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# The Approach and Safety of Esophageal Dilation for Treatment of Strictures in Children with Epidermolysis Bullosa

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## Abstract

**Objective:** To analyze a large series of esophageal balloon dilations in patients with Epidermolysis Bullosa (EB) to determine procedural approach and frequency of post-endoscopic adverse events (AE).

**Methods:** Retrospective chart review for AE occurrence and clinical outcomes in children and adolescents with EB, age 1–19, who underwent esophageal dilation for esophageal stricture(s) from January 2003- April 2016 at an academic, tertiary care, free-standing children's hospital. The primary outcome measure was occurrence of procedural AEs (defined as events occurring within 72 hours after endoscopic dilation procedure).

**Results:** 231 fluoroscopy-guided esophageal balloon dilation procedures (209 anterograde, 20 retrograde, 2 both) were performed in 24 patients. Strictures were more common in the proximal portion of the esophagus with median stricture location 13 cm from the lips. From 2003–2012, 4.1% of dilations were retrograde. From 2013–2016, 20.2% of dilations were retrograde. AEs attributable to dilation occurred after 10.0% of procedures, and the most common AEs were vomiting, pain, and fever. No esophageal perforations, serious bleeding events, or deaths occurred secondary to dilation. The rate of post-dilation hospitalization was 6.9%. Dilation approach (anterograde versus retrograde) did not impact the likelihood of AEs.

**Conclusions:** The characteristic esophageal lesion in EB is a single, proximal esophageal stricture. EB patients can safely undergo repeat pneumatic esophageal balloon dilations with minimal risk for severe complication. We observed a trend towards increased use of retrograde esophageal dilation.

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**Conflicts of Interest:** None declared.

**Keywords**

Esophageal Stricture; Adverse Event; retrograde

## Introduction

Epidermolysis bullosa (EB) is a family of genetic disorders characterized by fragility of the skin and mucous membranes.(1) Affected areas in this disorder include the skin, gastrointestinal, genitourinary, and ocular systems and without curative therapy available, treatment is currently supportive.(2, 3) Esophageal strictures are a complication of EB, primarily of the subtype recessive dystrophic EB (RDEB).(2, 4–7) In patients with RDEB, reduced or absent expression of type VII collagen leads to blisters and erosions of the squamous epithelium of the skin and mucosa of the esophagus.(2, 3, 6, 8) These lesions heal with scarring, leading to development of strictures (Figure 1).(1–3, 9) Esophageal strictures cause dysphagia and odynophagia, leading to restricted food intake and negatively impacting quality of life.(3, 7, 10) Reduced caloric intake, in concert with increased nutritional demands due to chronic wound healing, contributes to poor nutritional status in many patients with RDEB.(3, 10) Gastrostomy tube placement has been used as an adjunctive nutritional modality to improve energy balance.(11, 12)

Multiple treatment approaches have been proposed to prevent or minimize the impact of esophageal strictures on symptomatology, quality of life, and nutrition. Suggested dietary modifications have included avoidance of hot foods, hyperalimentation, and the use of soft foods.(13) Pharmacologic therapies to inhibit stricture formation, including corticosteroids, collagenase inhibitors (e.g. phenytoin), and calcium channel blockers have not shown significant benefit and have the potential for adverse events.(13–15) Although previously used as a treatment modality for EB-related strictures, bougienage dilation is now contraindicated in EB as it has been shown to lead to significant adverse events, mediated by the application of longitudinal esophageal traction forces that cause esophageal mucosal injury.

Balloon dilation of esophageal strictures is the standard of care for patients with EB-related strictures and can improve dysphagia and oral intake.(16) However, symptom improvement is frequently transient, necessitating repetitive esophageal dilations over time. Although balloon dilation has been described in patients with EB, and recommended techniques developed, the risks associated with esophageal dilation and the recurrence rates of stricture formation have not been systematically studied. (10, 17, 18)

Currently, limited data exist regarding the best dilation approach/technique and the frequency of adverse events (AEs) associated with pneumatic balloon dilation of esophageal stricture in EB. Understanding the relationship between procedural variables and patient outcomes, specifically the occurrence of procedural AEs, may help standardize esophageal dilation technique in patients with EB. Important variables to consider in performing esophageal dilation include stricture location, anterograde versus retrograde approach, presence of multiple strictures, intraprocedural balloon dilation time, and frequency of need for stricture dilation. The primary aims of this study were to retrospectively analyze

procedural approach and adverse event occurrence associated with esophageal dilation in patients with EB at a tertiary academic pediatric hospital.

