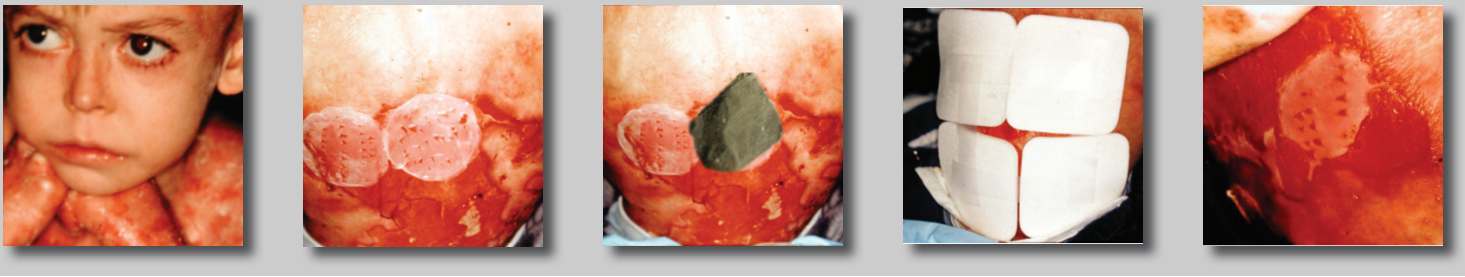
A Consensus Approach to Wound Care in Epidermolysis Bullosa



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Abstract

Epidermolysis Bullosa (EB) is a group of inherited diseases with 4 subtypes. This disorder is a model for fragile skin with some affected individuals having chronic, difficult to heal wounds. The assessment and treatment of wounds in persons with Epidermolysis Bullosa can be guided by the Wound Bed Preparation model. This holistic patient approach evaluates factors that may delay healing and patient centered concerns including pain, itch and activities of daily living. Local wound care is a challenge to optimize wound debridement, infection/inflammation and moisture balance. Stalled but healable chronic wounds may be stimulated by advanced therapies (Edge Effect) or optimizing patient care for replacement of defective genes (e.g. increased Type 7 collagen production post bone marrow transplant).

This review evaluates the clinical features that distinguish the various subtypes of Epidermolysis Bullosa, the frequent medical complications and prognosis. The care is best provided by an interprofessional team.

The treatment of chronic wounds is outlined with a quick reference guide of 12 recommendations from the 13 expert panel members. These recommendations have been reviewed by a computer-facilitated modified Delphi process where 15 external reviewers (68.8% of reviewers reported having 11 or more years experience with EB care) independently had a score of 80% strongly agreed or somewhat agreed with each of the recommendations.

FRONT COVER IMAGES

Application of Apligraf in a patient with recessive dystrophic EB

A person with recessive dystrophic EB had 50% of his back ulcerated for 3 years. He had 2 pieces of a living skin equivalent applied (Apligraf human dermal fibroblasts + bovine type 1 collagen under a human epidermal cell layer). One piece had silver dressing plus moisture-balancing foam, while the other piece had only a moisture-balancing foam. One week later, only the piece with the silver dressing plus foam survived (bacterial balance + moisture balance of wound bed preparation).

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Persons with Epidermolysis Bullosa and Wound Bed Preparation

R. Gary Sibbald and Elena Pope, Co-Chairs on behalf of the Epidermolysis Bullosa–Wound Bed Preparation panel

Persons with Epidermolysis Bullosa (EB), particularly the Recessive Dystrophic EB (RDEB) and Junctional subtypes, are plagued with lifelong chronic wounds and infections. This best practice consensus paper examines the issue of Wound Bed Preparation that was literally "born on the back" of Alex, a person with EB. We now have extended this knowledge for the benefit of all persons with EB.

This project united Epidermolysis Bullosa experts with wound healers (basic scientists, physicians and nurse clinicians) with a pioneer in Bone Marrow Transplantation. Our aim was to facilitate the knowledge of the 4 different subtypes of Epidermolysis Bullosa so that affected individuals are recognized early and receive appropriate symptomatic treatment, including optimal local wound care to prevent life-threatening infections and failure to thrive. Clinicians also need to be aware of complications such as cardiomyopathy and squamous cell carcinomas (persistent inflammation leads to malignant transformation) that may occur even in childhood.

In January 1997, Canada was the first county in the world to approve an artificial skin substitute grown *in vitro* (Graftskin: bovine type 1 collagen with human fibroblasts & an epidermal cell layer). In February 1997, Alex had 2 pieces of Graftskin (Apligraf, Organogenesis, Canton MA) placed on the upper part of his extensive back ulceration (covering 50% of his back for 3 years). One week post application, the skin substitute (with fluid release slits to maintain contact) under the silver + foam dressing was intact. In contrast, the other skin substitute piece without the bacterial balancing silver was destroyed by the local collagenase partly produced by the pseudomonas organisms. Subsequent applications of both vicryl skin substitute populated with human fibroblasts (Dermagraft, Advanced Biohealing, La Jolla CA) & Graftskin, resulted in complete wound healing of Alex's back. Although Alex is no longer with us as a result of cardiomyopathy, his contribution to our better understanding of local wound care has shaped what clinicians know today.

We have subsequently published the Wound Bed Preparation Model (WBP: Sibbald *et al.* 2000, 2003, 2006-7-10, 2011)[1-4]. The WBP model includes treating the whole patient, patient centered concerns and local wound care. Ideally, treatment of the cause involves replacing type 7 collagen for RDEB patients through bone marrow transplants or other gene modifying therapies. Treating the cause also includes optimizing other co-factors involved in healing, such as nutrition (e.g. supplements and early insertion of feeding tubes) and correction of anemia. The components of local wound care are: DIM before DIME: **D**ebridement, **I**nfection/**I**nflammation control, **M**oisture balance before the **E**dge effect for advanced therapies (e.g. skin substitutes for stalled but healable wounds). Local wound care has been improved with local silicone mesh products, soft silicone foam coatings and silicone tape.

Wagner *et al.* published a seminal article in the *New England Journal of Medicine* in August 2010 reporting on the first 7 patients with RDEB undergoing immunoablative chemotherapy and allogeneic stem cell transplant[5]. Of the 7 patients, one died of cardiomyopathy pre-transplant & a second patient died of infection and transplant rejection 183 days post-transplantation. All recipients had a reduction in new blister formation between days 30 and 130 post transplantation. Five of the 6 recipients had an increase in type 7 collagen without forming the complete normally seen anchoring fibrils.

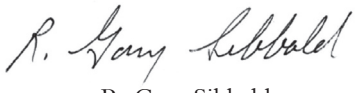
There are two concerns for transplantation procedures. First, the small number of individuals eligible for transplant may develop HLA antigens from the allogeneic cells in the skin transplant increasing the potential for rejection of a BM transplant. Second, older individuals with RDEB (especially after age 20) are very susceptible to aggressive squamous cell carcinomas and the immunosuppression associated with allogeneic stem-cell transplantation may increase this susceptibility.

We currently have come full circle to apply the principles of wound bed preparation, specifically for persons with Epidermolysis Bullosa, not only to optimize healing but also to prevent infections and other complications pre and post bone marrow transplantation. We are also suggesting strategies for persons with EB and their circle of care (parents and health-care providers) in resource poor areas where linkages to EB experts will help improve diagnosis and treatment.

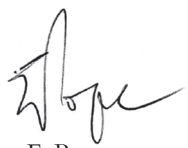
EB also represents a model for fragile skin found in the elderly, Skin Changes at Life's End (SCALE) & other persons suffering from chronic disease or immunosuppression, therefore the principles discussed in this document can be applied to other patient populations with skin fragility.

This supplement is dedicated to all persons suffering with EB in an attempt to improve their quality of life. We would specifically thank Alex Melkic & Deanna Molinaro from whom we have learned so much.

References:
1. Sibbald et al. WBP 2000 OWM
2. Sibbald et al. WBP 2003 OWM
3. Sibbald et al. WBP 2006 Wound Care Canada, Advances (2007) WHO (2010)
4. Sibbald et al. WBP 2011 Advances and WCC
5. Wagner NEJM 2011



R. Gary Sibbald



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A Consensus Approach to Wound Care in Epidermolysis Bullosa

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EB Team and Affiliates

Collaboration of...Knowledge and Expertise

Introduction

Epidermolysis Bullosa (EB) is a group of inherited diseases characterized by mechanical fragility of the skin and mucous membranes. **There are four different subtypes of EB** resulting from structural protein gene mutations at the cutaneous basement membrane zone (BMZ) or the relatively rare, suprabasal cell-cell adhesion desmosomal proteins. The recent consensus classification divides EB into four main types according to the plane of blister formation at the dermal-epidermal junction (DEJ) (simplex, junctional, dystrophic and mixed), with each type determined by the specific protein defect[1]. The severity of mucocutaneous and other organ disease varies considerably between types of EB. In the various subtypes of EB, mucocutaneous and other organ distribution is largely determined by the nature of mutations and the gene penetration resulting in different expression profiles of causative EB genes[2,3].

When possible, **the complex care of patients with EB is best provided by an interprofessional specialized team**. In the absence of a cure, supportive wound care and early recognition and treatment of complications are the mainstays of patient management.

Wound care in EB populations poses unique challenges. A highly individualized treatment plan is needed for each patient due to the clinical variability of the many types and subtypes of EB. Overall cost to the family and health units must be considered in deciding how to treat the widespread skin involvement common to many patients. The clinical decision process is further complicated by the myriad of available wound care products.

To date, there are no specific wound care guidelines that address the unique problems of the EB population. A group of international experts in the field of EB, wound care, microbiology, infectious diseases and bone marrow transplantation met for three days in Alton, Ontario, Canada and developed a list of 12 recommendations for addressing wound care in patients with EB. Using an online-based modified Delphi method of generating consensus, the list was translated into a survey that was completed by 15 other experts around the world (Table 1) and then further refined into a list of recommendations (Table 2).

