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Foot care in epidermolysis bullosa: evidence-based guideline

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Summary

This guideline was designed to provide service providers and users with an evidence-based set of current best practice guidelines for people and their families and carers, living with epidermolysis bullosa (EB). A systematic literature review relating to the podiatric care of patients with EB was undertaken. Search terms were used, for which the most recent articles relating to podiatric treatment were identified from as early as 1979 to the present day, across seven electronic search engines: MEDLINE, Wiley Online Library, Google Scholar, Athens, ResearchGate, Net and PubFacts.com. The Scottish Intercollegiate Guidelines Network (SIGN) methodology was used. The first guideline draft was analysed and discussed by clinical experts, methodologists and patients and their representatives at four panel meetings. The resulting document went through an external review process by a panel of experts, other healthcare professionals, patient representatives and lay reviewers. The final document will be piloted in three different centres in the U.K. and Australia. Following an EB community international survey the outcomes indicated six main areas that the community indicated as a priority to foot management. These include blistering and wound management, exploring the most suitable footwear and hosiery for EB, management of dystrophic nails, hyperkeratosis (callus), maintaining mobility and fusion of toes (pseudosyndactyly). The evidence here is limited but several interventions currently practised by podiatrists show positive outcomes.

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Conflicts of interest
Marigold Footcare Limited is family owned by one author (M.T.K.); however, M.T.K. does not have any financial interests and acts as a company consultant on an honorary basis. M.T.K., R.F. and M.W. are consultants for a project called REBOOT but have no financial interests in any shoe supplier or distributor; and K.M.-C. is an associate to DEBRA International. M.W. and K.M.-C. were therefore not involved in the final editions of the recommendation manuscript, editions post-review or panel feedback. The reviewers declared no potential conflicts of interest with respect to the publication of this guideline.

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Background

The Dystrophic Epidermolysis Bullosa Research Association (DEBRA) International is a worldwide network of national groups working for people affected by the genetic skin blistering condition EB. EB is a group of rare heritable skin fragility disorders, typically presenting as blistering of the skin from minor trauma.[1] While there are currently over 30 known subtypes of EB, there are four primary types: EB simplex (EBS), dystrophic EB (DEB), junctional EB (JEB) and Kindler syndrome (KS).[1,2] EB can be the result of either inherited or spontaneous dominant mutations, as seen in most forms of EBS and dominant DEB (DDEB), or from inherited recessive mutations as is the case with rare forms of EBS, recessive DEB (RDEB), JEB and KS (Table 1).[2] Ninety per cent of patients with EB have one or more podiatric manifestations, including blistering, hyperkeratosis, flat feet, nail dystrophy or structural abnormalities affecting foot positioning.[3,4] EB requires specialized podiatric care, but because of its rarity many podiatrists have limited knowledge of the disorder. Furthermore, there is a dearth of evidence regarding podiatric care of EB, and management decisions are usually based on experience and expert opinion.

The recommendations outlined in this clinical practice guideline (CPG) contain general information on foot care of people living with EB (Tables 2 and 3). They explain the precautions that should be taken when treating people with EB, as well as recommendations for podiatry treatment.

Objectives of the clinical practice guideline

- To describe foot problems in people of all ages with EB.
- To outline current EB podiatry practice in the U.K. and Australia.
- To highlight specific considerations for different subtypes of EB.
- To provide guidance for foot care in EB

User and target group

These guidelines are intended for podiatrists, other health professionals, people with EB (all ages and subtypes), their families and carers, teachers, employers, shoe manufacturers, stakeholders and policy makers. These guidelines comprise information relating to people with EB of all ages and subtypes.

Declaration

The recommendations contained in these guidelines do not indicate an exclusive course of action, or serve as standard medical care. Variations, taking individual circumstances into account, may be appropriate. The authors of these guidelines have made considerable effort to ensure that the information upon which they are based is accurate and up to date. Users of these guidelines are strongly recommended to confirm the information contained within them. The authors, DEBRA U.K. and DEBRA International accept no responsibility for any inaccuracies or information perceived as misleading, or the success of any treatment regimen detailed in the guidelines.

Recommendations

The key recommendations of this guideline are summarized in Table 2, with grades of evidence explained in Table 3. Detailed recommendations are provided below.

Blistering and wound management

Podiatric education

We strongly recommend offering podiatry education programmes to prevent blistering and wounds (*Strength of recommendation grade*: B).

Foot blistering is a common problem in all subtypes of EB, and patients of all age groups may be affected (Quality evidence level ranging from 4 to 2+).[4–8] Blistering in EB usually results from friction or minor trauma.[3,9] Blisters on the feet can be caused by a dressing, sock, shoe or boot rubbing against the skin,[3] but they sometimes appear spontaneously. The size of a blister depends on the type of EB and the degree and duration of friction.[3] In EB, defective skin adhesion means that a shearing force causes skin components to separate, creating a space that fills with fluid. The resulting blister easily enlarges under pressure because there is a plane of weakness in the skin, so it should be burst to avoid this (Appendix S1a; see Supporting Information).

