# Surgical management of epidermolysis bullosa: Proceedings of the IInd International Symposium on Epidermolysis Bullosa, Santiago, Chile, 2005

**Richard G. Azizkhan, MD, Jacqueline E. Denyer, RGN, RSCN, RHV, Jemima E. Mellerio, BSc, MD, MRCP, Robinson González, MD, Magdalena Bacigalupo, Arturo Kantor, MD, Gianfranco Passalacqua, DDS, Francis Palisson, MD, and Anne W. Lucky, MD**

From the Division of General and Thoracic Pediatric Surgery, Division of Pediatric Dermatology, and the Epidermolysis Bullosa Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, Great Ormond Street Hospital for Children, London, UK, St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK, Departments of Hand Surgery and Dentistry, Clínica Alemana, Santiago, Chile, Dystrophic Epidermolysis Bullosa Research Association (DebRA) Chile Foundation, Santiago, Chile, Department of Occupational Therapy of Mutual Safe-Deposit C.Ch.C, Santiago, Chile, Department of Ophthalmology, Clínica Las Condes and Universidad de Chile, Santiago, Chile, and Facultad de Medicina Clínica Alemana, Universidad del Desarrollo, Santiago, Chile

**Correspondence**
Richard G. Azizkhan, MD
Cincinnati Children's Hospital Medical Center
Division of General and Thoracic Pediatric Surgery
3333 Burnet Avenue
ML 3018, Cincinnati, OH 45229-3039
E-mail: Richard.Azizkhan@cchmc.org

## Introduction

The presentations described in this paper focus on the various components comprising the perioperative management of patients with epidermolysis bullosa (EB), emphasizing the need for a well-integrated interdisciplinary approach. The special preparations for anesthesia and techniques for anesthesia delivery are described. In the light of the high incidence of esophageal strictures in patients with recessive dystrophic epidermolysis bullosa (RDEB) and the concomitant nutritional issues that affect these patients, the indications and techniques used for esophageal dilatation, as well as for gastrostomy placement, at two internationally recognized pediatric institutions are presented. The psychosocial impact of associated hand deformities, such as pseudosyndactyly, is discussed, and the various surgical treatment approaches for these deformities are enumerated, stressing the important role played by occupational and physical therapists in helping patients to gain and maintain their autonomy. Relevant data pertaining to skin cancers in patients with EB are presented, with particular emphasis on the clinical behavior of squamous cell carcinoma (SCC) and current treatment options. In addition, both the ophthalmologic and oral manifestations of EB are described, with presenters focusing on the impact of eye and dental health, respectively, on the overall wellbeing of patients with EB and the related current management strategies.

## Anesthesia and perioperative care

Patients with EB undergoing surgery present the anesthesiologist with significant challenges that require thorough preoperative planning and meticulous perioperative care.[1] The management of a potentially difficult airway and the fragility of the skin and mucous membranes are of the highest priority. To avoid unanticipated difficulties with intubation, a thorough preoperative airway evaluation must be performed. When possible, endotracheal anesthesia is prudent. This is the safest and most effective technique, protecting against aspiration. In patients with microstomia, the tongue is often scarred down to the floor of the mouth and the teeth are often angled inward, making endotracheal intubation more difficult (Fig. 1). This difficultly increases with age as the cycle of scarring progresses. In some patients with microstomia, oral fiberoptic intubation may be necessary.

