Laryngoscope Investigative Otolaryngology

Office-Based Corticosteroid Injections as Adjuvant Therapy for Subglottic Stenosis

Debbie R. Pan, BA; David E. Rosow, MD

Objective: Subglottic stenosis (SGS) is a serious, potentially life-threatening disorder that is difficult to treat due to significant recurrence rates. While conventional treatment of SGS relies heavily on serial endoscopic dilation procedures, this study aims to characterize the efficacy of incorporating subglottic corticosteroid injections in increasing surgery-free intervals (SFIs) for a cohort of patients at a university-based medical system.

Study Design: Retrospective chart review.

Methods: All SGS patients who underwent endoscopic dilation and at least one adjuvant office-based serial intralesional steroid injection (SILSI) were reviewed. Patients were excluded if they had synchronous airway lesions or stenosis outside of the subglottis. Charts were reviewed for demographic and treatment-specific data. The SFI was calculated for patients both prior to the initiation of SILSI and after. Groups were compared via Mann–Whitney *U* test, with $P < .05$ as the threshold for significance.

Results: Thirteen patients met criteria, with mean age 50.1 ± 14.1 years and 7:6 female to male ratio. Eight of the thirteen (61.5%) had intubation-related stenosis, while 4/13 were idiopathic and 1/13 was due to Wegener's granulomatosis. Mean follow-up was 20.4 months. Patients underwent an average of 4.2 ± 2.2 postoperative injections, beginning 45.9 ± 19.0 days after surgery. The mean SFI prior to initiating SILSI was 288.6 ± 362.0 days; while after receiving SILSI, the mean interval was significantly longer (545.5 ± 152.7 days, $P = .0041$).

Conclusions: We demonstrate that office-based corticosteroid injection for SGS was associated with a statistically significant improvement in the SFI and is a promising adjuvant approach. Future prospective studies should evaluate if the efficacy is reproducible on a large scale and if SILSI can and/or should be incorporated into the standard management paradigm for SGS treatment.

Key Words: Subglottic stenosis, corticosteroid injections, office surgery, outcomes.

Level of Evidence: 4

INTRODUCTION

Subglottic stenosis (SGS) is a rare, but potentially life-threatening disorder that is characterized by the narrowing of the airway below the vocal folds, causing dyspnea with potentially devastating consequences for patients. Other common symptomatic manifestations can include dysphonia, stridor, coughing, and fatigue.[1,2] SGS can be idiopathic in nature or result from iatrogenic causes, including prolonged intubation, tracheostomy, or other tracheal surgeries, autoimmune disorders such as Wegener's granulomatosis, prior caustic exposure, trauma, or neoplasm.[3] Regardless of etiology, SGS is usually treated surgically, either with endoscopic dilation or open airway reconstruction. Patients typically prefer the less-invasive endoscopic dilations, but these often need to be repeated due to high rates of restenosis, likely due to mucosal inflammation and localized fibrotic scarring.[4] The need for repeat surgery can pose emotional and economical burdens on patients, who often experience stenosis recurrence rates as high as 40%–70% over months to years, with many requiring multiple endoscopic dilations at an interval spanning from 8 to 14 months on average.[4–6] If patients experience restenosis often enough, open airway reconstruction or tracheostomy may be necessary to maintain airway patency. However, there are currently neither standardized treatment protocols for managing SGS nor definitive cures, making it a frustrating disorder for both affected patients and their physicians.

Adjuvant treatments have been examined to determine whether they might improve outcomes following endoscopic dilation. Numerous therapies including mitomycin C application, proton-pump inhibitors, antibiotics, and inhaled corticosteroids have been studied. Only within the past few years have groups begun investigating the role of office-based corticosteroid injections as primary or adjuvant therapy to postpone or potentially eliminate the need for serial endoscopic dilations. Franco et al and Hoffman et al both evaluated the efficacy of in-office serial intralesional steroid injections (SILSIs) for treating idiopathic SGS and reported promising improvements in airway patency and time to next endoscopic dilation.[7,8] Because SGS is a fibroinflammatory disease, the injection

From the Department of Otolaryngology (D.R.P., D.E.R.), University of Miami Miller School of Medicine, Miami, Florida, U.S.A.