The usual technique is to lance intact blisters with a sterile needle at their lowest point to facilitate fluid drainage by

Table 1 Foot manifestations in epidermolysis bullosa (EB)

Primary types of EB	Blistering and scarring	Dystrophic nails	Hyperkeratosis, callus and corns	Pseudosyndactyly and mitten deformities
EB simplex	Yes		Yes	
Dominant dystrophic EB	Yes	Yes	Yes	
Recessive dystrophic EB	Yes	Yes		Yes
Junctional EB	Yes	Yes		
Kindler syndrome	Yes	Yes		

Table 2 Summary of key recommendations for podiatry management of foot and nail disorders in epidermolysis bullosa

Key recommendation	Grade strength of recommendation	Quality of evidence (rate average)	Key references[a]
Desirable consequences clearly outweigh undesirable consequences in most settings, and for this reason we recommend offering these options			
Avoidance of blistering and wounds: a podiatry education programme should be offered from birth, enabling carers, patients and staff to recognize and avoid causes of blistering and wounds, including • Footwear • Dressings • Foot biomechanics • Heat and sweating	B	2+	3–10
Management of dystrophic nails: podiatric support can include • Topical keratolytics • Trimming, reducing or removing nails	B	2+	3, 4, 8, 12–15
Management of hyperkeratosis (callus): podiatric support should include • Assessment and monitoring of weight distribution • Appropriate cushioning to prevent hyperkeratosis • Use of a validated assessment tool (Appendix S2)	B	2+	3–5, 7, 8, 10, 11
Footwear advice: information should be provided regarding suitable shoes and the appropriate use of • Insoles • Cushioning materials • Orthotics	C	3	3–5, 7–9, 21
Assessment and monitoring of mobility: podiatric care should focus on maintaining mobility, adapting to the specific needs of different subtypes and different age groups, within a multidisciplinary team	C	3	3–9, 18–28
The balance between desirable and undesirable consequences was uncertain, and for this reason we suggest consideration of this option			
Assessment of pseudosyndactyly and contractures: podiatric support should include • Advice on preventative measures • Assessment of functional impairment • Referral for surgical correction • Postoperative management to prevent recurrence and promote mobility	D	3	22, 29–34

[a]Reference 10 contained no EB population.

gravity[9] and to stop blisters from refilling.[3] Some patients prefer to use sterile scissors. Gauze or other absorbent material may be used to wick the fluid from the blister. A saline soak, nonmedicated and medicated dressings, and topical antiseptics or antibiotics could be used to prevent secondary infection until the skin heals (Quality evidence level ranging from 3 to 1−),[3,5] existing guideline ⇒[9] (expert opinion, *grade:* D).

Generally the management of EB tends to be supportive and is aimed at preventing blistering by reducing friction and the amount of mechanical trauma to the feet (Quality evidence level 3).[5] Prevention is key and involves minimizing friction and mechanical trauma to the feet (Quality evidence level 3).[5] The evidence here supports the training of staff, patients and carers to improve understanding of the causes of blistering and wounds on the feet.

Prevention of blisters is facilitated by an assessment tool that the podiatrist can use to address the adequacy of hosiery (silver-lined socks) and footwear (Quality evidence level 4).[4] That study[4] presented the development of a universal assessment tool, which requires validation (Section A in Appendix S2; see Supporting Information). The Foot Health Status Questionnaire (FHSQ) is seen as a validated universal assessment tool, which is not specific to EB (Quality evidence level 1−),[10,11] (Section B in Appendix S2; see Supporting Information).

In a cohort of 57 patients with a localized form of EBS, all reported localized pain in the feet related to blisters. Six patients (11%) tried lidocaine 5% plasters on their feet, with good efficacy (Quality evidence level 2+).[6]

Footwear and foot biomechanics

Selection of appropriate footwear and the use of appropriate insoles can help to reduce blisters and improve foot function in patients with EB. In a prospective study of six patients with EBS, three reported no new blisters while wearing shock-absorbing moulded orthoses (Quality evidence level 3).[5]

Table 3 Grades of evidence

Grade	
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	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
Rate	
2++	High-quality systematic reviews of case–control or cohort 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
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
3	Nonanalytical studies, e.g. case reports or case series
✓	Recommended best practice based on the clinical experience of the guideline development group[36]

Descriptions are in accordance with SIGN.[36] Note that there was no disagreement on the quality of the appraised articles or the strength of the recommendations.

In a qualitative study of 79 adults with all subtypes of EB, all patients improved in two to four key variables when using shock-absorbing insoles, custom orthotics and bespoke footwear. The investigators used a gait analysis system to capture the static and dynamic in-shoe foot pressure of bespoke footwear in seven patients, and provided an objective, quantifiable technique to identify biomechanical discrepancies and pathological foot function and to assess gait. Furthermore, the improved mobility and independence correlated to the reduced numbers and severity of blisters (Quality evidence level 2−)[7] demonstrating that the use of insoles and orthotics is also important (Quality evidence level 2−),[4] (Appendixes S3 and S4; see Supporting Information).

- Socks are helpful to provide ventilation, wick away moisture and reduce friction (Quality evidence level ranging from 4 to 2−).[3,4]
- Footwear for patients with EB should ideally be firm and comfortably fitting, with appropriate length and width, a rounded toe and a flexible flat sole with heel support. It should also have laces or straps or equivalent to prevent excessive movement or slipping of the foot inside the shoe, and have a seamless internal lining (Quality evidence level ranging from 4 to 2−).[3,4]

Practical point: although it is not mentioned in the literature, healthcare professionals and patients alike have reported the benefit of using cornflour on the soles of the feet and in between the toes to help control excessive moisture and reduce friction. Both of these measures can help control blistering on a day-to-day basis.

