CME

Rules Are Meant to Be Broken: Examining the ''Rule of 3'' for Esophageal Dilations in Pediatric Stricture Patients

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ABSTRACT

Background and Aims: The ''rule of 3'' is a 40-year-old expert opinion that suggests dilating an esophageal stricture more than 3 mm is unsafe. Few studies have evaluated this tenet, and do not specify how much larger than 3 mm is reasonable. Our aim was to determine the optimal point for maximum dilation diameter with acceptable risk in a pediatric population.
Methods: A retrospective review in pediatric patients with esophageal strictures was performed. The number of millimeters the stricture was dilated, defined as delta dilation diameter (ΔDD), was determined by subtracting the initial stricture diameter from the diameter of the largest balloon used. Receiver operating characteristic curve analysis was used to evaluate the discriminatory ability of ΔDD. Youden *J* index was used to identify optimal cut-point in predicting perforation.
Results: Two hundred eighty-four patients underwent 1384 balloon dilations. Overall perforation rate was 1.66%. There were 8 perforations in 1075 dilations with ΔDD ≤5 mm (0.7%) and 15 perforations in 309 dilations with ΔDD >5 mm (4.9%). Youden *J* index found an optimal cutoff to be at a ΔDD of ≤5 mm. The cumulative rate of perforation for all dilations ≤5 mm was 0.74% whereas the cumulative risk of perforation for all dilations ≥6 mm was 4.85% ($P < 0.001$).
Conclusions: Balloon dilations that expand the initial esophageal anastomosis ≤5 mm in a pediatric population appear to not unduly increase the risk of perforation. Further prospective studies are needed to further investigate the potential for a new rule of 5 for balloon dilation.

Key Words: endoscopy, esophageal atresia, esophageal dilation, esophageal perforation, esophageal stricture, pediatrics

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What Is Known

- The ''rule of 3'' is an expert opinion limiting bougie and balloon dilations to <3 mm to minimize risk.
- Few studies have evaluated the accuracy of the rule of 3, and no studies have determined how much larger than 3 mm is safe.

What Is New

- Risk of dilating an esophago-esophageal anastomotic stricture in pediatric patients is evaluated for each dilation diameter.
- Dilating an esophago-esophageal anastomotic stricture up to 5 mm does not unduly increase the risk of perforation compared with dilating up to 3 mm.

Esophageal stricture is commonly treated with balloon or bougie dilation. Specific guidelines, however, about the best methods of achieving safe dilation are lacking. According to the 2006 American Society for Gastrointestinal Endoscopy guidelines on esophageal bougie dilation, once resistance is met (ie, at the stricture's initial diameter), dilation should not progress beyond 3 dilators in increments of 1 mm in a single endoscopy session so as to minimize the risk of perforation, the so-called ''rule of 3 (1).'' Although oral tradition may have extended this rule to balloon dilations as well, it was not until 2017 that a rule of 3 relating to balloon dilation was proposed in the literature as a ≤3 mm difference between the first and last balloon used to dilate a stricture (2).

Despite the existence of at least the bougie version of this ''rule'' for more than 40 years, no studies support it for bougies or balloons. Rather, several early studies suggested that dilation greater than 2 mm with bougie or balloon does not increase risk of perforation (3,4). More recently, a 2017 study found that bougie or balloon dilations >3 mm do not increase risk of perforations (2). All of these studies were done in adult populations; no studies have examined the rule of 3 in pediatric patients. In addition, although prior studies may have shown that dilating a stricture >3 mm with a bougie or balloon appears safe, there was no data looking at how large a dilation can be performed safely.

The aim of this study was to evaluate a cohort of pediatric patients with esophago-esophageal (E-E) anastomoses undergoing dilation to determine if dilating the anastomosis more than 3 mm increased risk of esophageal perforation. In addition, we sought to identify an actual point at which the risk of perforation outweighed possible benefit of dilation to offer data-driven guidelines for safely dilating esophageal strictures. Lastly, we evaluated the initial diameter of an anastomosis as a risk factor for perforation during dilation of an E-E stricture.

