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Gastrointestinal complications of epidermolysis bullosa in children

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Conflicts of interest
None declared.

Summary

Background Epidermolysis bullosa (EB) is a group of inherited disorders characterized by skin and mucous membrane fragility. Gastrointestinal (GI) complications have been described in many types of EB and are responsible for significant morbidity.

Objectives To delineate the nature and frequency of GI complications in a large cohort of paediatric patients with EB and to postulate why some complications occur more commonly in some specific subtypes.

Methods The case notes of 223 children with EB seen at a national referral centre were examined retrospectively for the presence of GI symptoms, investigations and interventions.

Results GI complications were present in 130/223 (58%) of all patients. In EB simplex, constipation and gastro-oesophageal reflux (GOR) were frequently observed. In junctional EB, failure to thrive and protein-losing enteropathy (PLE) were the prominent GI manifestations. Constipation was common in patients with dystrophic EB (DEB) requiring laxatives and in some cases fibre supplementation. GOR affected three-quarters of those with recessive DEB, two-thirds also having significant oesophageal strictures. Over half of patients with recessive DEB required gastrostomy insertion. Diarrhoea affected a small but significant proportion of children with recessive DEB with macroscopic and/or microscopic changes of colitis in the majority.

Conclusion GI problems in EB are very common with subtype specificity for some of these complications. The occurrence of diarrhoea, PLE and colitis in the context of EB has not been highlighted previously, and may arise secondarily to antigenic exposure in the gut lumen as a result of mucosal fragility.

Epidermolysis bullosa (EB) is a group of inherited disorders characterized by blistering of the skin following minor mechanical trauma.[1] It affects between one and three per 100 000 children each year and is broadly divided into three major types depending on the ultrastructural plane of cleavage at the cutaneous basement membrane zone: EB simplex (EBS), junctional EB (JEB) and dystrophic EB (DEB).[2] To date, mutations in 10 different genes encoding structural proteins at the dermal–epidermal junction, notably in the basal keratins and the hemidesmosome basement membrane proteins, have been implicated in different forms of EB (Table 1).[1] Many of these proteins are also expressed in a variety of different epithelia and, as a result, involvement of mucosal surfaces, including parts of the gastrointestinal, urogenital and respiratory tracts, may be fragile in different types of EB, resulting in extracutaneous complications. Kindler syndrome is an autosomal recessive genodermatosis sharing many clinical features with EB, notably skin fragility, resulting from defects of actin–cytoskeleton adhesion via focal contacts as a result of mutations in the kindlin-1 gene (Table 1).[3]

A number of gastrointestinal (GI) complications have been described in EB, notably the occurrence of oral mucosal involvement,[4–6] oesophageal strictures[5,7–12] and constipation[5,7,8,10,11,13] which may cause considerable morbidity for this patient group. Other features of gastrointestinal disease, including gastro-oesophageal reflux (GOR), failure to thrive (FTT; defined as weight loss across two centiles on a growth chart), protein-losing enteropathy (PLE) and diarrhoea have not been well described in EB. In this study, we reviewed features of GI disease in a large group (n = 223) of paediatric

Table 1 A brief classification of epidermolysis bullosa (EB) and Kindler syndrome (KS)

Major type	Inheritance	Subtype	Protein defect	Gene defect
EBS	AD	Weber–Cockayne Koebner Dowling–Meara	Keratin 5 or keratin 14	*KRT5* or *KRT14*
	AR		Keratin 14	*KRT14*
EBS-MD	AR		Plectin	*PLEC1*
JEB	AR	Herlitz	Laminin 332 (formerly laminin 5)	*LAMA3*, *LAMB3* or *LAMC2*
		Non-Herlitz	Type XVII collagen or laminin 332	*COL17A1*, *LAMA3*, *LAMB3* or *LAMC2*
JEB-PA	AR		α6β4 integrin (or plectin)	*ITGA6*, *ITGB4* (or *PLEC1* or *COL17A1*)
DEB	AR or AD		Type VII collagen	*COL7A1*
KS	AR		Kindlin-1	*KIND1*

EBS, EB simplex; EBS-MD, EB simplex with muscular dystrophy; JEB, junctional EB; JEB-PA, junctional EB with pyloric atresia; DEB, dystrophic EB; AD, autosomal dominant; AR, autosomal recessive.

patients with EB seen at Great Ormond Street Hospital for Children, London, a national referral centre for EB. We have correlated the patterns of involvement seen in different forms of EB and postulate why certain patterns of disease occur.