Dystrophic nails

We strongly recommend offering podiatry support to treat and manage EB dystrophic nails (*Strength of recommendation grade*: B).

- Dystrophic nails can be very problematic in EB and may affect patients with all EB subtypes (Quality evidence level 2−).[12–15]
- Dystrophic nails may be effectively managed by the application of a topical keratolytic agent, and the nail thickness can be further reduced by an expert podiatrist (Quality evidence level 2−).[3,4,12–15]

Nail changes occur in all subtypes of EB. In an Australian EB registry study involving male and female patients from childhood onwards, dystrophic nails were reported in 33% of patients with EBS, 90% with JEB, 83% with DDEB and 95% with RDEB (Quality evidence level 3).[12] Most reports focus on toenails rather than fingernails, although both can be dealt with by podiatrists (Box 1). A retrospective qualitative study reported on 201 adults (Quality evidence level 2+);[8] most other reports discuss the diagnosis, characteristics and familial inheritance in childhood.

Toenails should be preserved where possible because they protect the tips of the digits from friction and pressure (Quality evidence level ranging from 4 to 2−).[3,4] The treatment and management of dystrophic nails presented the strongest evidence in this CPG, and podiatrists are encouraged to be involved with all patients with EB (Quality evidence level ranging from 4 to 2−).[3,4] As EB nails are a rare condition, community podiatrists are unlikely to have the disease-specific knowledge and expertise to deal with EB-related complications (Quality evidence level 2+).[8] Therefore podiatry is an essential component of EB multidisciplinary care (Quality evidence level 2+),[8] (Appendix S1b; see Supporting Information).

EB podiatrists should be available to assess newly diagnosed patients, develop care plans, offer treatment at the specialist centre, and recommend appropriately trained podiatry services near the patient's home.

Patients with EB with dystrophic nails should be advised as follows (Quality evidence level ranging from 4 to 2−).[3,4]

- Keep toenails trimmed straight across.
- File nail surfaces with an emery board after softening the nails by soaking in warm saline water or a bath.
- Daily to weekly, depending on the age of the individual and thickness of the nail, apply a urea-based cream, such as a keratolytic agent, to reduce the thickness of the

Box 1

Disclaimer: Podiatrists are sometimes asked to deal with fingernails as well as toenails by their EB consultant. Podiatrists should ensure that this activity is within the scope of the podiatric practice act for their country and find out whether certification is required.

keratin layer and hydrate the nail (Quality evidence level 4: expert opinion).
- Removal of the toenails can be performed via chemical or laser ablation to prevent future problems. If an EB podiatrist does not undertake this procedure it is advisable for them to provide some guidance or advice to the podiatrist who is performing the nail surgery (Quality evidence level 2−).[4]
- Surgical procedures can be carried out; please refer to the pseudosyndactyly section.

Hyperkeratosis (callus)

We strongly recommend assessment of hyperkeratosis with a validated tool to facilitate monitoring. (*Strength of recommendation grade: B*).

- Hyperkeratosis and fissuring of the feet have been reported in all EB subtypes (Quality evidence level 2+).[8]
- The use of a validated tool can help to monitor, evaluate and manage EB hyperkeratosis (Quality evidence level 1−).[10,11]
- Pressure redistribution and cushioning are helpful to prevent development of hyperkeratosis (Quality evidence level 2−).[3,4,7,8]

Hyperkeratosis (also called keratoderma or callus) has been reported in all subtypes of EB. EBS is often associated with mild-to-moderate hyperkeratosis (palmoplantar keratoderma), particularly of the soles.[4,5,7] In a retrospective qualitative study, carried out in an EB podiatry clinic covering both male and female patients with all subtypes from childhood onwards, 74 of 201 patients (36·8%) were treated for hyperkeratosis (Quality evidence level 2−).[8]

Hyperkeratosis may be defined as hard, thickened areas of the skin located on the tip of toes or between the toes and soles underneath the metatarsal heads.[3] If the skin is hard and yellow with a nucleus or plug of keratin, it is called a corn or helom.[3] A corn or callus will appear red if it is inflamed.[3] The central core of a corn extends downwards in a cone-shaped point and can cause notable pain and discomfort. Patients will often compare this to walking on a small stone or pebble.[3] A corn or callus enlarges if there is continuing friction as a direct hyperproliferative response of keratinocytes.[3] Hyperkeratosis is, to a limited extent, protective.[3] However, in EB, blisters can form under the thickened tissue and painful cracks can develop (Appendix S1a; see Supporting Information). The FHSQ is currently being used in studies with patients with EB with hyperkeratosis (Quality evidence level 1−).[10]

Podiatric management of hyperkeratosis and corns involves the following.[3]

- Debridement of the lesions is a procedure performed regularly by podiatrists using manual debridement or paring of hyperkeratosis (Quality evidence level 2+).[8] The forms of debridement can include self-management using an emery board or nailfile. If the area is too painful or too thick, patients need to be seen by a podiatrist for a blade or scalpel debridement. However, in dealing with patients with EB, podiatrists are advised to be more conservative in their approach, as overdebridement can make the underlying skin susceptible to increased blistering and tenderness. After debridement, emollients and nonadherent dressings should be used carefully to protect the debrided skin.
- **Practical point**: in the experience of the panel, many patients with EB have reported bad experiences regarding overdebridement from podiatrists who have not understood the nature of the condition or have sought advice from the patients themselves. This is why podiatry education in EB has been highlighted as a priority by DEBRA, and a specific training programme is currently being developed.
- Assessment and correction of weight distribution, with cushioning to try to reduce hyperkeratosis build-up (Quality evidence level ranging from 2− to 2+).[4,7,8]
- The use of EB-specific assessment tools (e.g. pressure assessment platforms and FHSQ; section B in Appendix S2; see Supporting Information). These assess the distribution of pressure on the skin leading to hyperkeratosis and evaluate how best to manage the condition by further assessing the quality of everyday function (Quality evidence level ranging from 2− to 1−).[4,7,8,10]

