Introduction

Epidermolysis bullosa (EB) is the term used to describe a number of rare genetically determined skin conditions characterised by a tendency for the skin to blister or shear away in response to minimal friction and trauma.

Diagnosis

In the majority of cases the type of EB can be determined by analysis of skin biopsy taken under local anaesthesia. There are 3 broad categories of EB depending on the level of the split within the skin. These are EB simplex, junctional EB and dystrophic EB. Within each of these categories there are several subtypes.

Inheritance

Junctional EB (JEB) is a recessively inherited disorder. Both parents are carriers of the mutation, each having one defective copy of the gene. The risk of an affected child is 1:4 in every pregnancy. Carrier status is not generally recognised until an affected child is born.

Types of junctional EB

1. Herlitz JEB
2. Non-Herlitz JEB
3. JEB with associated pyloric atresia

All forms of JEB reflect mutations in genes encoding components of the hemidesmosomes-anchoring filaments that help with binding basal keratinocytes to the lamina densa. Junctional EB results from a defect in the protein laminin 332.
Laminin 332 is made from three glue-like proteins, LAMA3, LAMB3 and LAMC2. These stick the epidermis to the dermis.

**Herlitz JEB** is caused by complete loss of one of the parts of the laminin 332 protein.

**Non Herlitz JEB** results from a mutation in laminin 332 or in type XV11 collagen.

**Junctional EB with pyloric atresia** is caused by defects in the α6 or β4 integrin proteins.

**Herlitz JEB**

This is the most common type of JEB, in which death is probable within the first two years of life. Many will die in early infancy.

Often there is only minimal blistering apparent at birth, usually presenting as inflammation around the nail beds. This may give false hope that the infant has a mild type of EB. Blistering under and around the nappy is a common feature. Mouth blistering may be present at birth, or quickly develops once feeding commences. Often blisters readily appear on the skin as the infant is handled. Some infants are born with absent skin on the limbs as a result of intra uterine movements. These wounds are typically slow to heal.

Over time the lesions become widespread, blistered areas develop into chronic ulceration which is reluctant to heal.

Causes of death are the effects of the disease on the larynx and the gastro intestinal tract, resulting in increasing respiratory distress and failure to thrive.

**Non Herlitz JEB**

Non Herlitz JEB may resemble the Herlitz type initially and outcome cannot be predicted before analysis of the skin biopsy. Infants may have widespread blistering and skin loss at birth.

Laryngeal disease and failure to thrive are rarely seen in those with Non Herlitz JEB but these features have been described. The risk of death in the first few years of life is much lower than in the Herlitz type, but this has been reported in infants severely affected with Non Herlitz JEB.

More commonly, the skin is slow to heal and results in atrophic scarring. Protein-losing enteropathy may be a feature requiring modified feeds.

Urinary tract involvement can cause stricture formation and renal damage if left untreated. We recommend annual renal ultrasound and regular urinalysis to identify early problems. Supra - pubic catheterisation or urinary diversionary surgery in the form of a mitroffanof is occasionally required to relieve urinary retention and painful micturition in severe cases.
JEB with pyloric atresia.

This is a rare form of JEB. Infants are frequently born prematurely and may have ear lobe defects. Gastrointestinal atresia can be single or multiple and may occur in the pylorus or duodenum. Surgical correction is often successful but the prognosis is generally poor. There are however a few survivors, often with minimal skin problems. Protein losing enteropathy can occur. Urinary tract involvement is common in the survivors and is managed as above.

Care and management of infants and children with JEB.

Handling.

The infant should be nursed on a soft pad tested for safety in small babies. We recommend a Spenco incubator pad which can be covered with a Parafricta pillowcase to reduce shear and friction. Parafricta products are available from your DebRA nurses or can be purchased directly from www.parafricta.com. To lift the baby from the Spenco mattress, apply a roll and lift technique to avoid damage from friction and shearing forces – roll the baby onto his side, place one hand behind the head, the other under the nappy area, allow him to roll back onto your flat hands and lift.

