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Principles of Wound Care in Patients with Epidermolysis Bullosa

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Abstract: **Epidermolysis bullosa comprises a series of hereditary skin fragility disorders characterized by blister formation in response to minor friction or trauma. Acute and chronic wounds are part of the daily life of many epidermolysis bullosa patients. To offer proper care, health care providers need to understand the wound healing process, recognize the different types of wounds these patients may present, and be able to select among a wide variety of wound care products to optimize healing.**

Epidermolysis bullosa (EB) refers to a heterogeneous group of genetic skin fragility disorders, clinically characterized by blistering of the skin in response to minor friction or trauma. The most recent classification separates this condition into four subtypes: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler Syndrome (1).

Regardless of their subtype, the common factor in all EB patients is the skin blistering and therefore constant presence of wounds. In patients with this debilitating condition, special considerations regarding the host, the wound healing process and the wound itself, have to be considered to facilitate the healing processes. This article will review the wound healing stages and discuss the particularities of wound healing and care in patients with EB.

THE WOUND HEALING PROCESS

A wound is healed once it has completed the three stages of repair: inflammation (primarily dominated by neutrophilic and macrophage action), proliferation (predominated by endothelial cells and fibroblasts), and maturation/remodeling (governed by collagen deposition). In addition, normal wound healing requires adequate circulation, nutrition, a normal immune status, and avoidance of negative mechanical forces that may disturb the healing process (2).

Traditionally, the three phases of wound healing were thought to be very distinct steps, but currently are known to overlap. The first action the body takes after a wound develops is to control bleeding and fluid loss, initially by vasoconstriction of damaged blood vessels and then by formation of a clot. This clot, formed by fibronectin, platelets, collagen and thrombin, will release and serve as a reservoir of cytokines and growth factors that will initiate inflammation (3,4). Neutrophils predominate at this stage, and are responsible for producing proteolytic enzymes, that help clear bacteria and debris, as well as oxygen free radicals that assist in the sterilization of the wound (5). Neutrophils are replaced by macrophages making the transition to the proliferative phase.

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Macrophages produce nitric oxide (NO) that kills bacteria and matrix metalloproteinases (MMP) that facilitate elimination of cellular debris in addition to phagocytosis of bacteria, cellular debris and neutrophils (6). It was once thought that the inflammatory process "burns itself out" (7); new insights into this process have revealed the existence of cellular mediators of the eicosanoid family, named lipoxins, which are the "stop signals" of the inflammation (8,9). The proliferative phase consists of epithelization, angiogenesis and provisional matrix formation of the wound. Epithelial cells on the skin edge start proliferating and sending out projections that establish a protective barrier. The primary stimulus for this process is the release of endothelial growth factor (EGF) and transforming growth factor alpha (TGF-α) produced by the platelets and macrophages (10). The endothelial cells and fibroblasts are the predominant cells. The fibroblasts synthesize and secrete keratinocyte growth factor-1 and -2 and interleukin-6 that stimulate keratinocytes to migrate, proliferate and differentiate in the epidermis (11,12). The endothelial cells begin forming new capillary tubes and produce NO to stimulate more vascular endothelial growth factor (5). During this time the provisional matrix is formed, consisting of collagen type III, glycosaminoglycans and fibronectin (13). This process is guided by TGF-β, which decreases matrix degradation and production of MMP, causes fibroblasts to synthesize type I collagen and increases the production of cell adhesion proteins (6). The turn off signal of this proliferative phase is given by interferon-inducible protein (IP-10) that inhibits EGF-induced fibroblast motility, limits fibroblast recruitment and has a negative mitogenic effect on fibroblasts (14).

The last part of the wound healing process is remodeling and maturation, and consists of collagen deposition. The initial matrix is going to be disorganized, but it is replaced with a stronger, organized collagen matrix. Fibroblasts differentiate into myofibroblasts, that have the capacity of increasing contractility, and as these are anchored, they allow leverage for contracture of the wound (5). The collagen in the scar will never become as organized as the collagen in the uninjured skin and the wound strength will never return to 100% (it achieves a final strength of 80% of the original one after 3 mos) (15).

Cellular, structural, and functional processes in all three stages of wound repair are highly dependent on the supply of micro- (vitamins and minerals) and macronutrients (carbohydrates, fats, and protein). For instance, vitamin A and C, zinc, iron, and proteins are necessary for collagen synthesis and re-epithelization. Similarly, a healthy immune response, antibody activation, macrophage migration and the clearance of necrotic tissue are all dependent on an adequate nutrient supply (16).

