Management of oesophageal strictures in inherited epidermolysis bullosa: a clinical practice guideline

Running head: CPG for management of oesophageal strictures in epidermolysis bullosa

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What is already known about this topic?

- Oesophageal strictures (OS) are a frequent and severe complication of epidermolysis bullosa (EB), in particular of the dystrophic and Kindler types
- OS present with progressive dysphagia, odynophagia, regurgitation, food impaction, vomiting, and sialorrhea, which contribute to malnutrition, chronic anaemia and growth delay
- OS diagnosis is suspected clinically and confirmed by radiological investigations
- OS can be treated by oesophageal dilatation, which can be repeated in case of OS recurrence

What does this study add?

- Recommendations on diagnostic procedures to confirm the presence and characteristics of OS in EB
- Recommendations on non-pharmacologic and pharmacologic measures for preventing or delaying the onset, progression or recurrence of OS
- Indications and modalities of oesophageal dilatation associated, whenever needed, with gastrostomy for OS management
- Inclusion of patient and caregiver education
- Overall, improved effectiveness, safety, quality and equity of care for EB patients with OS

Abstract

Inherited epidermolysis bullosa (EB) is a group of rare and complex genetic disorders characterized by fragility of the skin and mucous membranes. Specifically, the gastrointestinal tract is commonly involved with a range of complications, one of the most disabling being oesophageal strictures (OS). OS manifest with progressive dysphagia, which in turn contributes to malnutrition, chronic anaemia and growth delay, with high impact on quality of life of patients and their families. DEBRA International has supported the development of clinical practice guidelines (CPG) for different aspects of EB care. The present CPG aims to provide healthcare professionals and affected individuals and their caregivers with recommendations on diagnostic procedures, preventative measures and treatment of OS. An international multidisciplinary panel comprising clinical experts and Patient and Public Involvement (PPI) representatives developed the CPG, following an international PPI survey and literature review. The GRADE methodology was adopted to define Population, Intervention, Comparison, Outcome (PICO) questions, implement literature appraisal process and prepare recommendations. Two recommendations are focused on OS diagnosis, and eight on preventative non-pharmacologic (diet, oral care, and therapeutic education) and pharmacologic measures (topical corticosteroids), and treatment procedures, in particular oesophageal dilatation and how to delay and manage disease relapses. It is expected that this CPG will contribute to improve the quality and equity of care for individuals affected with EB, and will hopefully foster clinical research to increase evidence, in particular on non-invasive OS treatment to prevent complications and delay relapses.

Introduction

Inherited epidermolysis bullosa (EB) is a group of rare genetic disorders characterized by fragility and blistering of the skin and mucous membranes.[1,2] Four major types- EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB)- are distinguished, based on the level of blister formation.[1,2] The major subtypes are further defined according to the inheritance mode and clinical features.[1,2]

Among mucous membranes, the entire gastrointestinal tract can be involved with a variable frequency and severity depending on the EB subtype.[3,4] Acute obstructive blisters sometimes develop in the hypopharynx and oesophagus, presenting with acute dysphagia and inability to swallow that can require emergency treatment.[5] A rare emergency situation is sloughing of the oesophageal mucosa that is coughed up as casts with vomiting and hematemesis.[6] Chronic dysphagia is common, in particular in recessive DEB (RDEB) and KEB,[3,4,7] and is usually due to oesophageal strictures (OS). These are thought to mainly result from repeated food-induced shearing trauma and blistering of the oesophageal epithelium, leading to chronic inflammation, fibrosis and scarring.[3,4] If untreated, OS can progress to oesophageal obstruction. OS and associated symptoms, i.e. dysphagia, odynophagia, regurgitation, food impaction, vomiting, and sialorrhea, are one of the most feared EB complications, greatly impacting the quality of life (QoL) and contributing to nutritional impairment and, in turn, to chronic anaemia and growth delay.[3,8]

Though international guidelines for the management of OS exist,[9] OS management in EB requires highly specialised care pathways with specific preventative and treatment measures.

Purpose and scope

This Clinical Practice Guideline (CPG) deals with diagnostic, preventative and therapeutic options for OS. Recommendations were developed following Patient and Public Involvement (PPI) through an international survey, literature review, and a multidisciplinary international expert consensus including PPI representatives. The aim of this CPG is to inform and support clinicians caring for EB individuals with regard to the management of OS.

User and target groups

The users of the CPG are all healthcare professionals involved in the management of OS (Appendix S1). The CPG target group includes EB patients of any age and their caregivers.

Aims

- To provide detailed and clear information for OS global care based on available literature evidence and multidisciplinary expert/PPI consensus.
- To deliver an early diagnosis in order to prevent/reduce OS complications.
- To highlight preventative non-pharmacologic and pharmacologic measures aimed at delaying OS progression and relapses.
- To define appropriate treatment of OS and their relapses based on current knowledge.

Methodology

The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was adopted for CPG development. The multidisciplinary panel members, including PPI representatives, recruited through DEBRA International are listed in Appendix S2 (Table S2a). The methodology for CPG development and implementation is summarized in Appendix S3, including the international PPI survey description, the identification of Population, Intervention, Comparison, and Outcome (PICO) questions and the literature search and appraisal process. Future research topics are outlined in Appendix S4. The CPG development process established ten specific PICOs pertinent to the guideline scope (Table 1).

Results

A literature search identified 1,967 papers (Figure 1). After duplicate removal, screening, selection and appraisal, and one updated search in March 2024, a total number of 42 papers were included, comprising two previous CPGs and two expert consensus on related topics. See Appendix S3, Table S3b, for appraised article allocation per outcome. Additionally, results from the PPI survey (Appendix S3 and Table S3a) and current reference centre practice were used to support recommendations.

Recommendations

The CPG describes the diagnostic procedures, preventative measures and treatment of OS in EB. Recommendations are listed in Table 2.