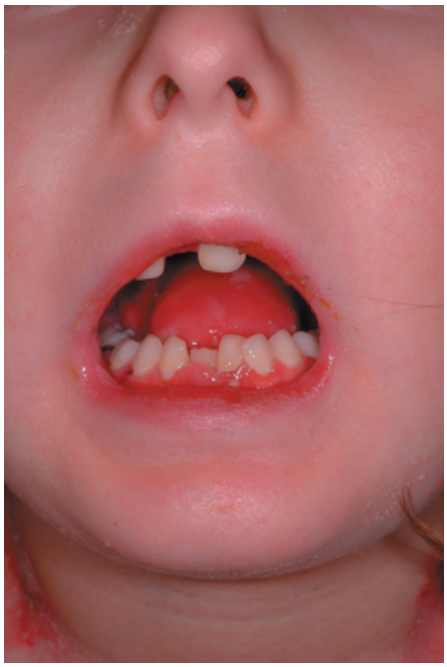

**Figure 1** Small child with recessive dystrophic epidermolysis bullosa and significant microstomia

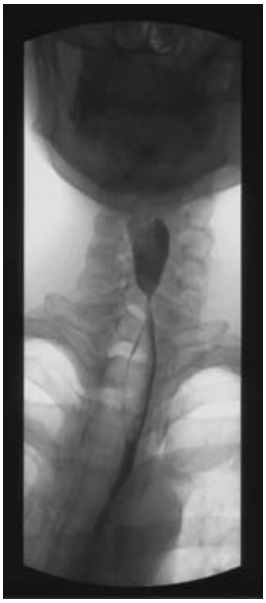

**Figure 2** Barium swallow in adolescent with recessive dystrophic epidermolysis bullosa. Note the tight proximal cervical esophageal stricture

To minimize trauma to the skin and mucous membranes, patients are placed on and remain on an egg-crate foam mattress for the entire procedure. Premedication with oral midazolam helps to promote a calm anesthetic induction with minimal anxiety, movement, and restlessness. Because of repeated blistering and scarring, establishing peripheral venous access can be difficult. Anesthesia, especially in young children, is thus usually induced by mask with inhalation anesthetics. Alternatively, if peripheral veins are accessible and the patient is cooperative, a peripheral intravenous line may be placed with the patient awake prior to intravenous induction of anesthesia. Intravenous lines are secured with a nonadhesive dressing and gently wrapped with gauze and Coban™ wrap. Silicone-based atraumatic adhesive covers, such as Mepiform® and Mepitac® (Mölnlycke Health Care, Goteborg, Sweden), are also used to secure these lines. The anesthesia mask is gently handled and lubricated with a bland emollient, such as Aquaphor® ointment (Beiersdorf, Hamburg, Germany), or protected with Mepilex® foam applied to the mask as well as to the skin of the submandibular, perioral, neck, and nasal areas. Gentle laryngoscopy with a lubricated blade is important to minimize oral trauma. When used, the endotracheal tube is secured with cotton tape that is initially placed behind the neck; the ends are then tied around the endotracheal tube at the level of the lips. The eyes are lubricated with a lanolin and preservative-free ointment and covered with saline-moistened gauze pads. No adhesive tape of any kind is used. Skin fragility also requires special precautions in the use of routine anesthesia monitors. Oxygen saturation is measured with a clip pulse oximeter probe rather than the adhesive style probes; the blood pressure cuff is applied over clothing, light gauze, or Mepilex® foam wrapped around the extremity. Electrocardiogram leads, if used, must have the adhesive portions removed and are secured to the patient with gauze or other nonadhesive wraps. The precordial stethoscope should be placed on the chest without adhesive and, if necessary, can be secured to the skin with a layer of nonadherent silicone dressing, such as Mepiform®, over the stethoscope.

At Cincinnati Children's Hospital, a combination of intravenous and inhalation anesthetics is used. Muscle relaxants may help facilitate intubation, and antiemetics are given to prevent postoperative nausea and vomiting. Although awake extubation at the end of the procedure may be associated with coughing, it minimizes the risk of aspiration and the need for continued mask pressure on the face after extubation.

## Esophageal dilatation

More than 70% of patients with RDEB are likely to have esophageal strictures by the age of 25 years. These strictures are primarily located in the proximal esophagus, but are also seen in the mid- and distal esophagus. Esophageal dilatation is indicated when strictures lead to dysphagia, varying degrees of obstruction, and/or an odor from accumulated food or saliva above the level of the stricture. A barium esophagram assists in evaluating the number, severity, and level of esophageal strictures (Fig. 2). It is essential to specifically request an

evaluation of the entire esophagus from the oropharynx through to the gastroesophageal junction. Significant strictures in the proximal cervical esophagus can be overlooked if an appropriate technique is not followed.