METHODS

An institutional review board–approved retrospective chart review of the histories of patients with strictures of an E-E surgical anastomosis seen at the Esophageal and Airway Treatment Center at

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Boston Children's Hospital between January 2016 and April 2019 was performed. Pertinent clinical data from patient charts, particularly endoscopy, surgical, and radiology reports, were collected in a comprehensive endoscopy database. Recorded patient information included sex, age, gestational age at birth, trisomy 21, number of balloon dilations, number of days out from the surgery that resulted in the anastomosis, diagnosis that resulted in the anastomosis, long gap esophageal atresia (LGEA) diagnosis (defined as esophageal atresia [EA] that cannot be primarily repaired because of inability to approximate the upper and lower pouches), stricture diameter, intralesional steroid injections (ISI), and adverse events, in particular, esophageal perforation (Table 1). EA patients had undergone primary repair, whereas LGEA patients underwent the Foker growth procedure (5). These patients may have had surgery at other institutions or in the distant past; postop day of the first endoscopy performed at our institution in our study population ranged from 0 (in a patient who was dilated intraoperatively to demonstrate distal anatomy to the surgical team) to 6702 days, though in some patients coming from overseas the day of surgery was unknown. Procedures during which endoscopic incisional therapy was performed or a surgical leak was discovered at the start of the procedure were excluded.

Perforation was defined as a tear extending completely through the esophageal wall, with confirmation of contrast leak on fluoroscopy study performed immediately following dilation in the operating room. The initial diameter of the esophagus was determined by the endoscopist before dilation and recorded in the operative note. An intraoperative contrast esophagram with half-strength Ioversol 68% (Optiray 320, Mallinckrodt Pharmaceuticals, Hazelwood, MO) was performed before balloon dilation (CRE 5.5-cm balloons, Boston Scientific, Marlborough, MA) with a radiopaque ruler placed under the patient. The anastomotic diameter was measured using the fluoroscopic image with the greatest anastomotic diameter; the radiopaque ruler and scope diameter were used as size references. The endoscope diameter and/or known width of open and closed biopsy forceps were used to determine diameter of the anastomosis in cases with poor contrast distention. Delta dilation diameter (ΔDD) was defined as the number of millimeters that a stricture was dilated; it was determined by subtracting the initial stricture diameter from the diameter of the largest balloon used.

ISI as adjunct therapy to balloon dilation typically entailed injecting triamcinolone acetonide 10 mg/mL (Kenalog-10, Bristol-Myers Squibb, Princeton, NJ) at a dose of 1 to 2 mg/kg with a maximum dose of 40 mg into the esophageal stricture. Typically, the steroid was injected into 4 quadrants but was sometimes targeted to specific quadrants if an abundance of scar tissue was concentrated in 1 area (6).

Continuous data are presented as median (interquartile range), and categorical data are presented as frequency (percentage). Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminatory ability of ΔDD in distinguishing patients with and without iatrogenic perforation among patients with E-E anastomoses. Results from ROC analyses are summarized using the area under the ROC curve (AUC) with 95% confidence interval (CI) and *P* value. Youden J index was used to identify the optimal cut-point of ΔDD in predicting perforation by maximizing sensitivity and specificity. Comparisons of leak rate and risk of perforation were done using the chi-square test, Fisher exact test, and the Mann-Whitney *U*-test for categorical and continuous data, as appropriate. Logistic regression analysis was used to assess the perforation rate for endoscopies that included steroid injections of the stricture, with results presented as odds ratio (OR), 95% CI and Wald test *P* value. All statistical analyses were performed using Stata version 15.0 (Stata Corp, College Station, TX). A 2-tailed alpha level of 0.05 was used to determine statistical significance.