When a chronic wound develops the caloric demands increase by about 50%, and the protein intake requirements by as much as 2.5 times its baseline (17). Research in different chronic wounds revealed that the presence of a nonhealing ulcer results in increased metabolic demands on the individual and initiates a cascade of catabolic events and simultaneous down-regulation of anabolic hormones. This stress response leads to breakdown of body's tissues, including stored fat and protein, to generate raw materials to meet the increased demand for energy, initiate wound closure and replace potential losses during the wound healing process. Albumin was noted to play a role in the inflammatory and proliferative stages of wound healing. In addition to high requirements, albumin can be lost through the chronic wound exudates (18), further diminishing body's ability to heal. Hypoalbuminemia should be considered as a contributor to poor wound healing.

Adequate tissue perfusion (normal vascular supply and normal hemoglobin) that allows nutrients, oxygen and cytokines to reach the wound is also very important for proper wound healing. It has been documented that patients with pressure ulcers which have a hemoglobin levels of $\leq$100 g/L experience delayed healing (19).

WOUND CHARACTERISTICS IN EB

The clinical presentation of individuals with EB is quite variable (20). Some individuals may only have minor blister [EBS and dominant DEB (DDEB)] or present with severe debilitating disease as seen in JEB and recessive DEB (RDEB). Even within a given subtype, clinical findings may differ among patients; different genetic mutations seem to explain, in part, different clinical phenotypes (21,22).

In mild cases of EBS, blisters tend to appear only in areas of frictional trauma such as hands and feet; most of them heal without any scarring or with minor pigmentary changes. In the more severe cases of EBS, blistering can be more generalized. Wounds in patients with JEB are different from the other types of EB in their predominant peri-orificial (around mouth, eyes or nose) and periungal distribution and exuberant, hypergranulation tissue within the wound base. Patients with DDEB tend to present with less severe blistering than RDEB, but because of the depth of the blisters they will also heal with scarring. Milia formation is significant, particularly over the bony prominences. In individuals with RDEB, blistering is quite severe and this can lead to extensive areas of chronic ulceration.

The presentation of the EB wounds depends on wound and host factors. The wound-dependent characteristics include the size of the area involved, location and the presence of bacterial colonization or infection. The host-dependent characteristics are influenced by the host's nutritional status (hemoglobin levels, albumin levels, as well as other nutrients), the underlying genetic defect and other predisposing factors (e.g., decreased mobility that makes some areas more susceptible to trauma).

One of the most important wound-dependent characteristics is the bacterial load. A pathogenic organism has to be present in an excess of 100,000 bacteria per gram of tissue for a clinical infection to occur (23,24). Bacterial loads of more than 10^5 bacteria per gram of tissue are associated with potential nonhealing of a wound (25). Initially, open wounds are infected by aerobic organisms, most commonly *Staphylococci* and *Streptococci* species (26). Clinically infected chronic wounds also contain anaerobes and thus are described as polymicrobial (mixed aerobe/anaerobe populations); however, the predominant organisms in these sites are *Staphylococcus aureus*, *Staphylococcus epidermiditis*, and *Pseudomonas aeruginosa* (25). The most common organisms found in the wounds of EB patients are *S. aureus* and *P. aeruginosa*. The presence of these bacteria also plays a role in delayed healing (26).

MANAGEMENT OF BLISTERS IN EB

Initially, wounds in EB patients present as blisters or bullae. To prevent these from enlarging, it is important to carefully puncture the blister or bulla with a sterile needle to release the inner fluid to prevent further extension of the blister. It may be necessary to puncture the blister in various sites to optimize the fluid release. The fluid should be allowed to drain on its own, as excessive pressure at the site may lead to further extension of the blister/bullae. The overlying skin should never be removed as it acts like a natural dressing aiding to the healing.

To optimize the healing of new blisters or bullae, patients are advised to cover them with nonadhesive dressings. Silicone dressings are generally preferred as these tend not to stick to the wound and can be easily removed without further skin damage. In the absence of nonstick dressings, Telfa (Kendall Company Ltd., Mansfield, MA, USA), and petrolatum-impregnated gauze may also be used provided that caution is exercised when removed, as they may adhere to the wound. Depending on the area of the body affected, some dressings may work better than others (Table 1).