## Methods:

Retrospective cohort chart review of all esophageal dilation procedures performed on patients with EB at Children's Hospital Colorado between January 2003 and April 2016, a time interval chosen because of availability of the electronic health record for data abstraction. The study was approved by the Colorado Multiple Institutional Review Board.

### Study Population

Inclusion criteria included known diagnosis of recessive dystrophic Epidermolysis Bullosa or Kindler syndrome (a subtype of EB), age 0–19 years, and pneumatic esophageal balloon dilation procedure performed at our hospital within the selected study timeframe. Dilations were performed as needed for patient complaint of worsening dysphagia. Stricture diagnosis in this cohort was based on presence of symptoms and previous history of esophageal stricture and/or fluoroscopic esophagram.

### Description of Dilation Procedure

All procedures were performed under general anesthesia provided by a dedicated EB anesthesia team. Fiberoptic nasotracheal intubation was used as the sole method of providing general anesthesia. Stricture management approach was based on prior esophagram imaging and/or the patient's previous location of esophageal strictures. For initial stricture dilation in a patient, and rarely for some repeat stricture dilations, a small diameter endoscope (GIF-XP180N or GIF N180 Gastroscope, Olympus Corporation of the Americas, Center Valley, PA) was first passed into the esophagus. These small diameter endoscopes do not have a working channel sufficiently large to pass endoscopic balloon catheters. The stricture distance was determined visually, a guide wire placed across the stricture, and the endoscope was removed leaving the guide wire in place. Then, an over the wire (OTW) CRE 5.5cm pneumatic esophageal dilation balloon catheter (Boston Scientific, Marlborough MA) was then loaded on the wire and passed into the esophagus and placed such that the mid-point of the balloon was positioned across the stricture. The esophageal balloon catheter diameter was chosen based on child age and size. For the large majority of patients undergoing repeat esophageal dilation, endoscopy was deferred until after esophageal dilation was performed. In these cases, the initial maneuver was to blindly place an OTW dilation balloon into the esophagus and position at the location of the previous stricture(s). Esophageal position was always confirmed by x-ray prior to balloon inflation. After dilation, the endoscope would then in most cases be passed secondarily to visualize disrupted stricture tissue and to confirm that all strictures had been successfully dilated.

In children with a gastrostomy tube, when microstomia (a common and progressive complication of RDEB) was so severe that anterograde passage of an endoscope was impossible, a retrograde approach to dilation was pursued. The retrograde approach to dilation first requires removal of the gastrostomy tube, followed by intubation of the stomach with the endoscope via the gastrostomy. The endoscope is then directed across the

gastroesophageal junction to the lowest visible stricture in the esophagus. A 0.035 cm, 160cm Jagwire guide wire (Boston Scientific, Marlborough MA) was passed through the endoscope across the stricture and out the mouth. With the endoscope in place the balloon catheter was loaded on the wire and passed through the mouth. Positioning across the stricture was confirmed by direct visualization. Following dilation, the balloon was removed and retrograde endoscopy of the entire esophagus was performed.

Independent of the method for positioning the esophageal dilation balloon, the balloon catheter was inflated with contrast under fluoroscopic visualization until eradication of the stricture waist was visualized and then was immediately deflated (Figure 1).

