Anastomotic Stricture after Esophageal Atresia Repair: A Critical Review of Recent Literature

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Abstract
Anastomotic strictures (ASs) complicate the postoperative course of roughly one-third of all patients with esophageal atresia with or without tracheoesophageal fistula. Its development is multifactorial, but is due in part to tension on the anastomosis, gastroesophageal reflux disease, and the presence of a leak in the early postoperative period. Efforts at reducing the rate of AS have been largely unsuccessful, although meticulous technique and aggressive acid suppression remain the cornerstones of perioperative care. Once an AS has been confirmed, the first-line treatment remains a course of esophageal dilatation. Adjuncts to dilatation are frequently required, including steroid injection or the topical application of mitomycin C. Currently, there is insufficient evidence to promote one at the expense of the other. Esophageal stenting has recently been added to the algorithm of treatment, although additional literature is required to confirm its safety and efficacy. Finally, stricture resection followed by primary esophageal anastomosis or, rarely, esophageal replacement with an interposition graft remain options for AS refractory to all other forms of treatment.

Keywords
► esophageal atresia
► anastomotic stricture
► esophageal stenting
► mitomycin C
► steroid injection

Introduction
Esophageal atresia (EA) with or without tracheoesophageal fistula (TEF) remains one of the most common surgically correctable gastrointestinal malformations, and has demonstrated improving survival rates since the original description of repair and primary anastomosis in 1943 by Haight.¹ However, anastomotic strictures (ASs) continue to complicate the long-term management of these patients, and publications evaluating long-term outcomes demonstrate no significant improvement over time.²–⁴ This review will evaluate the recent literature surrounding AS, including its definition and incidence, as well as the various medical and surgical preventive and treatment strategies in existence.

Epidemiology and Definition of Anastomotic Stricture

Definition
An AS after EA repair is generally defined as a narrowing that results in symptoms or signs such as dysphagia, regurgitation, oxygen desaturation during feeding, aspiration, and failure to thrive. However, several distinct complications may lead to similar symptoms in EA patients, including esophageal dysmotility, recurrent TEF, gastroesophageal reflux disease (GERD), chordee, tracheomalacia, laryngeal clefts, and vocal cord dysfunction.⁵–⁸ The clinician must therefore evaluate the degree of narrowing seen on fluoroscopy or endoscopy in the context of each of the other possible complications, many of which may be simultaneously present. Importantly, the
Table 1 Definition of refractory and recurrent esophageal stricture

<table>
<thead>
<tr>
<th></th>
<th>Adult definition</th>
<th>Proposed pediatric definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory</td>
<td>Inability to dilate to 14 mm diameter over five sessions at 2-week interval</td>
<td>SI remains &gt; 10% after five sessions</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Inability to maintain a satisfactory diameter &gt; 4 weeks once 14 mm reached</td>
<td>Recurrence of symptoms or SI &gt; 50% after &gt; 4 weeks after SI &lt; 10% achieved</td>
</tr>
</tbody>
</table>

Note: SI, stricture index, defined by Said et al \(^{13}\) as \((D - d)/D \times 100\), where \(D\) is the diameter of esophagus below the stricture and \(d\) the diameter of the stricture.

Table 2 Summary of existing literature from 1990 to present evaluating the incidence of anastomotic stricture after open esophageal atresia repair