Over the past two decades, endoscopically guided balloon dilatation has become the first line of treatment for esophageal strictures, replacing older, more invasive approaches, such as bougienage.[2–4] There is general consensus amongst clinicians that this widely used approach is superior to bougienage, in that it avoids the morbidity caused by longitudinal shearing forces that can affect the entire length of the esophagus. A less commonly known alternative approach, fluoroscopy-guided hydrostatic balloon dilatation, eliminates the routine use of the endoscope, thereby minimizing the risk of iatrogenic trauma.[1] This approach also achieves a greater dilatation diameter. An overview of the data on each of these treatment approaches is presented below.

### Great Ormond Street Hospital experience

As reported by Jacqueline Denyer, 31 pediatric patients underwent 118 fluoroscopically guided balloon dilatation procedures under general anesthesia at Great Ormond Street Hospital (London, UK) over a 4-year period (1999–2003). The number of procedures ranged from one to nine per patient, with 13 patients requiring four or more procedures. Dilatations were achieved with balloons varying in diameter from 8 to 12 mm. The median age at first dilatation was 7 years (range, 22 months to 16 years). The 13 patients who required multiple (≥ 4) procedures had a median interval of 10 months (range, 15 days to 3.4 years) between their last two procedures, and 11 of 13 patients had an interval of more than 7 months.

### Cincinnati Children's Hospital Medical Center experience

Dr Richard Azizkhan (Cincinnati, OH) related his 12-year (1993–2005) experience with the fluoroscopically guided balloon dilatation approach.[1] Thirty patients, ranging in age from 2 to 42 years, underwent 105 dilatation procedures under general anesthesia during this period. Since 2001, patients have received steroids (at a dose of 1–2 mg/kg/day of prednisone) at the time of dilatation. This is followed by a 5-day tapered daily dose of liquid prednisolone, with the initial dose being 1–2 mg/kg. To reduce gastric acidity, patients also receive a proton pump inhibitor or H-2 blocker. The number of procedures ranged from one to 14 per patient. Dilatations were achieved with balloons varying in diameter from 12 to 26 mm, with a median diameter of 18 mm (Fig. 3a,b). The mean interval between dilatations was 13 months (range, 2 months to 6 years), and one patient remained symptom free for 6 years.

### Outcome comparisons

Both approaches appear to be safe and effective, with no reported perforations in either study. Moreover, both approaches result in the relief of symptoms with dramatic changes in social behavior, the ability to enjoy food, and a better overall quality of life. Nevertheless, by eliminating the use of the endoscope, hydrostatic balloon dilatation minimizes oropharyngeal trauma. In addition, it allows the