## Classification of Adverse Event (AE) Primary Outcome

Adverse events were defined using our previously described procedural adverse event monitoring system.(19) Each esophageal dilation was reviewed retrospectively analyzing for symptoms and documentation of adverse events. Post-endoscopy adverse events were monitored and recorded using documentation obtained from procedure, anesthesia, emergency, hospitalization, or telephone encounters collected through the hospital EMR. All patient encounters documented in the medical record occurring within 72 hours of procedure were reviewed. AEs were classified and categorized by symptom type and severity.(19) AEs included but were not limited to the following symptoms: fever, chest pain, throat pain, vomiting, bleeding, respiratory complaints, infection, perforation, and death. The database of adverse events included only symptoms that were documented in the hospital EMR. Symptoms were reviewed and assigned by consensus of the authors (BA and DB) as adverse events attributable or not to the esophageal dilation procedure performed. Where multiple AE symptoms were recorded, a primary AE category was determined. AEs were graded from 1 to 5 in severity as previously reported (Grade 1: Home supportive care management; Grade 2: Ambulatory evaluation and treatment; Grade 3: Inpatient hospitalization or significant intervention (repeat endoscopy, etc.); Grade 4: Intensive care unit hospitalization or surgical intervention; and, Grade 5: Death).(19) AE’s of grade 2 or greater were considered significant in that they incurred increased medical costs and potential risks associated with subsequent evaluations.

## Statistical Analysis

Variables collected for each subject included age, gender, total dilations per patient, duration of interval between dilations, anterograde versus retrograde approach, stricture characteristics and location, use of endoscopy at the time of dilation, adverse events and adverse event severity. We generated basic descriptive statistics regarding the characteristics of subjects and their dilation procedure. To examine the relationship between procedural characteristics and our primary outcome of AE, we utilized Fisher’s exact and chi-squared tests; we used a p-value of $<0.05$ to signify statistical significance. All analyses were completed using Stata Version 15 software (College Station, TX).

## Results

Between January 2003 and April 2016, a total of 231 fluoroscopy-guided balloon dilation procedures were performed in 24 EB patients (23 recessive dystrophic (RDEB) and 1 Kindler syndrome) (Table 1). Median patient age at initial dilation was 4 years (interquartile range (IQR), 3–9 years). The median number of dilations per patient was 7 (IQR 5–12) and for those patients receiving repeat dilations (n=20) the median interval between procedures was 164 days (IQR 117–273). While there was some consistency of time intervals between dilations for an individual patient, there was considerable inter-patient variability in the interval between dilations (Supplementary Figure 1). Of the 231 total procedures, 90.5% involved an anterograde approach and 9.5% involved a retrograde approach. A single stricture was found in 73.2% of dilation procedures whereas multiple strictures were dilated in 26.8% of dilation procedures. Multiple strictures occurred more frequently in older subjects (12.7 years versus 8.3 years, $p<0.001$) and in subjects who had a longer median interval between dilations (330 days versus 192 days, $p<0.001$), but there was only a weak correlation between age and interval between dilations ($r=0.2$, $p=0.004$) (Table 1). Regardless of age, strictures were more common in the proximal portion of the esophagus (68.6%) with a median stricture location of 13 cm from the lips (Figure 2).

A pre-dilation endoscopy was performed in 25% of cases including all procedures by retrograde approach. Retrograde approach to dilation necessitates the presence of gastrostomy tube and 14 of our patients had gastrostomy tubes at some point during our study period. A total of 168 dilations (72.7%) were performed with presence of a gastrostomy tube. Of those subjects with a gastrostomy tube who had procedures performed from 2003–2012, retrograde dilation represented 4.5% of all dilations performed; whereas, from 2013–2016 the retrograde approach represented 29.8% of all dilations performed.

Of the 24 total patients, 46% had ≥1 AEs during one of their dilations; 54% had no AEs during any of their dilations. A total of 23 dilations, representing 10% of all dilation procedures, were associated with development of 29 AEs. Significant AEs (defined as grade ≥2) occurred in 8.7% of all dilation procedures. The most common symptoms associated with AEs of grades ≥ 2 were fever, pain, and vomiting (Figure 3). Grade 3 AEs requiring hospitalization occurred in 6.9% of dilation procedures (n=16). Reasons for hospitalization were vomiting, inability to drink sufficient liquid, fever, and/or pain control. All hospitalized patients were discharged the day after their procedure. Of note, no esophageal perforations, serious bleeding events, or deaths occurred secondary to procedure. Dilation approach (anterograde versus retrograde), inclusion of endoscopic visualization as part of the procedure, and number of strictures dilated (single versus multiple) were not significantly associated with the occurrence of AEs (Table 1).