TABLE 1. Patient demographics

Variable		N (%)
Number of patients		284
Number of dilations		1384
Female		141 (50%)
Gestational age (weeks)		36 (33,38)*
Trisomy 21		17 (6%)
Diagnosis	Number of patients (%) (N = 284)	Number of dilations (%) (N = 1384)
EA (nonlong gap)	151 (53%)	567 (41%)
EA type A	1 (0.4%)	6 (0.4%)
EA type B	1 (0.4%)	3 (0.2%)
EA type C	132 (46%)	501 (36%)
EA type D	2 (0.7%)	6 (0.4%)
EA unknown type	15 (5%)	51 (4%)
LGEA	129 (45%)	793 (57%)
LGEA type A	75 (26%)	452 (33%)
LGEA type B	20 (7%)	110 (8%)
LGEA type C	29 (10%)	197 (14%)
LGEA type D	1 (0.4%)	1 (0.1%)
LGEA unknown type	4 (1%)	33 (2%)
VACTERL association**	84 (30%)	373 (27%)
Congenital stricture**	9 (3%)	31 (2%)
Caustic stricture resection	1 (0.4%)	1 (0.07%)
History of esophageal perforation	3 (1%)	23 (2%)

EA = esophageal atresia; LGEA = long gap esophageal atresia.
*Values are median (interquartile range).
**All patients with congenital esophageal stricture or VACTERL association also all have diagnoses of EA or LGEA.

RESULTS

Demographics

A total of 284 patients met study criteria and had a total of 1384 balloon dilations performed on E-E anastomoses. Of these 1384 dilations, 919 were balloon dilations without any adjunct treatment of the stricture, and 465 dilations included ISI of the stricture as adjunct therapy to the dilation. Table 1 lists pertinent demographic data as well as the patient's diagnosis that led to their surgery. We are a large referral center for EA, so most of the patients in this cohort had EA (98%); 45% of the EA patients met criteria for LGEA. Nine patients with EA or LGEA also carried the diagnosis of congenital esophageal stricture, and 84 had VACTERL association. Five additional patients had stricture resection surgery for caustic ingestion or iatrogenic perforation of the esophagus.

Perforation Rate with Steroid Injections

To determine if dilations that had ISI could be included in the overall study population, we evaluated endoscopies in which steroid injections had also occurred to see if the risk of perforation increased. We identified a cohort of 919 endoscopies that involved esophageal stricture dilations without any adjunct treatment of the stricture. The perforation rate of these endoscopies was 2.1% (N = 19). The cohort of 465 dilations that included ISI of the stricture in addition to dilation had a reported perforation rate of 1.1% (N = 5; odds ratio [OR] = 0.51; 95% CI 0.19–1.39; *P* = 0.189). As there was no statistical difference between both groups, endoscopies with ISI were incorporated into the overall study cohort, bringing the total number of dilations to be further analyzed to 1384.

TABLE 2. Perforation rate by delta dilation diameter

Delta dilation diameter, mm	Number of dilations	Perforations	Perforation rate
0–1	54	0	0.00%
>1–2	206	0	0.00%
>2–3	306	3	0.98%
>3–4	292	2	0.68%
>4–5	217	3	1.38%
>5–6	172	8	4.65%
>6–7	87	3	3.45%
>7–8	33	1	3.03%
>8–9	8	1	12.50%
>9-10	9	2	22.22%

Perforation Rate by Delta Dilation Diameter

The overall perforation rate for all endoscopies in the study group was found to be 1.66%. Endoscopies were sorted by ΔDD in 1-mm increments. The perforation rate for each ΔDD increment is listed in Table 2. The perforation rate was 0% for dilations with a ΔDD of up to and including 2 mm. Dilations following the rule of 3 with a ΔDD up to 3 mm had a perforation rate of 0.98%. The first large jump in perforation rate occurred between ΔDD >4 to 5 mm and >5 to 6 mm, increasing from 1.38% to 4.65%. The perforation rate increased to more than 20% when the ΔDD dilation diameter was >9 mm in size.

There were 16 dilations in which the ΔDD was ≥9 mm in size. The median initial diameter in this subset was 2 mm (interquartile range [IQR] 1–3), and in patients with smaller initial diameters, we will consider a more aggressive dilation in an attempt to better remediate the stricture. Initial diameter was >5 mm in only 2 of these 16 dilations, and 1 of these was in a clinically symptomatic patient over 20 years of age.