Editor's Note: This Manuscript was accepted for publication 24 May, 2019.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Presented at the 2019 Triological Society Combined Sections Meeting, Coronado, CA, U.S.A., January 24–26.

Send correspondence to David E. Rosow, Department of Otolaryngology, University of Miami Miller School of Medicine, 1120 NW 14th Street, 5th Floor, Miami, FL 33136-1015. Email: drosow@med.miami.edu

DOI: 10.1002/lio2.284

of corticosteroids into the sites of stenosis or scarring targets the pathophysiologic mediators of disease progression and serves as a theoretically sound approach in management. Intralesional corticosteroid injections under general anesthesia at the time of endoscopic dilation have been long been suggested to benefit SGS patients,[1,2,9] but this newly trending concept of serial in-office delivery of injections is noteworthy to explore because it can significantly reduce the surgical burden on SGS patients and revolutionize standard of care.[7,8] As both aforementioned studies solely examined efficacy in patients with idiopathic SGS, there is a gap in current knowledge about how this approach could benefit patients with other etiologies of SGS.

To our knowledge, there is only one published study to date[10] which examines the efficacy of adjuvant serial in-office steroid injections to treat SGS patients of multiple etiologies. Our group has been performing these injections in idiopathic, postintubation, and Wegener's granulomatosis SGS patients undergoing endoscopic dilations for the past 3 years with our experience thus far also supportive of its utilization in clinical practice. With this study, we seek to add our institutional experience to the scarcity of literature that exists surrounding this topic. Our primary aim is to characterize the efficacy of incorporating subglottic corticosteroid injections in increasing surgery-free intervals (SFIs) for a cohort of SGS patients at a university-based medical system. Furthermore, we hope our institutional experience can present preliminary findings to drive future discussion on timing and execution of SGS management.

MATERIALS AND METHODS

The study protocol for retrospective chart review was approved by the Institutional Review Board of the University of Miami Miller School of Medicine. Beginning in late 2015 at our institution, all patients with SGS treated with endoscopic dilation surgery were given the option of receiving adjuvant SILSI as a part of disease management. A review of medical records was conducted to identify all SGS patients 18 years and older who underwent endoscopic dilation and at least one adjuvant SILSI within a 3-year period from 2015 to 2018 within the University of Miami Health System. Patients were excluded if they had synchronous airway lesions or stenosis outside of the subglottis. Ultimately, 13 patients met appropriate criteria.

Patients within our cohort were given corticosteroid injections with proper counseling and appropriate sniffing position posture. Injections were conducted in-office by the senior author (D.E.R.) with anesthetic preparation including nasal spray (4% lidocaine with 0.05% oxymetazoline), oral tetracaine/benzocaine spray, and local anesthesia of the larynx with inhaled 4% lidocaine. After dilution of 40 mg of Kenalog into 3 cc of saline, the solution was injected into several points directly within the subglottic scar under flexible laryngoscopic guidance via the cricothyroid membrane. Tissue blanching could easily be seen, indicating correct placement of the injection. The degree of stenosis was rated by the senior author immediately before first injection along with all subsequent office visits.

Charts were reviewed for demographic and treatment-specific data. Descriptive data including demographic information, etiology, medical comorbidities, and treatment details were recorded. The mean number of days between endoscopic dilations, representing the SFI, before and after the initiation of SILSI was calculated for our cohort. Groups were compared via Mann–Whitney U test, with $P < .05$ as the threshold for significance.

RESULTS

Thirteen patients met criteria, with mean age 50.1 ± 14.1 years and 7:6 female to male ratio. Eight of the thirteen (61.5%) had intubation-related stenosis, while four (30.8%) were idiopathic and one (7.7%) was due to Wegener's granulomatosis. Common comorbidities included obesity (7/13 patients; 53.8%), hypertension (7/13 patients; 53.8%), and gastroesophageal reflux disease (5/13 patients; 38.5%). All 13 patients presented with dyspnea with four additionally experiencing concurrent dysphonia, one with concurrent globus sensation, and one with concurrent mild inspiratory airway noise noted by the physician. Refer to Table I for demographic and clinical details of the patient cohort.