OS diagnosis

R1. ↑↑ *We recommend the use of radiologic investigations to diagnose OS and their characteristics in EB patients with suggestive clinical signs and symptoms.*

- *Radiologic investigations should carefully examine the entire oesophagus, paying attention to the cervical portion, to define the location, length, diameter and number of strictures.*
- *Radiological modalities used for the diagnosis of OS include oesophagogram and video-fluoroscopy.*

OS are clinically suspected when EB patients present with chronic dysphagia (inability to swallow solid or even liquids, sialorrhea, regurgitation, and food impaction), and odynophagia.[3,4,8,10] Strictures are more commonly seen in the cervical oesophagus, followed by the thoracic and then the abdominal tracts.[3,4,8,10] They can be single or, less commonly, multiple, and their length is variable. Although the diagnosis is suspected based on suggestive clinical signs and symptoms, radiologic investigations, i.e. oesophagogram (also known as contrast swallow) and video-fluoroscopy, are recommended to confirm the presence, location, length and number of stricture(s).[11]

Video-fluoroscopy provides a direct dynamic view of oral-pharyngeal and upper oesophageal function, while oesophagogram allows morphologic evaluation of the entire oesophagus. Specifically, oesophagogram, with attention to the cervical tract, has proven effective in detecting OS in EB.[8,10-24] Moreover, this non-invasive test has very rare adverse events in standard practice. Nowadays, water-soluble contrast media are increasingly used for oesophagogram.[5,25]

R2. ↓↓ *We recommend against using endoscopy examination in EB patients for a diagnosis of OS.*

The endoscope may traumatize the fragile oropharyngeal and oesophageal mucosa resulting in new blister formation, and further scarring and narrowing. More serious complications, in particular oesophageal perforation, have also been reported.[26,27] Furthermore, endoscopy may be difficult to perform in patients with microstomia and oral scarring. Thus, the risks of diagnostic endoscopy are not balanced by benefits, also considering that diagnostic radiologic procedures are available, effective and safe. In very rare symptomatic cases in which properly performed radiological investigations fail to identify OS or if endoscopy is the only modality available, it should be undertaken by experienced

endoscopists, familiar with EB, to prevent damage or excessive blistering. Surgical expertise and facilities should be available in case of oesophageal perforation.

R3. ↑↑ *We recommend prompt detection of OS in EB patients with suggestive signs and symptoms.*

- *Early signs and symptoms of OS include intermittent dysphagia for solid and sometimes liquid food, increased meal duration, intermittent regurgitation, and/or sialorrhea. Starting from an early age (ideally infancy), personalized information should be provided about the possibility of developing OS, and their early signs and symptoms, to individuals with specific EB subtypes, in particular RDEB and KEB, caregivers and their paediatrician/general practitioner. Early detection of OS may allow implementation of preventative measures, facilitating maintenance of adequate nutrition and delaying stricture progression and related complications.*

  Individuals with signs and symptoms suggestive of OS should be promptly referred to an EB expert centre and managed by a multidisciplinary team, which optimally comprises dermatologist, nutritionist/dietitian, gastroenterologist, (interventional) radiologist, digestive/paediatric surgeon, dentist, anaesthetist, psychologist, and specialized nurse.

OS can occur at an early age, with a reported cumulative risk of OS development of 6.73% and 35.19% by age 1 and 5 years, respectively, in severe RDEB.[3]

Though no literature comparing the benefits and risks of prompt versus delayed diagnosis of OS is available, this recommendation has been based on indirect evidence,[14,28] expert[3] and panel opinion, and results of the PPI survey that scored "Early diagnosis of OS" as the second highest priority topic (Appendix S3, Table S3a).

OS treatment: preventative and pharmacologic measures, dilatations and surgical procedures

R4. ↑ *We conditionally recommend considering non-pharmacological measures for preventing/or delaying the onset/or progression of the OS in people living with EB.*

- *An early referral to dietitian/nutritionist at the point of diagnosis is recommended for appropriate dietary advice with regular follow-ups.*
- *An early referral to dentist (ideally at 3 to 6 months of age) with regular follow-up is recommended for education of the parents and caregivers: preventive advice on oral hygiene routines, fluorides, and oral manifestations of EB.*
- *Collaboration between dietitian/nutritionist, dentist and the patient/parents is recommended to ensure the advice is consistent and the care is person-centred.*

Despite very low evidence, experts and PPI agree that different non-pharmacological measures may contribute to delay the onset/progression of OS in EB. In addition, "Preventive measures to avoid/ delay development of OS" was the highest priority topic according to the PPI survey (Appendix S32, Table S3a).

Dietetic/nutritional advice may include modification of food textures to reduce trauma to the oral and oesophageal mucosa.[5,16] Attention should be paid to ensure nutritional intake is not compromised by the prolonged use of blended meals with poor nutrient content.[16,29,30] Advice may include adapting cooking methods, energy dense, soft food choices and adding more fluids to soften foods. The advice should be individualized to reflect the patients' EB subtype/risk of OS, nutritional requirements, and personal preference. Appropriate information may prevent incorrect dietary customs due to mistaken beliefs.

A properly cared oral mucosa and dentition will enhance the patients' ability to chew and swallow, optimising their intake of a variety of foods and reducing oral and oesophageal tissue damage. For details, refer to the CPG on oral healthcare in EB.[31]

R5. ↑ *We conditionally recommend to consider the use of pharmacologic measures for preventing/or delaying the onset/or progression of OS in EB.*

- *Pharmacological measures can include: i) topical treatment of oral lesions, ii) fluoride-containing products applied to teeth, and, if required, systemic supplementation, iii) oral viscous budesonide, and iv) treatment of gastro-oesophageal reflux disease (GORD), when present.*

- *Prompt gastroenterology referral at the first signs and symptoms of oesophageal involvement is recommended to assess and treat GORD and to consider oral viscous budesonide.*

GORD can occur in all EB types, in particular in RDEB, and might contribute to the formation of distal OS.[3,4] Independent of a pathogenic role in OS, GORD should be considered in EB patients and treated according to current guidelines.[32-34] Typical GORD symptoms may respond to lifestyle and dietary modifications alone or, when ineffective, combined with proton-pump inhibitors as first line treatment.

