Outcomes and Predictors for Re-stenosis of Esophageal Stricture in Epidermolysis Bullosa: A Multicenter Cohort Study

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ABSTRACT

Background: Esophageal strictures are the common gastrointestinal complications in patients with epidermolysis bullosa (EB) requiring dilation. There is limited information on the best type of intervention, outcomes, and predictors for re-stenosis.

Objectives: We aimed to investigate the frequency, clinical presentation of esophageal strictures in EB patients, and to ascertain the predictors of re-stenosis.

Methods: We conducted a retrospective, multicenter cohort study involving 7 specialized, international EB centers on patients who were 0 to 50 years of age. Descriptive statistics and hazard risks for re-stenosis were calculated.

Results: We identified 125 patients with 497 esophageal stricture episodes over a mean period of observation of 17 (standard deviation [SD] = 11.91) years. Dilations were attempted in 90.74% of episodes, using guided fluoroscopy 45.23%, retrograde endoscopy 33.04%, and antegrade endoscopy 19.07%. Successful dilation was accomplished in 99.33% of attempts. Patients experienced a median of 2 (interquartile range [IQR]: 1–7) stricture episodes with a median interval between dilations of 7 (IQR: 4–12) months. Predictors for re-stenosis included: number of strictures (2 vs 1 stricture: $\chi^2 = 4.293$, $P = 0.038$, hazard ratio [HR] = 1.294 (95% confidence interval [CI]: 1.014–1.652 and 3 vs 1 stricture: $\chi^2 = 7.986$, $P = 0.005$, HR = 1.785 [95% CI: 1.194, 2.667]) and a long ($\geq$1 cm) segment stricture ($\chi^2 = 4.599$, $P = 0.032$, HR = 1.347 (95% CI: 1.026–1.769). Complications were more common with the endoscopic approach (8/86, antegrade endoscopy; 2/149, retrograde endoscopy vs 2/204, fluoroscopy; $\chi^2 = 17.39$, P-value <0.000).

Conclusions: We found excellent dilation outcomes irrespective of the dilation procedure; however, with higher complications in the endoscopic approach. Long (>1 cm) segment involvement and multiple locations were predictive of stricture reoccurrence.

Key Words: epidermolysis bullosa, esophageal dilation, esophageal strictures

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What Is Known

- Recurrent esophageal strictures are the common gastrointestinal complications in patients with epidermolysis bullosa.
- Instrumental dilation is needed.
- There is limited information on the best type of intervention, outcomes, and predictors for re-stenosis.

What Is New

- Dilation is successful irrespective of the type of procedure.
- Higher complications may occur with the endoscopic approach.
- Long (>1 cm) segment involvement and multiple locations are predictive of stricture reoccurrence.

Epidermolysis bullosa (EB) is a group of rare genetic skin disorders characterized by fragile stratified squamous epithelial tissue that blisters and potentially scars in response to minor trauma. It has been classified into 4 types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (1).

One of the most common and severe gastrointestinal complications in EB patients is esophageal stricture. According to National EB registry (NEBR) data, the frequency of esophageal strictures is 86.7% in Recessive Dystrophic EB (RDEB) inversa

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subtype, 79.1% in RDEB- severe generalized, 37.2% in mild generalized RDEB, 14.3% in patients with JEB-severe-generalized subtype, and much lower in the remaining subtypes (2,3). The frequency of strictures increases with age in all groups but is the most common in the RDEB-severe generalized patients with more than half presenting with symptoms by age 10 years (3). The youngest reported cases were 2 years of age (4,5).

Treatment options for esophageal strictures usually begin with dietary alterations, followed by a combination of esophageal dilation, gastrostomy, medical therapy, and surgery (4–14). In a large cohort, Feinstein et al (15) reported that 55.5% of 283 patients with RDEB had an esophageal dilatation at a median age of 6.6 (IQR: 3.5–10.7) years (15). Although fluoroscopically guided balloon dilation is the most common approach, there is still debate about which method should be utilized with risks and benefits associated with both endoscopy and fluoroscopy-guided dilations (4,5,7,11,16,17). Even more, we do not currently know the short- and long-term outcomes of each intervention and the clinical predictors for intervention success, limiting our understanding of the ideal treatment paradigm for esophageal strictures in EB patients. The aim of this study was to investigate the frequency, clinical presentation, and re-stenosis risk and predictors in a large cohort of EB patients to best inform management practices in this patient population.