The frequency of the dressing changes may vary, but in general only patients with excessive wound drainage or infection may require daily dressing changes. Keeping the dressing in place for several days may minimize trauma and aid in the healing. Another option to reduce trauma during dressing change is to use two dressings; a primary one that allows for assessment of the wound without being removed (e.g., mesh silicone dressing such as Mepitel-Mölnlycke Health Care or Restore, Hollister) and application of medications, and a secondary dressing, applied on top of the primary one that can be changed more frequently. If the dressing routinely sticks to the wound base, soaking the area with sterile water or using a nonirritating adhesive remover (such as Apeel® or Niltac®) is helpful.

The use of daily topical antibiotics is not necessary for clean, noninfected wounds. When topical antibiotics are used, we recommend limiting the application to short intervals, using only nonsensitizing antibiotics and alternating two or more (monthly or every 2 mos) to prevent resistance. Their application is less painful if a tongue depressor is used to "butter" the primary dressing before applying it to the skin. Other methods used to reduce bacterial loads are vinegar and bleach baths, we recommend one cup of either vinegar or bleach in one bathtub for baths or one in nine parts of water if locally applied. The use of honey or honey impregnated dressings and silver dressings have are also used for their antibacterial properties and seem to be well tolerated by EB patient. Rarely patients may also need anti-candidal topical treatment. Table 2 presents a step-wise approach to blister management in EB patients.

ACUTE AND CHRONIC WOUNDS IN EB

The general principles of wound care apply to both acute and chronic wounds in the EB population. Acute and chronic wounds are illustrated in Figs. 1 and 2.

In 2002, the International Advisory Panel on Wound Bed Preparation developed a practical framework that guides practitioners through the trajectory of wound healing (27,28). The principles can be remembered by the mnemonic tissue, infection/inflammation, moisture balance, epidermal margin, or extracellular matrix.

Tissue

This refers to nonviable tissue such as slough or escar within the wound bed or its periphery. In the non-EB patient, if these elements were present, debridement would be the treatment of choice. In the EB patients, because of their skin fragility, debridement is rarely recommended. If required, gentle debridement using a hydrolytic agent can be performed.

TABLE 1. *Dressing Types and Their Use in Epidermolysis Bullosa Patients*

Dressing type	Dressing characteristics	Advantages	Disadvantages	Use in EB
Hydrocolloids Restore*	Dressing made out of carboxymethylcellulose, gelatin, pectin, elastomers, and adhesives that become a gel when moist	Occlusive (keeps moisture in wound area and protects from contamination) Inert May be safely used for several days Provides autolytic debridement of necrotic tissue Available as pads, powder, and paste	Excessive hydration may lead to maceration	Useful in noninfected wounds that require hydration
Foams Silicone foams Mepilex† Mepilex border† Mepilex border lite†	Can be made out of silicone or hydrophilic polyurethane/polymer or gel-coated dressings	Provides cushioning effect Nonadherent Provides autolytic debridement of necrotic tissue (but not as much as alginates)	Variable absorption capacity Semi-occlusive	Helpful to provide padding for wounds in easily traumatized areas
Hydrogels Duoderm gel‡ IntraSite gel§	Composed mostly of water in a complex network or fibers that keep the polymer gel intact	Provides moisture Can be used as vehicle for antibiotics High debridement ability	Requires dressings to cover and keep in place	Can be used for crusted lesions that need hydration
Alginates Aquacel‡ Kaltostat‡ SeaSorb¶	Dressing made out of calcium alginate (component of seaweed), that when in contact with wound is exchanged with sodium from wound fluid and turns dressing into a gel Subset are hydrofiber dressings (absorb more)	Very absorbent Maintains moisture Provides debridement Available as pads or fiber sheets or ribbons	If used in wounds that have little exudate, it leads to dryness and scabbing Requires frequent dressing changes	Useful in highly exudating wounds
Others Telfa**	Perforated plastic film dressings that consists of a thin layer of absorbent cotton fibers enclosed in sleeve of poly(ethylene terephthalate) that is perforated in a regular pattern and sealed along two edges	Does not stick to the wound surface Water resistant	Requires burn net or cling to keep it in place	Useful in lightly to moderately exudating wounds
Silicone mesh Mepitel†	Porous, semi-transparent, flexible polyamide net coated with soft silicone	Allows to apply topical medications without being removed Nonadherent Does not require frequent dressing changes	Requires secondary dressing	Ideal to use when topical medications should be applied to wound and dressing change trauma wants to be minimized
Silver dressings Aquacel Ag‡ Contreet¶ Mepilex AG† Acticote§ Silvasorb†† Restore AG*	Silver containing dressings can be alginates, foams, gauze, hydrogels, or hydrofibers. These release silver into the wound	Anti-microbial effects No resistance to silver is developed	Patient may experience burning, or pain in the wound area May lead to irritation Requires moist environment in order to release silver Argyria Silver can affect keratinocytes, so it should be reserved for wounds with increased bacterial burden	Critically colonized or infected wounds in EB patients may benefit from the use of silver dressings
Gauze	Open weave fabric made of cotton	Not expensive Widely available	Sticks to the skin as it becomes dry (may damage wound bed when removed) Not an effective barrier Requires to be more frequently changed	Petrolatum-impregnated gauze being less adherent than gauze alone may be a less costly option in EB