Skin Care

**Blisters** must be lanced with a hypodermic needle to prevent their spread. The roof should be left on the blister and the area dusted with cornflour to help dry up the blister. Cornflour is chemically inert and soluble providing a safe alternative to commercial powders.

Nappy area care

The skin should be cleaned with water or if ulceration is extensive and stinging results from contact with water, clean with 50% white soft paraffin/50% liquid paraffin.

Blisters should be lanced as described above, but cornflour not applied as contact with urine will turn it to a paste. Blistered and vulnerable areas should be protected by a thick layer of Bepanthen ointment (Roche) which is reapplied at each nappy change. Open wounds are covered with the dressing Intrasite Conformable (Smith & Nephew). The nappy is lined with a soft material to cover the edges of the nappy to prevent it from rubbing. Suitable materials include Conti Cloth Supersoft and polyester fleece. The fleece can be washed and reused. Commercial nappy liners are also available from Plushpants at www.plushpants.com
Bathing

If there is extensive skin loss at birth we recommend delaying bathing until healing has taken place. This is because bathing will be a painful process and it is difficult to protect the infant from further skin damage when all the dressings are removed at once. Regular bathing may not be possible.

Clothing

Initially a front fastening babygro is ideal but unless flat-seamed will need to be worn inside out to prevent the seams from rubbing and causing blisters. Care must be taken to ensure the fasteners do not rub the chest. Older children can wear commercial garments providing there are no prominent seams and they are easy to put on and off. Clothing and bedding designed for children with EB can be purchased from “Blue Aliya” – for a catalogue please phone on 07876 684661 or email; sharmila@bluealiya.com

Wound care

Open wounds must be dressed to encourage healing and prevent adherence to clothing. Some dressings although described as atraumatic and suitable for those with other types of EB may cause blistering or extension of the wound.

Intrasite Conformable (Smith & Nephew) appears to be the most satisfactory dressing providing protection of the skin and enabling wound healing. The dressing is applied directly to the skin and secured with a small piece of tubular bandage such as Tubifast (Medlock). The Intrasite Conformable will need to be changed at least once a day and more frequently in hot weather to prevent it from drying out and adhering to the wound. Applying Bepanthen ointment (Roche) to the dressing prior to application will aid healing and help to keep the dressing moist.

Alternatively the wounds may be dressed with primary wound dressings including Mepitel (Mölnlycke Healthcare) and Urgotul (Urgo). Secondary dressings include Mepilex Lite, Mepilex Transfer and Mepilex (all Mölnlycke Healthcare). For ease of dressing changes Urgotul can be replaced with Urgotul Duo or Urgocell which combine a primary and secondary dressing. Choice of dressing is dependent on the nature of the wound, the amount of exudate and requirements for protection. For management of excessive exudate Eclypse dressings (Advancis) are supra absorbent.

Honey based products and dressings are helpful in controlling critical colonisation, reducing malodour and debriding wounds. Suitable products include Mesitran and Mesitran S ointments (Medlock) and Algivon (Advancis).
Finger and toe nails are often lost following blistering around the nail bed. The resulting open wound is reluctant to heal. Over granulation is very common in this area and can be reduced by short term application of a potent topical steroid. Finger tip wounds can be dressed with Mepitel as a primary wound dressing, covered with Mepilux Transfer or Mepilux Lite and secured with a small strip of adhesive tape, taking care the tape does not come into contact with the skin. If adhesive products accidentally adhere to the skin, or dressings are adherent, Appeel Medical Adhesive remover spray (Clinimed) will remove the product painlessly and without skin stripping.

Short term application of potent topical steroid can be helpful in other areas of over-granulation and is particularly useful where facial ulceration is troublesome.

Wounds readily become infected or critically colonised, reducing healing and causing addition pain. Topical application of products such as medical honey or Crystacide (1% stabilised hydrogen peroxide) can help reduce the bio-burden. When infection is suspected a broad spectrum antibiotic should be commenced whilst wound microbiology results are awaited.

If wounds are malodorous, which is a common problem with finger tip wounds, application of metronidazole gel will reduce the level of anaerobes which are responsible for the odour.