Although evidence supporting the efficacy of pharmacological measures in preventing or delaying the onset or progression of OS in EB patients is very low, oral viscous budesonide, characterized by low systemic exposure, is increasingly prescribed in expert centres,[5,6] extrapolated from its use in eosinophilic oesophagitis, a condition associated with dysphagia, subepithelial fibrosis and stricture formation.[35] In an open-label trial on six EB paediatric patients, a four-month treatment regimen of oral budesonide nebulizer solution (0.5 mg/2 ml twice a day) led to a clinical and radiological improvement of OS in five patients.[28] However, oesophageal *Candida* infection was observed in one patient,[28] and is also reported in a small percentage of patients during treatment of eosinophilic oesophagitis with topical corticosteroids.[35] Based on eosinophilic oesophagitis consensus guidelines, the suggested dose of oral budesonide varies between 1 and 2 mg/day in adult patients.[35] The availability of an orodispersible formulation of budesonide represents an additional treatment modality in adults.

Finally, pharmacological measures for oral cavity care are detailed in the CPG for oral healthcare in EB.[31]

R6. ↑↑ *We recommend to perform oesophageal dilatation associated, whenever needed, with surgical procedures, specifically gastrostomy, for the management of OS.*

- *Oesophageal dilatation and gastrostomy tube placement must be performed in EB reference centres, by experienced professionals as part of a multidisciplinary team.*
- *Oesophageal dilatation is recommended for patients who have failed pharmacologic treatment with oral budesonide and continue to present chronic dysphagia, sialorrhea, food impaction, and regurgitation.*

- *Gastrostomy is recommended for patients who present with intractable OS, those with failure to thrive, major problems in the oral cavity, severe chronic constipation and high stress levels during feeding.*
- *Complete and personalized information about the benefits and risks must be delivered to the patient and/or parents, and written informed consent should be obtained prior to any procedure.*

According to the PPI survey, OS treatment represents a priority (Appendix S3, Table S3a). Despite non-pharmacological and pharmacological measures, OS frequently progress with worsening symptoms [chronic and persistent dysphagia with inability to swallow even fluids, odynophagia, food impaction, regurgitation, rumination (i.e. rechewing food returned from oesophagus), vomiting, and increased sialorrhea] that require invasive treatments.[14,27]

Retrospective cohort studies and case series[8,10,14,15,17-19,21,23,24,36-42] stated a high success rate (>95%) of oesophageal dilatation with immediate symptomatic improvement following the procedure (disappearance or relief of dysphagia, increased feeding, and nutrition and weight gain), and a very low rate of serious complications. In a recent multicentre cohort study, major complications such as haemorrhage, tear, and chest pain, were reported in a minority of dilatations (2.66%, 12/451 procedures).[8]

Several retrospective cohort studies[43-48] and a systematic literature review[49] have then reported that gastrostomy contributes to improve nutritional and health status of EB patients presenting with malnutrition. Moreover, improved QoL and satisfaction among caregivers post-G-tube placement have been described.[45,47] Early gastrostomy may avert nutritional decline,[48] indicating that it should be considered timely to prevent/delay weight loss. Complications (excessive leakage, infection, pain, ulceration, chronic wound, and granulation tissue) have been reported in 20–70% of cases, leading to G-tube removal in approximately 10%.[49] Gastrostomy tube placement may be performed by either open/laparoscopic surgery or percutaneous gastrostomy.[18,20,39,40,43,44,46,48] In turn, the latter may be carried out by a transoesophageal endoscopic approach or an image-guided non-endoscopic technique.[18,20,40,48] Recently, a retrospective cohort study has documented the effectiveness and safety of a minimally invasive laparoscopic-assisted gastrostomy approach in 32 EB children.[46] However, the method of insertion and type of G-tube will depend on experience within the specialist centre.

R7. ↓↓ *We recommend against bougie (semi-rigid) dilatation for best outcomes in terms of safety in EB patients.*

Oesophageal dilatation can be performed using two main categories of devices: radial expanding balloon dilators and fixed-diameter semi-rigid push-type dilators (bougie dilators) (Table 3).[50]

Bougie dilators are passed across the stricture and dilatation is achieved by employing bougies of progressively increased diameter. In addition to exerting radial forces, the procedure also involves longitudinal forces that generate a significant shearing effect.

Balloon dilators can be positioned over a guidewire under fluoroscopic or endoscopic guidance. When fluoroscopy is used, successful dilatation is detected by the obliteration of the "hourglass shape" on the balloon, representing the stricture (Figure 2a-c).[51] Balloon dilators only exert radial forces that are delivered simultaneously over the entire length of the stricture.[51]

There are almost no data comparing the efficacy and safety of bougie versus balloon dilators to treat OS in EB. However, a recent multicentre cohort study reported that only three out of 451 dilatations were carried out using bougie dilators.[8] In addition, recent studies on oesophageal dilatation in EB employed balloon dilators almost exclusively.[17,18,21,23,24,37-42]

It is agreed by experts that bougies in EB are very likely to increase the mechanical trauma to the hypopharynx and the shearing trauma of the oesophageal mucosa, contributing to OS recurrence and increasing the risk of oesophageal perforation.[52] Accordingly, EB reference centres are using fluoroscopically- or endoscopic-guided balloon dilatation.

