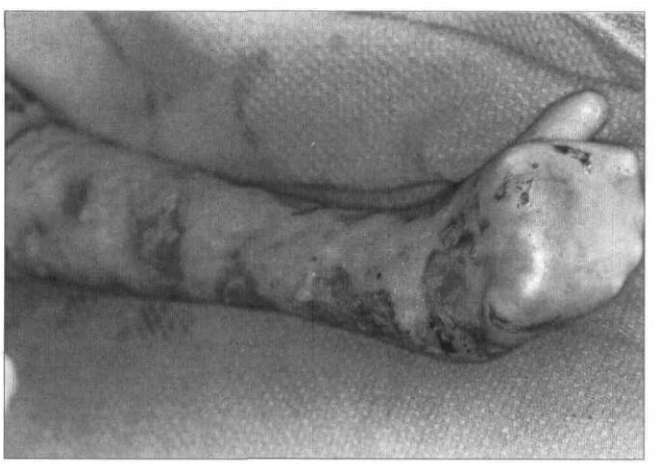

Fig 3. Digital webbing and severe mitten deformities result from the continual process of blistering and scarring around the digits. Complete enclosure of the digits in an ectodermal sac is characteristic of severe generalized recessive dystrophic EB.

mities of the hands and feet is characteristic of severe generalized recessive dystrophic EB (Fig 3), although rare patients with cicatrical junctional EB may exhibit similar or identical findings.

In some cases extracutaneous involvement can be so severe that it significantly alters an individual's lifestyle. For example esophageal involvement, most frequently associated with Herlitz junctional and severe generalized recessive dystrophic EB, may potentially lead to significant strictures, making the passage of food impossible.[19] Severe multifactorial anemia also is seen commonly in both of these EB types and is presumed to be secondary to malabsorption and chronic iron (blood) loss through mucosal erosions and ulcerations.[8,20] While growth retardation may be seen occasionally in several EB subtypes it is most often seen with the Herlitz variant of junctional EB and severe generalized recessive dystrophic EB. Patients with the latter are at particularly high risk during early adulthood of developing aggressive cutaneous squamous cell carcinomas, which may eventually lead to metastasis and death.[21]

Oral features

The character and extent of oral involvement varies greatly from one EB type to the next. In the milder forms of inherited EB the oral mucosa may suffer only occasional blistering with small discrete vesicles that heal rapidly without scarring and do not significantly alter the patient's life. In more severe cases, however, the entire oral mucosa is affected and may be characterized by severe intraoral blistering with subsequent scar formation, microstomia, obliteration of the oral vestibule, and ankyloglossia. Table 3 reviews the predominant oral features of the major EB subtypes.

Oral mucosa fragility, with subsequent development of intraoral soft tissue lesions, is common to all major EB types.[22] Prospective evaluation of enrollees in the Southeastern Clinical Center NEBR has demonstrated a much higher frequency of oral blistering with even mild forms of EB simplex than reported previously.[22–24] Although 35% of the localized and 59% of the generalized EB simplex patients develop intraoral blistering, these lesions tend to be few and small in size (< 1 cm), and tend to heal without scarring.[22] Whereas oral involvement in EB simplex appears to occur most commonly during the perinatal period, some individuals experience continued blistering into or beyond infancy or even late childhood.[22]

Most individuals with junctional or dominant dystrophic forms of inherited EB develop lesions involving their oral mucosa that are characteristically larger (> 1 cm), and more numerous than those observed in EB simplex, often become erosive, and are usually quite painful. Despite this propensity to develop clinically significant oral lesions, patients with these two major inherited EB forms usually heal without extensive intraoral scarring and, therefore do not typically develop ankyloglossia or vestibular obliteration (Fig 4).

Individuals with generalized recessive dystrophic EB exhibit the most severe oral involvement, which is characterized by complete obliteration of the vestibule and ankyloglossia (Fig 5). With increasing age, structures such as the palatal rugae and lingual papilla typically become unrecognizable because of the presence of continuous blister formation and scarring. In contrast, localized or mildly affected generalized recessive dystrophic cases do not show the same severity in oral scarring, loss of lingual papillae, and/or ankyloglossia observed in the severe generalized