METHODS

This was a retrospective, multicenter cohort study involving specialized EB centers from Canada (Toronto), USA (Cincinnati), England (London), Chile (Santiago), Australia (Sydney), Mexico (Monterey), and Colombia (Bogota). Each center had ethical approval to participate in the study.

Patients were included if they were 0 to 50 years of age with a clinical diagnosis of EB and with at least 1 and $\leq$10 consecutive episodes of esophageal stricture (upper limit was selected to maximize data while decreasing biases because of inevitable procedural practice changes over a large time span). Patients with incomplete or unavailable medical documentation were excluded. Collected data included demographic information, details about EB diagnosis and subtype, symptoms related to EB stricture, and radiological description of the strictures. Details of the dilation included the use of either of a balloon or bougienage, the type of visualization (fluoroscopy vs direct visualization using an endoscope) and the access point of the endoscope (oral vs gastrostomy). For the purpose of the analysis, the type of interventions was categorized as fluoroscopy-guided balloon dilation, antegrade endoscopy balloon dilation (oral insertion of an endoscope), retrograde endoscopy balloon dilation (insertion of the endoscope through a preexistent gastrostomy), and others (bougienage). Outcomes of dilation, such as success rate, complications, and recurrences were also collected.

The primary outcome measure of the study was the stricture-free intervals for patients with multiple events. The secondary outcome measures were frequency of strictures according to the EB subtype, frequencies of type of medical and/or surgical interventions, percentage of dilation success, frequency of complications pertaining to each procedure/intervention, and clinical predictors for re-stenosis.

Descriptive statistics were used to report discrete and continuous variables, such as counts, frequencies, means and standard deviations (SDs), medians and ranges, and interquartile ranges (IQRs). A conditional model-applied survival analysis was used to calculate predictors for re-stenosis. The model assumed that it was not possible to be at risk for a subsequent event (stricture) without having experienced the previous event and the time interval of a subsequent event started at the end of the time interval of the previous event. A univariate analysis was performed using the following variables: age at dilation, sex, number of stricture episodes, size and location of stricture, EB subtype, type of dilation procedure, and use of medication. The Cox multiple regression model used the variables that showed a significance of <0.25 in the univariate model. The overall significance level was set at 5%. Statistical analysis was performed using STATA 14.0 (TX) and SAS 9.4 (NC).

RESULTS

We collected data from 125 patients who had 497 esophageal stricture episodes over a mean period of observation of 16.96 (SD = 11.91) years. There was a slight male to female predominance (53% vs 47%). DEB was the most common type in 98.4% (123/125), the rest of the cohort being represented by JEB and Kindler syndrome with 1 patient each. Among DEB patients, esophageal strictures were found most commonly in recessive DEB (RDEB), severe generalized type—43.9% (54/123), followed by DEB unspecified—24.4% (30/123), RDEB severe intermediate—19.5% (24/123), and dominant DEB (DDEB) generalized—6.5% (8/123). The mean age at the first episode of esophageal stricture was at 12.67 (SD = 8.2) years, with the youngest subject being 1 years of age. Most patients were assessed as having severe malnutrition with a median body mass index (BMI) percentile of 6.3 (IQR: 0.57–23.32). Patients experienced a median of 2 (IQR: 1–7) stricture episodes. Additional findings were rare and included esophageal webs (6/497), hiatal hernias (3/497), ''corkscrew'' esophagus (3/497), and ulcerations (2/497). Twenty out of 497 patients had visualized gastro-esophageal reflux. Only in 18.51% (92/497) episodes was there documentation of proton pump inhibitor use at the time of diagnosis of esophageal stricture.

Esophageal Stricture Characteristics

Most common symptoms suggestive of stricture were dysphagia in 85.5% (425/497) of events, particularly inability to swallow solids—29.8% (133/497). Complications attributed to the presence of the strictures included malnutrition—64% and anemia—59.9%. Combined diagnostic and interventional video fluoroscopy were used to diagnose a stricture in 57.7% (287/497) patients, whereas barium swallow was used in 21.83% (109/497). Upper esophageal location of the stricture was found in 76.66% compared with thoracic (56.74%) and abdominal (9.66%) location and a long segment involvement (>1 cm in length) were the most common presentations. (Table 1).