Sensitivity and Specificity of Perforation

As a first step toward determining the point of maximum ΔDD dilation and minimum risk, we looked at sensitivity and specificity for perforation. Here, as what we are examining is the absence of perforation, the sensitivity and specificity definitions are as follows: sensitivity is all cumulative dilations up to a particular diameter that did not have a perforation, whereas specificity is all dilations more than a particular number that did have a perforation. We found that of all the dilations that did not have a perforation, 78.4% were dilated to ≤5 mm, whereas of all the dilations that did have a perforation, 65.22% were dilated to ≥6 mm (Table 3). There were 8 perforations in 1075 dilations with ΔDD ≤5 mm (0.7%) and 15 perforations in 309 dilations with ΔDD >5 mm (4.9%).

Next a ROC curve analysis was performed to determine Youden *J* index, the point where sensitivity and specificity are maximized—the optimal point to maximize ΔDD and minimize risk. This index point was identified at a ΔDD of ≤5 mm (ROC = 0.769; 95% CI 0.678–0.860; $P < 0.001$) (Fig. 1). Positive-predictive value (PPV) looks at the cumulative rate of a dilation up to a certain diameter not having a perforation; the PPV of a dilation ≤5 mm not having a perforation was 99.26%, or in other words, the cumulative rate of perforation for all dilations ≤5 mm was 0.74% (Table 3). The negative cumulative risk of perforation found the perforation rate for all dilations ≥6 mm was 4.85%, and this was statistically significant ($P < 0.001$).

Initial Anastomosis Diameter as a Risk Factor for Perforation

We next looked at initial diameter at time of dilation as a possible risk factor for esophageal perforation in the dilation cohort, as smaller, tighter strictures might be expected to be higher risk for perforation than larger, more compliant strictures. This was not statistically significant (Table 4), although it did approach statistical significance ($P = 0.073$).

DISCUSSION

The rule of 3 was first described in a letter to the editor in 1977 and advised ''limiting any one treatment session to a maximum of 3 dilators'' as a means of limiting risk of perforation (7). This recommendation was not based on actual evidence, however, and was merely an expert opinion. Originally intended for bougie dilations only, as balloon dilations are increasingly utilized, the rule of 3 has been applied to balloon dilations as well, which have been examined indirectly in several articles (2,3,8,9). Over the past decades and even to the present day, clinicians continue to

TABLE 3. Receiver operating characteristic analysis of delta dilation diameter in predicting freedom from perforation in esophago-esophageal anastomoses

Cut-point for ΔDD	Sensitivity	Specificity	Youden *J* index	LR+	LR −	PPV	NPV
< 0.5	0.00%	100.00%	0.00%	.	1.00	.	1.66%
≤ 0.5	0.81%	100.00%	0.81%	.	0.99	100.00%	1.67%
≤ 1	3.97%	100.00%	3.97%	.	0.96	100.00%	1.73%
≤ 2	19.10%	100.00%	19.10%	.	0.81	100.00%	2.04%
≤ 3	41.37%	86.96%	28.33%	3.17	0.67	99.47%	2.44%
≤ 4	62.67%	78.26%	40.93%	2.88	0.48	99.42%	3.42%
≤ 5	78.40%	65.22%	43.62%	2.25	0.33	99.26%	4.85%
≤ 6	90.45%	30.43%	20.88%	1.30	0.31	98.72%	5.10%
≤ 7	96.62%	17.39%	14.01%	1.17	0.19	98.58%	7.99%
≤ 8	98.97%	13.04%	12.01%	1.14	0.08	98.54%	17.61%
≤ 9	99.49%	8.70%	8.19%	1.09	0.06	98.47%	22.36%
≤ 10	100.00%	0.00%	0.00%	1.00	.	98.34%	.