Special considerations

- Heloma (corn): the common corn is heloma durum. Heloma miliare (seed corns) are frequently seen in EB due to toe and foot deformity. Heloma neurovascular are encountered but to a lesser degree (Quality evidence level 4: expert opinion).
- Neurovascular hyperkeratosis. This is a form of callus in which nerve endings and blood vessels become prominent in the epidermis in response to trauma and treatment. This condition can present in patients with EB (estimated < 1%). The area is sensitive, painful and difficult to treat, as normal debridement causes pain and bleeding. Although rare, it is very debilitating in the small number of patients with EB affected. It probably results from long-standing gross hyperkeratosis and usually affects skin overlying the calcaneum and hallux (Quality evidence level 4: expert opinion). Debridement of these lesions by a podiatrist is also recommended and can provide similar relief, but the patient should be advised that due to the nature of the lesion, treatment can often be more uncomfortable than is experienced with standard hyperkeratosis.

Footwear

We recommend suitable footwear and appropriate insoles or orthotics for management of the EB foot by podiatrists, patients, carers and healthcare professionals (*Strength of recommendation grade: C*).

Evidence that advice on footwear is beneficial has been reported in all subtypes of EB:[16–20] EBS,[4,5,8] JEB,[4,8] DDEB[8,21] and RDEB.[7,8]

EB footwear advice suggests that wherever appropriate, footwear should be supportive. Its primary focus should be aimed at minimizing blistering by reducing friction (Quality evidence level ranging from 3 to 2−).[3,5,7] Once blisters have formed, dressings and topical antiseptics or antibiotics may be used to prevent secondary infection until the wound heals (Quality evidence level ranging from 4[3] to existing guideline⇒[9]). Therefore, suitable shoes or footwear are essential to accommodate dressings and not lead to further trauma to the damaged area. Footwear that is adjustable may be beneficial in these circumstances.

Recommendations regarding footwear in EB are based on expert opinion, as evidence is lacking. The overriding recommendation is to minimize mechanical trauma to the feet by emphasizing the need for suitable footwear and appropriate insoles or orthotics (Quality evidence level 2−).[4]

Footwear advice should address the following:

- Socks should be selected to improve ventilation. Silver-fibred cotton socks and silver vinyl covering (for example CoolSorb) can be used with simple insoles and orthoses (Appendix S3; see Supporting Information). These conduct heat away from the feet, reducing sweating and friction (Quality evidence level ranging from 4 to 2−).[4] Silver-fibre socks also have additional antibacterial action (Quality evidence level 2−).[4] Silver sock technology is readily available across the world through hiking and trekking products. Additional options for patients living with EB include bamboo socks and double-layer socks.
- Shoes should ideally have the following features: firmness (Appendix 4; see Supporting Information), comfortable fit, appropriate length and width, rounded toe, plenty of room for the toes, flexibility, flat heel, heel support, laces or straps and flat or absent seams. These features are to prevent excessive movement or slipping of the foot inside the shoe (Quality evidence level 4).[4] The upper covering should be leather or fabric mesh to allow air to circulate, rather than plastic or synthetic (Quality evidence level 2−).[4]

The grey literature supports this by showing how different types of cushioning materials and insoles provide benefit in non-related diabetic foot ulcers. This can have a subjective relevance to support the benefits of footwear and orthotics in EB.[16–18]

Special considerations

- Care must be taken when a child starts walking, acknowledging that shoes are not always necessary indoors (Quality evidence level 4).[3] Allowing a child to walk barefoot or just in socks helps feet to grow normally and develops muscular joint strength. A child will also benefit from proprioceptive feedback when walking barefoot (Quality evidence level 4).[3] These benefits must be balanced against the risk of damage to the unprotected skin. Outside, children's feet should be protected in lightweight flexible footwear made of natural materials (Quality evidence level 4).[3] The soft cartilage within their feet can easily be bent while walking, and the layer of fat tissue will offer support and shock absorption, potentially masking abnormal development (Quality evidence level 4).[3]
- Babies with EB may have one foot smaller than the other due to prenatal loss of skin and subcutaneous tissue: this can be managed by correctly fitting shoes of different sizes (Quality evidence level 4).[3] The child's foot should be measured at a reputable shoe store every 2–4 months (Quality evidence level 4)[3] or at the EB clinic, and it may be necessary to change the shoes and the socks every few months to allow room for growth (Quality evidence level 4).[3] Children with severe types of EB needing bulky dressings to the feet may have difficulty finding shoes to fit and need to rely on lightweight plastic shoes such as Crocs (Appendix S4; see Supporting Information).
- All patients with severe EB should not be walking barefoot but should have layers of protective dressings. Special consideration should be given to the length of the Achilles tendon, which can tighten in response to pain on walking and application of dressings.
- Cost implication for appropriate footwear is a large consideration in the global EB world. Some countries may use specific funded services for shoes for 'suitable' patients, while others are unable to provide such a service. Recommending suitable footwear can have its limitations and cost implications due to the type of footwear available, the age of the individual, their foot deformity, the type of EB they have, their occupation and changes in fashion. Not all services will cover or have international availability. However, the improvement in mobility, independence and quality of life in the long term outweigh this (Quality evidence level 2−),[7] (Appendix S4; see Supporting Information).