Patients and methods

All patients with EB and Kindler syndrome attending Great Ormond Street Hospital for Children, a national referral centre for children with EB, were included in the study. A total of 223 children were identified and reviewed by two paediatric gastroenterologists, a paediatric dietician and two paediatric dermatologists. Their subtype of EB, as established from clinical features, skin biopsy and mutation analysis, where available, was recorded, and the presence of any GI symptoms, investigations and management was documented. Specifically, the presence of symptoms of GOR, oesophageal stricture formation, dysphagia, FTT, diarrhoea and constipation was assessed. The use of gastrostomy feeding was also recorded.

Results

A total of 223 children were identified in the study (aged between 0 and 18 years), of which 81 had EBS, 19 had JEB, 119 had DEB and four had Kindler syndrome. Results are summarized in Table 2.

Epidermolysis bullosa simplex

A total of 81 patients in this study had EBS (36% of total patients), of which 31 (38%) complained of gastrointestinal problems. Mild to moderate constipation was common, occurring in 21/81 (26%) of children with EBS. This was most notable in the Dowling–Meara group with 11/29 (38%) affected, and in children with EBS with muscular dystrophy (EBS-MD), two of four (50%) having symptoms of constipation. Most children had been treated with polyethylene glycol-based laxatives (one to two sachets twice daily) with the occasional addition of senna as a propulsive agent (5–10 ml twice daily), with good effect in almost all cases.

GOR, typified by persistent effortless vomiting, was observed in seven of 29 (24%) and two out of four (50%) patients with Dowling–Meara and EBS-MD, respectively. Domperidone as a prokinetic agent tended to be of limited value as monotherapy, with most children requiring additional treatment with ranitidine and/or a proton pump inhibitor (lansoprazole or omeprazole) in standard doses. Four patients with severe GOR had FTT due to nutritional losses from persistent vomiting. Twenty-four hour pH monitoring was performed on two children with EBS with severe reflux. The average reflux index in these cases was 18% (normal < 5%). These children responded to medical therapy with improvement in weight gain.

Junctional epidermolysis bullosa

JEB was the least common type of EB seen in our cohort affecting 19 of 223 children (9%). Of these, nine had Herlitz JEB (HJEB), seven had non-Herlitz JEB (NHJEB) and three had JEB with pyloric atresia (JEB-PA). Fourteen of these children (74%) had some features of GI involvement.

FTT was present in seven of nine (78%) children with HJEB, necessitating nutritional supplementation with nutrient-dense fibre-containing whole protein feed in three cases. One patient had a gastrostomy inserted and three were commenced on a hydrolysed formula feed, although compliance was suboptimal. In infants with HJEB in whom breastfeeding was established, continuation, exclusive or partial, was encouraged.

Two children in the HJEB group had severe hypoalbuminaemia of < 20 g dL^{-1} (normal range 35–50 g dL^{-1}) with raised stool α_1-antitrypsin levels greater than six to eight times above the normal range indicating PLE. Intestinal leakage of albumin is known to be associated with the loss of other small molecular weight proteins; IgG, IgA and IgM levels were low in the children with low albumin levels. Formula-fed infants were given hydrolysed feeds (as mentioned above) or whole

Table 2 Summary of types of epidermolysis bullosa (EB) and symptoms

	Total (n = 223) (%)	EBS (n = 81)					Junctional EB (n = 19)			Dystrophic EB (n = 119)			Kindler syndrome (n = 4)
		WC (n = 37)	DM (n = 29)	Rec (n = 3)	MD (n = 4)	Other (n = 8)	HJEB (n = 9)	NH JEB (n = 7)	JEB-PA (n = 3)	RD (n = 57)	DD (n = 54)	Unspec (n = 8)	
Any symptoms	130 (58·2)	7 (18·9)	17 (58·6)	2 (66·7)	4 (100)	1 (12·5)	8 (88·9)	3 (42·8)	3 (100)	50 (87·7)	30 (55·5)	3 (37·5)	2 (50)
Dysphagia	44 (19·7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	40 (70·1)	2 (3·7)	1 (12·5)	1 (25)
GOR	64 (28·7)	0 (0)	7 (24·1)	0 (0)	2 (50)	0 (0)	1 (11·1)	2 (28·6)	1 (33·3)	43 (75·4)	6 (11·1)	1 (12·5)	1 (25)
Strictures	39 (17·4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	37 (64·9)	0 (0)	1 (12·5)	1 (25)
Constipation	80 (35·9)	7 (18·9)	11 (37·9)	1 (33·3)	2 (50)	0 (0)	4 (44·4)	1 (14·3)	1 (33·3)	23 (40·3)	25 (46·3)	3 (37·5)	2 (50)
Diarrhoea	12 (5·4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12·5)	0 (0)	0 (0)	1 (33·3)	9 (15·8)	0 (0)	0 (0)	1 (25)
FTT	42 (18·8)	0 (0)	4 (13·8)	1 (33·3)	2 (50)	0 (0)	7 (77·8)	3 (42·8)	2 (66·6)	22 (38·6)	1 (1·85)	0 (0)	0 (0)
PLE	5 (2·2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (22·2)	1 (14·3)	2 (66·6)	0 (0)	0 (0)	0 (0)	0 (0)