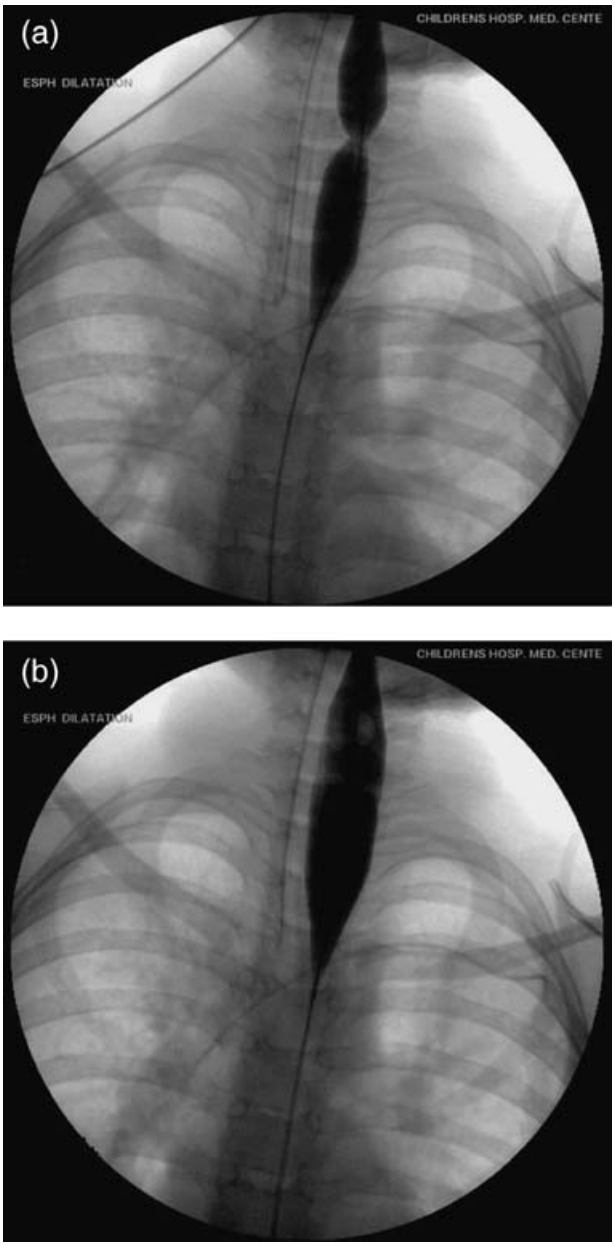


**Figure 3** (a) Hydrostatic balloon dilatation of a proximal esophageal stricture in a child with recessive dystrophic epidermolysis bullosa. Note the narrow waist at the site of the stricture when the balloon catheter is only partially filled with dilute water-soluble contrast. (b) The same patient with the balloon catheter fully inflated with total effacement of the stricture

use of much larger balloon sizes (up to 26 mm), achieving larger functional esophageal diameter. Most important in terms of the quality of life, the data indicate that the nonendoscopic approach results in a longer interval between dilatations.

## Gastrostomy tube placement

As current dilatation techniques are effective, less than one-third of patients require gastrostomy tube placement for enteral feeding.[1] This intervention is far more likely to be required in patients with RDEB. Failure to thrive is common and can be caused by reduced oral intake resulting from: (i) dysphagia and esophageal strictures; (ii) microstomia; (iii) oral ulceration; (iv) overcrowding of teeth; (v) dental caries; and (vi) diminished appetite associated with constipation. In addition, patients have increased nutritional requirements due to competition between wound healing and growth, as well as increased catabolism resulting from recurrent skin and mucous membrane infections.

### Techniques for gastrostomy tube placement

Dr Azizkhan described a number of approaches for gastrostomy tube placement that have been successfully used in patients with EB. Either open or percutaneous gastrostomy can be performed, with the latter carried out using either an endoscopic or nonendoscopic technique. After gastrostomy tracts have healed and are well established, original tubes can be replaced with low profile gastrostomy buttons that are better accepted by patients.

For patients requiring this intervention, gastrostomy tube placement has both advantages and disadvantages. Of primary importance, it guarantees an enteral feeding route for patients who are nutritionally compromised. It also helps to reduce constipation. In some older patients, however, gastrostomy tube placement is not always well accepted, and many dislike the need for button change. Moreover, leakage and irritation can occur around the gastrostomy site, incontinence can occur with overnight feeding, and gastroesophageal reflux can worsen. These nuisance complications require troubleshooting and the cooperative efforts of patients, families, and the entire EB team.