PPV and NPV were calculated while incorporating the prevalence of 98.34% of freedom from perforation using Bayes formula. Area under the ROC curve (AUC) = 0.769 (95% CI 0.678–0.860; $P < 0.001$). ΔDD = delta dilation diameter; LR − = negative likelihood ratio; LR+ = positive likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

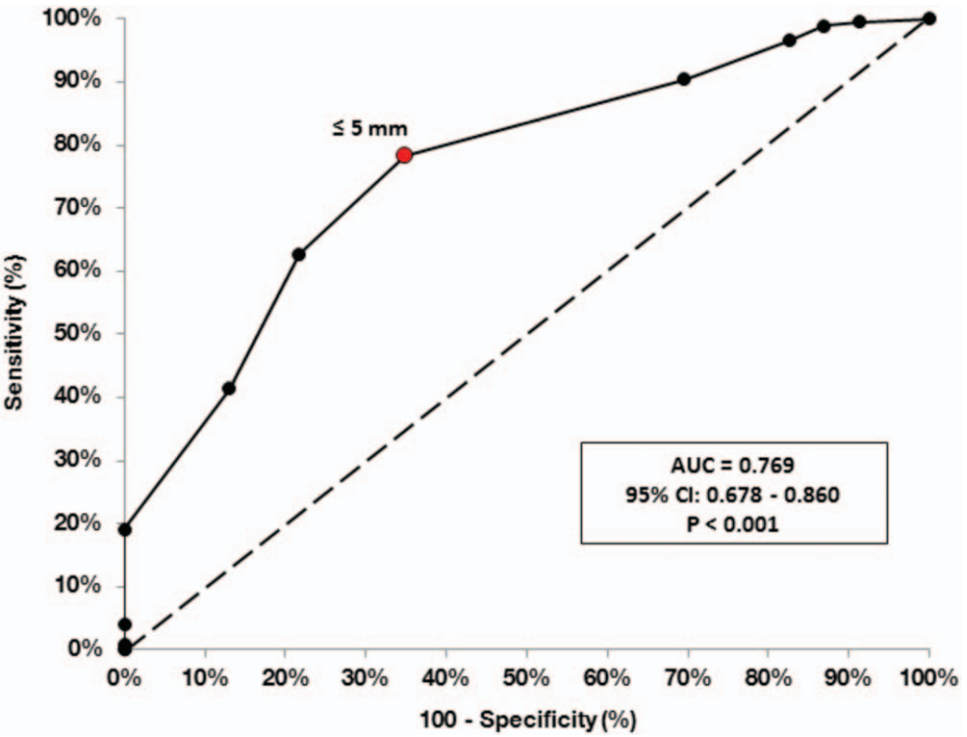

FIGURE 1. The optimal cutoff for maximum dilation diameter of esophageal strictures as determined by Youden *J* index was a delta dilation diameter of ≤5 mm (sensitivity =78%, specificity = 65%). Area under the receiver operating characteristic curve =0.769; 95% confidence interval = 0.678–0.860; $P < 0.001$.

recommend adherence to the rule of 3 despite a lack of evidence of its effectiveness (10).

There is a paucity of literature evaluating the rule of 3. Two very early studies obliquely looked at the risk of dilating a stricture with balloons by more than 3 mm (3,4). One study included 18 patients with ΔDD >3 mm in which there were no perforations (3).

TABLE 4. Analysis of initial stricture diameter as a risk factor for perforation of esophago-esophageal strictures during dilation

Initial diameter (mm)	No. patients	Perforations	Percent perforations	Median ΔDD (IQR)
<1	4	0	0.00%	8 (7–8)
1	49	2	4.08%	7 (6–7)
2	125	4	3.20%	6 (5–6)
3	102	2	1.96%	5 (5–7)
4	90	2	2.22%	4.5 (4–6)
5	152	7	4.61%	4 (3–5)
6	121	0	0.00%	4 (3–4)
7	158	2	1.27%	3 (3–4)
8	216	1	0.46%	3 (2–4)
9	127	2	1.57%	3 (3–5)
10	87	0	0.00%	2 (2–5)
11	44	0	0.00%	4 (3–5)
12	84	0	0.00%	3 (3–3)
13	22	0	0.00%	2 (2–3.5)
14	9	0	0.00%	4 (3–5)
15	24	1	4.17%	3 (3–5)
≥16	14	0	0.00%	2 (0.1–2)

Odds ratio = 0.89; 95% confidence interval 0.78–1.01; $P = 0.073$. ΔDD = delta diameter dilation.

