JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Endoscopic Management of Subglottic Stenosis

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IMPORTANCE Optimal management of subglottic stenosis has not been established. Endoscopic techniques include balloon dilation, radial incisions with carbon dioxide laser or cold knife, and combinations of techniques. Adjunctive measures include mitomycin application and glucocorticoid injection.

OBJECTIVE To determine whether surgical technique or adjunctive measures are associated with duration between surgical procedures.

DESIGN, SETTING, AND PARTICIPANTS Adult patients with subglottic stenosis treated endoscopically between 1995-2015 at a quaternary academic medical center were identified. Patients with isolated subglottic (cricotracheal) stenosis 18 years and older were included. Patients with prior open surgical procedures, prior laryngeal surgical procedures, glottic stenosis, or vocal fold paralysis were excluded.

INTERVENTIONS Patients underwent endoscopic procedures including laser radial incisions, balloon dilation, or both, with some patients receiving topical mitomycin, glucocorticoid injection, or both.

MAIN OUTCOMES AND MEASURES Time interval between endoscopic treatments.

RESULTS A total of 101 patients (mean [SD] age, 52.3 [15.9] years; 77.2% female) were included in the analysis, with etiologies including idiopathic (47 [46.5%]), intubation (31 [30.7%]), granulomatosis with polyangiitis (9 [8.9%]), and other autoimmune diseases (6 [5.9%]). Among the 219 operations, both laser and balloon dilation were used in 117 (53.4%), while balloon dilation alone was used in 96 (43.8%) and laser alone in 6 (2.7%). Mitomycin application and steroid injection were used in 144 (65.8%) and 93 (42.5%) cases, respectively. Mitomycin application was associated with improvement in the mean interval to next procedure from 317 to 474 days (absolute difference, 157 days; 95% CI, 15-299 days). Advanced grade of stenosis, dilation technique, and steroid injection did not significantly alter the surgical intervals.

CONCLUSIONS AND RELEVANCE Endoscopic surgery for subglottic stenosis is a critical aspect of patient management. Neither surgical technique nor grade of stenosis was seen to alter the surgical intervals. Mitomycin application was associated with an extended time interval between endoscopic treatments.

JAMA Otolaryngol Head Neck Surg. 2017;143(5):500-505. doi:10.1001/jamaoto.2016.4131
Published online February 23, 2017.

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Subglottic stenosis is a rare, progressive inflammatory disorder resulting in fibrotic narrowing at the level of the subglottis.[1-3] This complex disorder causes progressive dyspnea and may present emergently with severe respiratory distress. Surgical approaches are categorized as endoscopic, open neck surgery, and tracheotomy, and the optimal management has not been established.[4-8] Endoscopic techniques include balloon dilation, rigid dilation, radial incisions with carbon dioxide (CO_2) laser or cold knife, endoscopic scar excision without dilation, or, rarely, endoscopic stent placement. These approaches aim to provide long-term airway patency without dyspnea symptoms; however, they entail distinctive risk/benefit profiles. In particular, whereas endoscopic techniques are less invasive and better tolerated, patients are more likely to experience recurrent symptoms and multiple interventions as compared with definitive open surgical intervention.[9]

Adjunctive measures during endoscopic surgery include topical mitomycin application and glucocorticoid injection.[10-12] Mitomycin, an antibiotic from *Streptomyces caespitosus*, has antifibrinogenic and antineoplastic activity that has been shown to block fibroblast proliferation and thereby reduce scar formation.[13] Although prior studies have generally favored use of mitomycin, debate continues over its proper role and safety profile.[14] Fibroblast migration occurs weeks following intraoperative application, and the pharmacokinetics of the medication are unknown. Intralesional glucocorticoid injection has also been reported in several small case series with encouraging outcomes, as previously reviewed.[15]

We retrospectively reviewed our experience with endoscopic management of subglottic stenosis with the aim of evaluating optimal surgical techniques and adjunctive medical treatments with the measured treatment outcome of improving the interval between operations.

Key Points

Question Are surgical techniques or adjunctive intraoperative medical therapies associated with the length of time between endoscopic surgical procedures in treatment of subglottic stenosis?

Findings In this retrospective analysis of 101 patients, we did not identify a difference in duration between operations according to surgical technique or use of glucocorticoid injection. Application of topical mitomycin was associated with an increased duration between operations.