## Hand surgery and occupational and physical therapy

Hand deformities in patients with EB have a serious impact on psychomotor and social development, leading to low self-esteem, social isolation, and an overall poor quality of life. Hand involvement can be either cutaneous or articular.[5] Cutaneous involvement includes blisters, erosions, ulcerations, retractile scars, absence of nails, and pseudosyndactyly. Articular manifestations include flexion contractures of the fingers, abduction of the thumb, complete retraction of the fingers with the formation of a "skin cocoon", and flexion contracture of the wrist. The severity of these manifestations is graded (Fig. 4a–c) according to a scale developed by Glicenstein *et al*.[6] Optimally, patients should be cared for by an interdisciplinary team representing surgery, nursing, occupational therapy, and psychology.

Hand surgery should be performed before deformities become irreversible. Surgical approaches depend on the severity of involvement, and include the release of contractures, arthrolysis, tendon elongation, corrective osteotomies of the axis, and skin grafting. In his presentation, Dr Robinson González described an epidermal graft harvesting technique that has been successfully used to cover surgically created skin defects; the donor sites heal with no scarring. Successful postoperative care includes management with static and dynamic splints. Patient and family education and involvement are also essential.

The goals of occupational and physical therapy are to facilitate the development of the skills required for gaining autonomy, thus enabling patients to fully participate in social, educational, and work activities. Individualized treatment plans are aimed at slowing the progression of the deformity through therapeutic exercise programs and the use of customized static and dynamic orthotic devices. These devices are constructed of molded thermoplastic materials. Their framework comprises aluminum wires, Velcro straps, and soft quilted safety belts. Common glues, dressings that retain humidity, and materials that produce damage by friction or pressure are avoided. Dr González reported short-term success with this treatment approach. Unfortunately, however, long-term outcomes are not sustained, as many patients have recurrence of their deformities and require repeated surgical procedures to remain functional.

## Skin cancer

Data from the National EB Registry in the USA indicate that SCC continues to be a major cause of morbidity and mortality.[7] SCC is primarily associated with Hallopeau–Siemens RDEB; however, it is also seen with non-Herlitz junctional EB (JEB) and other recessive and dominant forms of DEB.[8] Patients with EB have no increased risk of basal cell carcinoma and, although melanomas have been reported, the number of cases is small.[9] Clinically and histologically, atypical EB nevi have also been reported, but there is no documentation of malignant transformation. With regard to extracutaneous malignancies, National EB Registry data indicate sporadic reports of hard palate SCC and esophageal carcinoma in patients with RDEB, as well as reports of transitional cell carcinoma in patients with non-Herlitz JEB, but there does not appear to be a significantly increased risk of these malignancies.