Table 1

EB EXTERNAL REVIEWERS	
Karen Wiss (USA)	Celia Moss (UK)
Edward Barrett (Canada)	Agnes Schwieger (Canada)
Rosemarie Watson (Ireland)	May El Hachem (Italy)
Anna Bruckner (USA)	Louise Fret-Lalonde (Canada)
Annmarie Ormonde (Italy)	Dedee Murrell (Australia)
Anne Lucky (USA)	Andrew Lin (Canada)
Michelle Lee (Canada)	Francis Palisson (Chile)
Gerry Kelly-Mancuso (USA)	

A. Treat the Cause

The cutaneous clinical findings in all types of EB are the result of **skin fragility leading to bullae formation**. There is a wide spectrum of presentations, varying from very mild forms [e.g. EB simplex (EBS), dominant dystrophic EB (DDEB)] to disfiguring disabling and life-limiting disease [e.g. Junctional EB (JEB), recessive dystrophic (RDEB)].

The clinical presentation, morbidity, and mortality of this group of conditions are the result of skin involvement and mucosal blistering (eyes[4,5], oral mucosa , gastrointestinal tract[6], genitourinary tract[7,8], respiratory tract). In addition, anemia, cardiomyopathy[9,10], renal failure, respiratory failure, osteoporosis including fractures[13], chronic malnutrition and growth failure[13] are frequently encountered in severe cases.

While traumatic blistering is the norm in EB, the extent, depth, and healing of the wounds is subject to wide inter-patient variations largely dependent on the type of EB. It is well recognized that many milder EBS patients have limited blistering and healing is the norm with minimal skin care or systemic intervention. ***In contrast, severe generalized RDEB patients have chronic, non-healing ulcers covering large areas of the skin that lead to scarring and contractures***. However, the severity, extent and location of blisters are subject to, but not predictive of the disease type. This is important to keep in mind particularly in the first few months of life, as the extent of the skin blistering can be underestimated. The ability to heal is also influenced by other factors such as bacterial load, malnutrition and low levels of hemoglobin.

Wound Bed Preparation is a framework for assessment, diagnosis and treatment of wounds along the continuum toward optimal healing[14]. This process includes the treatment of the cause and patient centered concerns prior to instituting best practices for local wound care (DIM before DIME: Debridement, Infection and Inflammation, Moisture Balance & Edge Effect for healable but "stalled" wounds).

Table 2: Wound Care Recommendations for Persons with Epidermolysis Bullosa

Main Themes	Specific Themes	Specific Recommendations
A. Treat the cause	1. Assess the patient's ability to heal	· Evaluate EB type specific involvement (simplex, junctional, dystrophic, Kindler syndrome) and co-morbidities · Consider age of the patient · Assess nutrition status: growth centiles, BMI · Monitor hemoglobin levels
	2. Develop individualized goals and plan of care	· Low hemoglobin consider: Fe supplementation, transfusion(s) · Low albumin: protein supplements, feeding tube, etc. · Address other specific sub-type involvement
B. Patient centered concerns	3. Address and support management of patient centered concerns to enable healing	Pain: · World Health Organization pain ladder for nociceptive pain · Neuropathic pain: consider tricyclics, gabapentin, pregabulin · Local or topical approaches · Non-pharmacological approaches Itch (only partly histamine mediated) · Combine non-sedating H1 antihistamine in the morning with sedating preparations at night · Consider liquid quick onset preparations for breakthrough Activities of Daily Living · Consider rehabilitation consult
	4. Provide education and support to the patient/parent and their circle of care to increase treatment adherence*	· Build confidence with patient and their circle of care individuals, to increase adherence · Develop interprofessional team · Explore the support from established EB centers Consult: · ebcare network (owner-ebcarenetwork@lists.stanford.edu) · dEBra foundations (www.debra-international.org; http://www.debra.org/international)
C. Local wound care	5. Assess wound locations and characteristics	· Location · Target wound or wounds · Longest length x widest width at right angles · MEASURE mnemonic
	6. Gently cleanse wounds with low toxicity solutions	· Saline, water or acetic acid (0.5%-1.0) · Consider baths, whirlpool +/- with salt, bleach, other antimicrobials
	7. Debridement	· Drain blisters with a sterile needle to prevent tracking BUT LEAVE ROOF ON BLISTER · Consider non-traumatic conservative debridement of slough
	8. Assess and treat	· Superficial critical colonization (NERDS) & abnormal inflammation · Deep/surrounding tissue infection (STONEES) / generalized inflammation
	9. Select an appropriate dressing/topical therapy based on the subtype of EB	· Autolytic debridement – alginates, hydrogels · Superficial critical colonization –silver, honey, PHMB · Moisture balance with silicone coatings to prevent trauma, pain
	10. Evaluate the expected rate of healing or reassess wound goals of care	Reassess individuals not healing at the expected rate: · Low hemoglobin · Low albumin · Infection · Systemic organ compromise

	11. Edge effect: If a wound is stalled or the edge/other areas appear atypical, consider a skin biopsy to rule out squamous cell carcinoma or other complications prior to considering active therapeutic options	· Determine if wound is healable but stalled
		· Consider advanced or active therapies
		  · Skin grafts
		  · Living skin equivalents (beware of potential HLA sensitization for future bone marrow transplant and other procedures)**
		  · Biological agents

D. Provide organizational support	12. Consider a health care system support structure including specialized nurses, interprofessional clinics and a structured approach to new cases	· Each new case needs diagnosis and typing/subtyping ASAP · Develop health care system support for new patients (existing models) · Individual patients need community virtual interprofessional team · http://www.internationalebforum.org

*For professionals requiring further support contact DEBRA or other established EB centers

**If cellular therapy candidate (identify early, especially JEB): Use filtered blood products; consider the risk of HLA exposure with any cellular products (e.g. allogeneic skin grafting); optimization of the vaccine strategies for potentially immunocompromised individuals

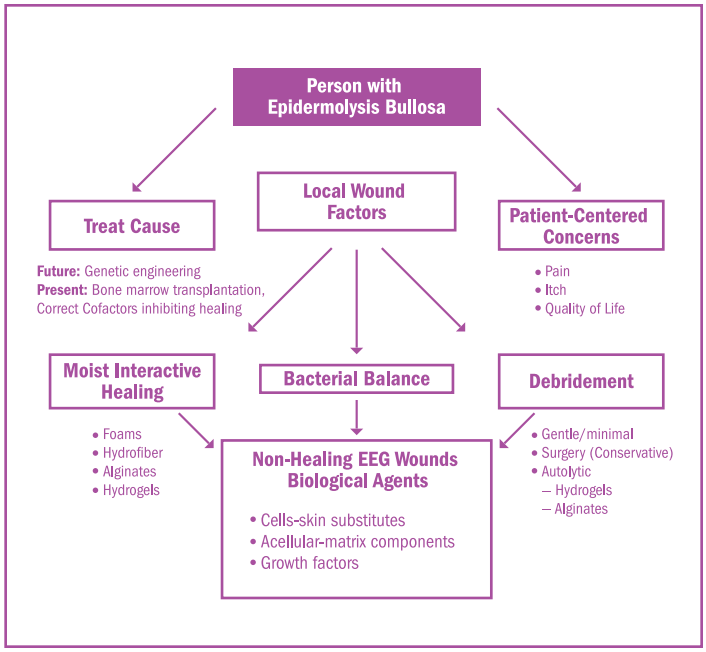
1. Assess the patient's ability to heal

1.1. Evaluate EB type specific involvement (simplex, junctional, dystrophic, Kindler syndrome) and co-morbidities.

In ***EB simplex (EBS)***, trauma-induced separation occurs within the epidermis. In the majority of cases this is at the level of basal keratinocytes, resulting from autosomal dominant mutations in either of the basal keratin genes (*KRT5* or *KRT14*, encoding keratin 5 or 14 respectively)[15]. Patients with the milder localized form of EBS (Weber-Cockayne) have predominantly acral blisters on the palms and soles, exacerbated by heat and friction. The more severe, generalized Dowling-Meara form of EBS is characterized by a classical presentation with grouped blisters that extend at the periphery resembling a string of pearls and acral blisters that lead to painful keratoderma. Dowling-Meara EBS may be very severe in infancy with a tendency for slow improvement in blistering over time. EBS with muscular dystrophy is an autosomal recessive form of EB starting with blistering from birth, followed by progressive muscle weakness after a variable interval of up to three decades. Mutations in the plectin gene (*PLEC1*) cause a deficiency of plectin, a hemidesmosomal inner plaque protein also expressed in skeletal muscle[16]. Rare recessive forms of EBS with suprabasal cleavage are caused by mutations in the desmosomal genes *PKP1* (encoding plakophilin 1, which causes skin fragility-ectodermal dysplasia syndrome)[17] or *DSP1* (encoding desmoplakin, resulting in a severe form of acantholytic EB) that is generally fatal in the neonatal period[18].

Junctional EB (JEB) is autosomal recessively inherited and characterized by blister formation at the level of the lamina lucida. Mutations in one of the three genes encoding laminin 332 (*LAMA3*, *LAMB3*, *LAMC2*) result in either the very severe Herlitz form of JEB (where severe mucocutaneous fragility, airway involvement and failure to thrive usually result in death in the first year or two of life), or the non-Herlitz form that may be severe in infancy but is generally compatible with a normal life-span[19]. The Herlitz variant of JEB has a pathognomonic presentation with peri-orificial blistering, exuberant hypergranulation tissue and periungal involvement with nail shedding. The diaper region is often particularly difficult to manage. Frequently, the presences of large denuded areas are difficult to protect from the urine and feces. When the blistering is very extensive, these patients have significant percutaneous fluid losses which can lead to anemia, hypoalbuminemia, electrolyte imbalances and increased risk of bacterial sepsis. Non-Herlitz JEB

Figure 1: Wound Bed Preparation adapted to the Person with Epidermolysis Bullosa.