Meaning Mitomycin may be a useful adjunctive therapy for patients with subglottic stenosis requiring endoscopic surgery, worthy of further study in prospective trials.

Methods

Institutional review board approval from the University of California Los Angeles was received for this study. A waiver of consent was granted from the medical branch of the institutional review board due to the retrospective nature of the study.

Adult patients, 18 years of age or older, with subglottic stenosis treated with endoscopic techniques between 1995 and 2015 at a quaternary academic medical center were identified on the basis of *International Classification of Diseases, Ninth Revision,* diagnosis codes. Patients with prior open surgical procedures, prior laryngeal surgical procedures, glottic stenosis, or vocal fold paralysis were excluded. To focus our analysis on subglottic stenosis, only patients with documented isolated subglottic (cricotracheal) stenosis were included; patients with mid/distal-tracheal stenosis or multilevel stenosis were excluded. Measured outcome was mean days to the next surgical procedure. Patient records were reviewed for clinical features, dates of operations, procedures performed, and adjunctive treatments. Cases with indeterminate stenosis grade were excluded from analyses requiring stratification by grade.

In the present institution, surgical techniques are chosen on the basis of surgeon preference and individual patient factors. In patients with mild stenosis or excellent laryngoscopic view, endotracheal intubation is generally performed with a 4.0 microdirect laryngoscopy endotracheal tube. In patients with severe stenosis or poor laryngoscopic view, the laryngeal mask anesthesia technique can be used without initial intubation with a technique as previously described.[16,17] Suspension microlaryngoscopy is achieved, and lidocaine hydrochloride, 4%, is applied topically to reduce laryngospasm. Airway examination is carried out with a Hopkins 0° telescope. When used, CO_2 laser radial incisions are performed under intermittent apnea conditions. Line-of-sight CO_2 laser (Lumenis) controlled with the operating microscope's micromanipulator can be used with good visualization; however, a flexible CO_2 laser fiber (OmniGuide) with extended length hand-pieces can be used in cases with challenging exposure and in all cases performed via laryngeal mask anesthesia. Typically, 4 to 6 radial incisions are performed. Balloon dilations are also performed under intermittent apnea with the controlled radial expansion pulmonary balloon dilator (Boston Scientific). Dilation is performed at least twice, but many times is performed a third time for 30 seconds. After the appropriate lumen diameter is achieved, adjunctive medications can be administered. Mitomycin at a dose of 0.4 mg/mL is applied topically with 2 lightly soaked cotton pledgets at the site of stenosis for 2 to 4 minutes, with replacement of the endotracheal tube following initial positioning of the pledget. For patients receiving glucocorticoid injection, triamcinolone acetonide, 40 mg/mL, is injected submucosally in a circumferential pattern using a 25-gauge butterfly needle controlled with microlaryngoscopy alligator forceps. Patients initially treated with laryngeal mask anesthesia technique are transitioned to microlaryngoscopy suspension to allow for medication administration to be performed in an identical manner.

Descriptive statistics were used to evaluate the study group's demographic and clinical characteristics. A 1-way analysis of variance test was used to compare intervals to subsequent operation. The effect size[18] was estimated using the η^2 test. An effect size of 0.02 or less was considered small; more than 0.02 to 0.13, medium; and more than 0.13 to 0.26, large[19]; the 90% confidence intervals are reported because the η^2 test is inherently 1 sided.[20] Statistical analyses were performed using SPSS, version 22 (IBM).

Table 1. Clinical Characteristics of Patients

Characteristic	No. (%) (N = 101)
Etiology	
Idiopathic	47 (46.5)
Intubation	31 (30.7)
Granulomatosis with polyangiitis	9 (8.9)
Other autoimmune	6 (5.9)
Radiation	5 (5.0)
Benign neoplasm	2 (2.0)
Other	1 (1.0)
Age, mean (SD), y	52.3 (15.9)
ASA score	
1	1 (1.0)
2	39 (38.6)
3	53 (52.5)
4	3 (3.0)
Unknown	5 (5.0)
Diabetes mellitus	
No	76 (75.2)
Yes	24 (23.8)
Unknown	1 (1.0)
Smoking	
No	80 (79.2)
Yes	18 (17.8)
Unknown	3 (3.0)
Tracheostomy ever performed	36 (35.6)
Stenosis grade, initial	
1	11 (10.9)
2	16 (15.8)
3	24 (23.8)
Unknown	50 (49.5)
Operations	219 (100)
Balloon dilation	96 (43.8)
Laser and balloon dilation	117 (53.4)
Laser	6 (2.7)
Mitomycin used	144 (65.8)
Glucocorticoid used	93 (42.5)

Abbreviation: ASA, American Society of Anesthesiology physical status score.

