Development of best clinical practice guidelines for epidermolysis bullosa


Authors:
Elizabeth Pillay and Jane Clapham

Epidermolysis bullosa (EB) is a rare genetic skin fragility disorder and the majority of patients live with life-long wounding. EB is not specific to any racial group and those affected by the disorder can be found all over the world. In contrast with many other countries, the UK is fortunate to have well-developed specialist services with experienced multidisciplinary teams who serve this patient group. Sharing of experience and expertise is particularly crucial in caring for those with rare conditions and this recognition led to the development of guidelines to be shared globally. In 2012 and, more recently, in 2016, London EB centres led on the development of best practice guidelines for skin and wound care in EB, with participation from EB professionals worldwide, patients and carers. This article outlines the process of developing the guidelines and the challenges of finding evidence to support management strategies in a complex rare condition.

The guidelines for skin and wound care in epidermolysis bullosa (EB) were developed to aid all clinicians who manage the skin and wound care of patients with the rare genetic skin fragility disorder EB, and to optimise the care that this patient group receives. The original guidelines were published in 2012 (Denyer, 2012) and were then updated in 2016 (Denyer, 2017).

EB requires expert multidisciplinary management. The guidelines represent the knowledge and experience of international practitioners, patients, their carers and published material. A literature review was undertaken and a synthesis of the findings from the review and expert opinion was used to develop the key recommendations. The recommendations fall broadly into the following categories: general principles of wound management, localised and systemic factors, wound assessment, blister management, pain, itch, risk of developing squamous cell carcinoma (SCC) and specific recommendations for the management of neonates and palliative care.

What is EB?

EB describes a group of rare, genetically inherited skin fragility disorders. Inheritance is either autosomal recessive or dominant, with the more severe forms being recessively inherited. The common presentation in all types of EB is the tendency for skin and mucous membranes to blister or shear away in response to minimal everyday friction and trauma. EB is an 'umbrella' term for a number of phenotypically distinct disorders that result from variations in the affected genes, proteins and skin structures. The affected genes are those which encode for a variety of proteins that are vital to the structure and stability of the layers of the skin. Hence, as an example those affected with dystrophic epidermolysis bullosa (DEB) are unable to make sufficient quantities of collagen VII which form the anchoring fibrils that act to bind the epidermis to the dermis. The skin is the largest organ in the body; its functions include protection from pathogens and damage, sensation through nerve endings that react to injury and temperature changes and heat regulation. In EB, the function of the skin (including in many forms the mucous membranes) is disrupted, and dependant on the severity of the EB the effects can be devastating and, in some forms, is life threatening.

The most recent classification for EB, agreed in 2014, names four categories of the condition defined by the level of cleavage at the dermal/epidermal junction (Fine et al, 2014). These are: EB simplex (EBS), junctional EB (JEB), DEB and Kindler syndrome. The severity of EB varies from simple blistering affecting the hands and feet, particularly in warm weather, to death in early infancy from the devastating combination of laryngeal disease and failure to thrive.

Elizabeth Pillay *is Advanced Nurse Practitioner, EB Research, Guys and St Thomas' NHS Foundation Trust;* ***Jane Clapham*** *is Lead EB CNS, Guys and St Thomas' NHS Foundation Trust, London, UK*

In people with more severe forms of EB, namely DEB and JEB, the skin is extremely fragile and patients can experience recurrent blistering and skin loss. There is often a tendency to develop chronic wounds resulting from the underlying gene defect, constant trauma and repeated infection. Other non-cutaneous factors will have a negative impact on healing and should be addressed.

In autosomal recessive DEB (RDEB) and JEB, the skin is extremely fragile, often with extensive blistering and wounding. Patients with these forms of EB will frequently develop hard-to-heal or never-to-heal areas, or areas that do heal, but can very quickly break down. Atrophic scarring and healing leading to disabling contractures are common. Pseudosyndactyly or mitten deformity of the hands is often present and may require repeated surgery to release the digits (Formsma et al, 2008; Bernardis and Box, 2010).