Table 3. Oral manifestations of inherited epidermolysis bullosa variants•

EB Type	*Subtype*	*Mucosal Erosions*	*Oral Scarring*	*Ankyloglossia*	*Microstomia*	*Enamel Hypolasia*	*Hypodontia Anodontia*	*Rampant Caries†*
Simplex	Localized (Weber-Cockayne)	Occasional	Absent	Absent	Absent	Absent	Absent	Absent
Simplex	Generalized (Koebner)	Occasional	Absent	Absent	Absent	Absent	Absent	Absent
Simplex	Herpetiformis (Dowling-Meara)	Common	Absent	Absent	Absent	Absent	Reported	Absent
Simplex	Localized with Hypodontia (Kallin)	Present?	Absent	Absent	Absent	Absent	Present	Absent
Junctional	Generalized (Herlitz; Gravis)	Common	Mild/ Variable	Absent/ Mild	Moderate	Severe	Absent	Severe
Junctional	Generalized (Mitis; Non-Herlitz)	Common	Absent/ Mild	Absent/ Mild	Absent	Moderate/ Severe	Absent	Moderate
Junctional	Localized (Minimus)	Common	Absent	Absent	Absent	Mild/ Moderate	Absent	?
Dystrophic	Generalized (Cockayne-Touraine)	Mild/ Moderate	Absent	Absent	Absent	Absent	Absent	Absent
Dystrophic	Generalized (Gravis & Pasini; Hallopeau-Siemens)	Severe	Severe	Severe	Severe	Absent	Absent	Severe

•Oral features are listed for 10 of the EB subtypes. The following references provide more complete reviews of all subtypes (Fine et al. 1991).

† Moderate and Severe indicates relative risk for developing dental caries. By no means will all individuals in a subtype listed as severe have rampant caries.

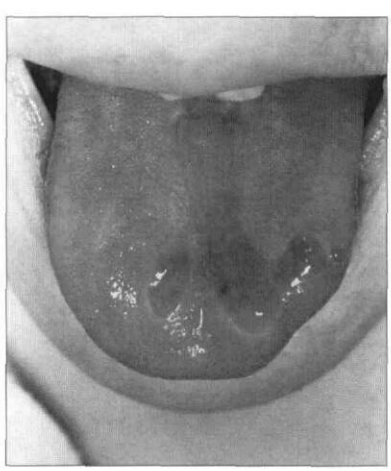

Fig 4. The lesions on the tongue of this individual with the Herlitz variant of generalized functional EB are large and painful but heal without scarring leaving the tongue with normal mobility.

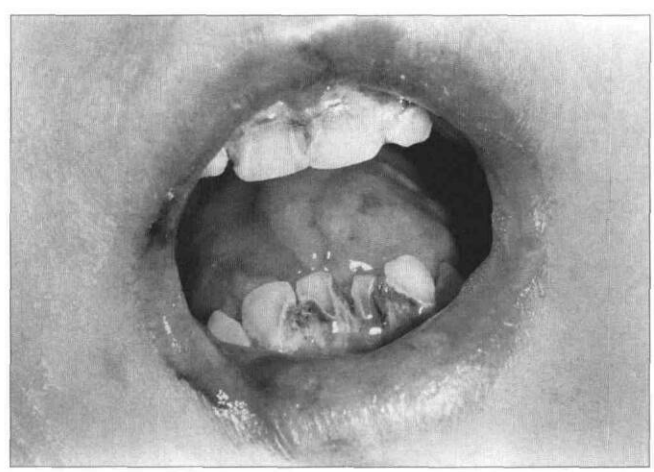

Fig 5. This individual with severe generalized recessive dystrophic EB has lost all the papillae on the tongue which is ankylosed and will not extend beyond the incisal edges of the mandibular incisors. Marked microstomia and dental caries also are clearly evident.

forms.[22] Squamous cell carcinoma of the tongue has been reported in several cases of recessive dystrophic EB, presumably due to the analogous tendency for such tumors to arise on skin sites subjected to repeated ulceration and re-epithelialization.[21,22]

Microstomia is most profound in severe generalized recessive dystrophic EB, but also may be common to individuals with the Herlitz variant of junctional EB.[22] In these two EB subtypes, microstomia apparently results from either intraoral or perioral blistering with subsequent scar formation. In generalized recessive dystrophic EB, microstomia appears to be the result of chronic, severe intraoral blistering. In contrast, while the Herlitz variant of junctional EB also demonstrates microstomia, vestibular obliteration and severe, intraoral scarring are characteristically absent. Instead, this EB subtype is classically associated with severe, chronic, perioral erosions and exuberant granulation tissue.[17]

The dentition may be affected severely by enamel hypoplasia and/or dental caries depending on the EB type. Examination of more than 100 individuals with EB by