(*COL17A1*)[20]. Dental enamel defects, nail involvement, patchy scarring alopecia and ocular involvement are common. A very rare form of JEB associated with gastrointestinal atresia, usually affecting the pylorus, EB with pyloric atresia (EB-PA), is caused by mutations in the genes encoding α6 or ß4 integrin (*ITGA6* or *ITGB4*) or, very rarely, plectin[21]. These proteins are co-expressed in gastrointestinal epithelia accounting for the phenotype of gut involvement. Most cases succumb in the early days or weeks although a milder clinical picture is recognized in a minority.

Dystrophic EB (DEB) may be dominantly or recessively inherited, but all forms are caused by mutations in the gene that encode type VII collagen (*COL7A1*), the major component of anchoring fibrils[22]. In contrast to other forms of EB, scarring and milia formation are a hallmark of DEB. The location of the blisters is variable from patient to patient but tends to affect trauma-prone areas. Patients with severe forms of RDEB commonly present with chronic wounds (lasting months, sometimes years) affecting large body surface areas. As the chances of critical colonization/infection increases with wound chronicity most of these patients have wounds that are "stalled" in an inflammatory phase which further delays healing. Esophageal strictures are a frequent complication, particularly in RDEB, which is generally more severe than dominant forms. Involvement of other mucosa membranes, notably the mouth and eyes, may result in blistering, ulceration and scarring.

Patients with DEB, particularly severe generalized recessive DEB, are at increased risk of developing aggressive cutaneous squamous cell carcinomas from adolescence onwards. This is the major cause of death in this subgroup of DEB patients[23].

Kindler syndrome (KS) is a rare autosomal recessive genodermatosis in which skin fragility early in life is gradually replaced by poikiloderma, scarring and photosensitivity of the skin along with gingival inflammation[24]. It is now included as a form of EB termed 'mixed', due to the variable plane of cleavage that can be seen ultrastructurally with a combination or all three levels occurring: simplex, junctional and dystrophic separation.

Before deciding on a particular wound care management strategy it is important to be able to take an inventory of the body surface area (BSA) affected, the type(s) of skin involvement (intact blisters, erosions, chronic wounds; exudative, non-exudative type) and the presence of critical colonization/infection. Ideal methods of serial assessment of wounds in EB patients are lacking. In addition, most patients are very reluctant to expose their entire skin at each visit. Often the care team needs to negotiate a rotating skin examination schedule that allows for the entire skin to be carefully inspected at least every six months. Serial photography may be beneficial for wounds that are particularly problematic. Signs of local infection such as increased redness, local pain, odour and exudate should be documented for each problematic wound.

1.2. Consider the age of the patient

The age of the patient is an important consideration when developing a wound care plan. Infants typically require a lot more control of their immediate environment in order to prevent trauma[25]. This includes, but is not limited to, techniques of gentle handling by the caregivers. In addition to selecting dressings for wounds, foam dressings should be considered to provide padding and protect bony prominences exposed to repeated trauma. The diaper area is particularly difficult to manage as it is prone to more physical and chemical trauma (friction from the diaper, frequent cleansing of the area, chemical irritation with urine and feces).

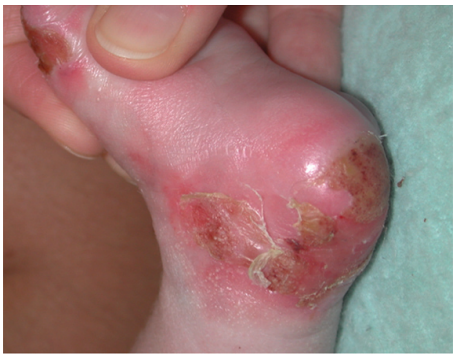
We recommend:

- Removing the elastic bands from diapers and covering them with a non-stick material.
- Avoidance of cleansing wipes to minimize friction

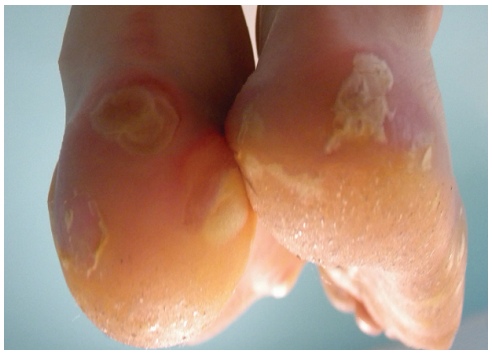
Some families of Herlitz JEB patients have found that zinc oxide paste is more soothing and effective than the use of dressings for the diaper area. As the child becomes more mobile, blistering predominantly affects the extremities. Special padding of the knees and increased attention to feet by providing padding and using special shoes may decrease the blistering. Older patients tend to have more chronic ulcers that are critically colonized and infected. Another consideration for older children and adults is the increased likelihood of colonization with antibiotic-resistant bacteria such as methicillin resistant staphylococcus aureus (MRSA). Patients with more severe forms of EB are at an ***increased risk of squamous cell carcinoma (SCC***), notably severe generalized RDEB, but to a lesser extent patient with other forms of DEB and JEB. Although this is an unusual occurrence before the second or third decade of life[26,27], it has been described in a child as young as six years old (personal communication from Dr. Mellerio).

1.3. Assess nutritional status: for children use growth centiles, for adults use BMI

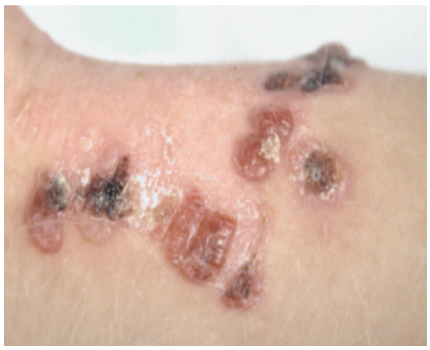
Wound healing can be delayed or interrupted in persons with existing co-morbidities. ***Malnutrition is very common in the severe types of EB***. It results from a combination of reduced intake (due to oral blisters, dysphagia, reduced mouth opening, dental pain, food aversion, esophageal strictures and gastro-esophageal reflux) and increased demands (wound healing, protein and blood loss, chronic inflammation and infection)[28,29]. The end results of malnutrition are failure to thrive, delayed puberty, and anemia. This leads to a cascade of clinical and biological events, decreasing the potential for wound healing and increasing potential further skin breakdown. Over time patients with EB can develop multiple deficiencies that contribute to delayed wound healing[29], mineral deficiencies (zinc, selenium)[30], vitamin deficiencies (A, B6, C, 25(OH), vitamin D3 and folate)[31]. A low protein intake or relative deficiency can prevent the production of granulation tissue contributing to a delay in or "stalled" healing progression. ***Albumin levels, a gross indicator of long-term nutritional deficit, less than 2.0–3.0 g/dL (normal: 3.0 to 5.4 g/dL)***[32] are associated with impaired healing. While albumin or pre-albumin levels may be helpful, blood sampling can be difficult in the severe EB population due to poor venous access. A more practical approach followed by many EB centers for assessment of the overall nutritional status is close monitoring of the growth curves in pediatric patients and BMIs in adults with EB. Regular nutritional consults (including calorimetry) to evaluate caloric needs are recommended[33].



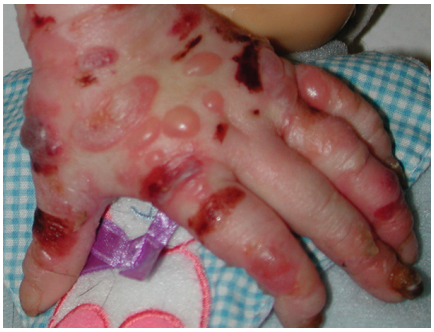
EB Simplex
heel-prick blistering



EBS
blistering and keratoderma



EBS
Dowling-Meara type
"herpetiform blistering"

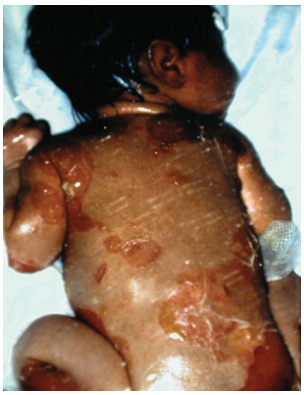


JEB
hand blistering

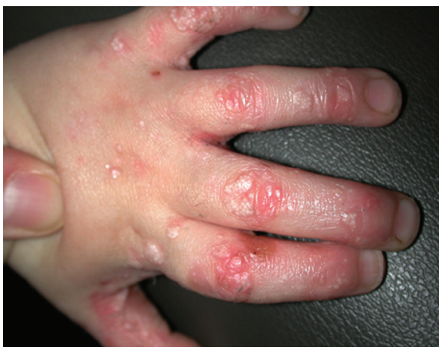
Figure 2:

EPIDERMOLYSIS BULLOSA

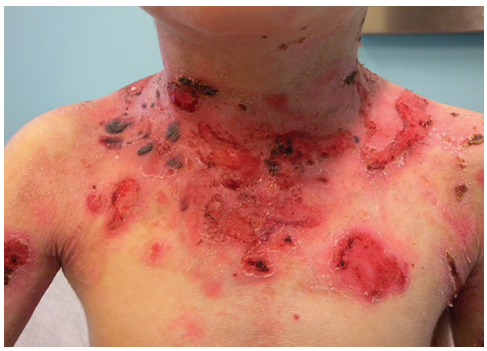
Type Specific Presentations



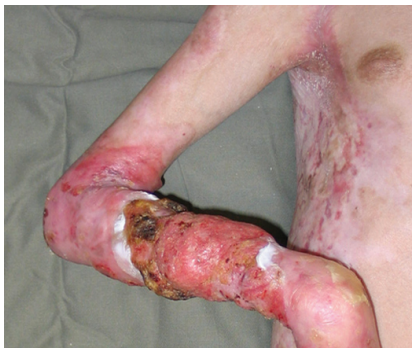
JEB
extensive neonatal blisters



Dominant DEB
milia formation



Recessive DEB
chronic neck blistering



RDEB
squamous cell carcinoma
in a chronic ulcer

1.4. Monitor hemoglobin levels: ideally over 80 g/L

Anemia is a frequent and serious complication of the severe types of EB such as RDEB and JEB. While its mechanisms are not fully understood multiple factors are likely involved:

- increased blood loss through the skin and GI tract
- decreased red cell production secondary to chronic inflammation
- iron deficiency and decreased iron utilization
- deficiencies of vitamin B12, folate and other minerals[27]

For persons with pressure ulcers, it has been proposed that hemoglobin less than 100 g/L may cause impaired wound healing due to decreased tissue oxygenation[34]. The low hemoglobin levels in EB patients are one of the factors that are likely to be associated with delay or "stalled" healing in these patients.