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Subjects, no. of type C</th>
<th>Stricture rate</th>
<th>Definition of stricture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chittmittrapap et al 1990 (^{23})</td>
<td>N = 184 (not reported)</td>
<td>37% (74)</td>
<td>Required dilatation</td>
</tr>
<tr>
<td>Poenaru et al 1991 (^{20})</td>
<td>N = 74 (74)</td>
<td>24% (18)</td>
<td>Required dilatation</td>
</tr>
<tr>
<td>Engum et al 1995 (^{4})</td>
<td>N = 215 (178)</td>
<td>35% (75)</td>
<td>Required dilatation</td>
</tr>
<tr>
<td>Konkin et al 2003 (^{116})</td>
<td>N = 136 (119)</td>
<td>52% (69)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lain et al 2007 (^{24})</td>
<td>N = 34 (29)</td>
<td>79% (27)</td>
<td>Required dilatation</td>
</tr>
<tr>
<td>Serhal et al 2010 (^{59})</td>
<td>N = 64 (64)</td>
<td>37% (23)</td>
<td>Contrast esophagram</td>
</tr>
<tr>
<td>Alshehri et al 2012 (^{3})</td>
<td>N = 50 (39)</td>
<td>36% (18)</td>
<td>Required dilatation</td>
</tr>
<tr>
<td>Koivusalo et al 2013 (^{4})</td>
<td>N = 127 (110)</td>
<td>78% (102)</td>
<td>Based on endoscopy</td>
</tr>
<tr>
<td>Total</td>
<td>884</td>
<td>40.0% (353)</td>
<td></td>
</tr>
</tbody>
</table>

Incidence

Table 2 provides a summary of case series reporting stricture rates in survivors after open EA repair, with no appreciable improvement in the stricture rate over time. Most of these studies used the need for dilatation as a sine qua non of the diagnosis, with approximately 40% occurrence overall. A recent comparative review of open and thoracoscopic EA repairs demonstrated an optimistic 9% stricture rate for the minimally invasive approach, \(^{16}\) although more contemporary series have documented stricture rates that approach the open rate (Table 2). A systematic review comparing open to thoracoscopic repair also demonstrated a wide variation in AS, from 9% to 45% after thoracotomy (defining AS as requiring \(> 1\) dilatation) and from 4.3% to 60% after thoracotomy (variable definition of AS) \(^{17}\); the author concluded that the incidence of AS was comparable between the two approaches and that a clear definition of AS would be important.

Prevention

Although an ounce of prevention is worth a pound of cure, numerous attempts at describing modifications to the technique of anastomosis have failed to demonstrate a durable solution to the development of AS. The end-to-side anastomosis that was used for much of the 1970s to 1980s by some surgeons may have reduced the stricture rate when compared with the end-to-end technique, \(^{18,19}\) but was shown to be associated with an increase in the refistulization and overall

initial anastomotic narrowing seen on postoperative contrast esophagram does not correlate with the development of a symptomatic AS;\(^9\); therefore, one must wait for the development of symptoms and have a low threshold for repeating an esophagram.

A symptomatic stricture may respond to a single dilatation, or may become refractory or recurrent. Kochman et al\(^{10}\) have proposed a definition for these two entities, which has been adopted by others, \(^{11,12}\) but it currently applies to adults. Table 1 represents an attempt at translating the adult definition to the pediatric context. Said et al described the anastomotic stricture index (SI) to quantify the severity of the stricture and monitor its subsequent response to treatment. \(^{13}\) The SI is defined as: \(SI = (D - d)/D \times 100\), where \(D\) is the diameter of esophagus below the stricture and \(d\) is the diameter of the stricture. All their patients were symptomatic and had a SI > 50% before dilatations were initiated. Nambirajan et al described an “anastomotic index” using the ratio of maximum upper pouch diameter to that of the anastomosis on contrast study. \(^{9}\) More recently, Parolini et al also used the upper pouch diameter in relation to the stricture diameter, based on endoscopic assessment, yet they called this the SI and quoted Said et al. \(^{14}\) None of these calculations have been widely used in a standardized fashion, but it would seem that using the distal esophageal diameter on contrast study more accurately reflects the true esophageal diameter (i.e., using the SI as originally described). \(^{13,15}\)
The development of AS after EA repair continues to be a vexing complication. End-to-end repair with minimal tension appears protective. Aggressive treatment of GERD is critical in minimizing stricture formation, including medical therapy and antireflux surgery if supported by evidence of uncontrolled reflux.

**Treatment**

**Dilatation**

Esophageal dilatation has been a well-established treatment modality for benign strictures in adults for more than 50 years. After the establishment of bougies or balloons in the treatment of peptic strictures in adults, their use in children soon followed. In general, strictures are characterized as simple (focal, straight, large diameter) or complex (long segment, i.e., > 2 cm, tortuous). Strictures secondary to caustic ingestion are typically complex in nature and challenging to treat while strictures secondary to EA nearly always result in a simple narrowing directly at the anastomotic site.