Guideline development process

The 2012 EB guidelines were developed following an international workshop held in London, which brought together healthcare professionals working in EB care. Participants ranged from novices who had small EB caseloads to those with more extensive caseloads and who had many years of experience in the field. A variety of wound care scenarios were discussed (using photographs) and participants put forward a range of management strategies. A limited literature review was undertaken, however, following the publication of an EB guideline development protocol, this was deemed to be inadequate and a further review (detailed below) was undertaken.

Literature review

Search methodology

As a basis for the guidelines, a systematic literature search was undertaken concluding in July 2016. The databases searched were Medline, Embase, British Nursing Index and CINAHL. The search limits were papers published from January 1980 to July 2016, papers published in English and involving humans. The initial search term used was 'epidermolysis bullosa' followed by separate searches on 'wound', 'erosion', 'dressing', 'exudate', 'pruritus', 'itch', 'odour', 'pain', 'cancer', 'malignancy', 'carcinoma', 'wound dressing', 'wound care', 'wound pain' and 'wound management'. The search terms were then individually combined with 'epidermolysis bullosa' using the Boolean operator, 'and'.

Search results

A total of 1,342 abstracts were retrieved and the following search results occurred:

- 422 were duplicates
- 920 unique results
- 102 further duplicates were removed manually
- 818 abstracts to review
- 636 abstracts rejected as not relevant; these were excluded because they did not relate to the topic (e.g. papers discussing EB Acquisita, surgical management or related purely to non-clinical issues)
- 182 were identified to be included in the review.

The papers were then appraised and graded by the reviewers as per the SIGN guidelines and a synopsis made of the information they contained.

SIGN grading system 1999–2012

The majority of the papers were graded level 3, being small-scale case studies with many others being level 4 (i.e. expert opinions). Given the rarity of EB and the many confounding factors that impact healing, it is difficult to conduct statistically valid studies to provide evidence to support the efficacy of any particular wound management strategy.

In looking at published evidence it is clear that there is variation in study methodology and outcome measures, and this was highlighted by 'Ly' in a review of EB wound management (Ly and Su, 2008). Additionally, while investigating the use of use of injected fibroblasts as a potential stimulus to wound healing in EB, 'Petrof' observed that the natural history of wound healing in EB is unknown, and that the chronic wounds previously assumed to be static can in fact change and reduce in size over time with no new treatment modality being introduced (Petrof et al, 2013).

The literature review revealed the paucity of published evidence to support any particular wound management strategy. Due to lack of robust published evidence the Best Practice Guidelines present a wide range of recommendations for wound management in EB across all subtypes and in a variety of scenarios. These range from management of the neonate to care at the end of life and are based on the published evidence and the sharing of information among professionals, patients and carers across a global network.

The guidelines were reviewed by an international panel of reviewers, consisting of professionals with extensive experience in EB care, and a patient/carer panel; their comments and corrections were incorporated into the published guidelines. Some limited examples of some of the recommendations made are included, however, readers are directed to the Best Practice Guidelines for comprehensive information *[Box 2]*.

Blisters management

A first principle in managing EB is to deal with any

Levels of evidence

1	++High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias + Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias - Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2	++ High-quality systematic reviews of case control or cohort or studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal + Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal - Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	A body of evidence rated level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice points

✔	Recommended best practice based on the clinical experience of the guideline development group

Box 1. SIGN 50 Guideline Developer's Handbook. NHS Scottish Intercollegiate Guidelines Network, 2014.

new blisters the patient may develop. Blisters occur in all types of EB following friction and relatively minor trauma. They can be present anywhere on the skin and the mucous membranes.

The location of a particular blister may be EB-type specific. For example, EBS localised blistering will occur mainly on the hands and feet whereas as other forms, such as dystrophic EB blisters, will occur on the areas subject to the most trauma, such as the bony prominences. The blisters can occur alone or in clusters depending on the initial degree of trauma and they may be filled with serous or blood-stained fluid.