The panel's consensus for EB related wounds was to aim for hemoglobin levels of 80 g/L or above as this is a more attainable goal and may avoid potential long-term complications of iron overload from intravenous iron therapy or red cell transfusions.

2. Develop Individualized Goals and Plan of Care

The interprofessional team should develop an individualized wound care plan after a thorough comprehensive assessment. The plan must be tailored to the individual and take into consideration his/her unique ***biopsychosocial needs.***

Biopsychosocial Need	Considerations
Individual personal preferences	· Reflect, respect & integrate experiences and feedback from the patient and those in circle of care
Risk factor	· EB subtype specific
Comorbidities	· Anemia · Malnutrition · Cardiomyopathy
Quality of life issues	· Pain management · Frequency of the dressing changes · Interference with daily activities · Schooling and/or employment
Support systems/ circle of care	· Consider who performs the skin care · Access to home care · Specialized EB teams
Access to care	· Specialized EB interprofessional team

Individualized patient preference must be respected and reflected in the plan of wound care[35]. Sackett *et al.* recognized three dimensions of equal importance: best available scientific evidence, clinical expertise and patient preference. It is common for EB families to have "time-tested" exceptional wound care routines that do not necessarily follow the currently accepted medical wisdom. Over the years we found that a flexible approach that includes the family and patient preferences is most likely to increase adherence, satisfaction with care, and improved outcomes.

With the new exciting, disease modifying cellular therapies that are currently emerging[36], it is also important to maximize the chances of each patient being a potential candidate for these therapies. Early recognition of JEB-Herlitz is one example.

Care for Potential Candidates of Disease Modifying Cellular Therapies	
Maintain overall health by preventing, recognizing & treating disease related complications	· Anemia · Malnutrition · Cardiomyopathy
Minimize risks of exposure to antibodies	· Use filtered blood products · Consider risks of HLA exposure with cellular products such as allogeneic skin grafting
Optimizing vaccination strategies for potentially immune-compromised individuals	· Ensure compliance with vaccination schedule before procedures

The wound care plan should be clearly outlined in a written document that is given to the family and copied to the health records, family practitioner and home care personnel. The care plan should also be evaluated and updated regularly.

2.1. Low hemoglobin consider: Fe supplementation, transfusion(s)

To date, there is not an ideal management strategy for dealing with anemia in EB patients. A pathogenic based approach is sensible, but not always possible. Using adequate skin care and preventing/ treating infection can minimize blood losses through the skin. Oral iron supplementation for correction of iron deficiency is widely used but its individual effectiveness varies. Patients frequently report gastrointestinal upset and constipation as reasons for non-adherence. Poor iron absorption may further limit how well replacements works[27]. Intravenous iron[37] plus erythropoietin has been documented as being beneficial in small studies of

RDEB patients[38]. Blood transfusions should be considered for cases where Hgb levels are consistent below 80 mg/dL and/or for symptomatic patients who do not respond to other measures.

2.2 Treat low albumin: optimize nutrition, protein supplements, feeding tube

In order to optimize nutritional status, EB patients may need a gastrostomy tube (G-tube). Although there are no clear guidelines for use in the EB population, indications for G-tube placement include: recurrent aspiration due to uncoordinated swallowing, ongoing difficulties with oral intake including administration of medication, significant weight loss or failure to gain weight and "falling off" growth curves for infants and children[29]. Gastrostomies are reported in up to 40% of patients with JEB-Herlitz and in 4.2% of patients with RDEB[39], although these numbers are currently likely to be higher[40]. With a G-tube in place it is easier to provide supplementary feeding at night while encouraging oral intake during the day. Supplementation of identified deficiencies is commonly suggested by many EB centers and 6 to 12 monthly monitoring to identify them is endorsed[29].

B. Patient Centered Concerns

3. Address and support management of patient centered concerns to enable healing

3.1. Pain

Patients have a disease, but experience an illness and related suffering. This is particularly applicable to pain.

Pain is the most common symptom experienced by patients with EB, irrespective of the subtype.

The frequency and severity of pain is often proportional to the disease severity, with up to 50% of the patients with the most extensive type of EB (RDEB) experiencing daily pain >5 (0 to 10 scale)[41]. While the cause of pain in EB is multifactorial, the skin and related EB lesions are by far the most significant source of pain. The pain can occur at rest due to pressure exerted on blisters and denuded skin, secondary infection, friction and shear from bandages with physical movements. Pain can also be triggered or exacerbated by trauma during dressing changes or bathing and other activities of daily living. The assessment of pain is conducted using various standardized tools that are age appropriate e.g. faces scales for young children and a visual analog scale or 0 to 10 numerical rating scale[42]. Multidimensional pain instruments should be considered for a comprehensive evaluation of pain and its impact on patients. Behavioral indicators of pain have also been developed for infants and those who cannot verbalize their pain. These tools are easy to administer in a variety of clinical circumstances, including at home by the family members. In order to develop an adequate pain management approach, pain levels should be recorded before, during and after dressing changes, bathing and other painful interventions[43].

Consideration of other patient-related factors (anxiety, previous experiences, lack of comfort, depression) is important in the understanding of pain experience. These factors should be recognized and treated separately from wound-related pain. The impact of chronic unrelenting pain can be devastating, eroding the individual's quality of life and constituting a significant amount of stress for patients and their families. Each patient is unique and may have individual preferences for approaches to manage pain including the use of medication (long acting, short acting, nociceptive and neuropathic agents) and other non-drug and complementary strategies (e.g. acupuncture, music, distraction, massage). It is considered best practice to assess pain on an ongoing basis, to compare pain between dressing changes to acute pain that is repetitive at dressing change or incidental pain with procedures including surgical debridement. Regular pain assessments also provide the temporal pattern and identify potential aggravating and alleviating factors for pain[44].

Increased levels of stress have been demonstrated to lower pain thresholds and decreased tolerance. The result is a vicious cycle of pain, stress/anxiety, anticipation of pain, and worsening of pain. Increased stress also activates the hypothalamic-pituitary adrenal (HPA) axis producing hormones that modulate the immune system, thus compromising normal wound healing[45].

The approach to pain in an EB patient includes preventative and therapeutic modalities[46]. Prevention strategies include, but are not limited to, the use of protective atraumatic dressings, padding of the trauma prone areas, releasing fluid from tense blisters, avoiding adhesive dressings or skin adhesive products, removing dressings in water to hydrate the surface and limit friction with removal and treatment of skin infections.

Adjunctive non-medication pain therapies that have been described as being beneficial include physical modalities such as ice packs, vibration, distraction, relaxation and music therapy.

Table 3: Pain Management Strategies

Pain Management Strategies	Goals/Types	Actions
Preventative	Avoid trauma Avoid blister expansion Prevent local infection	· Protection, use foam dressings, use soft sleeping and seating surfaces · Clothing and shoe modification · Release fluid from blister, maintain roof of blister over affected area · Cover open areas · Control local colonization · Use of hand cleansers by caregivers prior to dressing changes
Therapeutic	Pharmacological	Nociceptive: · mild pain: Acetaminophen ± NSAIDS · moderate pain: Acetaminophen ± NSAIDS + morphine · severe pain: Acetaminophen + NSAIDS + morphine/other strong opioids
	Non-pharmacological	Neuropathic: · tricyclics (nortriptyline, desipramine), gabapentin, pregabulin, other anti-epileptics · relaxation/distraction · biofeedback · physical modalities (e.g. vibration, cooling)

NSAIDS = non-steroidal anti-inflammatory drugs

In circumstances where pain is anticipated (e.g. dressing changes), adjunctive procedures should be considered in conjunction with medical therapy. Therapeutic pain medication can be delivered topically and systemically (Table 3). Some potentially useful topical options include: addition of salt to the bath water to make it isotonic[47]; and using dressings with silicone contact surfaces to prevent pain and trauma on removal (e.g. Mepitel®, Mepilex®, Molnlycke, Sweden) or expert opinion on the use of dressings that have analgesics (Foam dressing with slow release ibuprofen: Biatin-IBU, Coloplast, Denmark not available in the USA).

In order to decide on the best pharmaceutical intervention, the mechanism of pain should be explored. ***In general, wound-associated pain is both nociceptive and stimulus-dependent (gnawing, aching tender, throbbing) vs. neuropathic or non-stimulus-dependent or spontaneous pain (burning, stinging, shooting, stabbing)***. Nociceptive pain is treated with the WHO pain ladder medication starting with aspirin and non-steroidal anti-inflammatories and then progressing to weak and strong narcotics (Table 3)[48].