Mobility

We recommend measures to improve mobility, with assessment and monitoring for all subtypes of EB (*Strength of recommendation grade: C*).

- Longitudinal mobility assessment and monitoring are essential in EB, as disease-related factors such as scarring and contractures can change an individual's ability to mobilize over time (Quality evidence level ranging from 4 to 2+).[3,5,7,19,20]
- Gait analysis systems can be safely used in EB and can be helpful to diagnose pressure areas and walking patterns, and evaluate the effect of therapeutic interventions (Quality evidence level ranging from 2− to 2+).[6,7]
- Podiatry interventions differ between EB subtypes and must be tailored to the individual patients to prolong mobility (Quality evidence level ranging from 4 to 3).[3,5]

The evidence of podiatric care can improve mobility. Both children and adults with all subtypes of EB may have affected feet.[18] Problems such as blistering, hyperkeratosis (callus), nail loss, altered gait and deformity (Quality evidence level ranging

from 3 to 2+)[8,20,21] can result in reduced mobility and, eventually, wheelchair use (Quality evidence level ranging from 3 to 2+).[8,21] Preventing these problems can help children and adults with all subtypes of EB to stay mobile for longer and improve their quality of life.

A study of 425 patients with EB, of whom 140 were children, reported the percentages of children being able to walk independently or dependently within the different EB subtypes (Table 4).[19] The results showed children who were independent had differing walking abilities.[19] It was noted that DDEB showed a higher percentage of independent walking compared with EBS, JEB and RDEB.[19] The patients in the dependent groups showed very little ability to walk, with those with RDEB requiring the most support compared with EBS and JEB, and patients with DDEB requiring no support (Table 4).[19] The impact of dependency should not be diminished by these results, as the occasional use of wheelchairs is present among all forms of EB.[19]

Painful foot blistering is a common problem exacerbated by walking or standing in EB (Quality evidence level ranging from 3 to 2+).[6,19,22,23] A DDEB study reported that pain on walking was reduced in six of the seven patients by correcting the foot's balance and eliminating areas of abnormal weight bearing (Quality evidence level 3).[22] In a more recent cohort of cases of localized EBS, localized foot pain occurred before, during or after the onset of a blister (Quality evidence level 2+).[6] Blisters triggered by friction, walking, heat, trauma and hyperhidrosis tend to be worse in the summer (Quality evidence level 2+).[6]

Practical point: a case–control study reported that plantar injections of botulinum toxin effectively reduced pain from walking, and were a long-lasting and safe treatment for painful blistering and callosities in EBS (Quality evidence level 2−).[23] Blisters disappeared after botulinum toxin therapy and the pain reduction was sufficient to permit the patient to start walking more freely (Quality evidence level 2).[23] However, the procedure is painful and not tolerated by all patients (Quality evidence level 2−).[23]

Gait analysis and pressure measurement systems assess foot step pattern[2] (Quality evidence level 2−),[7] (section C in Appendix S2; see Supporting Information). Analysis of a person's manner of walking (gait) in EB facilitates the diagnosis and appropriate management of foot problems[3] (Quality evidence level 2−).[7] These platforms have proved essential in podiatry practice in diabetic foot management. The podiatrist can use gait assessment to identify areas that have more focused pressure when walking and translate this information into the development of patient-specific insoles (section C in Appendix S2). This practice can also be extended, where appropriate, to the development of bespoke footwear (Appendix S5; see Supporting Information). This is particularly useful when the type of EB results in such deformity that standard off-the-shelf footwear will not fit[3] (Quality evidence level 2−).[7]

The physiotherapist can also use gait analysis and assessment to help improve posture while walking and provide further advice and exercises to help develop core strength (Quality evidence level 4).[24] Furthermore, this approach can evaluate the effectiveness of the therapy (Quality evidence level 4).[24] From a practical view, gait platform mats are portable and can be fun to use, and above all do not damage the skin (Quality evidence level 4).[24]

The overarching recommendations here are as follows:

- Referral for podiatry assessment, treatment and monitoring to minimize blisters and pain while walking.
- Where appropriate and affordable, consideration of patient-specific insoles and bespoke shoes.
- Multidisciplinary therapy management should include the podiatrist, occupational therapist and physiotherapist to reduce pain while walking and encourage mobility (Quality evidence level ranging from 4 to 2++).[25–28]
- Use of a gait analysis system to assess the patient's walking pattern, and to monitor and evaluate therapy intervention (section C in Appendix S2; see Supporting Information).
- Plantar injections of botulinum toxin have been highlighted as providing therapeutic benefits in a small cohort of patients. Further research is required in this area, but it may be a consideration for adult patients with EBS who can tolerate the procedure, if conservative therapies have not worked.
- Tailoring podiatry interventions to the subtype of EB to prolong mobility.
    - Patients with EBS tend to require debridement of hyperkeratosis (callus), blister care management or simple insole and footwear advice.
    - Patients with JEB may require blister and wound management, and also simple insoles and footwear advice.
- All patients with EB require nail management from birth, plus wound care and footwear advice and insoles as they become older.