Patients underwent an average of 4.2 ± 2.2 total postoperative injections, beginning 45.9 ± 19.0 days after surgery. The primary outcome measure was the SFI split into two classifications: pre- and post-SILSI initiation. The pre-SILSI SFI is defined as the mean number of days between the date of endoscopic dilation prior to SILSI initiation and the most recent prior endoscopic dilation before that, if undertaken. Of the 13 patients, 3 (patients 6, 9, 13) did not have multiple prior endoscopic dilations and were therefore not included in the calculation of average pre-SILSI SFI. Post-SILSI SFI is defined as the mean number of days between the date of endoscopic dilation prior to SILSI initiation and the next repeat endoscopic dilation surgery, if undertaken. The mean SFI prior to initiating SILSI was 288.6 ± 362.0 days, while the mean interval was significantly longer (545.5 ± 152.7 days, $P = .0041$) after receiving SILSI as shown in Figure 1, with error bars representing respective standard errors.

Ultimately, 10 of the 13 total patients did not need to return to the operation room for repeat endoscopic dilation after receiving SILSI and so their post-SILSI SFI was calculated from time of most recent surgery that preceded SILSI initiation to time of final data review (December 31, 2018). Mean follow-up was 20.4 months. Seven of these 10 patients improved by way of decreased degree of stenosis after one or two rounds of SILSI and of these, 3 of 7 achieved minimal residual stenosis (<5% circumferential stenosis noted via laryngoscopy). The remaining 3 of these 10 patients who did not require a repeat dilation achieved stable stenosis after SILSI initiation. Patients 7, 8, and 13 underwent repeat endoscopic dilation surgery after SILSI initiation because of worsened conditions as evidenced by an increase in stenosis severity. Patient 7 worsened from 35% to 80% stenosis and required surgery within approximately 11 months after initiating SILSI treatment. Patient 8 worsened to the point of having repeated stenosis >50% and requiring surgical dilations every 1–2 months for the past 6 months with a tracheostomy tube placement scheduled for the near future. Patient 13 worsened from 5%–10% to 40% stenosis within approximately 21 months after initiating SILSI but since the repeat surgery, has had a stable residual stenosis of 5%. There were no reported complications or adverse events

TABLE I.
Demographic and Clinical Characteristics of Patient Cohort.

Patient	Sex	Age	Etiology	BMI	Comorbidities	Presenting Symptoms	Number of Dilation Surgeries Prior to SILSI	Total Number of SILSI	Initiation of SILSI (Days after Surgery)	Change in SFI after Initiating SILSI (days)
1	F	69	Intubation	22.8	GERD, HTN, hypothyroidism, Crohn's disease	Dyspnea, dysphonia	5	2	47	+444
2	F	48	Intubation	24.9	—	Dyspnea, inspiratory airway noise	3	7	36	–554
3	F	71	Idiopathic	19.9	GERD, HTN	Dyspnea, globus sensation	4	2	56	+297
4	F	42	Intubation	36.3	GERD	Dyspnea	2	3	33	+54
5	M	65	Intubation	29.5	HTN	Dyspnea	2	3	33	+535
6	F	38	Idiopathic	31.8	—	Dyspnea, dysphonia	1	3	34	NA
7	M	44	Wegener's	30.5	Asthma	Dyspnea	3	7	65	+120
8	F	53	Intubation	29.7	HTN, CHF	Dyspnea	3	7	50	+96
9	F	36	Idiopathic	39.4	GERD	Dyspnea	1	6	37	NA
10	M	39	Intubation	32.5	HTN, anxiety	Dyspnea	2	2	30	+384
11	M	23	Intubation	40.7	HTN	Dyspnea, dysphonia	5	3	22	+389
12	M	64	Intubation	30.8	HTN, DMII	Dyspnea	2	5	57	+563
13	M	55	Idiopathic	27.8	GERD	Dyspnea, dysphonia	1	3	97	NA

BMI = body mass index; CHF = congestive heart failure; DMII = diabetes type 2; GERD = gastroesophageal reflux disease; HTN = hypertension; NA = not applicable; SFI = surgery-free interval; SILSI = serial intralesional steroid injection.

resulting from the corticosteroid injections per the medical charts.