Short acting agents are often used to determine the dose of longer-acting agents with the short-acting agents then reserved for breakthrough pain including administration 30 to 60 minutes before dressing change. Neuropathic pain often responds to tricyclic agents, particularly second-generation agents high in anti-noradrenalin activity. Nortriptyline and desipramine are often better than amitriptyline. For non-responders results may be better with alternative agents such as gabapentin, pregabalin or other anti-epileptics[48].

Procedural pain (e.g. before dressing changes, bathing) should be managed with an interprofessional approach, reflected upon and communicated to those within the circle of care. This is especially important in the care of EB children as they often required repeated unpleasant procedures. If procedural pain is not adequately managed, long-lasting negative outcomes may result and the therapeutic relationship could be jeopardized, therefore care planning is essential to procedural pain management. Oral sucrose 24% is a useful, short-acting analgesic that is effective for children under two years of age[49]. For older children and adults, acetaminophen or morphine administered 30 minutes prior to the procedure may be used. Non-pharmacological modalities (Table 3) are also helpful in combination with the pharmacological measures listed above. In the general population, music therapy has been found to improve patients' moods when experiencing anxiety during care delivery[50] and for depression[51]. Music therapy has been used successfully in several EB clinics to manage the pain and anxiety associated with wound care assessments.

3.2. Itch

Itch, also known as pruritus, can be a most distressing experience for any individual with skin disorders and is often affiliated with depression, sleep impairment and overall distress [52]. Kini *et al.*(2011) commented on their study findings: "Chronic pruritus has a substantial impact on Quality of Life (QoL), one that may be comparable to that of pain. The severity of symptoms and the use of support networks are the main factors that determine the degree to which patients are affected by their symptoms. Addressing support networks in addition to developing new therapies may improve the QoL of itchy patients."

Itch is a common symptom in the EB population. The exact mechanism is not known: abnormal persistent skin inflammation, overheating due to dressings, local sensitizers, and the use of systemic opioids that are histamine releasers are all potential contributors[46]. The pruritus leads to more skin blistering from skin trauma, which in turn exacerbates the pruritus. Itch is often a poorly controlled symptom in most patients with EB as there is not one modality that targets all potential pathogenic components including histamine, slow reacting substances or prostaglandins.

Management should start with a thorough history to identify the timing when itch is more severe and factors that will exacerbate itch. Occasionally changing the topical routine (switching dressings or discontinuing topical antibiotics) may be sufficient to bring the pruritus down to a manageable level. Establishing the time of the day when itching is most significant is also important.

Itching at night may be related to body overheating and can be treated with sedating antihistamines (e.g. Hydroxyzine) or a tricyclic antidepressant with prominent H1 antihistamine action (e.g. doxepin). Apart from sedation, the advantage of using tricyclics is their mild antidepressant effects (doxepin at higher doses).

Daytime pruritus requires the addition of a non-sedating antihistamine H1-blocker such as Cetirizine or Loratadine. Using H1 antihistamines from different chemical classes can give a synergistic effect on the competitive blocking of the H1 blocker with some other agents such as Ketotophen having additional mast cell stabilizing properties as well. Liquid preparations are always preferable for breakthroughs as they have a shorter onset of action, are easier to swallow and can be administered via G-tubes. For persistent itching there are anecdotal reports of successful use of Ondansetron or low dose Gabapentin[46]. Clinicians should be aware of potential sensitizers that can trigger itch in dressing and other topical preparation. According to studies fragrance is one of the most common skin sensitizers[53].

3.3. Activities of daily living

Pain, odor, mobility limitations have a significant impact on the EB patients and their daily living. The disease burden may include a difficulty performing personal care, difficulty in engaging in school or employment activities, increased financial burden and ultimately impacts on engagement in and enjoyment of life. Depression and anxiety are also common[54] and further contribute to social isolation. Fostering independence and safety during activities of daily living may help to decrease the burden of disease, and reduce dependence on others. ***Significant environmental modifications (e.g., special seating in baths, wheelchairs, footwear) have to be put in place to diminish the amount of trauma and suffering that these patients experience and to make their environment functional for their needs***. A rehabilitation consult early on with frequent re-evaluations is recommended.

EB can have a detrimental aspect on individual's image of self. In addition to appearance, odour and leakage from wounds often prohibit patients from engaging in social activities that people would take for granted. It is important to remember that most patients grow up with the disease and the impact of social isolation and disruption of daily routine (e.g. schooling) on personality development can be tremendous.

4. Provide education and support to the patient/parent and their circle of care to increase treatment adherence (compliance)

In order to provide support and education to an EB patient, ***one has to gain the trust of the patient and his/her family by developing a therapeutic relationship***. This occurs when trust, communication and open dialogue allow the patient and those in their circle of care to understand that each person involved has a meaningful contribution. Having a patient assist with the decision-making process provides reassurance that the team is working with them. A constant dialogue with all key players is very important. EB families often develop highly individualized unconventional routines that are very difficult to change either because of the feasibility of implementing new treatment modalities or because of a learned distrust of the medical community.

EB is a complex multisystem disease; therefore communication among various health care professionals is paramount. We realized that a centralized, interprofessional approach that includes care coordination including open communication with the general practitioner and homecare team is the most effective way of caring for these patients. The burden of caring for these patients is taxing for the health teams. As not all patients can be looked after in specialized centers, non-EB practitioners should seek support from established EB centers, EB care network, or DEBRA foundations.

C. Local Wound Care

5. Assess wound location(s) and characteristics

An inventory of the Body Surface Area (BSA) involved and the type of wounds (intact blisters, open blisters, erosions, ulcers, acute vs. chronic wounds, exudative vs. non-exudative) is the first step in the developing a wound care plan. There are very limited tools available for determining the extent of skin involvement. Classical methods such as the palm method, used for burn patients[55], are not feasible given the multiple stages of skin blistering and difficulties in examining the entire skin at each visit. Digital photography may be helpful particularly for assessing and monitoring the progress of problematic lesions. Another objective method is the **MEASURE**[56] paradigm used for assessment of chronic wounds where **M**easure is size- longest length with the widest width at right angles, **E**xudate- amount (none, scant, moderate, heavy) and characteristics (serous, sanguinous, pustular or combinations), **A**ppearance (base: necrotic [black], fibrin [firm yellow], slough [soft yellow], or granulation tissue [pink and healthy vs. red and friable=easy bleeding], **S**uffering (pain), **U**ndermining (measure in cm and use hands of clock to document: 6 o'clock, etc.), **R**e-evaluate, & **E**dge (hyperkeratotic, macerated, normal). This method, modified for the EB population by eliminating the undermining (still MEASURE but suffering gets SU rather than S), could be used for particularly problematic non-healing wounds for the purpose of developing a wound care plan and monitoring the response over time.

The decision about the type of skin care includes the location of the wound. Other considerations are extra padding and protection, specialized dressings and feasibility for everyday use (Tables 4, 5, 6).

6. Gently cleanse wounds with low toxicity solutions

The standard of care for wound cleansing is to use solutions that are as gentle and non-cytotoxic to the wound as possible: e.g. saline, water or acetic acid (0.5-1.0%)[14]. Research has shown that certain solutions can be cytotoxic to healing cells such as fibroblasts, *in vitro*. A 2008 Cochrane Review[57] stated "***There is not strong evidence that cleansing wounds per se increases healing or reduces infection***." The Cochrane Collaboration updated its evidence reviews (2011) on wound cleansing for pressure ulcers and concluded there is "no good evidence to support use of any particular wound cleansing solution or technique for pressure ulcers"[58]. Until further evidence is available, expert opinion recommends caution for immune compromised individuals or if the tap water is not of drinkable quality. ***Avoiding cytotoxic solutions (such as Dakin's and Povidone-iodine) to cleanse healable wounds or using them only for limited periods of time is a reasonably prudent practice***. Although there is a place for these agents in the management of highly exudative wounds in order to control bioburden and odor, their applicability in the EB population is limited due to skin fragility and the pain associated with open wounds. **We recommend gentle cleansing with a body temperature adjusted saline solution or water**. Patients may experience "sticking" with non-silicone coated dressings. Soaking each individual wound for 5-10 minutes or removing the dressings in the bathtub may help reduce pain and trauma associated with the tear force at dressing removal. A dilute acetic solution (5% is white vinegar diluted to 0.25%-1.0%) will acidify water and help decreased bacteria) or bleach (5-10 ml in 5 L by acidification, releasing hypochlorous acid and coagulating protein) may decrease the bacterial carriage, and therefore be beneficial particularly if used infrequently[27].

Bathing is the preferred method of skin care for patients with EB as showering is associated with more pain[47]. Bathing will facilitate cleansing with the additional advantages of relatively non-traumatic dressing removal and supplemental antibacterial control with antimicrobials (e.g. dilute acetic acid or bleach). There is a theoretical concern that bathing may increase the bacterial pathogen colonization of previously commensally colonized skin; however, this disadvantage is outweighed by its benefits.

