

Endoscopic Management of Subglottic Stenosis

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 Invited Commentary

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.

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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 (CO₂) 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.

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.

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.

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, CO₂ laser radial incisions are performed under intermittent apnea conditions. Line-of-sight CO₂ laser (Lumenis) controlled with the operating microscope's micromanipulator can be used with good visualization; however, a flexible CO₂ 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 size¹⁸ 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, large¹⁹; 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).

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.

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

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	
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.

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 ($\eta^2 = 0$; 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%

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

Surgical Technique	No. (%)				Both Mitomycin and Glucocorticoid Concomitantly
	Mitomycin		Glucocorticoid		
	No	Yes	No	Yes	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)	

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.

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 ($\eta^2 = 0.010$; 90% CI, 0 to 0.037) (Table 4).

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 al²¹ 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 al²¹ 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 al³ 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 al²² 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 al²³ 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 al²⁴ 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.

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REFERENCES

- Park SS, Streitz JM Jr, Rebeiz EE, Shapshay SM. Idiopathic subglottic stenosis. *Arch Otolaryngol Head Neck Surg.* 1995;121(8):894-897.
- Lorenz RR. Adult laryngotracheal stenosis: etiology and surgical management. *Curr Opin Otolaryngol Head Neck Surg.* 2003;11(6):467-472.
- Gelbard A, Francis DO, Sandulache VC, Simmons JC, Donovan DT, Ongkasuwan J. Causes and consequences of adult laryngotracheal stenosis. *Laryngoscope.* 2015;125(5):1137-1143.
- Lee KH, Rutter MJ. Role of balloon dilation in the management of adult idiopathic subglottic stenosis. *Ann Otol Rhinol Laryngol.* 2008;117(2):81-84.
- Monnier P, George M, Monod M-L, Lang F. The role of the CO₂ laser in the management of laryngotracheal stenosis: a survey of 100 cases. *Eur Arch Otorhinolaryngol.* 2005;262(8):602-608.
- Ashiku SK, Kuzucu A, Grillo HC, et al. Idiopathic laryngotracheal stenosis: effective definitive treatment with laryngotracheal resection. *J Thorac Cardiovasc Surg.* 2004;127(1):99-107.
- Roediger FC, Orloff LA, Courey MS. Adult subglottic stenosis: management with laser incisions and mitomycin-C. *Laryngoscope.* 2008;118(9):1542-1546.
- D'Andrilli A, Maurizi G, Andreotti C, et al. Long-term results of laryngotracheal resection for benign stenosis from a series of 109 consecutive patients. *Eur J Cardiothorac Surg.* 2016;50(1):105-109.
- Gelbard A, Donovan DT, Ongkasuwan J, et al. Disease homogeneity and treatment heterogeneity in idiopathic subglottic stenosis. *Laryngoscope.* 2016;126(6):1390-1396.
- Eliashar R, Eliachar I, Esclamado R, Gramlich T, Strome M. Can topical mitomycin prevent laryngotracheal stenosis? *Laryngoscope.* 1999;109(10):1594-1600.
- Rahbar R, Valdez TA, Shapshay SM. Preliminary results of intraoperative mitomycin-C in the treatment and prevention of glottic and subglottic stenosis. *J Voice.* 2000;14(2):282-286.
- Whited CW, Dailey SH. Is mitomycin C useful as an adjuvant therapy in endoscopic treatment of laryngotracheal stenosis? *Laryngoscope.* 2015;125(10):2243-2244.
- Veen EJD, Dikkers FG. Topical use of MMC in the upper aerodigestive tract: a review on the side effects. *Eur Arch Otorhinolaryngol.* 2010;267(3):327-334.
- Smith ME, Elstad M. Mitomycin C and the endoscopic treatment of laryngotracheal stenosis: are two applications better than one? *Laryngoscope.* 2009;119(2):272-283.
- Hirshoren N, Eliashar R. Wound-healing modulation in upper airway stenosis—myths and facts. *Head Neck.* 2009;31(1):111-126.
- Chhetri DK, Long JL. Airway management and CO₂ laser treatment of subglottic and tracheal stenosis using flexible bronchoscope and laryngeal mask anesthesia. *Oper Tech Otolaryngol Head Neck Surg.* 2011;22(2):131-134.
- Vorasubin N, Vira D, Jamal N, Chhetri DK. Airway management and endoscopic treatment of subglottic and tracheal stenosis: the laryngeal mask airway technique. *Ann Otol Rhinol Laryngol.* 2014;123(4):293-298.
- Piccirillo JF. Improving the quality of the reporting of research results. *JAMA Otolaryngol Head Neck Surg.* 2016;142(10):937-939.
- Bakeman R. Recommended effect size statistics for repeated measures designs. *Behav Res Methods.* 2005;37(3):379-384.
- Steiger JH. Beyond the F test: effect size confidence intervals and tests of close fit in the analysis of variance and contrast analysis. *Psychol Methods.* 2004;9(2):164-182.
- Hseu AF, Benninger MS, Haffey TM, Lorenz R. Subglottic stenosis: a ten-year review of treatment outcomes. *Laryngoscope.* 2014;124(3):736-741.
- Gu J, Mao X, Li C, Ao H, Yang X. A novel therapy for laryngotracheal stenosis: treatment with ethosomes containing 5-fluorouracil. *Ann Otol Rhinol Laryngol.* 2015;124(7):561-566.
- Mizokami D, Araki K, Tanaka N, et al. Tacrolimus prevents laryngotracheal stenosis in an acute-injury rat model. *Laryngoscope.* 2015;125(6):E210-E215.
- Namba DR, Ma G, Samad I, et al. Rapamycin inhibits human laryngotracheal stenosis-derived fibroblast proliferation, metabolism, and function in vitro. *Otolaryngol Head Neck Surg.* 2015;152(5):881-888.
- Hueman EM, Simpson CB. Airway complications from topical mitomycin C. *Otolaryngol Head Neck Surg.* 2005;133(6):831-835.
- Ubell ML, Ettema SL, Toohill RJ, Simpson CB, Merati AL. Mitomycin-C application in airway stenosis surgery: analysis of safety and costs. *Otolaryngol Head Neck Surg.* 2006;134(3):403-406.
- Franco RA, Paddle P, Husain I, Reder LS. Serial intra-lesional steroid injections as a treatment for idiopathic subglottic stenosis. Paper presented at: American Laryngological Association 136th Annual Meeting; April 23, 2015; Boston, MA.
- Maldonado F, Loissele A, Depew ZS, et al. Idiopathic subglottic stenosis: an evolving therapeutic algorithm. *Laryngoscope.* 2014;124(2):498-503.