The degree of stenosis for each patient was reported by the same provider (D.E.R.) in the medical charts for all visits. Photo-documentation by laryngoscopy was done at each visit; in some cases, marked differences could be appreciated as early as one injection (Figs. 2 and 3). Any observable trends between stenosis severity and management were examined and reported in Table II, along with treatment-specific details of SILSI administration. The mean number of injections in one round of SILSI was 2.5 injections, with an average interval of 50.6 days between injections (Table II).

DISCUSSION

SGS can be an unrelenting disease with a natural course marked by recurrent, potentially life-threatening bouts of inflammation and scarring and has been traditionally managed by either repeated endoscopic surgical dilations or definitive open tracheal reconstructive surgery. Recent studies have prompted the consideration that better treatment modalities exist outside the surgical realm, used in combination or possibly even standalone, to achieve successful management of SGS. The concept of adjuvant therapy has already been well investigated for SGS with anti-inflammatory/immunomodulating agents such as mitomycin C, inhaled corticosteroids, proton-pump inhibitors, antibiotics, and methotrexate based on the principle that SGS pathophysiology is heavily driven by inflammation and fibroblast proliferation.[3,5,11–14] In Maldonado et al study, a trend between aggressive medical treatment (anti-reflux medications, inhaled corticosteroids, and trimethoprim-sulfamethoxazole) and lowered idiopathic SGS recurrence rate was identified demonstrating a relative risk of 0.52, $P = .051$ with adjuvant treatments versus no further treatments after endoscopic surgery.[11] However, concerns for toxicity as well as inconclusive results between studies have prevented these agents from becoming mainstay modalities in SGS management.

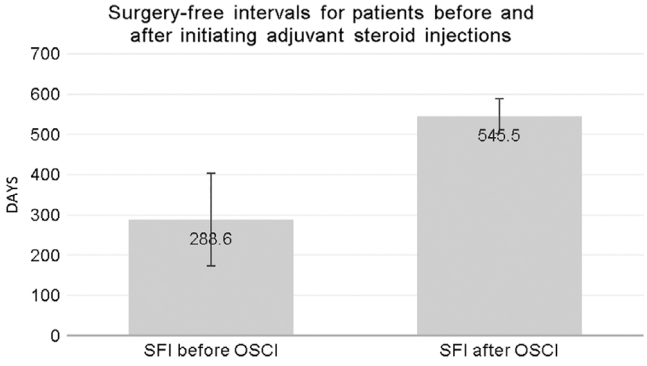

Fig. 1. Effect of office SILSIs on increasing SFIs for subglottic stenosis patients. SFI = surgery-free interval; SILSI = serial intralesional steroid injection.

Investigation of corticosteroid injections in an office-based setting is a growing topic of interest in SGS research, as it is well tolerated and provides presumed cost-effective advantages of nonsedation techniques, shorter procedure times, and reduced need for operative intervention with no cited adverse effects.[10] Given the body of literature demonstrating the efficacy of intralesional corticosteroid injections in the operating room setting,[1,2,9] the ability to provide these same injections in an office setting can revolutionize the way in which we approach clinical management of SGS.

Our institutional experience supports the use of office-based subglottic corticosteroid injections as an