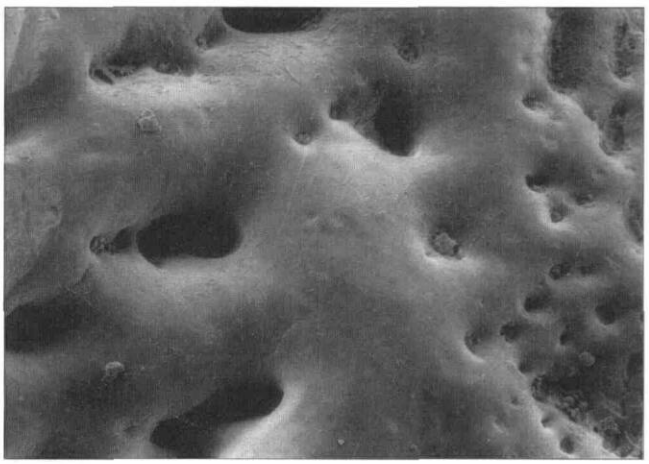

Fig 6. This scanning electron micrograph shows the diverse size and shapes of the hypoplastic pits seen in the enamel of a permanent molar removed from an individual affected with the Herlitz variant of generalized junctional EB (Original magnification 25x).

Gedde-Dahl indicated that all patients with junctional EB suffered from enamel hypoplasia.[25] It has since been confirmed in a large prospective study that generalized enamel hypoplasia is limited to junctional EB types.[26] Among the junctional EB patients, however, considerable variation may be noted in the nature of the enamel hypoplasia with some individuals having generalized pitting hypoplasia while others display very thin enamel with marked furrows (Fig 6). Rampant dental caries in patients with junctional EB seems to occur, at least in part, as a result of enamel hypoplasia, which decreases the tooth's intrinsic disease resistance.

Rampant dental caries is frequently seen in patients with severe generalized recessive dystrophic EB despite appearing to have normal dentition development.[26] It has been hypothesized that excessive dental caries is a result of the presence and severity of the soft tissue involvement, which leads to alterations in the diet (soft and frequently high carbohydrate), increases oral clearance time (secondary to limited tongue mobility and vestibular constriction), and creates an abnormal tooth/soft tissue relationship (i.e., buccal and lingual mucosa, which is firmly positioned against the tooth.)[27] Furthermore, these individuals often lack the ability to routinely practice normal preventive measures such as oral hygiene or the use of oral rinses.

General management

Treating inherited EB still consists primarily of palliative topical care. There are no known cures and most systemic therapeutic approaches have proved to be ineffective. For example, although initial reports suggested that phenytoin might prove to be beneficial in reducing the tissue collagenase levels in recessive dystrophic EB and thereby reduce blistering, a subsequent double-blind study failed to confirm the efficacy of this particular agent.[28–30] Eroded skin surfaces are best covered with nonadherent dressings after applying a topical antibiotic such as bacitracin, silver sulfadiazine, or mupirocin.[12] Oral nutritional supplements including iron and zinc may be partially beneficial in managing individuals suffering from anemia, and liquid preparations high in protein and calories may help patients with growth retardation.[31–32] Nutritional counseling also should take into account and address the control of dietary cariogenicity since individuals with severely affected oral mucosa and/or esophageal strictures usually consume soft or pureed foods high in calories; in addition they frequently eat very slowly, thereby further extending the dentition's exposure to potentially caries-promoting substrate.

Surgical intervention helps to correct mitten deformities and digit webbing, although webbing usually recurs, necessitating repeated surgeries.[33] Esophageal stenosis may be managed with dilatation, which again usually must be repeated to maintain luminal patency.[19] Although most interventions remain palliative and temporary, collectively they have permitted many severely affected EB patients to live beyond early childhood, thus producing a population of individuals requiring refined and aggressive dental treatment and interventions.[12]

Oral management

Individuals with milder forms of EB require few alterations in their dental care and may be treated much like any other patient. For example, the majority of individuals with EB simplex will tolerate dental procedures without difficulty. The practitioner should, however, carefully question any individual with EB as to their mucosal fragility, since dental therapy can precipitate oral blistering even in some mildly affected patients. Conversely, an altered approach to oral rehabilitation and anesthetic management may be required in individuals with enamel hypoplasia or rampant caries, extreme fragility of the mucosa, and/or the presence of microstomia (eg. Herlitz junctional EB and severe generalized recessive dystrophic EB).[9] Routine outpatient dental treatment with local anesthesia is possible in patients with minimal soft tissue involvement or limited treatment needs. Individuals with severe soft tissue involvement requiring multiple restorative and/or surgical procedures typically are best managed with general anesthesia.