Results

There were 207 patients undergoing endoscopic balloon dilation and/or laser surgery for airway stenosis during the years 1995 through 2015. We excluded patients with carcinoma (n = 20), glottic stenosis (n = 25), tracheal stenosis (n = 53), and insufficient follow-up data (n = 8). The remaining 101 patients with subglottic stenosis were included in the present analysis. The stenosis etiologies included idiopathic (47 [46.5%]), intubation (31 [30.7%]), granulomatosis with polyangiitis (9 [8.9%]), and other autoimmune diseases (6 [5.9%]) (**Table 1**). The mean (SD) age at presentation was 52.3 (15.9) years. A minority of patients had a history of diabetes mellitus (24 [23.8%]) or prior smoking (18 [17.8%]). The American Society of Anesthesiologists physical status classification score was 1 in 1 (1.0%), 2 in 39 (38.6%), 3 in 53 (52.5%), and 4 in 3 (3.0%). Tracheotomy had been performed prior to referral in 35 patients (34.7%). One patient required tracheotomy placement for pulmonary toilet during follow-up. Stenosis severity was classified with the Cotton-Myer grading scale. The stenosis grade was noted to be grade 1 in 11 (10.9%; <50% stenosis), grade 2 in 16 (15.8%; 50%-70% stenosis), and grade 3 in 24 (23.8%; 71%-99% stenosis). No patients with grade 4 stenosis were treated endoscopically.

Table 2. Use of Adjunctive Medical Measures According to Selected Surgical Technique

Surgical Technique	No. (%) Mitomycin No	Mitomycin Yes	Glucocorticoid No	Glucocorticoid Yes	Both Mitomycin and Glucocorticoid Concomitantly Yes
Balloon dilation	51 (68.0)	45 (31.3)	86 (68.3)	10 (10.8)	4 (4.2)
Laser and balloon dilation	19 (25.3)	98 (68.1)	35 (27.8)	82 (88.2)	72 (61.5)
Laser	5 (6.7)	1 (0.7)	5 (4.0)	1 (1.1)	0
Total	75 (100)	144 (100)	126 (100)	93 (100)	

The 101 patients underwent 219 endoscopic operations during follow-up. The mean duration of follow-up was 2.8 years (range, 6 months to 11.75 years). Among the 219 operations, both laser and balloon dilation were used in 117 (53.4%), while balloon dilation alone was used in 96 (43.8%) and laser alone in 6 (2.7%). Mitomycin application and steroid injection were used in 144 (65.8%) and 93 (42.5%) cases, respectively. Mitomycin was more frequently applied in cases with both laser and balloon dilation (98 [68.1%]) than in those with balloon dilation alone (45 [31.3%]; absolute difference, 36.8%; 95% CI, 24.3%-49.3%) (**Table 2**). Glucocorticoids were also more frequently used for cases with both laser and balloon dilation (82 [88.2%]) than in those with balloon dilation alone (10 [10.8%]; absolute difference, 77.4%; 95% CI, 68.9%-85.9%). Both medications were concomitantly administered more frequently for cases with both laser and balloon dilation (72 [61.5%]) than in those with balloon dilation alone (4 [4.2%]; absolute difference, 57.3%; 95% CI, 47.6%-67.0%). The mean (SD) interval to the subsequent operation among all patients was 420 (510) days (**Table 3**).

Of the patients who received mitomycin application, the mean (SD) interval to the subsequent operation was 474 (570) days, while those who did not receive mitomycin had a mean (SD) interval of only 317 (351) days (absolute difference, 157 days; 95% CI, 15 to 299 days; $\eta^2 = 0.021$; 90% CI, 0.001 to 0.063) (Table 3). The difference of 157 days is clinically significant, and the η^2 value of 0.021 suggests that the effect size is small. However, the upper bound of the confidence interval of 299 days and an η^2 value of 0.063 does not rule out a very strong clinical effect with a medium η^2-defined effect, while the lower bound value of 15 days and η^2 value of 0.001 suggests that the observed effect may not be much different from 0. There was no significant difference among the interval to subsequent operation for patients receiving mitomycin at the first operation or those receiving mitomycin during subsequent operations.