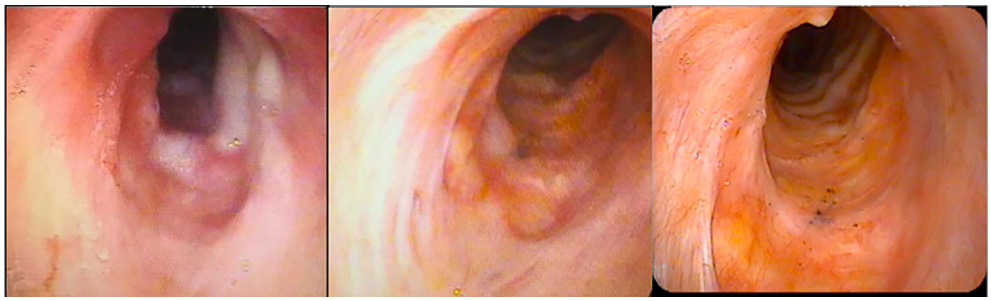

Fig. 2. Pre/post-office subglottic corticosteroid injection laryngoscopy images. This sequence demonstrates initial stenosis 4 weeks after surgery at the time of initial injection (left), the change after two serial injections spaced approximately 1 month apart (center), and the appearance 6 months after third and final injection (right).

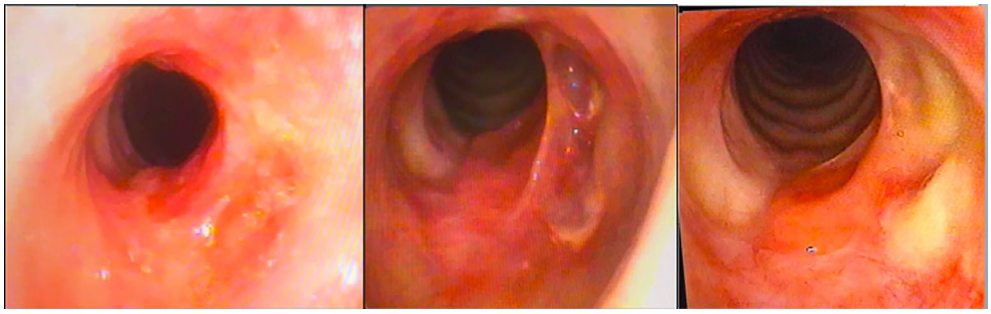

Fig. 3. Pre/post-office subglottic corticosteroid injection laryngoscopy images. This sequence demonstrates initial stenosis 6 weeks after surgery at the time of initial injection (left), the change after one injection (center), and the change after two injections, spaced approximately 1 month apart (right).

effective adjuvant treatment to endoscopic dilations in SGS patients as reported in the few studies published in current literature.[7,8,10] In Bertelsen et al study, among 24 identified SGS patients with at least two consecutive in-office intralesional steroid injections who fulfilled eligibility criteria for comparison of SFI before and after intralesional steroid injections (n = 8), the SFI improved from 10.1 months to 22.6 months (mean difference = 12.5 months; 95% confidence interval = −2.1 to 27.2 months), with 75% of patients individually experiencing longer SFIs before

TABLE II.
Treatment Specific Details Involving Timing and Number of Injections, Next Therapeutic Steps, and Stenosis Severity.

	Mean	Standard Deviation	Range	Comments
Number of days between surgery and initiation of SILSI	45.9 days	19.0 days	30–97 days	
Number of injections in one round of SILSI	2.5	1.0	1–4	
Time interval between each injection in one round of SILSI	50.6 days	17.4 days	28–97 days	
Nine patients proceeded with MWL; time interval between each visit	86.3 days	30.1 days	32–126 days	Range of stenosis severity (%) at end of first round of SILSI: 0%–25%*
Four patients proceeded with next round of SILSI	—	—	—	Two patients initiated MWL, then began second round of SILSI at 20% and 35% stenosis. The remaining two patients were at 30% stenosis at start of second round of SILSI
Three patients received repeat endoscopic dilation surgery	—	—	—	One patient initiated second round of SILSI and between second and third injections, stenosis increased from 35% to 80%, and surgery was done. The remaining two patients were at 40% and 50% stenosis at time of repeat surgery
Total number of SILSI	4.2	2.2	2–8	

*Patient 10 proceeded with MWL likely due to lack of symptoms per medical record "patient feels comfortable, denies stridor, reports his breathing is quite good" although having an estimated 40% stenosis after two injections in the first round of SILSI; we omitted this outlier here because within 4 months after the first MWL visit, the stenosis had regressed to a point where it "could not be visualized" per note.