R8. ↑ *We conditionally recommend to offer fluoroscopically-guided balloon dilatation as first line treatment option for best outcomes in terms of safety.*

- *Endoscopy-guided dilatation should be considered in specific situations/settings: presence of a gastrostomy tube, characteristics of the stricture, local resources, and, importantly, physician's expertise and skills in the use of endoscope for treatment of OS.*

Placement of the balloon dilator across the stricture and hydrostatic dilatation can be carried out under fluoroscopic or endoscopic guidance or combinations of the two techniques (Table 3). There is no international consensus on how to perform these procedures which may lead to variations between centres.

Several retrospective cohort studies[4,8,24,39,42] and case series[15,17,18,20,21,23,36,38,40,41] reported on efficacy and safety using fluoroscopically- and/or endoscopically-guided balloon dilatation for treatment of OS in EB. Of these, one cohort study[42] and 4 case series[21,23,38,40] routinely used the endoscopic-guided approach.

Both procedures led to OS symptom relief and QoL improvement. Limited complications are described for both techniques including transient swallowing difficulty after the procedure, pain, and fever[15,41] with only rare cases of oesophageal perforation.[42] A single multicentre study compared the outcomes of the two procedures, concluding that they have a comparable efficacy, but more complications may occur with the endoscopic technique due to the mechanical trauma secondary to the passage of the endoscope.[8] Overall, fluoroscopically-guided balloon dilatation may be preferable for treatment of OS in EB in terms of safety.

Endoscopy-guided balloon dilatation can be considered in specific conditions:

- Patients with a gastrostomy can have a retrograde approach for OS balloon dilatation using an endoscope passed through the existing gastrostomy.[8,41] However, the retrograde approach may be exploited also for fluoroscopically-guided dilatation. Indeed, this approach allows to overcome difficulties related to microstomia, common in RDEB.
- Strictures which are both narrow and tortuous require attention and expertise to avoid iatrogenic oesophageal injury. In these cases, passing the guidewire under endoscopic visualization may reduce the risk of perforation and allow dilatation.[52]
- Physician's expertise in the use of endoscope for treatment of OS, and available local resources.

The available techniques and their preferential use are summarized in Table 3 and illustrated in Figures 2 and 3. Independent of the method for dilatation balloon positioning, fluoroscopy should be employed during all dilatation procedures to verify the guidewire placement. Finally, a crucial factor in technique choice remains the local expertise.

R9. ↑ *We conditionally recommend to consider pharmacological and non-pharmacological measures for preventing OS relapse.*

- *Pharmacological and non-pharmacological measures include: dietary interventions, adherence to standard GORD treatment if required, and corticosteroid therapy.*
- *Gastroenterologists should assess the possibility of incorporating pharmacologic treatments on a case-by-case basis, tailoring interventions to individual needs and circumstances.*
- *Information about the possibility of stricture relapses and related preventative measures should be provided to the patients, their parents, and the primary care paediatricians/general practitioners. Patients should undergo regular follow-ups to check adherence to preventative measures as well as to promptly detect and treat OS relapses.*

Although there is scarce evidence to substantiate the efficacy of non-pharmacologic measures in preventing or postponing OS relapses in EB, panel members, and PPI survey findings suggest the relevance of dietary interventions. It is essential, however, to customize these measures on a case-by-case basis to avert nutritional complications. Recommendations for oral healthcare measures should be provided.[31]

In the realm of pharmacologic interventions, adhering to standard GORD treatment in EB remains essential.[4-6] Several centres employ short-term systemic corticosteroids immediately after dilatation to alleviate post-procedural pain and swelling, potentially minimizing the inflammation that contributes to subsequent scarring and re-stenosis. However, there is a lack of data to substantiate their effectiveness as a preventative method for re-stenosis.[8,17,32] Oral viscous budesonide, previously reported in a few cases to decrease stricture indices and to space the need for dilatation, [5,8,28], is increasingly used in reference centres.[6] Finally, losartan, a sartan antihypertensive drug with inhibitory effects on the profibrotic factor TGF-ß1, has been recently reported to reduce OS relapses in the short term in a small case-control study.[53] However, further studies are needed to support its efficacy.

R10. ↑↑ *We recommend that oesophageal dilatations be used for the treatment of OS recurrence in individuals with EB.*

- *In case of OS relapse, patients should be referred to an EB expert centre for complete re-evaluation, and planning of dilatation and follow-up, also taking into account patient preferences.*

Recurrence of OS is well-described in EB patients and frequently requires repeat dilatations.[8,17,20,21,24,37,39,40,42,54] Although controlled prospective studies comparing the effects of repeated dilatations versus no dilatation are lacking, retrospective cohort studies and case series reported that repeated dilatations are effective and relatively safe.[8,17,20,21,24,37,39,40,42,54] According to the literature, the median interval between dilatation varies largely, ranging from 7 months (interquartile range: IQR 4-12) to 18 months (IQR 14 days - 24.5 months).[8,21] The median number of dilatations per patient is also highly variable.[17,20,21] In a large cohort study, relapses have been associated with long (≥ 1cm) segment strictures and multiple OS, suggesting the need for closer follow-up and a lower threshold for treatment in the presence of symptoms.[8]

Fluoroscopically-guided balloon dilatations for recurrent OS treatment are effective and well-tolerated, with minimal risk of severe complications.[17,23,41,55] However, due to the susceptibility to squamous cell carcinoma (SCC) development in this population, protocols should be implemented to reduce the radiation exposure in individuals with recurrent strictures.[17] Finally, oesophageal SCC has been rarely reported in RDEB patients with chronic OS.[3,56] Thus, patients complaining acute symptom worsening should undergo prompt endoscopy and/or imaging re-evaluation.