TABLE 1. *(Continued)*

Dressing type	Dressing characteristics	Advantages	Disadvantages	Use in EB
Burn net or Cling	Elastic cotton mesh	Nonadherent elastic		Used to hold dressings in place (securing)

*Hollister.
†Mölnlycke Health Care.
‡Convatec.
§Smith & Nephew.
¶Coloplast.
**Kendall Company Ltd.
††Medline Industries.

Infection or Inflammation

Bacteria act as impediments to normal wound healing. While all wounds are either colonized or contaminated, true infection only occurs when the replicating organisms cause harm to the host. The risk of infection is proportional to the virulence and dose of the organism and inversely related to the resistance of the host. A decrease in the bacterial burden is essential for healing of any acute or chronic wound (29–32).

Because all chronic wounds are either colonized or contaminated, it is important to remember that wound infection is a clinical diagnosis. The presence of beefy red areas, purulent exudates, malodor, and increasing pain are generally signs of true infection. In general, superficial infections can be treated with topical agents, whereas deeper infections typically require systemic antibiotics (29). Wound cultures are rarely helpful on their own without a solid clinical diagnosis and may lead to inappropriate antibiotic usage. If oral antibiotics were required, their bioavailability may be impaired in the patients with severe EB secondary to malabsorption.

Chronic wounds do not follow the normal healing trajectory, being "stuck" in the inflammatory phase, characterized by continued expression of cytokines that cause injury of the host (33). Recent advances in the wound care products can, in part, alleviate the problems associated with the ongoing pro-inflammatory process. One of the newer advances has been the development of collagen based dressings. These dressing are designed to lay down a more "normal" extracellular matrix which allows for better keratinocyte migration as well as the inhibition of the more deleterious MMP. Use of collagen based products has been reported to reverse the pro-inflammatory cytokines and aid in wound healing (34).

Moisture Balance

Approximately 4,000 different wound care products were available on the market. Many of these products have been developed to address moisture balance. It is well known that moist wounds, whether chronic or acute, heal faster and are less painful than dry wounds (28). This applies to all wounds in the EB population, with the exception of Dowling-Meara EBS patients, who do better by keeping their wounds dry accomplished through the application of cornstarch after the fluid has been released from the blisters.

In the EB population, it is important that irrespective of the dressing used, the primary contact layer does not adhere to the wound or to the peri-lesional skin (35), because removal of the adherent dressings leads to further blistering and breakdown of the skin.

TABLE 2. *Step-Wise Approach to Blisters in Epidermolysis Bullosa Patients*

1. Blister/bulla management may be painful; if necessary provide pain control measures 20–30 minutes prior to popping blisters/bullae
2. Use clean, not sterile technique (wash hands, use gloves)
3. Very carefully puncture the blister with a sterile needle
4. Aim for the blister's lower edge so that gravity can allow more complete fluid drainage
5. The blisters may need to be punctured in multiple areas for optimal fluid drainage
6. Do not apply pressure on top of the blister to prevent enlargement
7. Let the fluid drain and collect with gauze, leave the overlying skin in place
8. Repeat this as often as new blisters are noticed; daily check-ups are recommended

Figure 1. Blisters and acute wound in epidermolysis bullosa patient.

Figure 2. Chronic wound in epidermolysis bullosa patient.

In general, dressings can be separated into those that provide moisture, and those that provide absorption. The presence of dry crust or necrotic tissue requires using a dressing that provides moisture, such as hydrogels or petrolatum-impregnated gauze. On the other hand, the presence of excessive moisture or exudates requires dressings with absorption capacity such as hydrocolloids, foams, or alginates (Table 2 provides a summary of dressing types and their characteristics).