MWL = maintenance with laryngoscopy; SILSI = serial intralesional steroid injection.

and after injections.[10] Our data corroborate these findings. For our cohort of 13 SGS patients, the mean SFI was significantly longer after initiating SILSI (545.5 ± 152.7 days; approximately 17.9 months) compared to the mean SFI before initiating SILSI (288.6 ± 362.0 days; approximately 9.5 months, P = .0041). On an individual level, the SFI interval increased for 90% of the patients for whom there was a pre-SILSI SFI to compare with (n = 10). Our patients underwent an average of 4.2 ± 2.2 total postoperative injections, comparable to 4.08 ± 1.91 and 4.4 ± 1.5 injections in Hoffman et al and Bertelsen et al, respectively.[8,10]

Regarding patient characteristics, our study comprised SGS patients from various etiologies with distributions of gender, etiology, symptomatology, and comorbidities also consistent with historical data. According to Gelbard et al, one of the largest study cohorts of adult laryngotracheal stenosis patients with data collected over a 15-year period, the most common etiology was iatrogenic, within 2 years of intubation or after tracheostomy, followed by idiopathic, autoimmune, and traumatic causes.[15] Among the various etiologies of SGS, there is also a well-known gender predilection toward females for cases of idiopathic SGS which is postulated to be related to hormonal alterations or a reflux-mediated process.[16] We observed that among the common comorbidities present within our patient cohort, GERD was described in 75% of patients with idiopathic SGS. Overall, 75% (3/4) of our idiopathic SGS patient were female compared to 50% (4/8) female in our intubation SGS group and a single male with Wegener's granulomatosis etiology, demonstrating a female predilection within the idiopathic cohort. The most common presenting symptom among SGS patients was dyspnea (100%), as described in prior studies.[1,2]

In the Franco et al. study, researchers presented a flowchart depicting the clinical pathway for idiopathic SGS patients treated with serial steroid injections with the recommendation to repeat injections every 3–5 weeks until 5–7 injections have been delivered followed by regular office visits to monitor via spirometry.[7] Our institutional experience, as summarized in Table II, encouraged the initiation of SILSI within 2 months of an endoscopic dilation procedure as series of 2–3 injections spaced 1–2 months apart. This is based on the principle that SGS pathophysiology is caused by aberrant wound-healing processes that involve inflammation and pathologic scar formation akin to hypertrophic scars or keloids.[7,14] This suggests the necessity for serial steroid injections rather than single injections for each round of SILSI initiation. While it is generally understood that hypertrophic scarring develops usually within 6–8 weeks after injury, a recently published rat model study for tracheal stenosis demonstrated that maximal luminal narrowing occurred at day 21 after injury was induced by electrocauterization[17]; this prompts the consideration that injections should be done at intervals frequent enough to disrupt scar formation. Regular monitoring via laryngoscopy at longer intervals of 2–4 months between visits was conducted for patients with improved symptoms or mild residual stenosis. Management included either initiating another round of SILSI or preparing the patient for endoscopic dilation in the setting of concerning symptoms or persistent stenosis.

Some limitations of our study include small sample size, short follow-up time, and the retrospective nature of the study design. Although we included SGS patients of multiple etiologies, we recognize that comparison analyses of outcomes between the different etiologies could not be conducted because of the low number of patients per etiological category. While we have included an objective indirect measure of airway improvement by way of SFIs, our study lacks an objective direct measure of airway status before and after SILSI initiation such as spirometry. We acknowledge this to be due to limitations of what data were available in the medical record upon retrospective review. Additionally, accurately assessing the degree of airway stenosis is inherently difficult and is a challenge that may also be complicated by the fact that severe stenosis ratings may not linearly correlate with clinically significant symptoms for a given patient. Future studies designed with larger sample sizes, longer follow-ups, control groups, and randomization are needed to optimize SILSI conditions such as frequency, timing, and dosing. Because there is currently no standardized management approach to treat SGS, we hope our institutional experience can contribute to meaningful discussions to establish such an algorithm moving forward.