Management of the Strictures

Dilation of the strictures was attempted in 90.54% (451/497) of episodes, based on the patient's preference. The preferred modality of treatment was balloon dilation using guided fluoroscopy—45.23% (204/451). A retrograde approach, consisting of direct visualization using an endoscope passed through an existing gastrostomy tube was employed in 33.04% (149/451) of episodes, whereas antegrade endoscopy (passed through the mouth) was used only in 19.07% (86/451). A general anesthetic that required intubation was preferred for most of the procedures in 87.58% (395/451). Medication use around dilation with the purpose to enhance the results or prevent complications was documented in 46.8% (214/451) of events, in the form of corticosteroids—90.7% (194/208) (various preparation of oral corticosteroid formulations—189/194, inhaled budesonide preparation used orally—5/194, and antibiotics—9.3% [20/214]). The mean duration of corticosteroid treatment was 5.17 (SD = 5.68) days starting on the day of the procedure. Successful dilation determined through direct visualization or fluoroscopy was accomplished in 99.33% (448/451), 96%

TABLE 1. Esophageal strictures characteristics; N = 497 events; (n) if different from N

Category	Characteristics	Values n (%)
Symptoms at presentation	Dysphagia	425 (85.5)
	Inability to swallow solids	133 (29.8)
	Odynophagia	58 (11.7)
	Inability swallow liquids	36 (7.24)
	Regurgitation	25 (5)
	Cough	24 (4.83)
	Food impaction (n = 470)	24 (8)
	Dyspepsia	14 (2.8)
	Regurgitation	25 (5)
Methods of evaluation (n = 475)	Video fluoroscopy	281 (56.54)
	Barium swallow	109 (21.83)
	Combined methods	22 (4.43)
	Clinical symptoms	45 (9.05)
	Endoscopy	9 (1.81)
	No evaluation	9 (1.81)
Level of stricture	Cervical esophagus	381 (76.66)
	Thoracic esophagus	282 (56.74)
	Abdominal esophagus	48 (9.66)
Length of stricture (n = 166)	Long (≥1 cm)	126 (76)
	Short (<1 cm)	40 (24)

with full dilation to caliber of esophagus and 3.33% with only partial dilation. There was no difference in the outcome based on the method of dilatation, 10 patients in the fluoroscopy versus 8 patients using endoscopy had a partial or not successful dilation. Transient complications were reported rarely in only 2.66% (12/451) (hemorrhage, 3; tear, 1; chest pain, 2; and nonspecified, 9) (Table 2). Complications were more commonly seen using the endoscopical approach (8/86, antegrade endoscopy; 2/149, retrograde endoscopy vs 2/204, fluoroscopy), $\chi^2 = 17.39$, P value <0.000.

Predictors for Esophageal Stricture Reoccurrence

Our cohort had a median interval between dilations of 7 (IQR: 4–12) months. The variables initially thought to predict esophageal stricture reoccurrences were age at dilation, sex, number of strictures, size and location of stricture, EB subtype, type of dilation procedure, and use of medication. Of these variables, only the EB subtype categories failed to reach the 0.25 threshold of being included in the multiple regression model (Table 3). Lower compared with upper esophageal location was protective for reoccurrence ($\chi^2 = 3.626$, $P = 0.057$, HR = 0.675 (95% CI: 0.450–1.012), although it did not reach statistical significance. The best predictors for stricture reoccurrence were: higher number of strictures found during a single episode [2 vs 1 stricture: $\chi^2 = 4.293$, $P = 0.038$, HR = 1.294 (95% CI: 1.014–1.652 and 3 vs 1 stricture: $\chi^2 = 7.986$, $P = 0.005$, HR = 1.785 [95% CI: 1.194–2.667]) and a long (≥1 cm) segment stricture ($\chi^2 = 4.599$, $P = 0.032$, HR = 1.347 [95% CI: 1.026–1.769]).

DISCUSSION

Our study, summarizing the data from the largest cohort of patients with EB with esophageal strictures, demonstrated excellent dilation outcomes irrespective of the dilatation procedure. It also highlighted stricture characteristics (long segment involvement, upper esophageal location and multiple strictures in 1 episode) predictive of stricture reoccurrence. As upper esophageal locations are the most common, barium swallow imaging should include the neck to avoid missing a cervical stricture.