Conclusion

Early diagnosis and treatment of OS is essential to improve nutritional status and QoL of EB individuals and their families. A well-coordinated multidisciplinary team at an EB expert centre is a prerequisite to ensure appropriate management of this severe and highly disabling complication. Equally important are the continuing delivery of therapeutic education to the patient/caregiver and regular follow-ups in order to improve adherence to preventative measures, and prompt recognition and reporting of OS symptoms. It is hoped that the present CPG will foster clinical research and quality-improvement initiatives related to OS management and will reduce variation in clinical practice internationally increasing equity of care.

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Figure legends

Figure 1. Flow-chart summarizing literature search process and findings.

Figure 2. Fluoroscopically-guided balloon dilatation of an oesophageal stricture in a 4-year-old child affected with recessive dystrophic epidermolysis bullosa. Naso-gastric guidewire positioning under fluoroscopic guidance (a). Fluoroscopic monitoring allows visualization of the typical “hourglass” appearance of oesophageal stricture at starting of balloon inflation, the arrow points to the stricture which appears as the narrow passage between the two pear-shaped bulbs of an hourglass (b), and of the effacement of the stricture after complete balloon dilatation (c).

Figure 3. Endoscopic-guided balloon dilatation combined with fluoroscopy. (a) Oro-gastric guidewire positioning under endoscopic and fluoroscopic guidance. (b) Hydrostatic balloon dilatation of the oesophageal stricture.

Table 1. PICO questions identified by the multidisciplinary panel and PPI representatives

A. Should radiologic investigations be used to diagnose oesophageal strictures (OS) and their characteristics in epidermolysis bullosa (EB) individuals with suggestive signs and symptoms?
B. Should endoscopy be used to diagnose OS in EB individuals?
C. Should prompt vs delayed detection of OS be used for reducing complications in EB individuals?
D. Should non-pharmacologic measures (like soft food and oral health care) vs no modifications be used for preventing or delaying the onset or progression of OS in EB individuals?
E. Should pharmacologic vs no pharmacologic treatment be used for preventing or delaying the onset or progression of OS in EB individuals?
F. Should dilatations/surgical procedures vs non-invasive treatments only be used for the management of OS?
G. Should bougie (semi-rigid) dilatation vs fluoroscopically-guided balloon dilatations be used for best outcomes in terms of effectiveness and safety in EB individuals?
H. Should fluoroscopically-guided balloon dilatations vs endoscopy-guided dilatation be used for best outcomes in terms of effectiveness and safety in EB individuals?
I. Should pharmacological measures and non-pharmacological measures vs. no measures be used for preventing OS relapse?
J. Should repeated oesophageal dilatations vs no dilatations be used for the treatment of OS recurrence?

Table 2. Summary of recommendations for oesophageal stricture (OS) management

Recommendations	Strength	Level of evidence	Key references
R1 We recommend the use of radiologic investigations to diagnose OS and their characteristics in epidermolysis bullosa (EB) individuals with suggestive clinical signs and symptoms. Radiologic investigations should carefully examine the entire oesophagus, paying attention to the cervical portion, to define the location, length, diameter and number of strictures. Radiological modalities used for the diagnosis of OS include oesophagogram and video-fluoroscopy.	↑↑	⊕⊕⊕◯	3, 4, 8, 10-18, 20-24
R2 We recommend against using endoscopy examination in EB patients for a diagnosis of OS.	↓↓	⊕◯◯◯	26, 27
R3 We recommend prompt detection of OS in EB patients with suggestive signs and symptoms. Early signs and symptoms of OS include intermittent dysphagia for solid and sometimes liquid food, increased meal duration, intermittent regurgitation, and/or sialorrhea. Starting from an early age (ideally infancy), personalized information should be provided about the possibility of developing OS, and their early signs and symptoms, to individuals with specific EB subtypes, in particular RDEB and KEB, caregivers and their paediatrician/general practitioner. Early detection of OS may allow implementation of preventative measures, facilitating maintenance of adequate nutrition and delaying stricture progression and related complications. Individuals with signs and symptoms suggestive of OS should be promptly referred to an EB expert centre and managed by a multidisciplinary team, which optimally comprises dermatologist, nutritionist/dietitian, gastroenterologist, (interventional) radiologist, digestive/paediatric surgeon, dentist, anaesthetist, psychologist, and specialized nurse.	↑↑	⊕⊕◯◯	3, 14, 28
R4 We conditionally recommend considering non-pharmacological measures for preventing/or delaying the onset/or progression of the OS in people living with EB. An early referral to dietitian/nutritionist at the point of diagnosis is recommended for appropriate dietary advice with regular follow-ups. An early referral to dentist (ideally at 3 to 6 months of age) with regular follow-up is recommended for education of the parents and caregivers: preventive advice on oral hygiene routines, fluorides, and oral manifestations of EB. Collaboration between dietitian/nutritionist, dentist and the patient/parents is recommended to ensure the advice is consistent and the care is person-centred.	↑	⊕◯◯◯	5, 14, 16, 31
R5 We conditionally recommend to consider the use of pharmacologic measures for preventing/or delaying the onset/or progression of OS in EB.	↑	⊕⊕◯◯	3-6, 28, 31, 32