Table 4 Percentages of children with epidermolysis bullosa (EB) who reported independence and dependence for major activities for daily living[19]

Walking	EBS	JEB	DDEB	RDEB
Independent	31·2	30·8	66·7	24·4
Dependent	2·1	7·7	0	13·3

EBS, EB simplex; JEB, junctional EB; DDEB, dominant dystrophic EB; RDEB, recessive dystrophic EB.

Pseudosyndactyly

We suggest consideration of surgery for pseudosyndactyly and mitten deformities of the feet, as well as for contractures of the lower extremities in patients with DEB (*Strength of recommendation grade: D*).

- Foot surgery for joint contracture deformity release and digital amputation can be successfully performed in EB

and may benefit patients by reducing pain, improving ability to wear shoes and improving mobility (Quality evidence level 3).[22,29–32]

The evidence for the surgical management of pseudosyndactyly, mitten deformities and contractures of the lower extremities largely concerns patients with DEB. The relevant literature is heterogeneous and consists mainly of case reports and case series. Surgery in this patient cohort is primarily undertaken in the hand to improve function. Surgery can be considered for pseudosyndactyly, mitten deformities and contractures of the lower extremities in patients with DEB. However, due to the relative short-term nature of any cosmetic improvement and limited functional improvement (if any), other surgical procedures that will help accommodate the foot in certain footwear, such as selective digital amputation, may be more appropriate. Patients should therefore consider any benefits vs. risks very carefully. Similar complications from other EB subtypes do not cause mitten deformities or pseudosyndactyly deformities and are therefore not highlighted in any of the literature (Appendix S1a; see Supporting Information).

RDEB generalized severe is characterized by progressive fusion of digits leading to pseudosyndactyly and a mitten-like deformity of the hands and feet. These complications occur to a lesser degree and later in RDEB generalized intermediate. Cutaneous scarring can also lead to joint contractures and deformities in the feet, resulting in reduced mobility and pain (Quality evidence level 3).[22,29–31]

Procedures reported

- Clawed toes were surgically released in three patients, by making extensive transverse incisions across the dorsal and/or plantar surface of the toes and distal forefoot, extending into the subcutaneous tissue (Quality evidence level 3).[22] This improved the foot contour, reduced pain on walking and allowed shoes to be worn (Quality evidence level 3).[22] The release of pseudosyndactyly makes it easier to wear normal footwear and it is of psychological benefit to the patient to observe a 'normal' foot with five toes (Quality evidence level 3).[22] Improvements were seen for several years, but due to the progression of the EB reoccurrence was likely.
- Despite the long-term complications of surgery, early extension procedures to address contractures of the toes and equinus and cavus deformities using soft-tissue surgery were recommended by the experts reviewing six cases (Quality evidence level 3).[30]
- In a case study of foot syndactyly in six patients with RDEB, the main foot surgery goal was to reduce extreme flexion or extension contractures to allow the patient to wear shoes and ambulate comfortably (Quality evidence level 3).[29]
- Most surgical procedures to the foot in EB involved mitten release, although this procedure is used more for hands (Quality evidence level 4).[32] Syndactyly release to the foot reduced pain or difficulty in standing and walking, and improved ability to wear shoes due to hyperextension contractures of the toes (Quality evidence level 4).[32] The numbers are small, with only six patients benefiting out of 25 who had surgery in a New York cohort, and six of 50 patients in the St Thomas Hospital cohort who underwent foot surgery (Quality evidence level 4).[32]
- Contractures almost always recur, and because of the lack of long-term benefit patients often refused further surgical interventions (Quality evidence level 3).[33]
- RDEB mouse models have shown that losartan reduced tumour necrosis factor-β-mediated inflammation and supported matrix remodelling. Losartan administration in the RDEB mice with injured forepaws seemed to prevent digit fusion (Quality evidence level 2++).[34] A clinical trial to establish the safety, tolerance and efficacy of losartan in children with RBED is currently ongoing.[35]

Podiatrist professional development

Enhanced proficiency in the functional treatment of people with EB is recommended. It is expected that clinicians always use great care as an integral part of their professionalism as a podiatric clinician. However, EB is a condition requiring specialist intervention beyond just 'being more careful'. It necessitates specialist training and provision and recognition by podiatric practitioners of the extent of their practice and experience. This has important ramifications for undergraduate podiatry training in relation to informed knowledge of interprofessional referral pathways in instances where newly qualified students may inadvertently meet patients with EB for the first time.

Podiatrists managing EB must avoid causing secondary injury, by:

- Handling feet and limbs with great care.
- Avoiding the use of highly adhesive tapes, dressings and felt padding.
- Removing any adherent dressings, ideally with silicone spray.

Continued professional development for podiatrists is encouraged, for example undertaking a specialist EB podiatric management course to integrate their professional knowledge and clinical skills in managing EB-related podiatric conditions.

This guideline is focused on helping people living with EB and their families to manage their foot problems. In countries where podiatrists are unavailable or not part of the healthcare system, a healthcare professional can aid to some degree. Nurses can offer expertise with wound care management, and they can offer advice on footwear and foot care with the guideline as a reference. There are restrictions with blade debridement, as this is not part of their scope of practice. Specialist podiatric knowledge to address biomechanical issues of the feet and prescription orthotics can only be delivered by a podiatrist, physiotherapist or musculoskeletal doctor. These key areas may also be addressed by a dermatologist,

paediatrician, surgeon or 'doctor'. In countries where there is no podiatric support, the healthcare professional offering this care should make sure that they legally adhere to that country's scope for their profession.