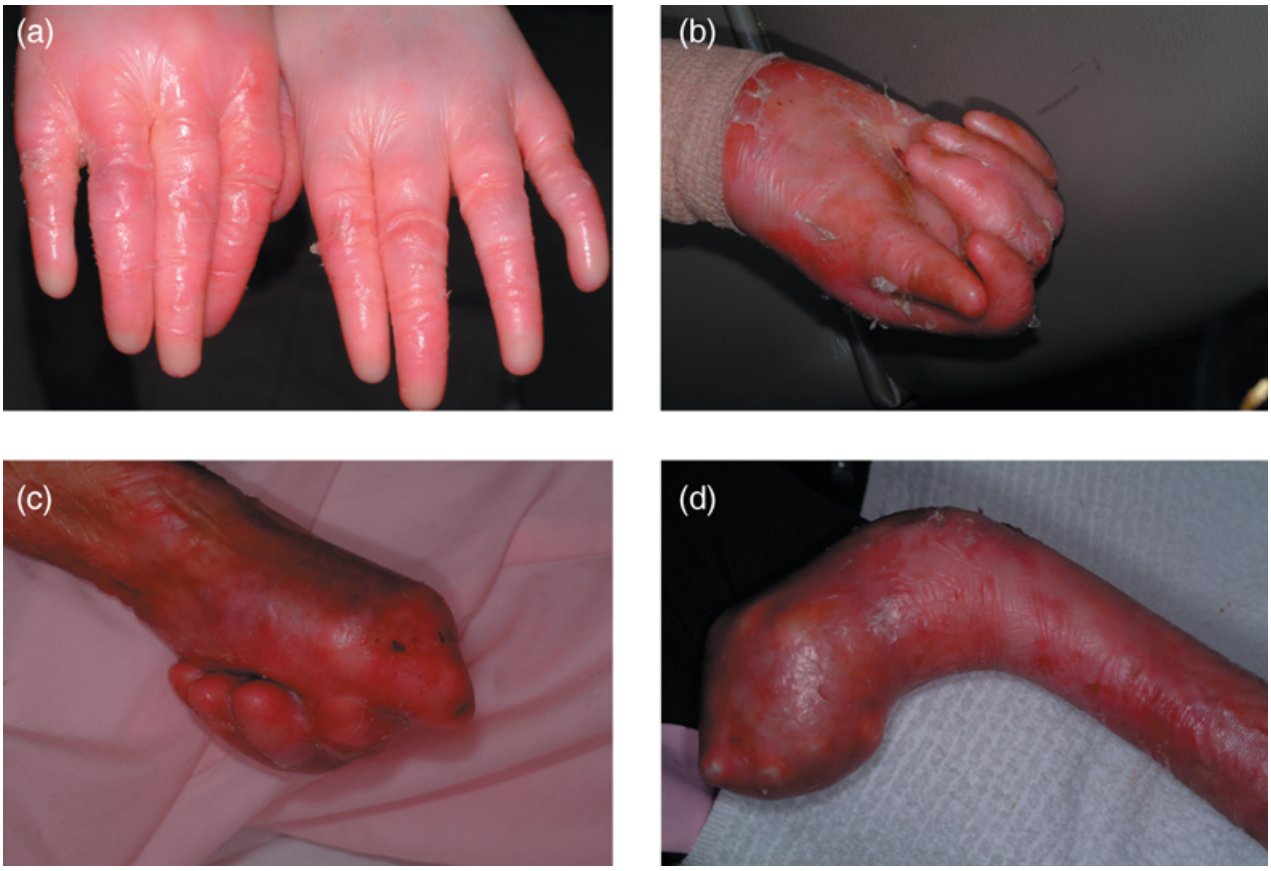


**Figure 4** Different degrees of hand involvement in patients with recessive dystrophic epidermolysis bullosa. (a) Near-normal extension and flexion of the fingers and metacarpal region. (b) Contractures of the metacarpal and phalangeal region of the hand with fusion of some of the digits. This patient still retained significant thumb and forefinger oppositional function. (c) Severe pseudosyndactyly and contractures. (d) Severe pseudosyndactyly with total clubbing of the hand and wrist contractures

SCC is predominantly seen in patients with Hallopeau–Siemens RDEB,[9] occurring mainly over bony prominences and commonly having multifocal primary sites.[10] Tumors have a wide spectrum of appearance, varying from that of nonhealing ulcers to exophytic or hyperkeratotic lesions (Fig. 5a). Several biopsies may be required to confirm or discount the presence of tumor within a suspicious area.

Although often well differentiated, SCC in these patients behaves aggressively, and even wide local excision with clear margins does not prevent metastasis (Fig. 5b). SCC has not been reported in EB patients younger than 12 years.[11] The risk of developing SCC in Hallopeau–Siemens RDEB increases with age: 6% by 20 years and 85% by 45 years.[7] These risks should be discussed with patients and their families early in treatment.