Table 4: Dressing choices according to indications/type of wounds

Type of Wound/indication	Primary dressing	Secondary dressing	Topical therapy
Protection	· Soft silicone foams · Modified absorbent pads · Lipidocolloid dressings · Contact layers	· Burn net to keep in place (if feasible)	· None
Open non-exudative	· Soft silicone foams · Modified absorbent pads · Lipidocolloid dressings · Contact layers	· Burn net to keep in place (if feasible)	· None
Exudative	· Soft silicone foams · Lipidocolloid dressings · Hydrofibers	· Burn net to keep in place (if feasible)	· Topical antibiotics (avoid allergens)
Eschar	· Hydrogels · Biosynthetic cellulose	· Foams · Modified absorbent pads	· None
Critically colonized or infected	Contact layer + Ag or other anti-microbial · Atraumatic foams · Hydrofibers · Alginates	· Foams · Modified absorbent pads	· Topical antibiotics (avoid allergens)
Pain	· Soft silicone coating (e.g. Safetac® Technology) · Biosynthetic cellulose · Hydrogel sheets	· Foams · Modified absorbent pads	· Topical NSAIDs
Itch	· Soft silicone coating Biosynthetic cellulose · Hydrogel sheets	· Foams · Modified absorbent pads	· Short course of topical mid-potency corticosteroids
Hypergranulation	· Contact layer +/- silver or other antimicrobial	· Foams · Modified absorbent pads	· Short course of topical potent corticosteroids

Table 5: Dressings categories, properties, indications

Type of Wound/indication	Primary dressing	Secondary dressing	Topical therapy
Foams	· Mepilex®[3] · Mepilex Lite®[3] · Mepilex Border®[3] · Mepilex Border Lite®[3] · PolyMem[2] (expert opinion from panel members)	· Contains silicone layer to make these non-adherent · Generally made from hydrophilic polyurethane · Non-occlusive. Semi-permeable surface allows exudate into the dressing and foam traps moisture	· Allow large amounts of fluid and wound drainage to be absorbed · Provide padding and protection to wounds · Depending on the amount of exudate, can be left in place up to 7 days · Some require secondary dressing to hold in place · Bordered dressing may sometimes be too sticky and should be used with caution
Hydrogels	· Gels: · Duoderm[4] · Intrasite[5] · Sheets (Cool dressings): · ActiFoamCool[6] · Intrasite Conformable[5]	· Made out of insoluble polymers that expand in water and hydrate wounds · Provide autolytic debridement	· For wounds with minimal or no exudate · Due to hydrating capacity, these offer cooling effect and may aid in relief of pain, itch and discomfort
Alginates (calcium or calcium/sodium)	· Kaltostat[7]	· Made of non-woven fibers derived from seaweed · Turn into a non-sticky gel when in contact with wound drainage	· Requires exudate · Does not work on dry wounds or wounds with eschar · Calcium alginate dressings release calcium ions that help stop bleeding
Hydrofibers	· Aquacel[7]	· Made out of sodium carboxymethyl- cellulose that when in contact with wound drainage becomes a gel and provides a moist environment	· More absorbent than alginates · Consider in wounds with heavy drainage
Modified absorbent pads	· Telfa[8] · Restore[1] · Mesorb[3]	· Thin layer of absorbent cotton fibers that are enclosed in a sleeve of perforated polyethylene terephthalate and sealed along two edges · A plastic film prevents dressing from adhering to wound surface and perforated surface allows passage of exudate into the pad	
Contact layers	· Mepitel®[3] · Mepitac® · Silflex[9] · Adaptic touch[10] · Siltape[9]	· Protective, inert material that allows non-traumatic removal (*Mepitel® scientific studies, others expert opinion*)	
Biosynthetic cellulose	· Suprasorb X[11]	· Dressing consisting of cellulose, water and 0.085% chlorhexidine gluconate (preservative) that has ability to both absorb and donate moisture	· Also considered a cooling dressing, aids in pain reduction and adding moisture to wounds · May also reduce itch
Lipidocolloid dressings	· Urgotul[12] · Restore (North American equivalent to Urgotul)	· Composed of an open weave polyester mesh impregnated with hydrocolloid polymers dispersed within petrolatum · When in contact with exudate, the hydrocolloid polymers are hydrated and constitute with the petrolatum a lipidocolloid interface that provides a non-adherent surface	· For wounds with exudate. Also used for protection of vulnerable areas

[1] Hollister,[2] Ferris Mfg.,[3] Molnlycke Health Care,[4] ConvaTec,[5] Smith & Nephew,[6] Activa Healthcare,[7] ConvaTec,
[8] Kendall Company Ltd, [9] Advancis Medical,[10] Systagenix,[11] Activa Healthcare,[12] Urgo, [13] 3M Healthcare

Table 6: Dressing choices/topical therapy for special locations/indications

Location	Dressing / topical therapy	Properties	Expert comment (opinion)
Perianal area	· Restore contact layer	· Autolytic debridement · Provides moisture	· Difficult to keep in place · Can be used to line the diaper
	· Intrasite conformable	· Autolytic debridement · Provides moisture	· Difficult to keep in place · Can be used to line the diaper
	· Bepanthen (ointment with Pro Vitamin B5)	· Aids in moisture balance	
	· Cavilon (liquid barrier film)	· Creates breathable, transparent coating on the skin	· Does not sting · Alcohol free
	· Emollin 50/50 emollient spray (CD Medical Ltd) (white soft paraffin and liquid paraffin)	· Water-repellent · Provides barrier protection	· Does not sting
Oral mucosa	· BioXtra (salivary substitute)	· Provides moisture	
	· Difflam Spray (active ingredient is benzydamine hydrochloride, and NSAID)	· Reduces pain and inflammation · Also acts as local anesthetic	
	· Corsodyl (mouthwash containing chlorhexidine)	· Provides antiseptic and disinfectant properties	
	· Gelclair (bioadherent oral gel)	· Creates barrier that protects nerve endings, reducing pain	· Can be used prior to meals
Feeding tube sites	· AMD- PHMB foam fenestrated disc dressing (antimicrobial foam dressing)	· Moisture balance · Contains antiseptic · (Polyhexamethylene biguanide, PHMB) (Effective against MRSA, VRE, gram + and gram – bacteria, fungi and yeast	
	· 4% sucralfate mixed with Cavilon	· Protectant	
PC/C lines, fixator	· Mepitac®, Mepitel® Adaptic touch, Siltape	· Non-stick	
Adhesives	· Medical adhesive remover (Hollister) · Appeel (CliniMed Ltd)or Niltac (North American equivalent) · Adhesive remover spray (Coloplast)		· Adhesive remover is temporary. · These sprays are silicone-based.
Retention bandage	· Tubifast™ · Acti-Wrap cohesive retention bandage(Activa Healthcare)	· Secures dressings in place	· Useful to fix small dressings

7. Debridement

Initially, wounds in EB patients present as blisters. To prevent blisters from enlarging, it is important to carefully puncture the blister with a sterile needle to release the inner fluid and prevent blister extension with fluid tracking. It may be necessary to puncture the blister at 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/bulla. The overlying skin should never be removed as it acts like a natural dressing and aids healing, reducing pain, and minimizing the risk of exogenous infection.

When the wound is covered with a firm dehydrated eschar or soft slough the normal healing process is impaired. ***A firm eschar serves as a pro-inflammatory stimulus that inhibits healing***, while the slough acts as a culture media for bacterial proliferation debridement. Debridement promotes healing by removing senescent cells that are deficient in cellular activities and removing biofilms that maintain the inflammatory process[59]. Debridement in the EB population—in contrast to methods for other chronic wounds—should be extremely gentle and whenever possible involve non-physical methods (i.e. autolytically using hydrogel or calcium alginate dressings).

8. Assess and treat

8.1. Superficial critical colonization & abnormal inflammation

Chronic wounds contain bacteria; however, the presence of bacteria obtained from a surface swab does not define infection. The bacterial implications for healing are dependent on the bacterial load and virulence. Contamination refers to smaller bacterial loads on the wound surface and colonization refers to the establishment of bacterial colonies in the tissue, usually without interfering with healing. Critical colonization occurs when the bacterial proliferation causes local damage and the wound to get "stuck" or stalled precluding healing. Infection is determined by the overall bacterial load, typically defined as $>10^5$ colonies per gram of tissue (i.e. $1.0x10^6$ or higher), the nature of the invading bacteria and most importantly host resistance[60]. Surface critical colonization and deep and surrounding skin infection are clinical diagnoses. The mnemonics NERDS© and STONEES©[61,62], which represent the two levels of bacterial damage or infection, have been validated for use in chronic wounds. New or increasing pain is a symptom that worsens with bacterial damage to cause superficial critical colonization or deep and surrounding wound margin infection as validated by Gardiner *et al*[14].

Any three NERDS criteria are required for superficial critical colonization and the need for a topical antimicrobial:

- Non-healing: The wound is not getting larger or smaller
- Exudate is increasing (host response to noxious damage)
- Red friable tissue (indicating over production of blood vessels due to increased VEGF production stimulated by bacteria)
- Debris: New dead slough on the surface that needs to be distinguished from shed epidermal blister roof
- Smell: This indicates the presence of gram negatives and anaerobic organisms

For deeper or surrounding skin infection and systemic therapy any 3 of the STONEES criteria are required:

- Size increasing: This is due to bacteria destroying the wound margin and/or base
- Temperature: infrared thermometry is a good measure of surrounding tissue change (mirror image >3 degree Fahrenheit warmer)
- Os is Latin for bone: exposed or probing to bone
- New areas of breakdown that indicate satellite involvement with the wound
- Erythema and or Edema of the surrounding skin that are the clinical signs of cellulitis
- Exudate increase as in NERDS
- Smell as in NERDS: If exudate/smell are present, an additional criteria is needed to define bacterial damage as superficial, deep or both

Although these concepts need to be validated for persons with EB, the need for 3 criteria is useful to help distinguish infection from persistent inflammation. Persons with EB may not demonstrate all the classical signs of deep infection but these signs should help to identify more subtle changes associated with bacterial damage.

The most common bacteria isolated from chronic and most likely EB wounds are gram-positive organisms (*Staphylococcus Aureus* and *Streptococci* species), gram negatives (*Pseudomonas aeruginosa*) and anaerobes (personal communication from R. Gary Sibbald). Documenting critical colonization/infection in the EB population is rarely needed.