Blisters are not self-limiting and will fill with serous fluid and rapidly expand if left intact. In contrast to recommendations for other dermatological conditions or wound management, intact blisters should be lanced at their lowest point to limit tissue damage (Denyer, 2010). A sterile hypodermic needle should be used and, should be passed through the blister roof, parallel to the skin, to create an entry and exit hole through which fluid can be expelled. A soft gauze, can be used to gently compress the blister to encourage complete emptying. Some patients advocate using sterilised scissors to create a larger hole to prevent the blister from refilling. The roof should be left on the blister unless patient preference is to de-roof it to prevent refilling, but de-roofing can lead to additional pain, due to exposed nerve endings and should be discouraged if possible.

Wound assessment and management

As with any wound care, careful skin and wound assessment should be undertaken regularly. Management must be tailored to both the type of EB and wound characteristics. Any one patient may be using a large variety of dressings, all of which serve different purposes.

The presence of multiple wounds of varying duration combined with systemic factors, which can impact negatively on the ability to heal makes the management of EB wounds difficult and complex. The underlying principles are a holistic patient assessment, and the use an atraumatic dressing to prevent skin and wound bed damage during use and upon removal.

Box 1. Key recommendations are based on the results of the literature review and the experience of the guideline development group. The recommendations in this table are not arranged according to importance but rather in the order they occur in the main body of the document.

Key recommendations	Strength of recommendation	Level of evidence	Key references
EB is a lifelong disorder that requires specialist intervention and consideration to minimise complications and improve quality of life. Ideally, management should take place in a specialised centre by a multi-disciplinary team	D	4	Pillay, 2008; Denyer 2009; Pope et al, 2012; Badger et al, 2013; El Hachem et al, 2014
In severe EB the individual's ability to heal can be compromised by malnutrition, anaemia, pruritus and pain, and should be treated appropriately	D	4	Schober-Flores, 2003; Lara-Corrales et al, 2010; Mellerio, 2010; Pope et al, 2012; Badger et al, 2013; Pope et al, 2013; El Hachem et al, 2014;
Careful skin and wound assessment should be undertaken regularly. Management must be tailored to both the type of EB and wound characteristics	D	4	Schober-Flores 2003; Sibbald et al, 2005; Denyer 2009; Denyer 2010; Pope et al, 2012; 2013; Badger et al, 2013; Elluru et al, 2013; El Hachem et al, 2014
Atraumatic dressings should be used to prevent further blistering, skin and wound bed damage	D	4	Denyer, 2000; Mellerio et al, 2007; Abercrombie et al, 2008; Pillay, 2008; Lara-Corrales et al, 2010; Badger et al, 2013; Denyer, 2009; 2010; Pope et al, 2012; Elluru et al, 2013; Gonzalez 2013 El Hachem et al, 2014; Kirkorian et al, 2014
People with EB and their carers are experts in the management of their condition and their involvement is paramount	D	4	van et al, 2008; Pope et al, 2012; Badger et al, 2013
The choice of wound management strategies should balance efficacy, patient choice and quality of life with cost-effectiveness	D	3,4	Sibbald et al, 2005; Kirkorian et al, 2014; Stevens, 2014
Staff caring for EB patients must be trained in specific handling techniques to avoid further harm	D	4	Gonzalez, 2013
Blisters are not self-limiting and intact blisters should be lanced and drained	D	4	Herod et al, 2002; Schober-Flores, 2003; Pillay, 2008; Denyer, 2009; Lara-Corrales et al, 2010; Pope et al, 2012; Elluru et al, 2013; El Hachem et al, 2014
Management of EB wounds must address issues such as critical colonisation, infection, and protection from trauma	D	4	Schober-Flores, 2003; Sibbald et al, 2005; Azizkhan et al, 2007; Mellerio et al, 2007; Denyer 2009; 2010; Badger et al, 2013; El Hachem et al, 2014;
Every effort should be made to treat the intense pruritus seen in EB and thereby minimise scratching that leads to further skin damage	C	2+4	Pillay, 2008; Snauwaert et al, 2011; 2014; Badger et al, 2013; Pope et al, 2013; El Hachem et al, 2014; Danial et al, 2015a; 2015b
Silicone medical adhesive removers (SMARS) should be used when removing adherent dressings or clothing	D	3,4	Mather and Denyer, 2008; Stephen-Haynes, 2008; Denyer, 2009; 2010; Lara-Corrales et al, 2010; El Hachem et al, 2014;
To ensure adequate nutrition and optimise wound healing long-term, enteral feeding may be indicated in severe EB	D	4	Haynes 2010; Hubbard et al, 2011; Haynes et al, 2012; Pope et al, 2012; El Hachem et al, 2014;
Optimal pain management is vital for patients with all forms of EB and include pharmacological and non-pharmacological interventions	D	4	Herod et al, 2002; Howard et al, 2004; Mellerio et al, 2007; Denyer 2009; 2010; Goldschneider and Lucky, 2010; El Hachem et al, 2014; Watterson et al, 2014;