CONCLUSION

Our study supports the utilization of office-based SILSIs as adjuvant therapy to endoscopic dilation surgeries in the management of SGS of multiple etiologies. These serial injections administered after endoscopic dilation are well tolerated and demonstrate efficacy in increasing the SFI for patients compared to management characterized only by repeated dilations. We initiated in-office corticosteroid injections within 2 months of an endoscopic dilation procedure as a series of 2–3 injections spaced 1–2 months apart with regular monitoring via laryngoscopy to assess the severity of stenosis at each visit. Further studies including randomized control trials are needed to establish a successful and standardized treatment protocol that can alleviate the burden of this disorder.

BIBLIOGRAPHY

1. Wierzbicka M, Tokarski M, Puszczewicz M, Szyfter W. The efficacy of submucosal corticosteroid injection and dilatation in subglottic stenosis of different aetiology. *J Laryngol Otol* 2016;130(7):674–679.
2. Wolter NE, Ooi EH, Witterick IJ. Intralesional corticosteroid injection and dilatation provides effective management of subglottic stenosis in Wegener's granulomatosis. *Laryngoscope* 2010;120:2452–2455.
3. Rosow DE, Barbarite E. Review of adult laryngotracheal stenosis: pathogenesis, management, and outcomes. *Curr Opin Otolaryngol Head Neck Surg* 2016;24(6):489–493.
4. Gelbard A, Shyr Y, Berry L, et al. Treatment options in idiopathic subglottic stenosis: protocol for a prospective international multicenter pragmatic trial. *BMJ Open* 2018;8(4):e022243.
5. Simpson CB, James JC. The efficacy of mitomycin-C in the treatment of laryngotracheal stenosis. *Laryngoscope* 2006;116:1923–1925.
6. Hseu AF, Benninger MS, Haffey TM, Lorenz R. Subglottic stenosis: a ten-year review of treatment outcomes. *Laryngoscope* 2014;124:736–741.
7. Franco RA Jr, Husain I, Reder L, Paddle P. Awake serial intralesional steroid injections without surgery as a novel treatment for idiopathic subglottic stenosis. *Laryngoscope* 2018;128(3):610–617.
8. Hoffman MR, Coughlin AR, Dailey SH. Serial office-based steroid injections for treatment of idiopathic subglottic stenosis. *Laryngoscope* 2017;127(11):2475–2481.

9. Hoffman GS, Thomas-Golbanov CK, Chan J, Akst LM, Eliachar I. Treatment of subglottic stenosis, due to Wegener's granulomatosis, with intralesional corticosteroids and dilation. *J Rheumatol* 2003;30: 1017–1021.
10. Bertelsen C, Shoffel-Havakuk H, O'Dell K, Johns MM 3rd, Reder LS. Serial in-office intralesional steroid injections in airway stenosis. *JAMA Otolaryngol Head Neck Surg* 2018;144(3):203–210.
11. Maldonado F, Loiselle A, Depew ZS, et al. Idiopathic subglottic stenosis: an evolving therapeutic algorithm. *Laryngoscope* 2014;124:498–503.
12. Rosow DE, Ahmed J. Initial experience with low-dose methotrexate as an adjuvant treatment for rapidly recurrent nonvasculitic laryngotracheal stenosis. *JAMA Otolaryngol Head Neck Surg* 2017;143(2):125–130.
13. Gouveris H, Karaiskaki N, Koutsimpelas D, Chongolwatana C, Mann W. Treatment for adult idiopathic and Wegener-associated subglottic stenosis. *Eur Arch Otorhinolaryngol* 2013;270(3):989–993.
14. Hirshoren N, Eliashar R. Wound-healing modulation in upper airway stenosis—myths and facts. *Head Neck* 2009;31(1):111–126.
15. 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.
16. Blumin JH, Johnston N. Evidence of extraesophageal reflux in idiopathic subglottic stenosis. *Laryngoscope* 2011;121:1266–1273.
17. Hu T, Wei F, Sun W, et al. Strongly induced hypertrophic scar in a rat model of tracheal stenosis. *Int J Clin Exp Med* 2018;11(4):3679–3685.