## Discussion

This single-center, retrospective cohort study is the largest reported series of endoscopic balloon dilation procedures performed in patients with Epidermolysis Bullosa (EB). The characteristic stricture in patients with EB is a single, proximal esophageal stricture. No esophageal perforations, serious bleeding events, or deaths occurred secondary to

esophageal dilation procedure during this twelve-year, cohort, single-center study. However, the rate of inpatient hospitalization for symptomatic control (e.g. pain or vomiting) was not inconsequential at 6.9%.

The therapeutic approach to pediatric esophageal stricture dilation is different in patients with EB than in other patient populations. Common types of pediatric esophageal stricture, including congenital, peptic, caustic, and anastomotic strictures, typically require disruption of a submucosal fibrotic component for dilation to be successful with balloon inflation times lasting minutes.(20–22) In contrast, esophageal strictures in EB appear to require less application of radial force for disruption. Our experience from fluoroscopically visualized dilation procedures is that esophageal balloon dilation resolves EB strictures in seconds instead of minutes. With less application of radial force to the esophageal wall, we believe that dilation of EB strictures is less likely to cause esophageal perforation. Indeed, we experienced zero instances of esophageal perforation in our cohort compared to published rates of up to 17% in the series of pediatric patients undergoing esophageal dilation of benign strictures.(21, 23)

We found that the retrograde approach to dilation was as effective as anterograde approach in delaying need for future dilation without and did not increase incidence of AEs as compared to anterograde approach. The retrograde approach may lead to a decrease in overall oral manipulation during the procedure, which may be beneficial in terms of post-procedure discomfort. Based on our experience, we feel that retrograde esophageal stricture dilation is a safe, first-line approach for strictures in patients with EB and existing gastrostomy tube.

Limitations of this study include retrospective study design, low power for retrograde dilation analysis, and small patient population size. A strength of this study was the longitudinal follow-up of individual patients, providing important data regarding stricture recurrence. An additional strength of this study was the extended period of AE monitoring (72 hours), increasing sensitivity to catch delayed presentation of symptoms related to esophageal dilation procedures. We considered AE rates for grade ≥ 2 to be clinically significant as in these cases patients required additional evaluation and possibly treatment or hospitalization post- esophageal dilation. We conclude that patients with EB can safely undergo repeat dilations with minimal risk of severe complications. We believe that our reported AE data can guide clinical decision making and pre-procedural counseling to help set realistic expectations for families and patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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**What is Known / What is New**

What is Known?

- Dysphagia due to esophageal stricture(s) negatively impacts quality of life and nutritional status in children with Epidermolysis Bullosa (EB).
- Reported dilation techniques in EB patients have varied in their approach with minimal data on recurrence rates and complications.

What is New?

- The characteristic EB stricture is a single, proximal esophageal stricture.
- Patients with EB can safely undergo repeat dilations with minimal risk of severe complications.
- Retrograde approach to dilation was safe and no more likely to lead to stricture recurrence.