Nutrition

Infants may be reluctant to feed due to soreness from blistering on the gums, tongue and palate. A Haberman feeder is often helpful as the valve ensures a good delivery of milk despite a weak suck which results from a reluctance to compress the teat between the blistered surfaces. Application of teething gels to the teat or directly to the mucous membranes prior to feeding or a preparation such as Gelclair (Cambridge Laboratories) further reduces pain.

Breast feeding is often possible although the face may need to be protected with a layer of emollient to reduce friction from rooting.

In those with the Herlitz form of JEB failure to thrive is a common feature. Increasing the nutrient value of the feed can help in the short term but improvement may not be sustained. Those with Non – Herlitz junctional EB are likely to need increased nutrients to compensate from losses through open wounds. Changes to the feed should always be made under the guidance of a dietician. Specialist advice can be obtained from EB dieticians at Great Ormond Street Hospital, London and Birmingham Children’s Hospital.

Gastrostomy insertion in infants and children with JEB can be helpful in those with the Non-Herlitz type, although problems with leakage have been reported. Gastrostomy feeding in those with HJEB is rarely offered as increased nutrients do not reverse the weight loss and the site of the gastrostomy rapidly ulcerates.

Constipation is a common problem in those with all types of EB, often resulting from blistering and soreness around the anal margin. This may respond to stool softeners such as Lactulose initially, but many require management with an osmotic laxative.
such as Movicol paediatric. Constipation may be further compounded by side effects from opiate pain management.

**Analgesia**

Sources of pain in EB are multifactoral. Pain results from blisters and wounds, in response to procedures such as dressing changes and nappy changes, oral and laryngeal lesions, bladder pain, dental pain, and pain from corneal abrasions. In view of the complexity of management we recommend regular assessment by a paediatric pain team. In general, many infants and children require simple analgesia such as paracetamol and ibuprofen, with opiate analgesia in the form of MST for background pain with additional morphine sulphate prior to procedures and for breakthrough pain.

Nerve pain can be managed by adding amitriptylline or gabapentin. Many require midazolam given as an anxiolytic and sedative together with the morphine sulphate prior to procedures.

Should swallowing become difficult, buccal preparations of morphine and midazolam should be used.

**Airway management**

Laryngeal blistering is a common feature in those with Herlitz JEB. The infant develops a hoarse cry within the first few weeks of life. This may be intermittent as blisters form and then burst. Breathing difficulties can be managed using nebulised budesonide or oral dexamethasone.

Acute respiratory distress responds to oral morphine and midazolam.

Copious secretions can be problematic and are managed by application of hyoscine patches. These should be removed using Appeel medical adhesive remover spray (Clinimed). Oral suction should be avoided where possible due to the risk of stripping of the oral mucosa.

Longer term survivors of Herlitz junctional EB have occasionally required a tracheostomy following repeated blistering and subsequent scarring of the airway.

**Dental**

Enamel hypoplasia is present in all types of JEB. Brushing should be encouraged with a soft toothbrush and fluoride supplements may be prescribed. Longer- term survivors may require extensive dental restoration.

**Eyes**

Blistering and ulceration of the cornea is a common feature of junctional EB. This painful condition can be triggered by rubbing the eyes, but often results from dry eyes resulting from a reduced tear film. Blepharitis is also common and may need treatment with FLM eye drops under the guidance of an ophthalmologist experienced in the care of children with EB. Regular application of artificial tears such as Viscotears during the day and ointment such as lacrilube at night can help keep the eyes moist and reduce the incidence of blistering. Once an abrasion has occurred the lubricants should be replaced by antibiotic eye drops. Occasionally a
severe abrasion results in loss of the entire conjunctiva and the ophthalmologist will need to insert a blanket contact lens to protect the eye whilst healing takes place.

The future

Sadly at present there is no cure for epidermolysis bullosa. Scientists are working hard towards finding gene therapy to correct the faulty proteins responsible, but at present treatment remains symptomatic.

Prenatal testing is available for parents who are carriers of junctional EB. The test is called a CVS (chorionic villous sampling) and involves a small piece of the placenta being taken for genetic testing after the 11th week of the pregnancy.