On the basis of accumulating evidence and observations, a predisposition to develop SCC may be associated with the following: (i) decreased immune surveillance of tumor cells in EB;[12,13] (ii) altered tumor suppressor genes in some EB tumors;[14] (iii) reduced insulin-like growth factor binding protein 3 (IGFBP-3) in EB SCCs vs. non-EB SCCs;[15] and (iv) growth-activated keratinocytes that promote tumorigenesis via cytokine stimuli.[16] It is also thought that the expression of part of type VII collagen may promote neoplasia.[17]

Management of EB patients with SCC comprises a number of integrated medical and surgical treatment options that require the combined expertise of an interdisciplinary team. Routine physical examinations (every 6 months in teenagers) are paramount and should focus on examining the entire skin surface for potential lesions. If SCC is diagnosed, the first line of treatment is wide local excision that preserves function as much as possible. Skin grafting is also used in these patients. If regional lymph nodes are enlarged, lymph node biopsy or fine needle aspiration is used to help stage the patient. The role of Mohs' surgery is yet to be defined, although it may be of use in selected patients. In addition to sentinel lymph node biopsies, computed tomography (CT) of the chest is important for ruling out lung metastasis. Both radiotherapy and

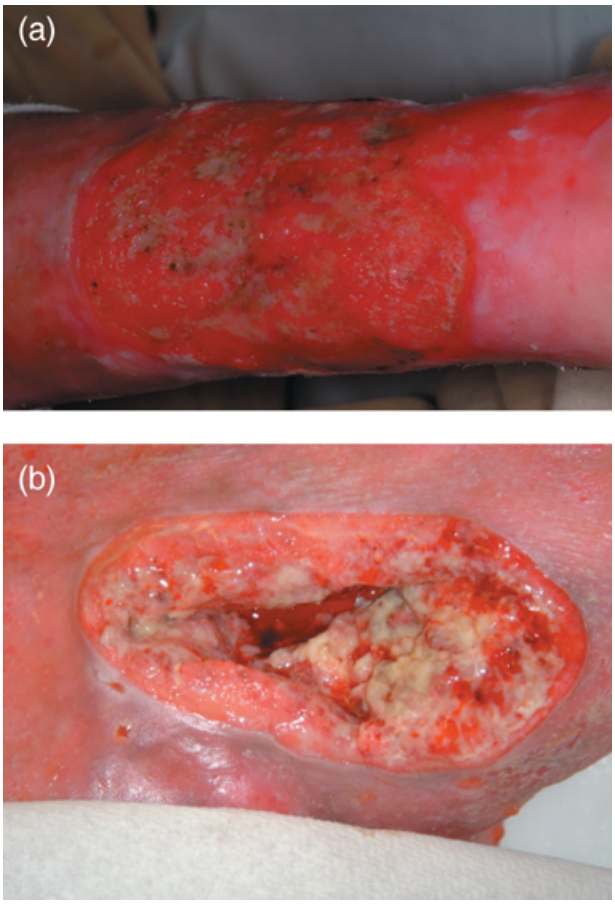


**Figure 5** Squamous cell carcinoma in a 20-year-old patient with recessive dystrophic epidermolysis bullosa. (a) Original ulceration on the left lower leg. (b) Necrotic, fungating metastatic mass which developed in the left thigh following a below-knee amputation

chemotherapy have limited effectiveness in treating SCC in these patients as tumors are usually poorly responsive, although these may be useful modalities for palliation. Radiotherapy may have a narrower therapeutic window because of the fragility of surrounding skin. Some patients require amputation to control local disease, although recurrence in the stump is common. Recently, anecdotal reports have suggested that a topical immune modulator, Imiquimod cream, is effective in shrinking or eliminating cutaneous lesions, although further studies are required to determine the effectiveness and tolerability of this treatment.

Despite active management, 80% of patients with severe RDEB and SCC die within 5 years of the initial tumor, and 55% of all patients with RDEB die from SCC by the age of 40 years.[7] The risk of developing SCC appears to parallel the severity of ulceration and scarring of skin, with SCC eventually developing at sites of repeated blistering and healing. As such, prevention of SCC entails an improvement in wound healing, nutrition, and anemia. Although not used routinely, retinoid chemoprevention for high-risk patients may be an option to consider.[18]