Box 1 (continued).

Key recommendations	Strength of recommendation	Level of evidence	Key references
When a surgical or interventional procedure is indicated adjustments to anaesthesia and theatre protocols will be required to minimise skin damage and protect the airway	D	4	Herod et al, 2002; Goldschneider et al, 2010; Elluru et al, 2013; El Hachem et al, 2014
The principles of wound bed preparation (WBP) are applicable to wounds seen in patients with EB, particularly wounds which have become chronic	D	4	Mellerio et al, 2007; Lara-Corrales et al, 2010; Pope et al, 2012; Pope et al, 2013; Sibbald et al, 2015
In patients with severe forms of EB there is a high risk of squamous cell carcinoma (SCC). Regular monitoring is essential with a low threshold for biopsy of suspect areas.*	D	4	Mellerio et al, 2007; Fine et al, 2009; Mellerio et al, 2016

* Although the evidence supplied by the US EB Registry (Fine et al, 2009) supported by a subsequent review in 2016 (Montaudie et al, 2016) for the high risk of SCC in severe forms of EB most notably RDEB-GS is unequivocal and are graded C -2+, the evidence for recommended actions are based on expert opinion.

Great care must be taken to ensure dressings do not slip and adhere to the clothing or bedding leading additional damage to the fragile skin or open wounds.

The retaining bandage or tape can also lead to additional blistering from movement or contact with the surrounding skin. Retention must allow for freedom of movement to discourage development of contractures in those with DEB. A range of EB-specific retention garments, Skinnies WEB™, have been developed with the aid of patients and carers (Grocott et al, 2013).

Dressings must be removed with great care to avoid further skin damage. If necessary, the dressing can be soaked off in the bath, hydrated with tepid water or saline or a silicone medical adhesive remover could be used (Denyer, 2011). In particular, this applies to patients with RDEB or those using a bordered dressing.

Management of EB wounds

Management of EB wounds must address issues such as critical colonisation, infection, and protection from trauma.

Dressing choice

Dressings are often extensive and large sizes must be sought in order to avoid blistering where two smaller dressings join. The chosen dressing should be appropriate to the level of exudate and should provide protection by absorbing exudate and holding the moisture within the dressing to avoid maceration and leakage. As with any chronic wound, odour can be a feature which must be addressed to avoid embarrassment and social compromise. Eradication can be impossible due to the high exudate levels, infection and, on occasion, odour of the dressing itself.

The most commonly used dressing in EB are those designed to be removed easily, such as those coated with soft silicone, foam or mesh, lipido-colloid and polymeric membrane. Many people with EB will change their dressings either daily or alternate days with frequent 'patch ups' and frequency of dressing changes will dictated by the patient. Changing of the dressings is part of their personal hygiene regime (akin to a daily shower), rather than being based on the recommended wear time of the dressings. The cost of dressings is often expensive.