Pharmacological measures can include: i) topical treatment of oral lesions, ii) fluoride-containing products applied to teeth, and, if required, systemic supplementation, iii) oral viscous budesonide, and iv) treatment of gastro-oesophageal reflux disease (GORD), when present. Prompt gastroenterology referral at the first signs and symptoms of oesophageal involvement is recommended to assess and treat GORD and to consider oral viscous budesonide.			
R6 We recommend to perform oesophageal dilatation associated, whenever needed, with surgical procedures, specifically gastrostomy, for the management of OS. Oesophageal dilatation and gastrostomy tube placement must be performed in EB reference centres, by experienced professionals as part of a multidisciplinary team. Oesophageal dilatation is recommended for patients who have failed pharmacologic treatment with oral budesonide and continue to present chronic dysphagia, sialorrhea, food impaction, and regurgitation. Gastrostomy is recommended for patients who present with intractable OS, those with failure to thrive, major problems in the oral cavity, severe chronic constipation and high stress levels during feeding. Complete and personalized information about the benefits and risks must be delivered to the patient and/or parents, and written informed consent should be obtained prior to any procedure.	↑↑	⊕⊕◯◯	8, 10, 14, 15, 17-19, 21, 23, 24, 27, 36-49
R7 We recommend against bougie (semi-rigid) dilatation for best outcomes in terms of safety in EB patients.	↓↓	⊕⊕◯◯	5, 8, 19, 54
R8 We conditionally recommend to offer fluoroscopically-guided balloon dilatation as first line treatment option for best outcomes in terms of safety. Endoscopy-guided dilatation can be considered in specific situations/settings: presence of a gastrostomy tube, characteristics of the stricture, local resources, and, importantly, physician's expertise and skills in the use of endoscope for treatment of OS..	↑	⊕⊕⊕◯	4, 8, 14, 15, 17, 18, 20, 21, 23, 24, 36, 38-42
R9 We conditionally recommend to consider pharmacological and non-pharmacological measures for preventing OS relapse. Pharmacological and non-pharmacological measures include: dietary interventions, adherence to standard GORD treatment if required, and corticosteroid therapy. Gastroenterologists should assess the possibility of incorporating pharmacologic treatments on a case-by-case basis, tailoring interventions to individual needs and circumstances. Information about the possibility of stricture relapses and related preventative measures should be provided to the patients, their parents, and the primary care paediatricians/general practitioners. Patients should undergo regular follow-ups to check adherence to preventative measures as well as to promptly detect and treat OS relapses.	↑	⊕⊕◯◯	4-6 8, 17, 18, 28, 31, 32, 53

R10 We recommend that oesophageal dilatations be used for the treatment of OS recurrence in individuals with EB. In case of OS relapse, patients should be referred to an EB expert centre for complete re-evaluation, and planning of dilatation and follow-up, also taking into account patient preferences.	↑↑	⊕◯◯◯	8, 17, 20, 21, 23, 24, 37, 39-42, 54, 55

1 Strength of recommendation rated using ↑ (weak recommendation for the use of an intervention), ↑↑ (strong recommendation for the use of an
2 intervention), ↓↓ (strong recommendation against the use of an intervention) as detailed in Supporting Information, Appendix S2 and Table S2c. The level of
3 evidence was assessed using GRADE and was measured as very low, low, moderate or high (see Supporting Information, Table S2d).
4

Table 3. Dilatation techniques and oesophageal dilators: preferential use for treatment of oesophageal strictures (OS) in individuals affected with epidermolysis bullosa

OESOPHAGEAL DILATOR TYPE	DILATATION TECHNIQUE		
	Fluoroscopically-guided dilatation	Endoscopy-guided dilatation combined with fluoroscopy*	Endoscopy-guided dilatation only**
BOUGIE	No	No	No
BALLOON	Yes***	Yes	No

* Fluoroscopy visualization of guidewire positioning. ** No fluoroscopy visualization of guidewire positioning.
*** Preferable for routine anterograde dilatation of OS.