Epidermal Margin/Extracellular Matrix

Keratinocytes are the backbone of the epidermis. In normal wound healing keratinocytes move across the wound bed to re-epithelialize. However, in nonhealing wounds keratinocytes are abnormal and are incapable of normal migration (27). In the non-EB wound this lack of migration is clinically represented as a hyperproliferative wound edge. This is typically not seen in chronic wounds in EB and if a hyperproliferative wound edge is encountered one always needs to be concerned about squamous cell carcinoma. The exception to this rule is the hypergranulation tissue seen in the patients with JEB. The exuberant tissue may benefit from a short course of class one topical corticosteroids. Tables 3 and 4 present a step-wise approach to acute and chronic wound management in EB.

OTHER MANAGEMENT ISSUES IN EB WOUND CARE

Pain management is essential in the overall EB care. Medications such as acetaminophen, ibuprofen or codeine can be administered 20–30 min before dressing changes to minimize the pain associated with handling of the skin. Topical nonsteroidal anti-inflammatories may be of benefit for some patients if applied prior to wound cleaning and dressing; however, their use may induce a burning sensation when applied to the open skin. A pain management specialist should also be considered as part of the interdisciplinary care of these patients.

Trying to minimize trauma is also important for these patients. Protection of the existing wounds, as well as avoiding pressure or friction to the wound are important to prevent further blistering in the area and to allow healing.

An early, proactive intervention to optimize nutritional status is encouraged not only as part of the well-being of these patients but also to insure proper wound healing. This may involve placing of a G-tube to facilitate meeting the caloric requirements, prophylaxis or treatment for constipation, prevention and treatment of

TABLE 3. *Step-Wise Approach to Acute Wounds in Epidermolysis Bullosa Patients*

1. Clean area with normal saline and gently pat skin dry
2. In noninfected wounds Aquaphor or petrolatum can be used before applying dressing, if indicated apply antibiotic cream (Polysporin—Warner Lambert Consumer Healthcare, Flamazine—Smith & Nephew or mupirocin) using a tongue depressor thinly and evenly on dressing to avoid friction. Avoid antibiotics that are highly sensitizing (for example Neosporin)
3. Silicone dressings are the best choice to cover acute wounds (example Mepilex, Mepitel, Mölnlycke Health Care)
4. Cover wound with selected dressings; if Mepitel (Mölnlycke Health Care) is used as primary dressing, a secondary dressing such as Telfa (Kendall Company Ltd.) can be used to cover the area and secure with Mepitac (Mölnlycke Health Care), Cling or burn net
5. Mepitel (Mölnlycke Health Care) can be washed using tap water and re-used if necessary
6. Silicone dressings can be used for up to 7 days
7. Do not use tape on skin. If tape is needed use silicone tape (for example Mepitac, Mölnlycke Health Care)
8. Demonstrate to caregivers a dressing application on an acute wound
9. If the dressing sticks to the skin reassess the bandage
10. Do not remove dressings that are stuck to the skin, soak with normal saline for about 15 min or until you feel the dressing will come off without lifting the skin or use spray that removes adhesiveness
11. Avoid daily dressings. If wounds are clean and healing well, daily changes are not necessary

gastro-esophageal reflux, assessment and dietary interventions by a nutritionist (36–38).

In addition, treatment of anemia either by iron supplementation and or blood transfusions is essential for proper wound healing. Figure 3 presents a global approach to wounds in EB.