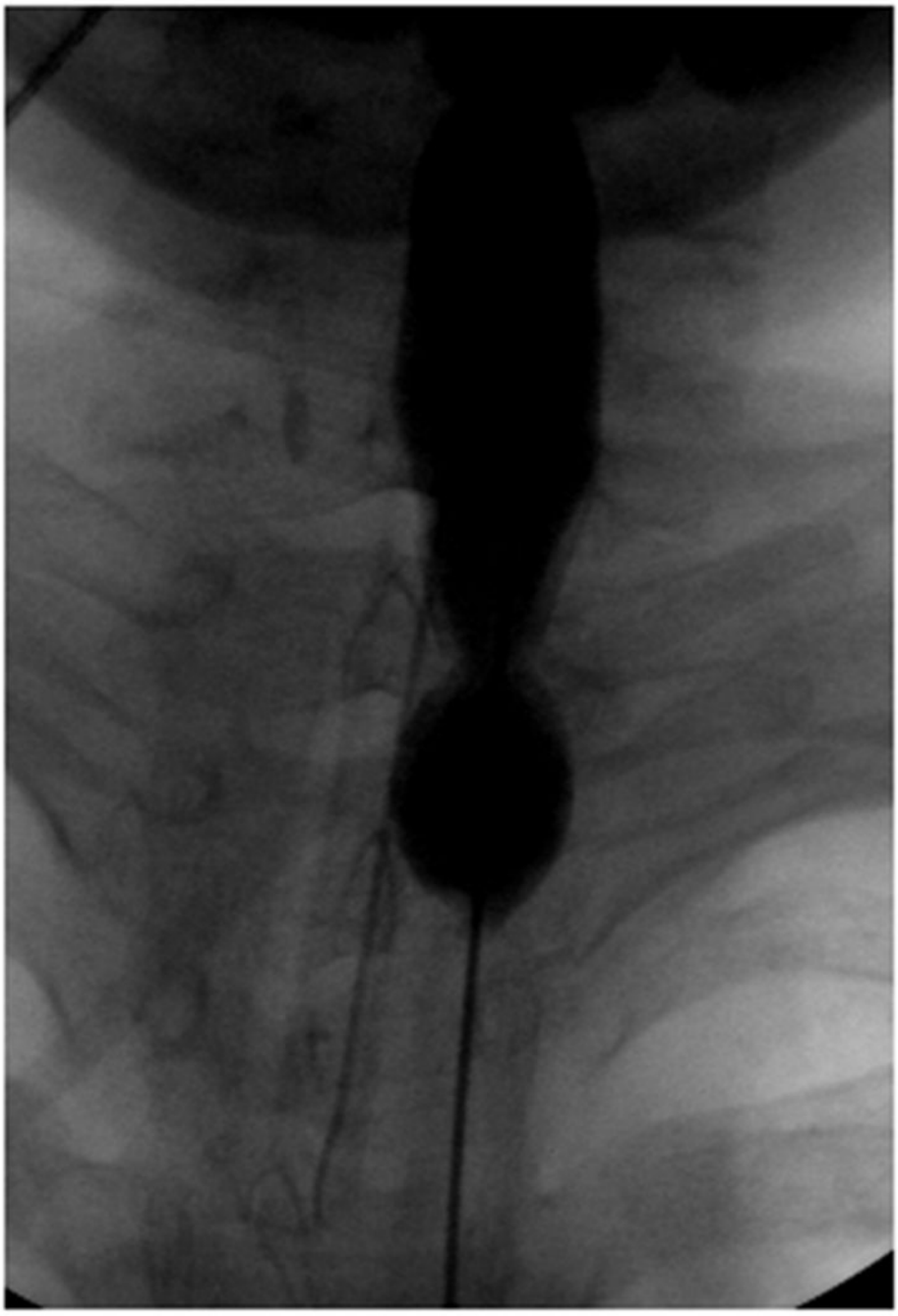

**Figure 1:**
Fluoroscopic image of anterograde esophageal balloon dilation. Contrast filling the esophageal dilation balloon shows a narrow waist in the inferior half of the balloon, representing a proximal esophageal stricture.