Key limitations

An extensive literature review of syndactyly surgery revealed mainly case studies, with few controlled studies. Recommendations are therefore based on expert opinion of current clinical practice.

Conclusions

We can conclude that podiatric intervention improves EB foot care. The key interventions of clinical debridement of hyperkeratotic (callused) skin, dressings of wounds and reduction and cutting of nails greatly improved the wellbeing of patients. Advice given by the podiatrist helped patients to identify suitable footwear, insoles and socks, benefiting patients on a daily basis. A podiatrist should routinely be included as part of the multidisciplinary management of EB. An overview of the evidence for each outcome is provided in Table 5.

Future research

This CPG highlights the need for further high-quality research (Table 6).

Implementation of guideline recommendations

DEBRA International aims to ensure that the EB guidelines address the needs of patients internationally. These guidelines will be translated into other languages and a patient version will be made to make them more accessible. These guidelines could be disseminated and promoted through the education of professionals, and eventually incorporated into clinical practice. This guideline was presented at the DEBRA Australia EB camp 2018. The implementation of these recommendations could be monitored and evaluated through audits, education programme registration and the CPG Evaluation Form: Pre implementation (Appendix S6; see Supporting Information). The panel recommends clinical sites to conduct a prepractice audit, implement the CPG and reaudit to test improvements. Audit tools can be used from SIGN.[36] DEBRA International would value your feedback on the site findings to continue to improve the quality of the CPG.

Development of the guideline and methodology used for formulating the recommendation

In 2016, an international panel of multidisciplinary health professionals and people living with EB was coordinated through DEBRA International, through voluntary membership. The panel represented people with clinical or personal experience of EB, covering both specific adult and paediatric knowledge bases. All panel members were encouraged to participate actively in all stages of the guideline development, so that the co-construction of knowledge and experience of the condition could be seen to move beyond tokenism in relation to the incorporation of the expert patients who live with EB on a daily basis.

Following the SIGN methodology[36] the panel decided on the clinical question, 'Can podiatry support help improve the quality of life of people living with EB?', and used this to focus their search through considering participants, interventions, comparisons and outcomes (PICOS) (Table S1; see Supporting Information).[36,37] This process was informed by priorities raised by people living with EB from an international survey using DEBRA International, EB-CLINET databases and distribution of hard copies of the survey in clinics in Australia (Appendix S7; see Supporting Information), and a preliminary literature search. The panel voted for the relative importance of the outcomes and selected the top six to seven priorities that matched those raised from the survey.[36,37]

Literature search

A systematic literature search was adopted with no language restrictions. The literature search was conducted by the two panel leads using seven electronic search engines: MEDLINE (PubMed MeSH), Wiley Online Library, Google Scholar, Athens, ResearchGate, Net and PubFacts.com. The search terms and inclusion criteria followed PICOS (Table S1; see Supporting Information). The Boolean AND and OR operators were used to combine these terms as appropriate. Searches of cited references were conducted on eligible papers. Updating of the available literature was continued up to publication. Forty-six full articles were identified, and 36 were finally included after exclusion of 10 duplicates.

Inclusion criteria were applied to all articles identified by the searches (Appendix S8; see Supporting Information). These were discerned from the papers' abstracts and titles, or the full articles in cases of uncertainty. Papers that were unpublished or did not meet the methodological filters were retained as grey literature. These were examined to provide context or considered divergence within the main recommendations.

Research appraisal

All published papers passing this filtering stage were then subjected to a systematic quality appraisal and risk-of-bias assessment. This appraisal was modified from the Critical Appraisal Skills Programme (http://www.casp-uk.net) and SIGN[36] quality ratings. This allowed both quantitative and qualitative research to be appraised using one list of questions, yielding one quality rating scale to allow a comparison of studies as required (Appendix S8; see Supporting Information). The study limitations and indirectness were taken into account through the appraisal tool. The precision and statistical consistency could not be evaluated as the EB articles had no statistical values. Most

Table 5 Overview of the evidence per outcome

Outcome	Allocated papers	Participants with EB in the articles	Methodology	Average quality rate[b]	Quality appraisal (range)	Benefits and limitations
Blistering and wound management	6	347[a] EBS 171 JEB 11 DDEB 31 RDEB 22	1 qualitative 1 quantitative 1 cohort 2 case studies 1 chapter	2+	58% (52–86%)	Blisters can be reduced in size and frequency, but expertise still limited to a few centres
Dystrophic nails	8	234[a] EBS 137 JEB 11 DDEB 38 RDEB 24	2 qualitative 1 quantitative 3 case studies 1 observational 1 chapter	2+	67% (17–90%)	Mainly toenails rather than fingernails and their use for diagnosis
Hyperkeratosis	5	286[a] EBS 137 JEB 11 DDEB 33 RDEB 22	1 qualitative 1 quantitative 2 case studies 1 chapter	2+	58% (52–64%)	Highlights occurrence in clinic, not complexity
Footwear	6	291[a] EBS 114 JEB 11 DDEB 31 RDEB 22	1 qualitative 1 quantitative 1 cohort 2 case studies 1 chapter	3	56% (48–69%)	Mainly on advice, no audits
Mobility	14	1067[a] EBS 396 JEB 71 DDEB 148 RDEB 105	3 qualitative 2 quantitative 1 cohort 3 observational 4 case studies 1 chapter	3	60% (48–90%)	Early stages of new approaches to assess and treat
Pseudosyndactyly	8	3401[a] DEB 96	Out of 96 cases of DEB only 7 were on toe fusion 1 laboratory biological and animal model	3	54% (24–95%)	Low evidence with only case reports or series of poor quality and high risk of bias