EBS, EB simplex; GOR, gastro-oesophageal reflux; FTT, failure to thrive; PLE, protein-losing enteropathy; WC, Weber–Cockayne; DM, Dowling–Meara; Rec, recessive; MD, muscular dystrophy; HJEB, Herlitz JEB; NJHEB, non-Herlitz JEB; PA, pyloric atresia; RD, recessive DEB; DD, dominant DEB; Unspec, unspecified DEB.

protein feeds containing mainly medium chain triglycerides (MCT) as the fat source. This resulted in normalization of albumin and immunoglobulin levels.

In the seven children with NHJEB, three (43%) had documented FTT, necessitating gastrostomy insertion in two cases. PLE was observed in one out of seven children with NHJEB (14%). A small bowel biopsy in this child demonstrated congested lymphatic vessels. He responded partially to oral steroids (initially 2 mg kg^{-1}) and an MCT-based feed.

Three patients with JEB-PA were included in the study. Two had FTT requiring nutritional supplementation, one via gastrostomy. In both children, endoscopic examination showed small bowel partial villous atrophy, and one also had a mild colitis. Two children also had PLE, which ultimately led to the death of one due to overwhelming sepsis.

GOR was observed not infrequently in children with HJEB (one of nine, 11%), NHJEB (two of seven, 29%) and JEB-PA (one of three, 33%). Affected children were treated with antireflux medication.

Patients with JEB also often experienced constipation: four out of nine (44%) with HJEB; one of seven (14%) with NHJEB; and one of three (33%) with JEB-PA. Management in most cases consisted of polyethylene glycol-based laxatives. In addition, some children were managed with fibre-containing feeds.

Dystrophic epidermolysis bullosa

A total of 119 (53%) patients with DEB were identified of whom 57 had recessive (RDEB), 54 had dominant (DDEB) and eight had unspecified DEB. A total of 83 (70%) in the DEB group complained of some GI symptoms, with the incidence higher in the RDEB group (50/57, 88%) compared with the DDEB group (30/54, 56%).

GOR was reported frequently in children with RDEB (43/57, 75%) but less commonly in those with DDEB (six of 54, 11%). Twenty-four hour pH monitoring was performed in four of these children. Three children with high reflux indices of > 25% were referred for Nissen's fundoplication which led to a temporary (< 1 year) reduction of GOR symptoms. Free reflux with an open lower oesophageal sphincter was demonstrated in six of 20 children with RDEB undergoing gastroscopy. All children with RDEB and GOR required antireflux medication in the form of domperidone (0·2–0·6 mg kg^{-1} per dose, up to three times daily), ranitidine (2–4 mg kg^{-1} once or twice daily) and/or a proton pump inhibitor, either lansoprazole (1 mg kg^{-1} once daily) or omeprazole (1–2·6 mg kg^{-1} once daily).

Dysphagia and oesophageal strictures were also seen most frequently in children with RDEB [40/57 (70%) and 37/57 (65%), respectively] compared with children with DDEB [two of 54 (4%) and none out of 54 (0%), respectively]. All children with oesophageal strictures (diagnosed radiologically with barium studies) required at least one fluoroscopically guided balloon dilatation.