In a survey of 40 patients with a diagnosis of RDEB the total annual costs for dressings alone were just under £1.9 million with an average of £46,397 being spent. This survey included some patients with milder forms of RDEB where few dressings are used; the lowest cost being £135. In those with more extensive skin damage, costs are significant, with one patient having dressings costs in excess of £500,000 (Unpublished data from the PEBLES Study, 2017). Less expensive alternatives are often not suitable and can cause additional skin damage.

Chronic wound management

A holistic assessment is needed when dealing with non-healing wounds to establish, if possible, the cause of chronicity. It is often easy in the context of severe EB to be overwhelmed by the wide variety of presenting wound-related problems.

Wound-related causes of chronicity

The most common causes of chronic wounds

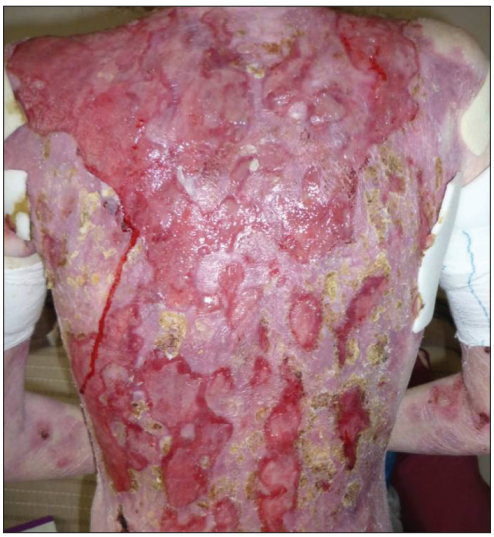

Figure 1. Chronic wound in a recessive dystrophic epidermolysis bullosa patient.

in EB are likely to be (Abercrombie et al, 2008; Pillay, 2008):

- High bioburden (critical colonisation)
- Frank infection due to the loss of the protective function of the skin with large wounded areas
- Presence of necrotic material, commonly soft slough
- Disordered cellular activity seen in all chronic wounds
- Poorly controlled exudate: extremely alkaline exudate is a wounding agent
- Intense pruritus leading to destructive scratching.

The presence of a biofilm will inhibit wound healing and should be suspected in non-healing EB wounds. The longevity/chronicity of wounds commonly seen in EB predisposes to biofilm formation. A biofilm is a multi-species microbial community that secretes a protective matrix. Biofilms interfere with normal wound healing by 'locking' the wound bed into the chronic inflammatory state that leads to elevated levels of proteases and reactive oxygen species, damaging the proteins and molecules essential for healing. Biofilms communities are often dormant and, therefore, tolerant to antimicrobials (Eberlein 2018).

The margins of chronic wounds in EB are frequently hyperkeratotic with the presence of dried crusty exudate and this devitalised tissue will inhibit the migration of epidermal cells from the wound edges.

In all patients with chronic wounds the periwound skin is vulnerable to further damage. This is particularly true in EB where a large area of the skin can be considered as periwound, while other unbroken areas are vulnerable to damage and breakdown because of the nature of the condition itself. Chronic wound exudate is potentially corrosive to intact skin and is itself a wounding agent causing increased pan. Maceration of the periwound skin with wound extension is common particularly in areas where exudate drains downward (Hollinworth, 2009).

Skin barrier products can be very useful in protecting the periwound skin and any hyperkeratosis around the wound edge can be softened with a moisturiser such as 50/50 to aid ease of removal.

On occasion, the aim of management may not be to heal a wound but to manage it. Focus may need to be on the effective management of wound-related symptoms, i.e. exudate, infection, odour and pain, as well as providing a dressing regimen that is acceptable to the patient and carer. In addition, there is evidence to support the notion that skin stem cells become 'exhausted' in their never-ending battle to heal wounds (Dellambra et al, 1998; Dowsett, 2008; Velarde et al, 2015).

The choice of wound management strategies should balance efficacy, patient choice and quality of life with cost effectiveness. People with EB and their carers are experts in the management of their condition and it is beneficial to all to involve them in the decision-making process; many will have a tried and tested dressing regimen that avoids injury.

Other considerations

Beyond the wound the whole patient must be considered and the context in which wound healing is failing to take place must be assessed and addressed.