Skin swabs are indicated only to determine antibiotic selection in cases where multi-resistant organisms or non-responsive infection is suspected. A proper technique is the Levine technique, i.e. rotating a bacterial swab 360 degrees over a clinically normal area of skin with just enough pressure to extract fluid[63]. The swab can be pre-moistened with the transport media if the wound surface is relatively dry. This technique requires that the wound surface be cleansed prior to collection[64].

Critical colonization can be controlled with topical agents. The bacterial load may be reduced by bathing with diluted bleach, applying compresses or using sprays with diluted vinegar[64]. Lipid-stabilized hydrogen peroxide cream (Crystacide available in the UK) is well tolerated and effective when applied directly on the wound or on the dressing that comes in contact with the colonized wound[25,63]. Topical antibiotics (e.g. Polysporin, Fucidic Acid, Mupirocin) should be used only for short periods of time and rotated every two to six weeks to prevent resistance, and clinicians should watch for sensitization. In addition, the use of potent topical sensitizers (e.g. neomycin) should be discouraged. There are a variety of dressings containing silver, honey, iodine in a cadexomer carbohydrate and polyethylene glycol slow release formulation, and PHMB (PolyHexaMethyleneBiguinide) that may facilitate a decrease of critical colonization. (Tables 4, 6). The use of antimicrobial dressings should be reviewed at regular intervals, preferably every two to four weeks, and discontinued if critical colonization has been corrected or if there is not a demonstrable beneficial effect[14]. There is currently a great tendency to overuse antimicrobial dressings, which is not cost effective.

Silver's broad spectrum of antimicrobial activity can be used in critically colonized chronic wounds that have the ability to heal. Silver must be ionized to exert an antimicrobial effect. Ionized silver requires an aqueous or water environment and should not be used in a maintenance or non-healable wound where the desired outcome is the combination of moisture reduction and bacterial reduction[14]. Silver should not be in close proximity to any oil-based products (e.g., petrolatum, zinc oxide), where the oil molecules may interfere with the ionization of the silver[14]. Products that produce a continuous supply of ionized silver are likely to be more effective and higher levels of silver release are often necessary to treat *pseudomonas*[14]. The amount of silver released from these dressings is a fraction of the silver released from silver sulfadiazine cream formulations. Silver sulfadiazine has been associated with argyria (permanent silver deposits in the dermis with a blue discoloration to the skin) and silver dressings have been associated with periwound staining but there are no published reports of argyria for patients that have not had silver sulfadiazine cream. There are anecdotal reports of high serum levels of silver after silver dressing use in Epidermolysis Bullosa (personal communication from Jemima Mellerio); therefore, despite the fact that they release less silver than silver sulfadiazine cream, their prolonged use should be discouraged especially if used on large areas or on individuals with a large surface area to total body weight.

There is evidence of effectiveness of other topical antibacterial agents in other wound indications including ***medical grade honey products*** (ointments, dressings). The honey preparations provide short-term benefit (low pH, high osmolality, hydrogen peroxide release) but their use can increase local pain and may temporarily increase exudate levels[65]. Once the honey becomes diluted with wound fluid, malodour will be associated with bacterial growth, including gram negatives and anaerobes.

8.2. Deep/surrounding tissue infection/ generalized inflammation

The signs of deep and surrounding tissue infection are outlined in the mnemonic STONEES where 3 or more criteria are an indication for systemic antimicrobial therapy. Regional and constitutional signs and symptoms (lymphadenopathy, fever, malaise) are important for prompt antimicrobial therapy initiation and the potential need for parental therapy. Empirical use of systemic antibiotics that cover common pathogens is recommended. The antibiotic choice can be further refined once the bacterial swab results identifying pathogenic organisms and their antimicrobial sensitivities. Administration via oral route may be sufficient, although longer treatment durations may be needed. ***Bacterial swabs positive for Streptococcus should be treated even in the absence of overt clinical infection due to the risk of complications (sepsis, toxin mediated disease, nephropathy)***[64].

For chronic non-healing wounds or frequent blister formation, systemic, low-dose anti-inflammatory antibacterial agents may be used for longer periods of time (e.g. trimethoprim, macrolides, and doxycycline). These agents are useful in controlling low grade bacterial damage combined with local and systemic inflammation[12] and have not commonly been associated with bacterial resistance (personal communication from Elena Pope). An alternating schedule of two to three months between any two or three agents is prudent.

9. Select an appropriate dressing/topical therapy that is appropriate for the needs of the patient and the caregiver based on the subtype of EB

The approach for dressing choices should be based on the type of EB, extent and location of the wound, dressing frequency, cost and availability. It is important to remember that given the various types of wounds that a particular EB patient may experience at one given time, the choice of dressing should be individualized for each wound. Chronic wounds are the most difficult ones to manage in patients with EB. Chronic wounds may be "stalled" in the inflammatory stage[14]. These wounds demonstrate marked increased activity of inflammatory cells and associated mediators such as matrix metalloproteinase (MMPs) and elastase[14]. Wound healing is stalled because degradation of extracellular matrix and growth factors occurs more rapidly when their synthesis is hindering the wound from progressing towards the proliferative phase and ultimately re-epithelialization[14,66].

Moore et al. reported that the longer a wound remains in the inflammatory phase, the more cellular defects are detected with potential delayed healing[66]. Recently, there has been a renewal of interest in wound diagnostic testing that will result in tests for increased metalloproteases at the bedside[14] and there are wound dressings with oxidized reduced collagen and cellulose that can trap metalloproteases and these dressings can be combined with antimicrobials such as silver. In the Sibbald cube[14], these specialized dressings can be combined antimicrobials depending on the presence of the NERDS (superficial antibacterial dressing criteria) or STONEES (systemic antibiotic) where the presence of increased inflammation can be treated topically or systemically.

Appropriate moisture is required to facilitate the action of growth factors, cytokines, and the migration of cells including fibroblasts and keratinocytes. Moisture equilibrium is a delicate balancing act. Excessive moisture can potentially cause damage to the skin surrounding a wound, leading to maceration of the keratin, increased bacterial proliferation and potential breakdown. Conversely, inadequate moisture in the wound environment can impede cellular activities and promote eschar formation resulting in delayed and poor quality of wound healing. A moisture-balanced wound environment is maintained primarily by using 'modern" dressings with occlusive, semi-occlusive, absorptive, hydrating, and haemostatic characteristics, depending on the drainage of the wound bed. Tables 4 and 5 provide a practical approach to wound dependent dressing choices for the EB population.

10. Evaluate the expected rate of healing or reassess wound goals of care (including potential maintenance status)

It is noted that a wound size reduction of 20% to 40% in two and four weeks is likely to be a reliable predictor of healing[67,68]. In a study with persons with diabetic foot ulcers using complete healing as the end point, a 30% reduction at week four was a good predictor for healing by week 12[69]. ***One measure of healing is clinical observation of the edge of the wound: nonhealing wounds often have a cliff like edge instead of the tapered sandy shore of a beach with a gradually sloping contour that is often purple due to new epithelialization***. If the wound edge is not migrating after appropriate wound bed preparation (debridement, bacterial balance, moisture balance) and healing is stalled, then advanced therapies should be considered to overcome the non-advancing Edge effect[70]. This may be considered after other causes and co-factors of delayed healing have been ruled out. Clinicians need to remember that wound healing is not always the primary outcome. ***Complete healing is particularly difficult in severe types of EB***. Other wound-related outcomes such as less pain, reduced bacterial load, fewer dressing changes with decreased exudate and odour, and/or an improved quality of life, may be more attainable.

11. Edge effect: If a wound is stalled or the edge or other areas appear atypical, consider a skin biopsy to rule out squamous cell carcinoma or other complications prior to considering active therapeutic options

Squamous cell carcinoma (SCC) is a major cause of morbidity and mortality in patients with EB, particularly those with RDEB. The cumulative risk of developing SCC in severe generalized RDEB by age 55 is 90.1%, much higher than that of the general aged matched population of the United States (9%-14% among men and 4%-9% in women)[71]. SCC tends to occur much earlier in the EB population is multifocal and more aggressive, leading to increased mortality (over 55% of severe generalized RDEB patients die from SCC by 40 years of age)[72,23]. As chronicity is the norm in many EB patients, a high degree of suspicion is required at the sites of chronic blistering, which may in fact be SCC. Any wounds that enlarge rapidly, have increased pain, appearance changes on serial photographic documentation or "feel different" for the patient should be biopsied[73].

D. Provide Organizational Support

12. Consider a health care system support structure including specialized nurses, interprofessional clinics and a structured approach to new cases

EB is not "just a skin disorder", therefore treating it requires involvement of a dedicated team with expertise in all aspects of care. The expression "it takes a village" (Figure 3) clearly illustrates not only the number of people who may need to be involved in patient's care, but also emphasizes that practitioners need to partner with patients and family in order to provide the best care.

Over the past decade EB specialized clinics have been opened worldwide in 16 countries. These clinics provide an interprofessional model of care utilizing the expertise of allied health professionals (nurses, physicians, occupational therapists, physical therapist, PT, social workers, dietitian, music therapists, etc.). These valuable teams of EB experts offers aspects of patient care that crosses all affected healthcare systems with strong community linkages. Isolated cases can be overwhelming to health practitioners particularly when referral to an established EB center is not feasible. Access to international EB experts via http://www.internationalebforum.org is possible and has changed the fabric of pre-existing professional isolation.