FTT was demonstrated in 22/57 (39%) children with RDEB but just one of 54 (2%) with DDEB. Factors contributing to this included: reduced dietary intake due to painful oral lesions and dental involvement; significant oesophageal strictures; and increased nutritional requirements due to extensive skin involvement. Thirty-three of 57 (58%) children with RDEB had a gastrostomy *in situ* to supplement oral feeding and to administer medications. Not all of these children had FTT, but in some cases a gastrostomy had been inserted to pre-empt this.

In keeping with other subtypes of EB, constipation was observed very commonly in patients with DEB: 23 of 57 (40%) children with RDEB and 25 of 54 (46%) with DDEB reported symptoms. As with children with EBS and JEB who had constipation, most were managed with polyethylene glycol-based laxatives (one to two sachets once or twice daily). Additionally, in some children with DEB, constipation was managed with fibre supplements or fibre-containing tube or sip feeds. In some children with DEB, however, larger doses of up to six sachets of Movicol Half or Movicol Paediatric were required daily to treat faecal impaction.

Diarrhoea was almost exclusively seen in patients with RDEB, occurring in nine of 57 (16%) of children, who passed up to eight to 10 loose stools per day, which was often explosive in nature. In seven of these nine children, colonoscopy and, where significant oesophageal strictures were not present, upper GI endoscopy, were undertaken. Histological features of six of these children have been reported previously.[14] Macroscopically discrete petechiae or an obvious colitis with mucosal friability was observed. Histological evaluation revealed a variety of features ranging from no abnormalities to moderately severe inflammatory changes including an increase in lamina propria inflammatory cell density, predominant eosinophils, and focal neutrophilic inflammation (Fig. 1). In four cases there was also prominent superficial lamina propria karyorrhectic cellular debris within the colon. In three cases, patchy granular brown pigment-containing macrophages were also identified within the lamina propria which stained positive with Perl's stain indicating haemosiderin deposition. In no cases was epidermal clefting or separation identified. These patients were treated with sulfasalazine (20 mg kg^{-1} twice daily) and occasionally also prednisolone (up to a maximum of 2 mg kg^{-1} per day or 40 mg, gradually weaning off over 3 months), which resulted in significant improvement of symptoms. In view of the likelihood of worsening colitis by food antigenic challenge, eight of the nine children were placed on a restricted diet free of cow's milk, egg, soya, and, in some cases, wheat.

Kindler syndrome

Of the four patients with Kindler syndrome included in the study, one had symptoms of GOR and had an oesophageal stricture requiring balloon dilatation. Two patients had constipation responding to conventional laxative regimes (see above). One child presented with blood and mucus in the stools. Endoscopic examination revealed a distal colitis which responded clinically to a 2-year course of sulfasalazine (20 mg kg^{-1} twice daily) and a cow's milk-free diet. After a 3-year follow-up period treatment was discontinued and the child remained symptom free.

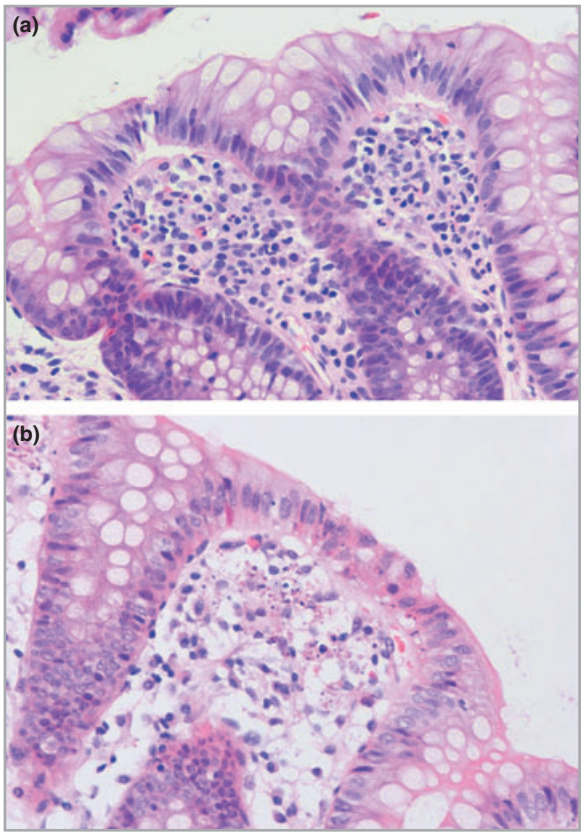

Fig 1. Photomicrographs of colonic mucosal biopsies showing (a) increased lamina propia inflammatory cells and (b) prominent superficial lamina propia apoptotic debris.