There was no significant difference in time interval according to receipt of steroid injection (η^2 = 0; 90% CI, 0-0.007) (Table 3). The responses to mitomycin application and steroid injection were also analyzed according to the etiology of stenosis; however, the results did not demonstrate statistical significance (data not shown). Patients with higher-grade stenosis tended to have a shorter interval to the next operation, with patients with grade 3 stenosis returning in a mean (SD) of 336 (277) days compared with patients with grade 1 stenosis returning in 461 (398) days (absolute difference, 125 days; 95% CI, −44 to 294 days) with the effect size η^2 of 0.024 (90% CI, 0 to 0.080) (**Table 4**). The difference of 125 days is clinically significant, and the η^2 value of 0.024 suggests that the effect is likely small. However, the upper bound of the CI of 294 days and an η^2 value of 0.080 does not rule out a very strong clinical effect and medium η^2-defined effect, while the lower bound value of −44 days (ie, the data are compatible with a 44-day interval difference favoring patients with grade 3 stenosis) suggests no benefit. Again, the wide confidence interval prevents any meaningful conclusion. Furthermore, there was no difference in the interval to subsequent operation according to the use of balloon dilation compared with laser radial incisions with balloon dilation or laser surgery alone (η^2 = 0.010; 90% CI, 0 to 0.037) (Table 4).

Table 3. Interval Until Subsequent Endoscopic Procedure by Adjunctive Medical Measure

Medicine	No.	Interval, Mean (SD), d	η^2 (90% CI)[a]
Mitomycin			
No	75	317 (351)	0.021 (0.001-0.063)
Yes	144	474 (570)	
During first operation	59	503 (589)	0.002 (0-0.030)
During subsequent operation	85	454 (558)	
Glucocorticoid			
No	126	424 (496)	0 (0-0.007)
Yes	93	415 (530)	
All surgical procedures	219	420 (510)	

[a] In the interpretation of η^2, effect size of 0.02 or less was considered small; more than 0.02 to 0.13, medium; and more than 0.13 to 0.26, large.

Table 4. Interval Until Subsequent Endoscopic Procedure by Cotton-Myer Grade of Stenosis and Surgical Technique

Characteristic	No.	Interval, Mean (SD), d	η^2 (90% CI)[a]
Grade of stenosis			
1	31	461 (398)	0.024 (0-0.080)
2	40	357 (325)	
3	34	336 (277)	
All patients	105	380 (335)	
Balloon dilation	96	463 (530)	0.010 (0-0.037)
Laser and balloon dilation	117	398 (502)	
Laser	6	179 (193)	
All surgical procedures	219	420 (510)	

[a] In the interpretation of η^2, effect size of 0.02 or less was considered small; more than 0.02 to 0.13, medium; and more than 0.13 to 0.26, large.

Discussion

Within the present study, we analyzed a large single-center cohort of patients with isolated subglottic stenosis. Based on the interpretation of η^2, the difference in the mean interval to subsequent operation among patients receiving mitomycin was associated with a small, clinically significant increase when compared with patients not receiving mitomycin; however, the wide confidence interval reflects the imprecision in this estimate, undermining definitive conclusions. There was no association noted for use of glucocorticoid, nor any difference based on the grade of stenosis or surgical technique. Hseu et al[21] examined 92 patients undergoing 247 endoscopic procedures and also noted that there was no difference in the interval to the next procedure between varying surgical techniques. In this study, no benefit to application of mitomycin was noted. The authors had a similar case distribution including granulomatosis with polyangiitis, intubation, and idiopathic etiologies. However, patients in this study could be included if the stenosis extended to the glottis or trachea, which may confound the applicability of these results to patients with stenosis limited to the subglottis. Furthermore, patients received glucocorticoid injection at the outset of the procedure before incisions or dilation, and then mitomycin application was performed as the final operative step; it is possible that steroid injection prior to mitomycin application prevents the mitomycin from reaching the appropriate tissues or desired cellular concentration. Hseu et al[21] did find that there was a plateau at 2.5 years whereby patients who did not require a procedure at 2.5 years after the prior operation were unlikely to need further surgery.