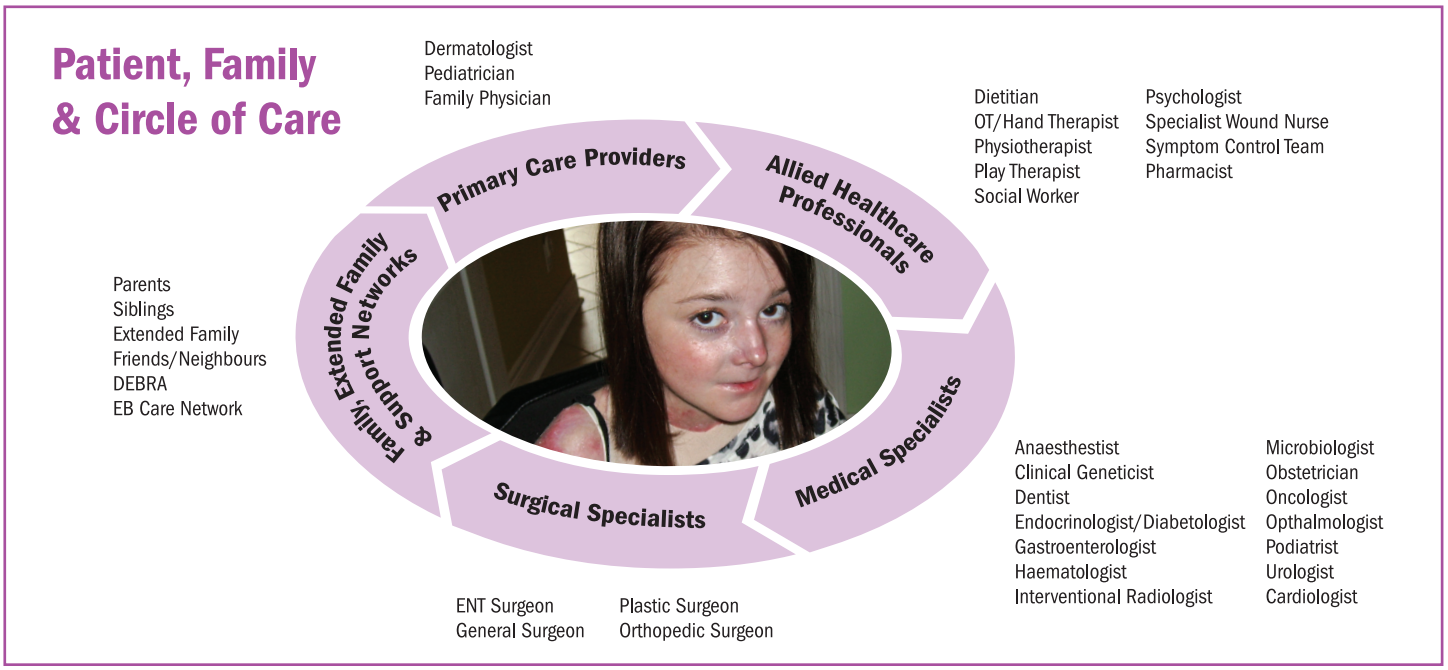
Other resources for patients and practitioners are DEBRA foundations that exist in many countries.

The birth of a child with EB is a traumatic event for a family. We find that imparting early education about the disease, determining the type/subtype of EB as soon as possible, and providing ongoing support from knowledgeable practitioners, allows a family to regroup and focus on providing the best care to their baby. We also find that a flexible approach at each visit that involves the family's agenda is more likely to lead to good care and building trust.

Conclusion

EB is one of the most complex diseases in medicine with severe EB types having devastating effects on the quality of life & life span of affected patients and their families. Wound care requires an interprofessional coordinated approach that addresses the patient as a whole. We have brought together experts in the field of EB, the science of wound care & clinical wound care practice to provide the best available approaches for optimal wound care to the EB individuals. Until a definitive cure becomes available, these practices' goals are to minimize suffering, improve wound healing and prepare patients for potential corrective procedures thereby improving the lives of afflicted individuals.

Figure 3: EB Care Team



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Pain and Wound Bed Preparation: From patient centered concerns to DIME

	D Debridement	I Inflammation/Infection	M Moisture Balance	E Edge Effect

Clinical presentation	· Wound bed covered with black eschar or loose necrotic slough
	· Exudate level may range from nil to high depending on wound bed dynamics
		· Chronic Inflammation
		· Superficial increase in Bacterial Burden (**NERDS**)
		  · **N**on-healing state or deterioration of wound condition
		  · **E**xudate level ↑
		  · **R**ed wound bed, bleeds easily
		  · **D**ebris In wound
		  · **S**mell ↑
		· Deep compartment infection (**STONEES**)
		  · **S**ize ↑
		  · **T**emperature ↑
		  · **O**S (probes to or exposed bone)
		  · **N**ew areas of breakdown
		  · **E**xudate, **E**rythema, **E**dema
		  · **S**mell ↑
			· Wounds may present with varying levels of exudate from nil to copious and from serous and serosanquineous to viscous or purulent depending on etiology, concomitant factors such as edema, inflammation, infection, etc. and nature and degree of tissue damage	· Epithelium fails to migrate across a firm and level granulation base
				· Epidermal edge may have a steep, cliff-like appearance or may be rolled under
				· Undermining maybe present

Critical considerations	· Assess healability · Remove debris where appropriate to increase rate of healing · Non-viable tissue may prolong the inflammatory process and provide a medium for bacterial growth	· Identify cause and co-factors · Bacterial damage can extend beyond the local wound bed · Extensive bacterial damage results in deeper and surrounding skin compartment infection that usually requires systemic antimicrobial treatment · Inflammation and infection inhibit collagen synthesis and epidermal migration and may lead to increased tissue damage · Infection prolongs inflammatory phase · Bacterial toxins in exudate may inhibit the wound repair process	· Assess healability. A moist wound environment may be contraindicated in non-healable or maintenance wounds · Fluid exuded from a wound is not inert. It has specific biologic and chemical properties that can hasten or prolong healing time · A moist wound environment hastens the healing process and promotes growth of new tissue · Excess moisture in the wound bed can impair the healing process and damage surrounding skin leading to peri-wound maceration · Promote optimum moisture balance	· Keratinocytes produce growth factors and play an important role in wound healing · Abnormal keratinocytes do not respond to wound healing signals · If a chronic wound is not 30% smaller at week 4, despite optimal local wound care it is unlikely to heal by week 12 and advanced therapies should be considered
Patient centered concerns	· Manage trauma and pain · Facilitate patient empowerment · Address quality of life issues	· Manage trauma and pain · Facilitate patient empowerment · Address quality of life issues	· Manage trauma and pain including peri-wound maceration and potential for skin stripping · Address quality of life and facilitate patient empowerment	· Address quality of life and facilitate patient empowerment, adherence and co-adherence · Manage Trauma and Pain including peri-wound maceration and potential for skin stripping
Local wound care	· Assess wound history and physical characteristics · Debride healable wounds · Assess and treat for increased bacterial burden	· Differentiate healability; classify as healable, maintenance or non-healable · Determine if bacterial imbalance exists and if the increased bacterial burden is in the superficial compartment or a deep compartment infection, or both · Support natural cleansing mechanisms of the wound · Decrease bacterial load · Protect against further invasion of organisms	· Select dressing appropriate to exudate level to promote optimal moisture balance · Evaluate need to fill cavity or dead space · Matched dressing characteristics to wound management requirements including fluid handling capacity, dressing change frequency and peri-wound skin health	· Consider cellular products and other complementary therapies · Support the cellular products with appropriate wound dressing to optimize management element relative to DIME paradigm
Treatment goals	· Support effective debridement · Minimize risk of infection · Promote patient comfort	· Support natural cleansing mechanisms of wound · Decrease bacterial load · Protect against further invasion of organisms	· Maintain optimal moisture balance · Protect the wound bed and support healing · Prevent contamination from external sources · Manage absorbed exudate and prevent contamination of external environment	· Enhanced cellular migration · Stimulate healing process in chronic wounds that have stalled · Restore cellular function · Support favourable wound healing environment · Protect peri-wound area

Product and treatment options	· Surgical/Sharp debridement
	· Autolytic debridement
	Hydrogel®
	  · Hypergel®
	· Mechanical debridement
	· Biological debridement – Maggot therapy
	· Enzymatic debridement
		· ***Non-healable and maintenance wounds***
		Topical Antiseptics
		· ***Inflammation***
		Hypertonic Saline
		  · Mesalt®
		· ***Superficial compartment bacterial imbalance***
		Antibacterial dressings
		  · Mepilex Ag®, Mepilex Border®, Melgisorb Ag®
		· ***Deep compartment infection***
		Systemic antimicrobial therapy
		Antibacterial dressings
		  · Mepilex Ag®, Mepilex Border®, Melgisorb Ag®
			· ***Moderately to highly absorbent***
			  · Foam – Mepilex®, Mepilex Border®
			  · Alginates & Hydofibers – Melgisorb®
			  · Dry hypertonic – Mesalt®
			  · Absorbent & Composite – Mesorb® Alldress
			· ***Low absorbent***
			  · Lite Foams – Mepilex Lite®, Mepilex Border Lite®
			  · Hydrocolloid
			  · Acrylic
			· ***Non-absorbent***
			  · Wound Contact Layers – Mepitel®, Mepilex Transfer®
			  · Transparent Film – Mepore Film®
			· ***Hydrating***
			  · Hydrogel – NormIgel®
				· ***Acellular preparations***
				  · Growth factors
				  · Extracellular matrices
				  · Matrix metalloproteinases
				· ***Cellular therapies***
				  · Grafting
				  · Autologous grafts
				  · Epidermal, dermal & composite products
				· ***Complementary therapies***
				  · Hyperbaric oxygen
				  · NPWT
				· ***Supporting products***
				  · Refer to product listing under moisture balance

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