## Ophthalmologic involvement

A spectrum of ophthalmic complications is seen in patients with EB. These complications may be acute or chronic. They vary in clinical severity depending on the EB subtype and commonly involve the cornea or conjunctiva.[19] This is not surprising as there are numerous biochemical and ultrastructural similarities between skin and cornea, particularly at the level of the plasma membrane and the epithelial–dermal basement membrane zone.[20]

The frequency of ocular manifestations mirrors the relative severity of skin disease, affecting 74% of all patients with RDEB. These manifestations include dry eye syndrome, corneal erosions or blisters, corneal ulcerations, corneal opacities, corneal scarring, acute and chronic conjunctival irritation, and conjunctival scarring. Blepharitis and lacrimal duct obstruction have also been reported. Corneal blister formation most often occurs in patients with the most severe types of EB: JEB and RDEB.

Dry eye syndrome is treated with lanolin-free ocular lubricants without preservatives. Soft contact lenses appear to protect the eyes from corneal erosions and also appear to reduce mild scarring and pannus formation, preventing possible blindness. Acute management of corneal erosions consists of supportive treatment with application of nontoxic antibiotic ointments, as long as no stromal infiltrates are seen. Gram stains and culture samples should be obtained otherwise. Patients who fail these approaches are sometimes treated with limbal and corneal transplants. These patients require systemic immunosuppressants to remain the integrity of transplants. A novel technique for corneal reconstruction uses tissue-engineered cell sheets derived from autologous oral mucosal epithelium. Another technique is to cover the cornea with amniotic membranes; this facilitates re-epithelialization of the cornea within a 4-week period. Chronic blepharitis can result in cicatricial ectropion and exposure keratitis. Moisture chambers and ocular lubricants are commonly used for management. This disorder is also treated with full-thickness skin grafting to the upper eyelid; however, complete correction is difficult to obtain.[21]

Given the clinical impact of external eye involvement in patients with EB, thorough semiannual to annual ophthalmologic evaluations should be considered and are an essential component of overall clinical management.

## Oral manifestations

The oral manifestations of EB differ according to the EB subtype.[22] Patients with EB simplex do not commonly present

with oral mucosal problems, but have a 50% incidence of dental caries. In contrast, patients with JEB tend to have a low incidence of decay. Both EB simplex and JEB are associated with three abnormalities in enamel formation: (i) generalized enamel hypoplasia; (ii) hypomaturation; and (iii) hypocalcification. Hypoplasia is a hereditary defect in which the enamel does not form to normal thickness. Teeth appear to be smaller than normal, with the surface of the enamel often having an irregular appearance. Hypomaturation is characterized by normal enamel thickness, with teeth having a mottled appearance. The enamel can be pierced or chipped on examination with a dental explorer and appears less radiolucent than the dentin on a radiograph. Hypocalcification is characterized by enamel that is normal in thickness, but that is soft and can easily wear away, leaving the dentin exposed. Yellow pigmented areas are present and teeth are highly temperature sensitive.

Patients with DEB, particularly those with RDEB, tend to develop progressive microstomia, contributing to their poor oral intake and making access to the mouth and gastrointestinal tract difficult. Microstomia can be caused by lesions and scars in the commissures, loss of vestibular space, and damage to the sphenomandibular ligaments during the eruption of second molars. By the age of 12 years, more than 60% of patients with RDEB have significant ankyloglossia. Many patients also develop a constricted palatal vault, limiting normal oral function. These patients also have significant abnormalities in the dental enamel and are prone to severe caries.

Early prevention and treatment, together with family-oriented education, are crucial to the overall quality of life of patients with EB. Maintaining oral health promotes healthy oral mucosa and improves mastication and nutrition. It also allows better functioning of the tongue, enabling improvement in deglutition, respiration, and speech. Applying fluoride varnish is recommended, as is the use of a small-head, soft-bristle toothbrush soaked in hot water to increase softness before use. Dental restorations and caps provide significant benefit to patients with caries. For children with microstomia, exercises can help to maximize the oral opening. Younger children often require general anesthesia to treat oral pathology.

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