Currently, 2 main methods of esophageal dilation are employed, periodic fluoroscopy-assisted pneumatic balloon dilation and direct visualization of the stricture through an endoscope and placement of a balloon over a wire. Each method could be performed using an antegrade approach, insertion of the guiding wire and balloon through the mouth or retrograde through a gastrostomy tube. The fluoroscopic method is the most frequently reported management strategy for EB patients (5–7,11,17) as it involves minimal instrumentation, reducing the risk of mechanical shearing trauma. Furthermore, balloon size is not limited by the caliber of an endoscope, thus allowing for maximum dilation and hypothetically decreasing the need for subsequent dilations (11). The success rate with this procedure is reported between 93.4% and 96.7% (7–11). One of the limitations of this approach is radiation exposure, especially if done repeatedly, theoretically increasing the risk of squamous cell carcinoma in an already susceptible population. The flexible endoscopy has the advantage of direct visualization of the stricture, observation of additional strictures, more precise estimates of the balloon's caliber, direct observation of complications (perforation, bleeding, etc), and no radiation exposure. The disadvantages relate to the potential increase in

TABLE 2. Management characteristics of patients who had a dilation; N = 451 events; (n) if different from N

Category	Characteristics	Values n (%) unless specified
Method of dilatation	Fluoroscopy-guided	204/451 (45.23)
	Retrograde endoscopy	149 (33.04)
	Antegrade endoscopy	86 (19.07)
	Bougienage	3 (0.01)
Type of anesthesia	General	395 (87.58)
	Sedation	11 (2.43)
	Not specified	45 (9.98)
Medication use (n = 214)	Corticosteroids	194 (90.7)
	Antibiotics	20 (9.3)
Outcome after dilatation	Completely resolved	433 (96)
	Partially resolved	15 (3.33)
	Not resolved	3 (0.01)
	Complications	12 (2.66)
Interval between dilatations	Median (IQR), months	7 (4,12)

IQR = interquartile range.

TABLE 3. Predictors/associations for event-free episodes; univariate analysis

Category	χ^2	*P* value	Hazard ratio (HR)	HR, 95% CI
Age	**1.39**	**0.239**	**0.987**	**0.966–1.009**
Female sex	**2.69**	**0.101**	**0.828**	**0.549–1.057**
DEB subtype	2.76	0.598		
Recessive severe generalized	0.14	0.709	1.145	0.561–2.337
Recessive not specified	0.77	0.379	1.344	0.695–2.596
Recessive severe intermediate	0.22	0.640	1.315	0.418–4.136
Dominant generalized	1.23	0.267	1.459	0.749–2.842
Recessive versus dominant	0.93	0.334	0.897	0.721–1.118
Severe recessive dystrophic versus others	1.31	0.253	0.822	0.588–1.150
Type of intervention	**6.49**	**0.039**		
Fluoroscopy	3.44	0.064	0.793	0.621–1.101
Endoscopy (ante- and retrograde)	5.14	0.023	0.6	0.385–0.933
Corticosteroid (CS) use	**5.57**	**0.062**		
Standard CS preparations	2.62	0.106	1.206	0.916–1.514
Budesonide	1.66	0.198	0.427	0.117–1.560
Stricture location	**24.99**	**<0.000**		
Cervical esophagus	17.11	<0.001	3.063	1.802–5.205
Thoracic esophagus	1.95	0.163	1.574	0.832–2.976
Abdominal esophagus	6.72	0.009	2.339	1.231–4.448
Length of the stricture ($\geq$ 1 cm vs <1 cm)	**8.38**	**0.004**	**1.474**	**1.13–1.91**
Number of strictures/episode	**8.45**	**0.015**		
2 vs 1	3.64	0.056	1.265	0.994–1.612
3 vs 1	6.48	0.011	1.504	1.098–2.059
Number of stricture episodes	**13.577**	**0.000**	**1.059**	**1.027–1.093**

Bolded variables included in the multiple regression model. CI = confidence interval; DEB, dystrophic epidermolysis bullosa.