The first dilatation for a repaired EA occurred 17 months after the first documented surgical repair by Haight, after which time the patient improved. Since then, encouraging case reports resulted in some centers incorporating dilatation into the routine postoperative management of EA patients. Although bougies were the first tools widely available to dilate esophageal strictures, balloon dilatation is now thought to be safer and more effective. The exception may be in patients with long or tortuous strictures (e.g., after caustic injuries) or very fibrotic strictures (e.g., after esophageal replacement), which is rarely the case for AS post-EA repair.

**Bougie**

Three main types of bougies exist: tapered (Maloney) or blunt-tipped (Hunt) dilators inserted blindly, wire-guided...
bougies (Savary-Gilliard), and string-guided dilators (Tucker). The group from Lille has reported twice their experience with bougienage for treating AS after EA repair. In 2001, 20 patients had undergone bougienage, with 2 ultimately failing dilatation and 1 patient perforating and dying as a consequence. In a subsequent group of patients reported in 2010, they demonstrated an 87% success rate with serial dilatations using the same Savary-Gilliard bougies in 23 patients, requiring a mean of 3.2 dilatations per child. No complications were reported. Other groups in Europe and other parts of the world continue to report good results with the same type of bougies. These are passed over a guidewire, which is introduced beyond the stricture by endoscopy or under fluoroscopy (or both); fluoroscopic guidance may also be used during dilatation. Maloney bougies (mercury or tungsten weighted) are now seldom used since their blind passage may lead to more perforations, especially in long complex strictures. Tucker dilators, which can be pulled in a retrograde fashion using a string, may be useful in patients who do not tolerate repeated general anesthesia, have a gastrostomy, and need frequent dilatations. The procedure can be performed at the bedside or as an outpatient under sedation.

**Balloon**

Successful balloon dilatation for esophageal stricturing in children was first reported in 1984. Balloon dilatations may be done under fluoroscopic guidance in the radiology suite under sedation or general anesthesia, or under endoscopic guidance in the operating room using general anesthesia, with or without fluoroscopy as an adjunct. Dr. Folkman’s group in Boston reported the first series of balloon dilatations as an alternative to bougienage for the treatment of AS after EA repair, demonstrating 66% resolution of symptoms with acceptable morbidity in nine patients. Other groups followed, including Said et al who reported a series of 25 patients with AS who were all managed with balloon dilatations under fluoroscopic guidance. After a mean of four sessions, 100% of patients achieved resolution of the stricture, albeit with two patients suffering esophageal perforations. Ko et al reported similar success using fluoroscopic balloon dilatation in 29 children, with three documented perforations. Over a 10-year period, Antoniou et al managed 59 patients using endoscopic balloon dilatation for the treatment of AS, with 80% of patients achieving a favorable outcome. Five patients required salvage (four had surgery and one was treated with a stent), and no perforations were reported. The maximal balloon inflation pressure used is either not reported or highly variable, from manual injection without measurement to 10 atm with the use of specially designed inflation systems (Table 4). A previous report has identified that esophageal rupture would occur at 280 pounds per square inch (19 atm), with a decreased margin of safety in a fibrotic stricture and presumably in younger children. Duration of inflation is also variable, most authors using 1 minute, then deflating and reinflating up to three times in the same session, and progressing by a maximum of two balloon sizes (2 to 3 mm total) at a time.

Some groups compared the two techniques (bougienage and balloon), and concluded that balloon reduced the number of dilatations required, increased success rate and decreased complications, however, the difference in complication rates were not statistically significant. On the contrary, others have reported equally good results with Savary-Gilliard bougies and balloon dilatation, although many of these reports are comprised primarily of patients with caustic injuries. Comparison between series is difficult, given the variability in the definition of stricture and successful dilatation and in the reporting of complications (per patient or per procedure). Finally, a recent review concluded that there were no significant differences between Savary bougies and balloon dilators for benign esophageal strictures in adults, but bougies were more cost effective since they were reusable.