EB, epidermolysis bullosa; EBS, EB simplex; JEB, junctional EB; DDEB, dominant dystrophic EB; RDEB, recessive dystrophic EB. [a]Total number of persons with EB in all papers combined. [b]Descriptions in accordance with SIGN:36 2+, well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 3, nonanalytical studies, e.g. case reports or case series.

studies reviewed had > 50% risk of bias, as EB is a rare condition, there are no double-blind randomized clinical studies and most people would know they have EB.

All selected papers were filtered and appraised by the two panel leads (M.T.K. and M.O'S.). In those instances where consensus could not be reached between the two panel leads, a third appraisal from the panel was allocated until this could be assured. This was conducted to reduce bias, to increase content validity checks of the literature, and most importantly to ensure the consistency of the reviews undertaken. The research quality score was obtained, with a high percentage being indicative of higher quality of the paper. Levels of bias were also measured in percentage values and all papers were graded in accordance with the SIGN method 'Level of Evidence and Grades of Recommendations' 1++ to 4 and grade A to D.[36]

The papers were then divided into outcome topics. All papers and grey literature were allocated to these outcomes. The two panel leads and a member summarized the appraisals per outcome and rated the strength of the recommendation. Outcome summary tables were presented to highlight the population subtypes, numbers of patients, study type, percentage quality and risk of bias in accordance with SIGN. The panel checked the emerging strength of the recommendation, desired and undesired effects, costs related to benefits and the feasibility of implementation. They confirmed and discussed the recommendations elicited using the GRADE framework for the recommendation table (http://www.gradeworkinggroup.org). All recommendation summaries were circulated to the panel, and final agreement and feedback were included. The AGREE II tool[38] was consulted to increase the quality of practice guidelines in rare diseases, and this CPG acknowledges existing guidelines by signposting with the symbol ⇒ throughout this manuscript.

The guidelines were peer reviewed by a representative cross-section of EB multidisciplinary team specialists and people living with EB. Five of eight health professionals and one

Table 6 Possible future research for each outcome

Blistering and wound management
• Comparative studies can be used to assess dressing types used on the feet in different EB groups
Dystrophic nails
• Evaluate the benefit of a podiatrist to manage both fingernails and toenails
• A review of the nail conditions affecting patients with EB is needed, and then a study to examine the treatment protocols, with topical keratolytic agents, urea-based agents and daily filing with an emollient to follow
Hyperkeratosis (callus)
• Evaluate the benefits of callus debridement between manual techniques (scalpel) over keratolytic agents
• Comparative studies to assess different keratolytic agents when treating hyperkeratosis in patients with EB
Footwear
• Examine different podiatry materials to offer shock absorption and redistribution within footwear being worn
• Studies on footwear for patients with EB and engagement with footwear and hosiery manufacturers to make friendly footwear and hosiery more accessible for a person with EB
• Evaluate specific footwear funding by the service for 'suitable' patients; the outcome of this would be useful
• A study would be required to show any quantifiable benefit of silver vinyl insole material
Mobility
• Further assessment with larger EB groups, monitoring mobility using gait analysis platforms and fitness trackers to assess total distances achieved.
• Patients can record their steps just using their mobile phones; this is not as accurate as a fitness tracker but it is less expensive, and not everyone can wear something around their wrist
• Assessing the impact that aids, suitable footwear, insoles and orthotics, and dressings have on aiding distances achieved by individuals with EB
Pseudosyndactyly
• Benefit of no surgical implementation of losartan in slowing down fibrosis in patients with RDEB
Other areas
• Botox injections in EBS
• Pedagogical implications for the contextual positioning of EB education and training in both undergraduate and continuous professional development and postgraduate podiatric specialisms

EB, epidermolysis bullosa; EBS, EB simplex; RDEB, recessive dystrophic EB.

person living with EB reviewed the guideline draft to assess the degree to which the recommendations presented addressed patients' concerns and identified good practice points (Table S2; see Supporting Information).

The lead and co-lead compiled a reviewer's feedback report for discussion with the guideline panel. Each point was addressed and any resulting change to the guideline was noted or, if no change was made, the reason for this was recorded. The panel conducted a final proofread of the manuscript before submission.

Guideline dissemination and update

The guidelines will be updated every 3–5 years or if there is a significant breakthrough in EB podiatry care from the publication date. We recommend iterative updating of search terms to see whether a full review is warranted at any stage.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 (a) Images of related foot and nail disorders in children and adults with epidermolysis bullosa. (b) Hand dystrophic nail management.

Appendix S2 Assessment tools.

Appendix S3 Foot care devices and products.

Appendix S4 Footwear and hosiery products for children and adults.

Appendix S5 Bespoke footwear information.

Appendix S6 Implementation survey.

Appendix S7 Epidermolysis bullosa survey.

Appendix S8 Appraisal and risk-of-bias tool.

Table S1 Literature search strategy.

Table S2 Members of the clinical practice guideline group.