Discussion

It is acknowledged that EB may be complicated by GI problems, in the main constipation and, in the case of DEB, oesophageal strictures, are well documented.[5,7–13] Other GI manifestations of EB, however, are less well described, for example, GOR, PLE and colitis. In this study, we report the GI complications in the largest series of paediatric patients with EB to date, including histopathological data, where available. Overall, 130 of 223 (58%) patients included had some symptoms of GI disease, with particular subtypes of EB associated with specific profiles of GI involvement. While simplex forms of EB were generally associated with GOR and constipation, patients with JEB and RDEB encountered more difficulties with FTT alongside these problems. Also, dysphagia and oesophageal strictures were almost exclusively seen in children with RDEB, whereas PLE was only observed in those with junctional forms of EB. Diarrhoea associated with macroscopic and/or microscopic colitis is described here in 16% of patients

with RDEB in addition to one child with JEB-PA and one with Kindler syndrome.

Symptoms of GOR were commonly encountered across the patient groups studied, occurring in 64 of 223 (29%) patients. In particular, children with RDEB experienced GOR very frequently (43/57, 75%) and two of these were additionally found to have a hiatus hernia.[8,10,11] Nissen's fundoplication, although providing some relief in three of these children initially, did not appear to have lasting benefit. GOR was also particularly problematic for a quarter of children with Dowling–Meara EBS and was felt to have contributed to FTT in infancy in some of these patients. Across all patient groups, infants and children with symptoms of GOR were managed medically with a prokinetic (usually domperidone 0·2–0·4 mg kg^{-1} up to four times daily) in addition to ranitidine (2–4 mg kg^{-1} once or twice daily) and/or a proton pump inhibitor such as lansoprazole (1 mg kg^{-1} once daily) or omeprazole (1–2·6 mg kg^{-1} once daily).

Dysphagia was also very common in this patient group, occurring almost exclusively in children with RDEB (40/57, 70%), with oesophageal strictures demonstrable in the vast majority. This is comparable with previously reported series.[5,7–12] The majority of strictures arise in the proximal part of the oesophagus and are thought to result from trauma due to shearing of the squamous lining of the oesophagus following ingestion of solid food. This leads to blistering and subsequent scarring and stricture formation. GOR may also contribute to the formation of more distal oesophageal strictures, causing scarring around the lower oesophageal sphincter which becomes fixed in an open position allowing constant free regurgitation of acidic gastric contents into the lower oesophagus, as was observed in a number of children in this study.

The treatment of choice for oesophageal strictures in EB is with balloon dilatation, usually carried out under fluoroscopic control although it may be done endoscopically.[12,15–20] This is generally a safe and well-tolerated procedure although in some patients treated in our centre, GOR has worsened following the procedure, presumably as removal of the stricture enables freer reflux of acidic gastric contents. We would recommend, therefore, that all patients with GOR and/or oesophageal strictures are also managed medically as described above. Treatment of oesophageal stricture by bougienage is no longer recommended due to the increased shearing stresses on the oesophageal mucosa with this technique and a higher risk of oesophageal perforation.[9] In cases where oesophageal stenoses are very tight, recurrent and poorly amenable to dilatation, colonic interposition has been advocated, although this procedure is associated with significant morbidity and mortality.[21–24]

Constipation was the most common GI complaint observed in our patients, occurring in 80 of 223 children (36%), which was particularly evident in the DEB group (51/119, 43%). Chronic constipation is a well-recognized complication of DEB and is thought to result from anal fissuring secondary to a diet relatively low in fibre, poor fluid intake and a learned postponement of defecation. A number of studies focusing on DEB have described constipation as a prominent feature but there are few data on other types of EB.[5,7,10,25] Interestingly, in our study, children with EBS were also frequently found to have constipation (21/81, 26%), a feature which has not been highlighted as a particular problem in these patients previously. Early detection and treatment of constipation is important to avoid anal fissuring and pain on defecation. In addition to measures where possible to increase dietary fibre in the diet, polyethylene glycol-based products one to two sachets per day with good oral fluid intake are highly effective in children with EB.