The outcome of subglottic stenosis treatment may also vary by etiology of stenosis. Gelbard et al[3] grouped patients with laryngotracheal stenosis by etiology, and those with iatrogenic and autoimmune etiologies were significantly more likely to remain tracheotomy dependent than those with traumatic or idiopathic disease. The patients with idiopathic disease were noted to have less severe degree of stenosis relative to autoimmune and iatrogenic groups. Endoscopic balloon dilation was carried out in 84% of cases. Patients with iatrogenic (intubation-related) stenosis were significantly more likely to have multiple comorbidities, including diabetes (39%), myocardial infarction (28%), congestive heart failure (13%), and cerebrovascular accident (7%). Patients with iatrogenic stenosis were also significantly more likely to have concomitant tracheomalacia (37% vs 8%).

Our analysis did not identify a difference in the interval to subsequent operation according to surgical technique. We did note that patients undergoing laser radial incisions and balloon dilation did have increased use of adjunctive mitomycin application and intralesional glucocorticoid injection relative to patients undergoing balloon dilation alone. The different use of techniques was related to both surgeon preference and individual patient factors. Familiarity with the variety of presentations and stenoses allows the surgeon to elect an appropriate technique for each patient.

There are encouraging results from previous studies of mitomycin application in humans; however, alternative medical therapies to prevent recurrent scarring are now under preclinical investigation. Gu et al[22] encapsulated fluorouracil within lipid vesicles (ethosomes) and injected the medication via the cricothyroid membrane in a rabbit model of laryngotracheal stenosis. The authors found that stenosis was reduced following 5 injections over 20 days, that the ethosome delivery vehicle was superior to fluorouracil alone, that smaller-sized ethosomes had a superior effect, and that there were no systemic adverse effects. Mizokami et al[23] explored the preventative effects of systemically delivered tacrolimus in a rat model of laryngotracheal stenosis. They found that low-dose systemic tacrolimus delivered for 5 consecutive days, starting 1 day before the induced injury, resulted in reduced stenosis, as well as reduced levels of cell proliferation markers. Namba et al[24] treated human fibroblasts cultured from patients with laryngotracheal stenosis with rapamycin in vitro, and there was an antifibroblast effect observed in most of the cell lines. These new therapies are important because of safety concerns regarding use of mitomycin. Patients treated with high-dose (10 mg/mL) and routine-dose (0.4 mg/mL) mitomycin were reported to have obstructive fibrinous debris at the application site,[25] and 1 patient developed inflammation and possible fungal infection ultimately resulting in the need for tracheotomy.[26]

Limitations

This study has several limitations. We performed a retrospective observational study, which is susceptible to biases associated with nonrandom assignment of intervention. A prospective, randomized clinical study would provide more reliable evidence. Using the data available, motivations for variations in practice among surgeons could not be assessed. It is possible that these differences may have resulted in selection bias, and there may be unmeasured confounding factors related to intraoperative and postoperative management. While our mean follow-up time was 2.8 years, some patients may have been lost to follow-up, and it is possible that some may have required subsequent operations outside our center that could not be factored within our analysis. The mitomycin dose achieved within the subglottic tissue was not measured, and differences in mitomycin preparation or application may have potentially resulted in different cellular doses, limiting the clinical application of our findings. Due to limitations in sample size, we could not perform multivariate analysis on the time interval incorporating all patient and treatment factors; however, these results will be available for use in future meta-analysis to be performed in studying this rare disease.

Within the present study, those who received glucocorticoids had this adjunctive treatment performed intraoperatively. There are recent reports of intralesional glucocorticoid injection performed as an awake, office-based procedure as a maintenance therapy to achieve persistent luminal patency in the postoperative setting.[27] Postoperative medical management may also prolong the surgical interval, with patients taking antireflux medications with or without inhaled corticosteroids or trimethoprim-sulfamethoxazole demonstrating a nonsignificant reduction in disease recurrence rate with a relative risk of 0.52.[28] These are promising avenues of research that have not been addressed by the present study. Further controlled studies are important to clarify the dose, timing, and duration of therapy needed to optimize patient outcomes.