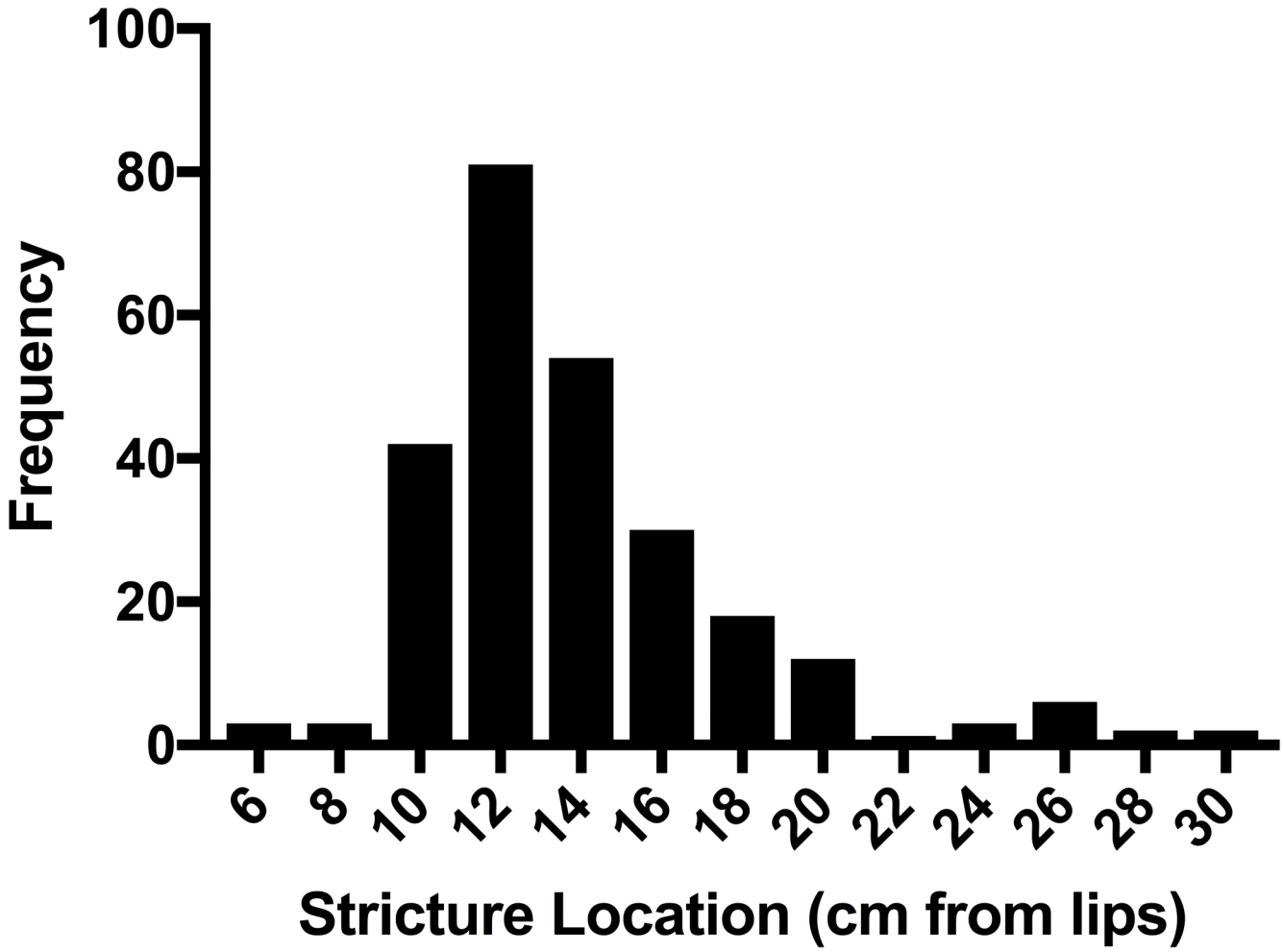


**Figure 2:**
Esophageal stricture location. Y-axis is the total number of dilations across all subjects and x-axis is stricture location from lips (cm).