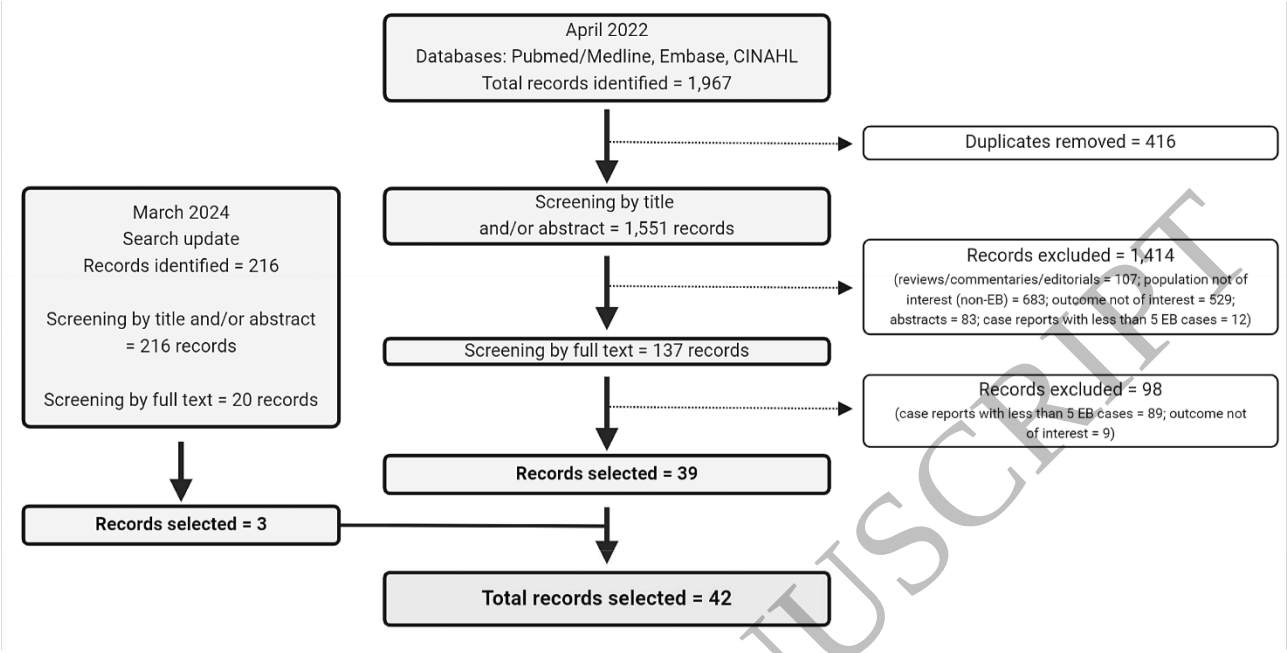

Figure 1
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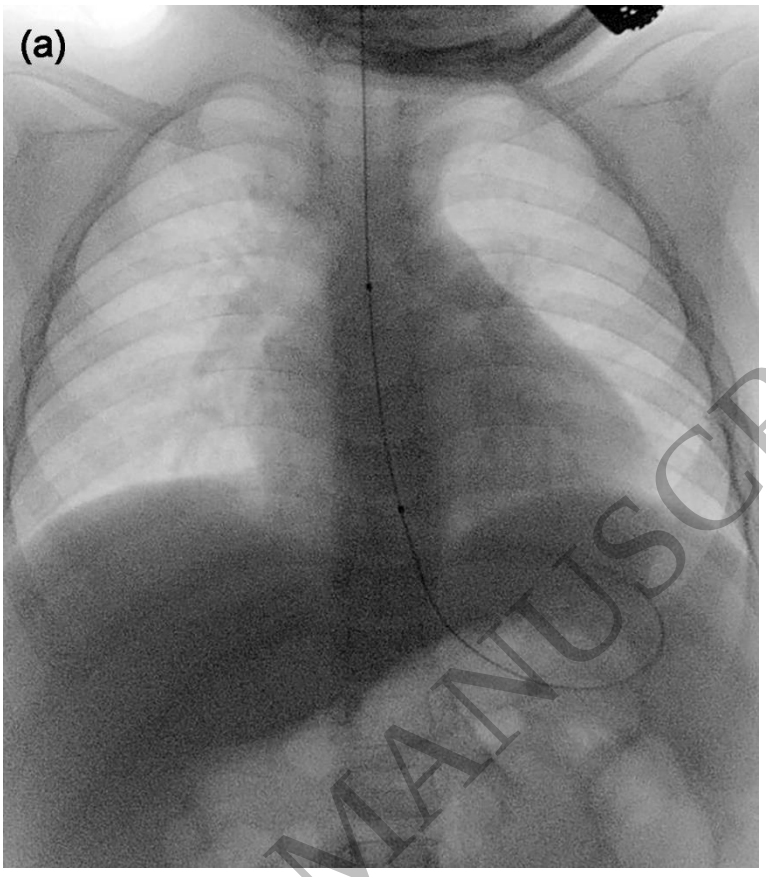

Figure 2a
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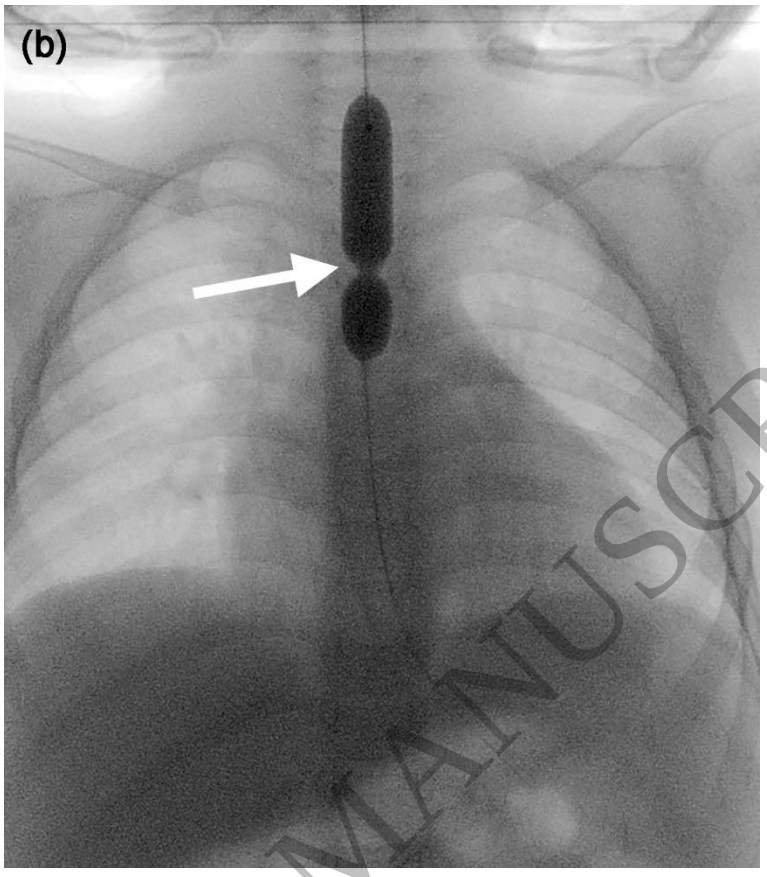