Conclusions

Subglottic stenosis may be effectively managed with endoscopic surgical techniques, yet in many cases it requires multiple operations. In our study, neither surgical technique nor grade of stenosis was seen to affect the interval between endoscopic treatments. Mitomycin application was associated with an increased time interval between endoscopic treatments, although imprecision in this estimate of the true effect from our data limits our making definitive conclusions about the impact of mitomycin treatment. The data presented should be used for future meta-analyses and prospective trials to define the optimal treatment strategy for subglottic stenosis.

ARTICLE INFORMATION

Accepted for Publication: January 10, 2017.

Published Online: February 23, 2017. doi:10.1001/jamaoto.2016.4131

Author Contributions: Drs Feinstein and Mendelsohn had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Feinstein, Goel, Chhetri, Berke, Mendelsohn.
Acquisition, analysis, or interpretation of data: Feinstein, Goel, Raghavan, Long, Chhetri, Mendelsohn.
Drafting of the manuscript: Feinstein, Goel, Chhetri, Mendelsohn.
Critical revision of the manuscript for important intellectual content: Feinstein, Raghavan, Long, Chhetri, Berke, Mendelsohn.
Statistical analysis: Feinstein, Goel, Raghavan.
Administrative, technical, or material support: Berke, Mendelsohn.
Supervision: Long, Chhetri, Berke, Mendelsohn.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Meeting Presentation: This article was presented at the annual meeting of the American Laryngological Association at the Combined Otolaryngology Spring Meetings; May 19, 2016; Chicago, Illinois.

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Invited Commentary

Expanding Perspectives in Airway Stenosis

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As surgeons, we take pride in our craft and, therefore, are biased toward our preferred techniques. Similarly, our clinical research is often guided by this motivation, steering us to share the outcomes of our favored techniques. This natural bias is evident in the literature. For example, at the time of publication, a PubMed search "Laryngostenosis/surgery[Mesh]" (which includes subglottic stenosis) revealed 1294 articles on surgical approaches to upper airway stenosis. In contrast, the search "Laryngostenosis/drug therapy[Mesh]" (which includes use of mitomycin and other adjuvant therapies) resulted in only 80 articles. The article by Feinstein et al[1] in this issue of *JAMA Otolaryngology–Head & Neck Surgery* joins several others to reinforce the concept that perhaps it is not the surgical finesse or latest technology used in endoscopic procedures to modify the structural airway anatomy that matters, but rather how we can manipulate the immunologic response and wound healing process afterward.[2-4] However, this is in contrast to more technically difficult open airway reconstruction, clearly demonstrating improved outcomes and higher "cure rate" in high-volume centers.[2]

The airway narrowing of subglottic stenosis can be managed by a variety of techniques, including rigid bronchoscopy, carbon dioxide laser, balloon dilation, cryotherapy, cold excision, microdebrider, open laryngotracheoplasty, and finally open cricotracheal resection. As the authors point out in the discussion of this article,[1] recent interest has been generated regarding adjuvant modulation of fibrosis with study of agents such as fluorouracil, tacrolimus, and sirolimus. Based on this and other studies, there does appear to be some beneficial effect of mitomycin treatment.[5,6] However, the tissue concentration and kinetics of topical drug delivery remains unknown. Furthermore, there are risks of using mitomycin, even at a standard concentration of 0.4 mg/mL. In patients without an alternate airway, such as a tracheotomy, there is a small but real risk of airway obstruction and death.[7] Mitomycin treatment appears to increase surgical intervals by a mean of 5 months in this heterogeneous population, with mean intervals increased from 11 to 16 months. While this is certainly a better outcome demonstrating statistical significance, the clinical significance to the patient may not be as tangible. There is room for study of the optimal adjuvant use of mitomycin maximizing the therapeutic effect based on pharmacokinetics. In contrast to this study, another recent study showed a benefit of intralesional steroid injection in patients with idiopathic subglottic stenosis, suggesting that there may be an etiology-specific treatment for this specific subset of patients with subglottic stenosis that addresses a unique inflammatory phenotype.[8] Although Feinstein et al[1] did not find significantly different outcomes by etiology, a recent study by Gelbard et al[9] showed varying rates of tracheostomy dependence by etiology, a surrogate marker for severity of stenosis. Specifically, this large study showed significantly more patients in the