In severe EB, nutrition is often compromised and will have a negative impact on the patient's ability to heal. To ensure adequate nutrition, patients should be managed by a dietician and long-term enteral feeding may be indicated. Iron deficiency anaemia and anaemia of inflammation will have a further negative impact on wound healing.

As would be expected with extensive open wounds, people with EB can suffer with severe pain that is often difficult to manage and will affect both the patient's ability to heal and quality of life. Comprehensive pain assessment must be undertaken and appropriate treatment instigated, with a recognition that pain may arise from sources other than the wounds. Both pharmacological and non-pharmacological interventions should be considered with input from a pain specialist where necessary (Goldschneider et al, 2014).

Recalcitrant pruritus can lead to destructive scratching and disruption to wound healing, frequently leading to the breakdown of newly healed or healing skin. Every effort should be made to treat this distressing symptom seen in most types of EB (Danial et al, 2013; 2015).

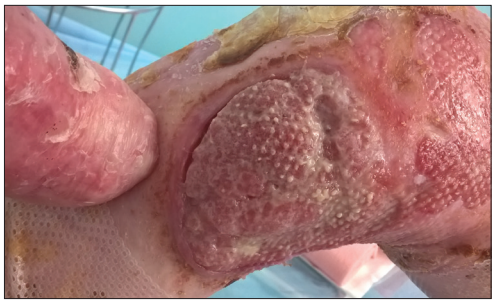

Figure 2. Squamous cell carcinoma in a recessive dystrophic epidermolysis bullosa patient.

There are many non-cutaneous complications, such as scarring and contractures, which result in microstomia and oesophageal strictures, while osteoporosis, growth failure and pubertal delay (Haynes, 2010; Hubbard et al, 2011) will further compromise wellbeing. There is also a greatly increased risk of aggressive SCC in those with severe forms of EB (Mellerio et al, 2016).

EB in neonates and children

There are special considerations that apply to the management of neonates and children with EB. There are three specialist centres in UK for the care of paediatrics with EB, London, Birmingham and Scotland. It is strongly recommended that their expert advice is sought early on in the child's care as they will provide diagnosis and condition specific information, together with an outreach service. In severe forms of EB, blisters and wounds are usually present at delivery or result from handling immediately after birth. In milder forms of disease these will often appear during the neonatal period.

There are several wound care, blister lancing and preventative techniques that can be used when caring for a new-born that may help lessen the real risk of infection and reduce procedural pain (Denyer, 2009).

More detailed information on these key recommendations can be found in the Best Practice Guidelines that provide advice on areas such as nursing care for the new born.

Squamous cell carcinoma

In patients with severe forms of EB there is a high risk of SCC, regular monitoring is essential with a low threshold for biopsy of suspect areas. A histopathologist with experience of EB skin cancers should ideally examine the tissue sample. Suspicion should be aroused if:

- The wound has been present for more than 3 months
- Exuberant tissue growth above the level of the surrounding skin
- The wound is ulcerated
- The wound has little feeling
- The wound is intensely painful
- The patient reports that the wound feels different.

Patients and their carers are frequently the first people to recognise that there is a problem and their concerns must be listened to. At the London EB Centres there is a low threshold for biopsy as it is recognised that even wounds that at first may appear insignificant can in fact harbour an SCC. It strongly recommend that any severely affect EB patient presenting with a suspicious area is referred to a specialist centre without delay (Mellerio et al, 2016).

In conclusion, EB can be a devastating lifelong disease in its worst forms, requiring expert multidisciplinary management. Patients with the condition become experts in the management of their skin and should be involved at every stage of decision making. Careful skin and wound assessment should be undertaken regularly and appropriate management implemented. Steps should be taken to avoid further skin damage caused by removal or application of dressings or inappropriate care. Patients often require dressings and treatment which are expensive to provide but this should not be a barrier to them accessing what is necessary for them to live a full life (Downe 2017). In common with the rest of the population people with EB want to live as normal life as possible and with good management a full and rewarding life can be achieved. WINT

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