**Initiation and Frequency of Dilatations**

The scheduling and underlying philosophy of esophageal dilatation has been investigated. Some European centers, after advocating for routine postoperative dilatation/calibration, compared routine with selective dilatation, demonstrating less procedures and comparable rates of dysphagia or other complications when dilatations are performed only on symptomatic patients. The timing of first dilatation is less controversial, with most publications waiting at least 3 weeks after repair due to the increased risk of esophageal perforation. Finally, there is insufficient evidence to support the ideal interval between dilatation sessions, with the published range between weekly and monthly, most using a shorter interval initially (every 2 weeks) and then spacing it out once

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### Table 4 Inflation pressure, success rate, and complications in selected series using balloon dilatation

<table>
<thead>
<tr>
<th>Study, year</th>
<th>N (total)</th>
<th>ATM</th>
<th>Success (%)</th>
<th>Perforation (%)</th>
<th>Surgery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lang et al 2001b55</td>
<td>22 (22)</td>
<td>1.5–6</td>
<td>100</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Lan et al 2003b79</td>
<td>63 (77)</td>
<td>10</td>
<td>97</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Said et al 2003b13</td>
<td>25 (25)</td>
<td>3</td>
<td>100</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Ko et al 2006b88</td>
<td>29 (29)</td>
<td>Manual</td>
<td>93</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Alshammari et al 2011b60</td>
<td>24 (49)</td>
<td>6</td>
<td>92b</td>
<td>8b</td>
<td>8b</td>
</tr>
</tbody>
</table>

Abbreviations: ATM, pressure (atmospheres); N, number of patients with esophageal atresia and total number treated in report.

aSuccess rate defined in various ways.
bSpecifically for esophageal atresia patients.
the area is not restricting at the next session (Table 5).

In summary, esophageal dilatation remains the mainstay of treatment for AS after EA repair. Current evidence appears to support the popularity of balloon dilatation over bougies, the latter remaining useful in certain circumstances and safe when used by experienced clinicians. The evidence also supports the investigation and treatment of strictures based on symptomatology as opposed to routine screening and dilatation.

Medical Adjuncts to Dilatation

Steroids
The use of steroid therapy as an adjunct to dilatation for esophageal stricture secondary to caustic ingestion in adults was described in 1967 by Knox et al, after several animal studies laid the groundwork for its use. It has now become a standard treatment modality for the treatment of corrosive esophageal stricture in adults. More recently, two randomized controlled trials have supported the use of steroid injection for the treatment of peptic strictures as well. Steroid injection generally results in a decreased need for further dilatation and/or an increased interval between dilatations. Holder et al reported steroid injection for pediatric esophageal strictures in 1969 and observed that longer strictures (> 1.5 cm) were more likely to fail triamcinolone treatment. Gandhi et al provided the first evidence of durable patency after dilatation and steroid injection after EA repair, describing 12 patients treated with a mean of four injections. All 12 achieved symptom-free status, with a mean follow-up of 6 years. The most recent report of steroid injection for the treatment of esophageal stricture dates from 1995 and includes a single patient with EA out of seven treated with triamcinolone; there are only scattered mentions of its use since then, even though other clinicians. The evidence also supports the investigation and treatment of strictures based on symptomatology as opposed to routine screening and dilatation.

Mitomycin C

Mitomycin C (MMC) is a natural antitumor antibiotic that decreases the production of fibroblasts and scar tissue. Its topical use was originally described in the treatment of bladder tumors, and it took many years before its potential in the use of aerodigestive disease was realized. In 2006, two patients were described with ASs after EA repair refractory to conventional dilatation that responded to MMC application. A recent comprehensive review identified 7 out of the 31 patients who had ASs after EA repair treated with topical MMC administration. Considerable variability in the dose (0.1–1.0 μg/mL), the application regimen (1–12 applications) and the route of administration were encountered (retrograde or antegrade, with or without a protective sheath). Importantly, the publication identified no reported complications, and 27 out of the 31 patients had good-excellent results albeit with a short follow-up. Fifty percent of the patients in the review by Berger et al derived from a single series by Rosseneu et al, which reported only a 50% success rate after 60-month follow-up. This raises the possibility that MMC and dilatation may not produce durable results, although further investigations are required to clarify this point. A recent randomized trial has further supported the short-term efficacy of MMC in the treatment of recalcitrant strictures. This article demonstrated a clear reduction in the number of dilatations, as well as a higher rate of symptom resolution, albeit in strictures secondary to caustic ingestion. No complications were reported. The largest series to date describes 28 patients (18 after EA); MMC was considered successful as it decreased the number of subsequent dilatations and improved symptoms in 75 to 80% of patients. The only concern with MMC raised so far was a comment about gastric metaplasia being present at the AS site in two of the six patients within a few years of using MMC.