BIOLOGIC DRESSINGS AND FUTURE DIRECTIONS

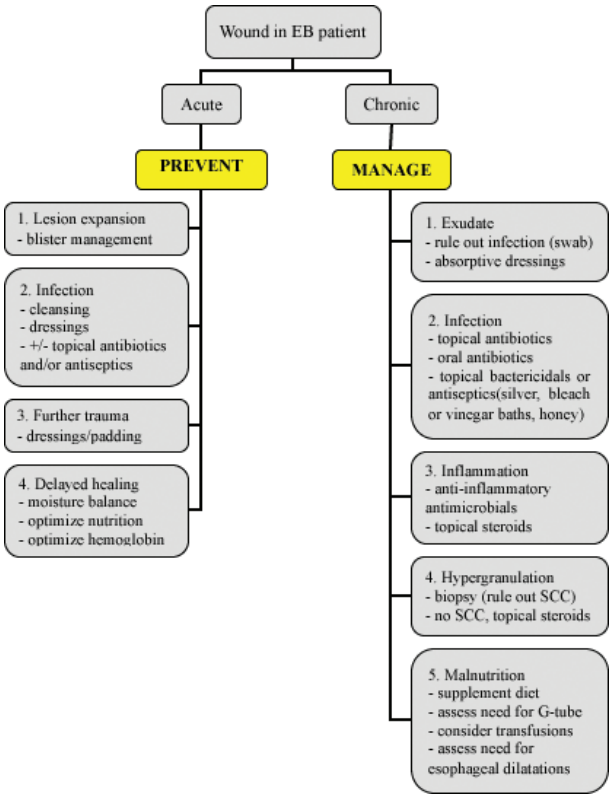

Figure 3. Approach to wounds in epidermolysis bullosa.

Treatment of difficult wounds may involve using artificial skin substitutes [dermal allografts (39), living bi-layered skin equivalents (e.g., Apligraft) (40)], biologic dressings [amniotic membrane grafting (41)], and growth factors such as platelet derived growth factor.

The development of bioengineered skin products had a positive effect in wound healing among a small number of EB patients. Dermagraft is a fibroblast-derived skin substitute example of this technology. This is a skin graft made of human fibroblasts harvested from neonatal foreskin (42). In a series of four patients with RDEB, 22 persistent wounds were treated with Dermagraft resulting in 20–100% epidermal coverage after 8 weeks (42).

Although the authors have no experience with these products, other biologically active dressing available include Apligraft (Organogenesis), Oasis (COOK Biotech, West Lafayette, IN, USA), Epicel (Genzyme Corporation, Cambridge, MA, USA), OrCel (Forticell Bioscience, Inc., New York, NY, USA), Integra bilayer matrix wound dressing (Integra NeuroSciences, Plainsboro, NJ, USA), and newer ones are currently being developed.

The use of amniotic membrane for EB has been reported in few patients, and remains promising (41,43,44). The amniotic membrane is thought to promote wound healing by preventing scarring, reducing inflammation, stopping the formation of blood vessels, and minimizing infection (45). The literature describes a patient with DEB who experienced spontaneous epithelialization after 1 week of the application of amniotic membrane, and reported pain and immobility improved in only a few hours (43). In another report, amniotic membrane was applied to nonhealing ulcers in three patients with RDEB, and they all experienced significant pain relief, with healthy granulation tissue appearing 3 days after

TABLE 4. *Step-Wise Approach to Chronic Wounds in Epidermolysis Bullosa Patients*

1.	Chronic wound management is generally painful; pain control may be needed more frequently and not only for dressing changes
2.	Clean technique should also be used for chronic wounds (hand-washing and gloves)
3.	Carefully remove dressings
4.	If dressings are stuck to the skin, soak with normal saline for about 15 min or until you feel the dressing will come off without lifting the skin or use spray that removes adhesiveness
5.	Very carefully assess area during each dressing change
6.	If odor, drainage, or increasing pain present, take swab for culture and consider oral antibiotics
7.	If nonhealing area looks worrisome, consider biopsy
8.	Clean area with normal saline
9.	Gently pat skin dry
10.	Apply the prescribed cream (Polysporin—Warner Lambert Consumer Healthcare, Flamazine—Smith & Nephew or mupirocin) using a tongue depressor thinly and evenly on the dressing. Avoid antibiotics that are highly sensitizing (for example Neosporin)
11.	Apply dressing. Silicone dressings are the best choice, but if wound presents crusted/dry areas consider hydrogels to provide moisture or if it has lots of exudate select dressings that provide absorption to avoid maceration. With infected chronic wounds also consider silver dressings
12.	Secure dressings with Cling or burn net
13.	In highly exudating chronic wounds dressing changes may be required more frequently than with dry wounds (daily vs every 3–7 days)
14.	In chronic wounds with hypergranulation tissue, patients may benefit from short course of high potency topical steroids to reduce inflammation. If these are used, monitor patients closely and prescribe small amounts of steroids

the application and it was noted within 2–10 weeks after (41). More recently, a report of eight applications of amniotic membrane in two patients with RDEB showed that a significant clinical response (defined as $>50\%$ improvement) was observed in four of eight applications (44). The use of amniotic membrane has been reported to be safe; however, further data are required to determine its efficacy in EB (46–49).

CONCLUSIONS

The treatment of wounds in patients with EB may be challenging for the health care professionals and the family providers. Understanding the wound healing process and special circumstances of the wounds in patients with EB is important for optimal treatment.

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