When administering intraoral local anesthesia, the anesthetic solution should be injected deeply into the tissues slowly enough to prevent tissue distortion, which may cause mechanical tissue separation and blistering. In our experience, nerve blocks are far less likely to form blisters since they do not place the mucosal surface under pressure by depositing a bolus of fluid near the tissue surface. When manipulating tissues of individuals with those EB types most prone to mucosal blistering (severe generalized recessive dystrophic EB), only compressive forces should be applied because these are less likely than lateral traction or other shear forces to induce tissue separation.

Lubricating the patient's lips and any tissue to be contacted also will reduce the likelihood of shear forces and tissue damage.[9]

General anesthesia allows for extensive reconstructive dental treatment and/or multiple extractions despite the severe soft tissue fragility. Clinicians have approached anesthetic management with great caution; their concern is the possiblility of developing airway obstruction due to blister formation and tissue damage. Anesthetic management for dental care has therefore varied greatly and included such techniques as IV ketamine, insufflation, and orotracheal and nasotracheal intubations.[34-37] It is clear, however, that even the most severely affected individuals may be treated using tracheal intubation, an approach that provides optimal airway protection during dental treatment.[9-38]

The generalized enamel hypoplasia characteristic of junctional EB often is best managed in the child with stainless steel crowns so as to protect all of the teeth. This therapy may be necessary at a very early age in individuals prone to rapid attrition and caries formation.[17] Adults with junctional EB also frequently benefit from conventional fixed prostheses that allow them to maintain their dentition and have optimal esthetics. Tissue-borne removable prostheses usually can be tolerated in those junctional EB patients who have lost their dentition.

Patients with severe generalized recessive dystrophic EB who develop extensive dental caries frequently require stainless steel crowns on all of the primary teeth. Similarly, because of marked mucosal abnormalities, microstomia, and vestibular obliteration, severely affected individuals with marked dental involvement often will be best served by placement of stainless steel crowns on the permanent dentition.[9] Patients with generalized recessive dystrophic EB rarely are considered candidates for removable prostheses, although occasionally even severely affected patients will tolerate tissue-borne appliances.[22]

While most individuals with EB can tolerate orthodontic therapy with only minor modifications designed to reduce soft tissue irritation, individuals with severe generalized recessive dystrophic EB are unlikely candidates for such treatment. Unfortunately, these patients are prone to develop a severely crowded dentition, apparently resulting from small alveolar arches (secondary to generalized growth retardation), and collapsed dental arches (secondary to soft tissue constriction) although no specific studies have critically addressed this hypothesis. The incisors often are inclined lingually and if the malocclusion remains untreated, severe crowding is likely to result. A program of serial extraction in those patients unable to receive other orthodontic therapy can greatly improve dental alignment if instituted during the appropriate stage of dental development.

Preventing dental caries is most challenging in individuals with severe mucosal involvement since they often are faced with an extremely cariogenic diet and are least able to perform routine preventive procedures. In patients prone to oral blistering oral hygiene may best be accomplished with a soft-bristled, small-headed toothbrush. In addition to systemic administration of fluorides, fluoride rinses also may help control caries.[27] However, many EB patients with mucosal lesions are sensitive to the strong flavoring agents and alcohol in most rinses; specially formulated rinses lacking these ingredients may be required. Chlorhexidine mouth rinses also may help control dental caries, but again the patient may be sensitive to the high alcohol content of commercially available rinses. This may be overcome by swabbing the chlorhexidine directly on the teeth. Diet constitutes a major difficulty in caries control. Due to the complex systemic nutritional demands of these patients, diet may best be managed with the help of a dietician.

Summary

While this diverse group of potentially debilitating inherited diseases remains a tremendous challenge for health care professionals, enormous strides have been made during the past decade toward partially unraveling some of the many questions and issues related to EB. Although specific therapies are not yet available for the cure or prevention of blisters in any of the EB types, the oral ravages associated with these diseases certainly can be controlled. If treatment is instituted early enough, even individuals with the most severe forms of EB can retain a functional dentition by using appropriate combinations of available anesthetic, restorative, and preventive measures. Maintaining the dentition not only reduces the potential for soft tissue trauma to the mucosa—and possibly the esophagus through more efficient mastication—but also may allow better nutrition. There is no question that dentists have the ability to help these patients keep a positive self image by providing them with optimal oral health.

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