In summary, while pharmacological adjuncts to dilatation have been popular for the treatment of AS, their evidence base

<table>
<thead>
<tr>
<th>Study, year</th>
<th>N (total)</th>
<th>Dilatation device</th>
<th>Interval between sessions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Said et al 2003</td>
<td>25 (25)</td>
<td>Balloon</td>
<td>1 week</td>
</tr>
<tr>
<td>Bittencourt et al 2006</td>
<td>54 (125)</td>
<td>Bougie</td>
<td>15 days</td>
</tr>
<tr>
<td>Koivusalo et al 2009</td>
<td>81 (81)</td>
<td>Balloon</td>
<td>1–3 weeks</td>
</tr>
<tr>
<td>Antoniou et al 2010</td>
<td>59 (59)</td>
<td>Balloon</td>
<td>15 days</td>
</tr>
</tbody>
</table>

Table 5 Summary of recent literature evaluating the interval between dilatation sessions for the treatment of anastomotic stricture after esophageal atresia repair

Abbreviation: N, number of patients with esophageal atresia and total number treated in report.
remains relatively weak. Steroid injection has been established for a greater period of time, but both steroid injection and topical MMC application appear reasonable first-line adjuncts once dilatation has been deemed a failure.

Procedural Adjuncts to Dilatation

Cauterization

The use of endoscopic electrocautery in the treatment of esophageal stenosis was first reported by Brandimarte and Tursi in 2002, who described six adults that were safely and successfully treated. A randomized trial in adult ASs demonstrated equivalency with bougienage. Okada et al reported three cases of AS after EA repair that were successfully treated, although further details of the technique were not available in their publication. At this time, there is insufficient evidence to endorse endoscopic cautery as a conventional treatment modality for AS after EA.

Stenting

The use of esophageal stenting has a long history in the prevention of stricture formation after caustic ingestion in adults and children, and has become a mainstay of care for obstructive esophageal cancer not amenable to resection. Its value in the treatment of severe stricture disease has greatly increased the esophageal salvage rate; an Italian group has suggested that replacement only be considered after failure of stenting. In 2003, Broto et al reported 10 cases of pediatric esophageal stenosis that were successfully managed with a siliconated polypropylene stent, of which one patient had AS after EA repair. Covered retrievable expandable stents have also been reported for caustic strictures, although migration has been appreciated. A series of seven patients was recently reported, six of whom had a successful outcome after treatment with a tracheobronchial covered stent. Five of these patients had refractory AS after EA repair. Additional stent material has included biodegradable models (The SX-Ella Esophageal Degradable BD Stent; ELLA-CS, Hradec Kralove, Czech Republic), as well as urologic double J stents and more recently a custom dynamic stent. The custom dynamic stent is fashioned from a nasogastric tube covered with silicone drainage tubing until the desired thickness is achieved. In total, 79 patients have been treated with this stent over 12 years, 21 of whom were AS after EA repair. Indication for stent placement was failure to resolve after > 5 dilatations. This group reported an 89% overall success rate, 81% in patients with AS secondary to EA.

Several complications have been reported with the use of esophageal stenting in the pediatric population as a whole. Gagging after insertion is common but typically self-limited. Stent displacement occurs in approximately 15% of insertions, and usually results in displacement distal to the site of stricture. Migration of the stent into the stomach has also been rarely observed. More significantly, stent erosion has been reported as a cause of arterioesophageal fistulae. Thus, while esophageal stenting may obviate the need for an operative intervention for recalcitrant AS, it is not without risk. Cross-sectional imaging appears warranted to evaluate the proximity of great vessels (with or without possible aberrancy) and to minimize the risk of catastrophic esxanguination.