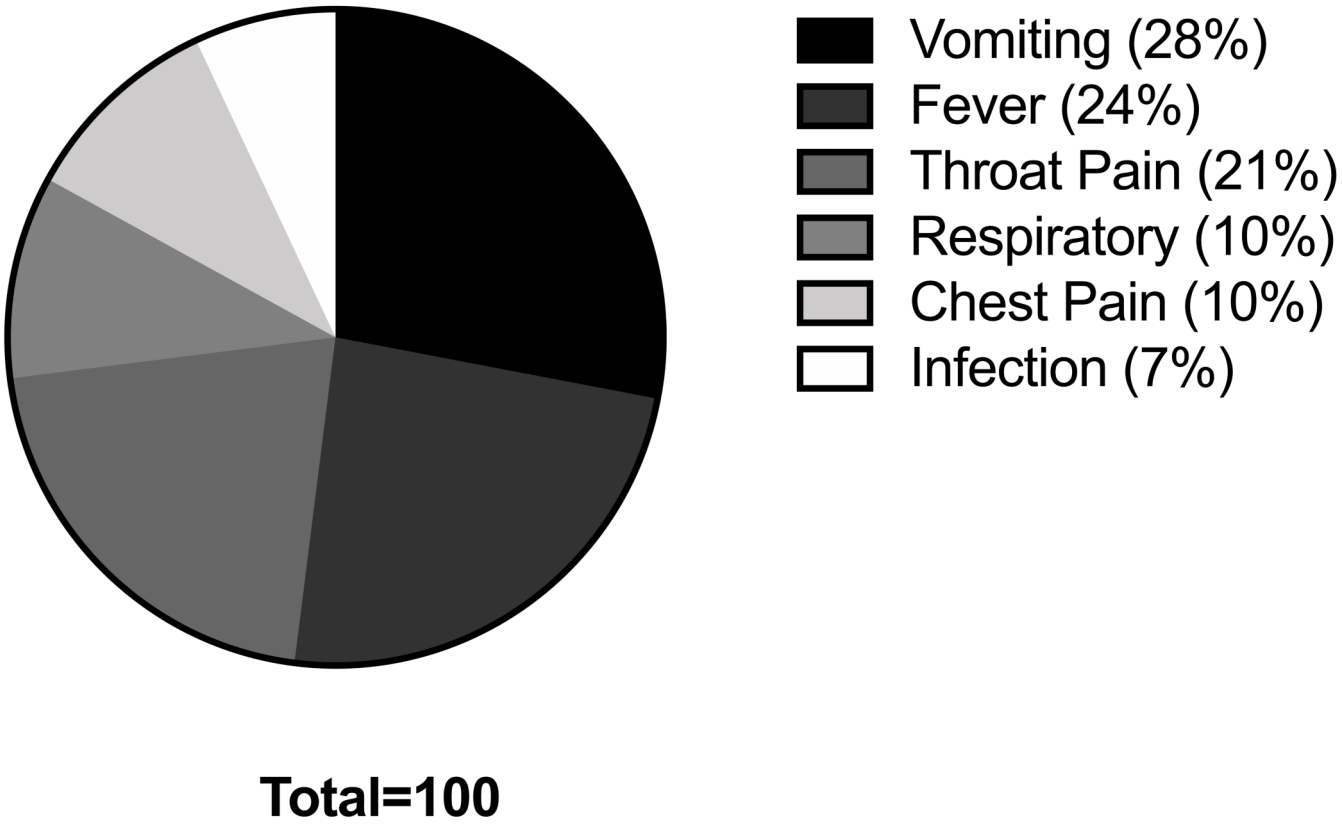


**Figure 3:**
Relative frequency of different types of adverse events (AEs) in subjects with AEs grades ≥2. Subjects could have multiple AEs occurring after a dilation procedure. A total of 29 adverse events occurred following 23 dilation procedures.

**Table 1:**

Patient Demographics and Frequency of Adverse Events by Procedural Characteristics

| | DILATION APPROACH | | | ENDOSCOPY | | | STRICTURE NUMBER | | |
|---|---|---|---|---|---|---|---|---|---|
| | **ANTEROGRADE** | **RETROGRADE** | **P value** | **YES** | **NO** | **P value** | **SINGLE** | **MULTIPLE** | **P value** |
| **TOTAL DILATIONS** | 209 | 22 | | 190 | 41 | | 169 | 62 | |
| **Mean Age (years)** | 9.3 | 10.8 | 0.182 | 9.8 | 8.0 | 0.033 | 8.3 | 12.7 | <0.001 |
| **Female (%)** | 66% | 50% | 0.353 | 63% | 73% | 0.201 | 65% | 65% | 0.998 |
| **Interval (days)** | 224 | 245 | 0.677 | 168 | 142 | 0.005 | 192 | 330 | <0.001 |
| **ADVERSE EVENTS** [1] | | | | | | | | | |
| **Grade 1** | 3 | 0 | | 2 | 1 | | 2 | 1 | |
| **Grade 2** | 3 | 1 | | 4 | 0 | | 2 | 2 | |
| **Grade 3** | 14 | 2 | | 15 | 1 | | 12 | 4 | |
| **Grade 4** | 0 | 0 | | 0 | 0 | | 0 | 0 | |
| **Grade 5** | 0 | 0 | | 0 | 0 | | 0 | 0 | |
| **AE- ALL GRADES** | 20 | 3 | | 21 | 2 | | 16 | 7 | |
| **AEs GRADES ≥2** | 17 | 3 | 0.417 | 19 | 1 | 0.215 | 14 | 6 | 0.793 |

[1]Subjects could have >1 type of AE at the same time. Among the 23 dilations associated with ≥1 AE, there were a total of 29 different types of AEs.