mechanical trauma and size restriction of the balloon that could be passed through an endoscope. Another possibility is using a slim endoscope and performing a wire-balloon exchange that eliminates the size restriction and potentially decreases the risks of complications resulting from use of a large endoscope (12). Although endoscopy approach has less reported data (4,12,18), it has advantages that in the hands of a skilled team in the right patient, may be a preferable dilation modality, especially using the retrograde approach, which may preclude the need for a general anesthetic (12). Complete strictures may be successfully dilated using a combined, retro and antegrade approach (19). In our cohort, irrespective of the modality of dilation, patients had a high success rate (99.33%), suggesting that the team experience is more predictive of success rather than the type of procedure attempted and no severe, permanent complications. The number of adverse effects, however, seemed to be higher in the endoscopy group, especially with the antegrade approach ($\chi^2 = 17.39$, P value <0.000) supporting the existing literature. These should be interpreted with caution as most were nonspecific and some of the complications, such as bleeding may occur with fluoroscopy also but fail detection, especially if small.

One of the aims of this study was to explore clinical and management characteristics that would be predictive of higher stricture recurrences. In the univariate model, the type of dilation procedure, use of corticosteroid medication, upper and mid-esophageal location of strictures, longer size strictures (>1 cm), number of strictures found and the need for repeated procedures warranted inclusion in a multiple regression model of analysis. Interestingly, the type of EB, which traditionally is thought to relate to an increased incidence of strictures, was not predictive in our model, suggesting that there may be other clinical characteristics that may influence re-stenosis risk once an initial stricture occurred. A lower esophageal stricture location was associated with a 67.5% decrease in the risk of stricture reoccurrence. A higher number of strictures found had a higher rate of re-stenosis: 2 strictures had a 29.4%, 3 or more strictures had a 78.5% risk. Stricture length of $\geq$1 cm was associated with 34.7% higher chances of re-stenosis compared with shorter strictures. Our data did not allow further analysis of whether the strictures reoccurred at the same site but highlighted the fact that patients with multiple and long segment strictures may need closer monitoring and a lower threshold for re-evaluation and treatment in the presence of symptoms.

An interesting question is the role of medical therapy in decreasing the risk of re-stenosis. Oral corticosteroids administered around the time of dilatation aim to reduce pain and swelling post-procedure and potentially decrease the inflammation leading to subsequent scarring and re-stenosis. Adjuvant treatment with dexamethasone- or prednisone-equivalent preparations (1–2 mg/kg per day for 5 days) has been advocated as being beneficial, although there were no data to support its use as a preventative method for re-stenosis (5,6,12). Oral budesonide (0.5 ml/2 ml nebulizer mixed with 5 gm of sweetener, administered twice a day) was previously reported in small cohorts as beneficial in decreasing the stricture indices and spacing the need for dilatation (8,10), with minimal side-effects (candidal infection in 1/8 patients) even with long-term use. This therapy is used in eosinophilic esophagitis, the proposed mechanism of action being decreased fibrosis through an inhibitory effect on TGF-β1 and vascular activation (20). Whether these are important in the pathogenesis of stricture formation in EB patients is not known. In our cohort, the use of corticosteroids in decreasing the risk of restenosis could not be replicated. The benefit observed with use of periprocedural 0and postprocedural budesonide was limited to a few patients, therefore, further conclusions could not be derived. Given limited opportunities to modify the natural history of the disease and risk of esophageal strictures, budesonide's role merits further exploration as preventative intervention in high-risk individuals.

Our study had several limitations. Data collection was retrospective, therefore, a portion of the events had incomplete information. As the sample size was not equal across contributing centers, management differences between centers could not be explored. Limiting the number of episodes to the most recent 10 for each patient may have also introduced bias; however, we feel that given that 7 was the highest number of strictures, this criterion did not influence our results. Small sample size could also not allow complex modeling looking at outcome differences between intervention taking into account multiple clinical characteristics.

Despite limitations, our study demonstrated high success rate irrespective of the dilation procedure, higher adverse events with an antegrade endoscopy approach, and underscored the higher risk of re-stenosis in patients with multiple and long-segment strictures. Further prospective studies are needed to explore the use of oral corticosteroids, especially budesonide peri and postprocedurally, as potential prevention strategy for re-stenosis.

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