For a small number of patients, diarrhoea was the most prominent lower GI problem affecting 12 of 223 (5%) patients overall, but nine of 57 (16%) of those with RDEB. Seven of these nine patients subsequently underwent colonoscopy, with histology showing chronic inflammatory changes with pigment-laden macrophages and prominent apoptotic debris (Fig. 1). To our knowledge, there is only one publication of a case of ulcerative colitis in a child with EBS,[26] and one previous report of diarrhoea and inflammatory bowel disease (IBD) in a patient with DEB.[27] The symptoms and histological findings in our group of patients with RDEB presenting with diarrhoea appear unique. As with all forms of DEB, RDEB is caused by mutations in the type VII collagen gene, *COL7A1*. Full-length type VII collagen is normally expressed in colonic epithelium.[28,29] EB acquisita (EBA) is an autoimmune blistering disease of the skin characterized by IgG autoantibodies against type VII collagen,[30] and is observed with greater than expected frequency in patients with Crohn disease[29,31–33] and is also reported with ulcerative colitis.[34] However, it is not understood why some patients with IBD develop EBA whereas others do not. It is postulated that autoantibodies against type VII collagen are formed following exposure in the colonic mucosa during the inflammatory process, by a mechanism of epitope spreading,[35] and that these autoantibodies then target type VII collagen in the skin resulting in blistering and scarring. In the patients with RDEB in our series, it is conceivable that lack of type VII collagen in the colonic mucosa leads to microscopic splitting and perturbation of the normal barrier function. This in turn might trigger inflammation and the observed colitic picture. Although all of the RDEB patients with diarrhoea have severe Hallopeau–Siemens disease, it is not clear why they have this problem whereas the majority of patients at our centre do not, and from the lack of reports from elsewhere, other patients do not appear to have this either.

In our study, PLE was a phenomenon observed only in children with junctional forms of EB. A quarter of the JEB group had hypoalbuminaemia and low serum immunoglobulin levels. In these patients stool α_1-antitrypsin levels were elevated six to eight times above the normal range. Feeds containing long-chain triglycerides (LCTs) can lead to increased lymphatic flow and a subsequent fall in albumin and a loss of circulating immunoglobulins.[36,37] MCT-based feeds are a better way of

feeding this group of patients by virtue of their pathway of absorption and transport via the portal vein.

In the normal small intestine, laminin 332 is mainly expressed at the base of the villous cell and redistribution of this axis to the crypts is a precursor to inflammation seen in conditions such as Crohn disease.[38–40] In children with laminin 332-deficient JEB, it is possible that similar abnormalities exist, predisposing to inflammation and PLE. However it is interesting to note that one patient with NHJEB with type XVII collagen deficiency had profound FTT and PLE. The distribution of type XVII collagen in the gut has not been well characterized but our patient's symptoms might suggest an important role in gut mucosal adhesion. This area may warrant further investigation. This child with type XVII collagen-deficient NHJEB had evidence of small bowel lacteal congestion on biopsy, consistent with the proposed mechanism of LCT-induced PLE.

PLE was also observed in two of the three children with JEB-PA, of whom, one also had diarrhoea. This particular subtype of JEB is usually caused by mutations in the genes encoding either subunit of α6β4 integrin. This protein is expressed not only at the cutaneous basement membrane zone, but also in a number of other stratified squamous and transitional epithelia,[41–43] notably the gut and urogenital tract. PLE and diarrhoea have been reported previously in a few of cases of JEB-PA,[44–46] and α6β4 integrin deficiency has been identified in an infant with total gut mucosal detachment, intractable diarrhoea, but no skin abnormalities.[47] It is possible that microscopic or macroscopic detachment of gut epithelium from the underlying lamina propria is responsible for the PLE observed in the patients with JEB in the present study. Histology from both patients with JEB-PA who underwent endoscopy showed partial villous atrophy, and one had mild colitis.

This study demonstrates a high prevalence of GI symptoms, affecting almost two-thirds of children with different forms of EB in this large cohort. Although some problems occur across EB types, for example constipation, GOR and, in more severe forms, FTT, other pathologies are more EB-type specific. Notably, dysphagia and oesophageal strictures are almost exclusively seen in patients with DEB, whereas diarrhoea is observed in a subset of children with DEB, Kindler syndrome and JEB-PA, and PLE is just observed in children with junctional forms of EB. Although the mechanisms for the observed subtype-specific GI involvement are not fully understood, it is likely that the underlying molecular pathology and the tissue expression of the causative proteins in the different types of EB are responsible. Further studies are needed to elucidate these mechanisms, and may lead to additional therapeutic interventions to improve GI symptoms in this patient group.

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