Surgical Resection

Although AS after EA repair continues to complicate the postoperative course of approximately one-third of all survivors, the number of reported patients who require resection of the stricture is remarkably small. Table 6 highlights the number of patients that progress to operative stricture resection. Most patients treated with a second end-to-end anastomosis require postoperative dilatation again, and no patient has been reported that has failed stricture revision and gone on to require a second operative revision, although this is not always easy to tease out from large series of complicated patients. Strictureplasty has been described for severe esophageal stenosis secondary to caustic ingestion, but has not been applied to patients after EA repair. Patch repair using a pedicled colonic graft has also been described. In a series of 15 patients reported by Othersen et al, two had developed AS after EA repair. Several significant complications were noted in the series (pseudodiverticulum formation, anastomotic leak, recurrent stricture), and this operation has not been widely adopted as a result. Interposition graft placement for the treatment of AS (as opposed to the treatment of long-gap EA) is exceedingly rare in the recent literature. Koivusalo et al describe one patient with AS treated with a pedicled jejunal flap. A recent review of jejunal interposition by Bax describes 19 patients undergoing the procedure—only one of which was performed to bridge a long stenosis. A recent large review (n = 97) of colonic replacement failed to identify any patients with an indication of refractory AS. Similarly, a multi-institutional review of gastric transposition failed to identify a single patient (n = 26) with the indication of stricture/stenosis. A larger series published by Spitz et al in 1987 identified 1 of the 32 EA

<table>
<thead>
<tr>
<th>Study, year</th>
<th>N (no. of type C)</th>
<th>Stricture N (%)</th>
<th>Stricture resection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louhimo and Lindahl 1983</td>
<td>273 (N/A)</td>
<td>Not reported</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Okada et al 1997</td>
<td>125 (N/A)</td>
<td>61 (49)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Mortell and Azizkhan 2009</td>
<td>86 (70)</td>
<td>27 (31)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Koivusalo et al 2013</td>
<td>130 (110)</td>
<td>102 (78)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: N, number of survivors; N/A, not available.
patients who required a gastric interposition because of an extensive stricture. Thus, interposition grafting appears to play an extremely limited role in the management of AS after EA. In the event that esophageal replacement is required, the choice of graft should be determined by individual and institutional expertise.

**Conclusion**

Although there has been a little improvement in the rate of the development of AS after EA repair, the armamentarium available for clinicians to treat this complication has continued to expand. Based on the available literature, the following algorithm is proposed by the authors (Fig. 1). Patients presenting with dysphagia, feeding intolerance, or respiratory symptoms should be promptly investigated with a contrast esophagram. AS remains the most likely complication to explain the aforementioned symptomatology; however, uncontrolled reflux without stricture, recurrent or missed TEF, vocal cord paralysis, laryngeal cleft, tracheomalacia, or other rarer sequelae or associated malformation must be considered. Once AS is confirmed, endoscopic dilatation remains the primary treatment modality, with adjuncts reserved for patients who fail treatment after three to five sessions. The use of steroids or MMC has clearly reduced the need for operative stricture resection; at this time, both adjuncts appear equivalent in terms of efficacy and morbidity. Esophageal stenting remains an exciting new option in the treatment of AS that reduces the repeated anesthetic requirements associated with multiple dilatations. Obviating an invasive, reoperative surgical procedure must be tempered by the availability of local expertise and the risk of significant complications. Stricture resection also remains an important option in good operative candidates, with end-to-end anastomosis the reconstructive option of choice.

Most of the treatments available to prevent and treat stricture formation at the site of esophageal anastomosis remain poorly investigated with little evidence to inform their use. Complication rates have been inadequately characterized to date, and the outcome of unpublished patients continues to cloud the true efficacy and morbidity of dilatation, adjunctive therapies, and stenting. Comparative studies of competing treatment strategies are sorely lacking. Additional prospective evidence is required to continue to optimize strategies to prevent, investigate, and effectively manage patients with AS after EA.

**Conflict of Interest**

None

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