A study of 716 dilation sessions with bougie and balloon dilators included 401 (56%) strictures with dilation of ≥45Fr (15 mm). In this entire patient population, there were 2 perforations during dilations for achalasia (4). The first article published in this century to look at this issue head-on was by Grooteman et al, who retrospectively examined 2216 dilations of 297 patients and found that bougie dilations that did not adhere to the rule of 3 did not have a higher risk of adverse effects or perforations. That team also set a rule of 3 for balloon dilations in which the difference between the first and last balloon was ≤3 mm, and found that balloon dilations >3 mm did not increase risk of adverse events (2). Although some of the authors of the above articles conclude that dilating >3 mm is ''safe,'' none specifically determined at what point ΔDD becomes unsafe. Our article is the first study to attempt to answer this question.

Our results find that balloon dilations that expand the initial E-E anastomosis ≤5 mm in a pediatric population do not unduly increase the risk of perforation. We found the risk of perforation when dilating up to 5 mm is 0.74%, while following the rule of 3 limited perforation rate to 0.53%. Increasing risk by one-fifth of a percentage point seemed reasonable, and this conclusion was supported by statistical analysis. Meanwhile, the data found that dilating to any diameter >5 mm raises the risk of perforation to 4.85%. ROC analysis demonstrated good discriminatory ability of ΔDD in predicting perforation at >5 mm. This study was also able to demonstrate that injecting steroids into an E-E anastomosis as adjunct therapy to balloon dilation did not increase the risk of perforation compared with balloon dilation alone.

We had hypothesized that strictures with smaller initial diameters might be more prone to perforation with dilation, as smaller initial diameters might call for more aggressive, larger dilations. We, however, found no statistically significant difference in starting esophageal diameter ($P = 0.073$). As this risk factor did

approach statistical significance, it could be that the study was underpowered to answer this question.

Limitations of the study include the fact that it was retrospective and that it evaluated only balloon dilations of E-E anastomoses in pediatric patients. The results may not apply in cases of bougie dilations. One benefit but also a limitation of the study was our homogeneous population, which adds weight to the conclusions when applied to the same population, but suggests that these conclusions may not be applicable to strictures of other etiologies (eg, peptic, caustic, or radiation-induced). In addition, we looked only at E-E anastomoses, so our data may not apply to other types of anastomoses. Furthermore, measurements of initial diameters are somewhat subjective, although we feel that the fact that we have only 2 endoscopists who are making these estimations limits variability. Our endoscopists have experience performing hundreds of dilations of pediatric E-E anastomoses annually, so other providers with differing levels of experience may not achieve these same results. We also did not make any allowance for a waist in the balloon at the end of dilation. A waist would signify that the stricture has not been dilated to the full diameter of the balloon, and this would decrease the ΔDD. Anecdotally, however, we can report that almost all of our dilations have minimal to no waist at the end of the dilation.

General thinking in performing a larger number of smaller dilations is that the risk of perforation is worse than the risk of multiple endoscopies. No studies have looked at improvement in an anastomosis based on ΔDD, so it is not known if smaller dilations are equally effective as larger dilations, and this warrants investigation. In a pediatric population, where general anesthesia is employed during EGDs, the long-term effects of anesthesia are not clear, but the FDA has issued a black box warning against repeated use of anesthesia in children under 3 years of age. Furthermore, significant time and cost are involved in undergoing numerous dilations. Reducing the number of dilations that a patient has, therefore, will likely benefit the patient and may prevent harm from anesthesia.

This article suggests that in a cohort of pediatric patients with E-E esophageal strictures, the optimal point between maximum dilation and minimum risk of adverse event is a ΔDD of $\leq$5 mm. It is important to remember that every case should be evaluated for its own merits; the data shows that dilating to 5 mm appears to be safe and is a reasonable option when the endoscopist determines it is clinically indicated. Future studies are needed to look at evaluating the new ''rule of 5'' prospectively for balloon dilation in patients with E-E anastomoses as well as other stricture etiologies in a multicenter study in order to ensure that this rule is applicable to patients with varying stricture types and to endoscopists of varying levels of experience.

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