Figure 2b
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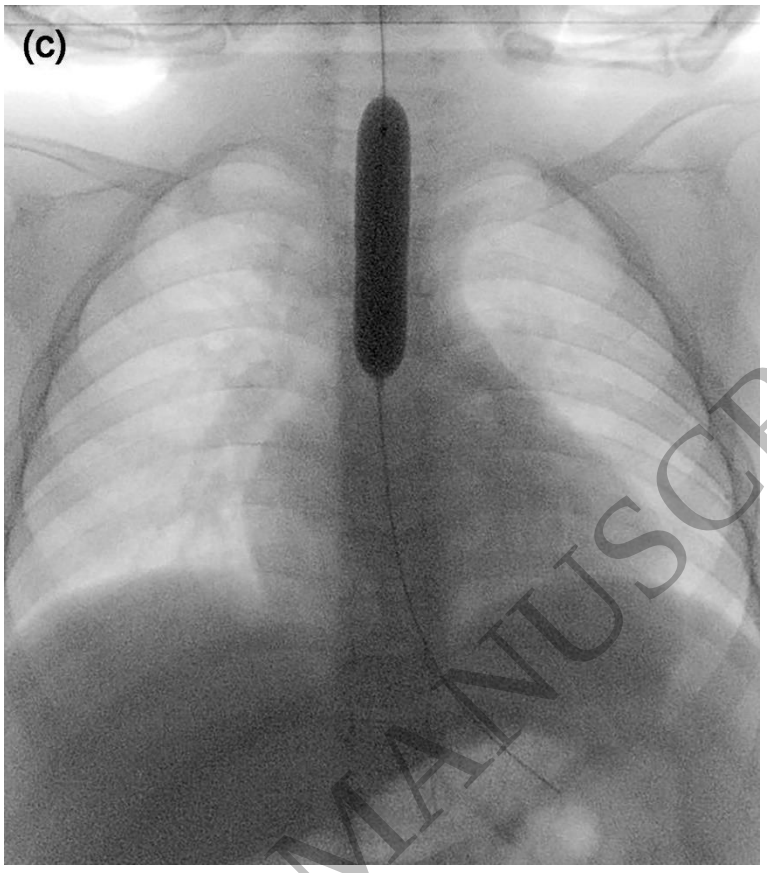

Figure 2c
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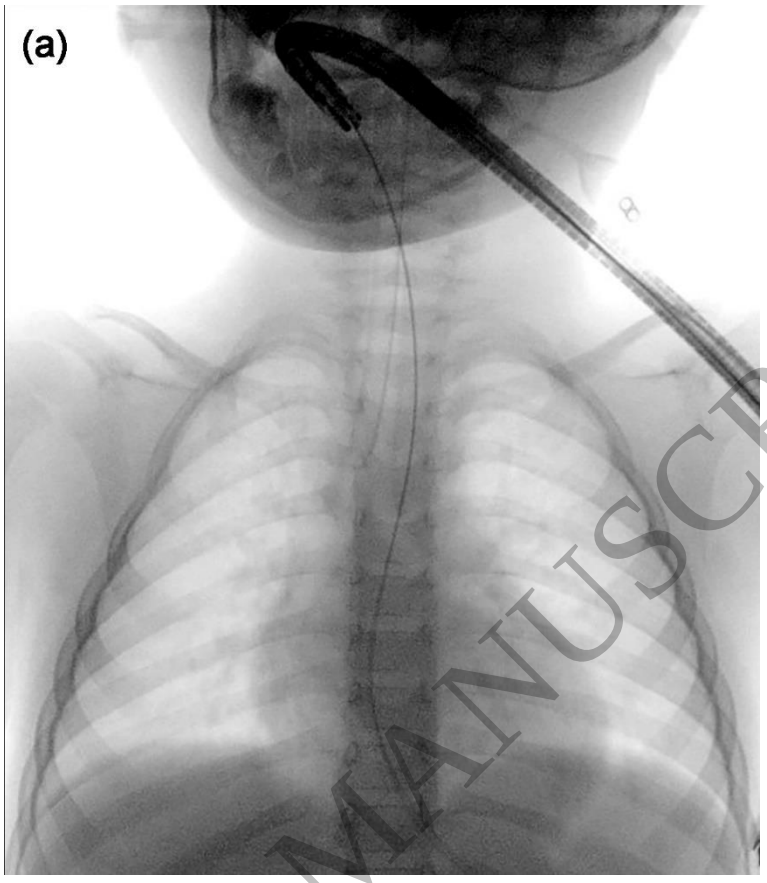

Figure 3a
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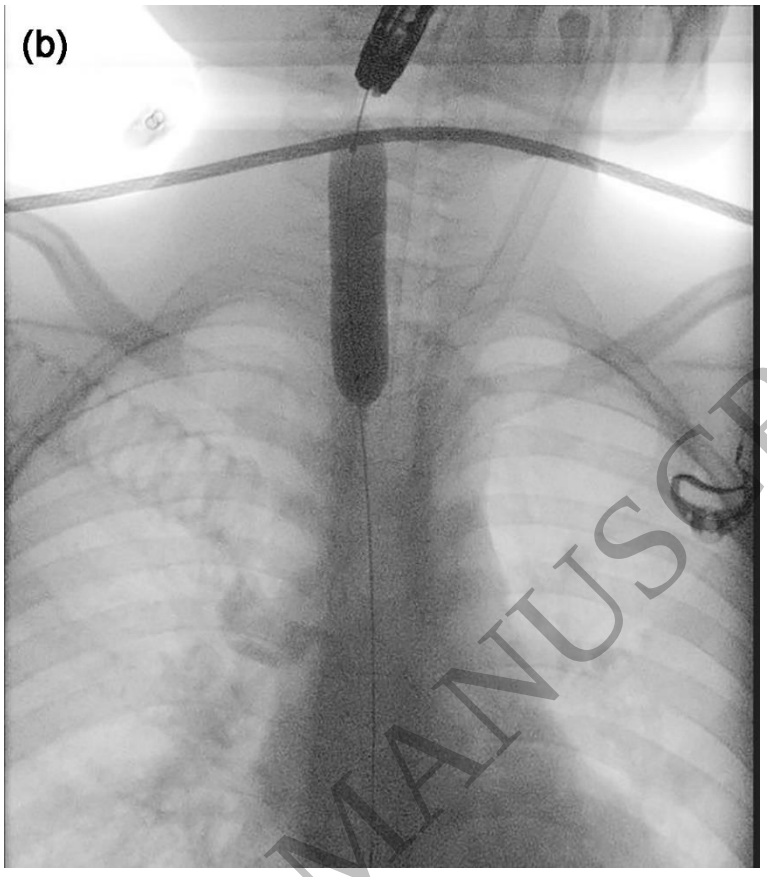

Figure 3b
100x114 mm (x DPI)