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An Updated Review of Subglottic Stenosis: Etiology, Evaluation, and Management

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Abstract

Purpose of Review To assimilate the newly published literature regarding subglottic stenosis (SGS), including basic science and translational research on mechanisms of etiology, clinical diagnostics, and therapeutic treatments.

Recent Findings The role of inflammation in development of iatrogenic and idiopathic SGS (iSGS) is continuing to be studied. The IL-23/IL-17A inflammatory axis appears to be a potential mechanism for development of iSGS. Additionally, as anticipated in an inflammatory milieu, PD-1/PD-L1 expression is upregulated. If the PD-1/PD-L1 axis is important in SGS pathogenesis, then it may represent a potential target for immunotherapeutic inhibition, given its success in cancer treatment. In terms of surgical management, prospective studies show that endoscopic approaches have more frequent recurrence compared to open techniques.

Summary SGS arises from various etiologies, and further understanding of its pathogenesis can aid in the development of novel therapies. It is imperative to obtain a thorough history for each patient presenting with respiratory complaints, as misdiagnosis can delay proper treatment. Endoscopic and open surgical techniques continue to be investigated in a growing number of prospective clinical trials to determine optimal treatment protocols. In-office injections are gaining popularity and show promise in the treatment of SGS.

Keywords Subglottic stenosis · Idiopathic · Iatrogenic · Review · Laryngotracheal stenosis

Introduction

Subglottic stenosis (SGS) refers to a condition in which the airway is narrowed inferior to the glottis. SGS is a component of laryngotracheal stenosis (LTS), which can occur at the level of the supraglottis, glottis, subglottis, or trachea. Each of these conditions may present and result in potentially life-threatening restriction in ventilation. Patients may present with a spectrum of respiratory symptoms, ranging from wheezing and shortness of breath to stridor and life-threatening airway compromise [1]. The diagnosis and management of SGS often requires coordinated teamwork among multidisciplinary aerodigestive teams including otolaryngologists, thoracic surgeons, general and interventional pulmonologists, gastroenterologists, and speech language pathologists.

There are multiple known causes of adult SGS, the most common of which is intubation- or tracheostomy-related (iatrogenic). The incidence of iatrogenic LTS is estimated to be about 1 in 200,000 adults annually, 50% of which are SGS [2, 3]. Iatrogenic trauma may cause about half (54.5%) of all LTS cases, and about half of those patients (59%) develop SGS [4]. Other causes of SGS include autoimmune disease and idiopathic, with laryngeal trauma and infection as less common causes. The North American Airway Collaborative (NoAAC) is an international network of clinical providers established in 2014 focused on improving the quality, safety, effectiveness, and cost of medical interventions in adult airway disorders. An international multi-institutional NoAAC study revealed the epidemiology of SGS subtypes varies, wherein idiopathic SGS (iSGS) patients are almost exclusively female (98.5%), Caucasian (95%), and otherwise healthy, with

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a mean age of 50 years [5]. iSGS is estimated to occur with an annual incidence of 1:400,000 [6]. Patients with iatrogenic LTS tend to have a more even sex distribution and higher rates of comorbidities [4]. Regardless of the etiology, SGS can be misdiagnosed easily as a pulmonary disease such as asthma, and delays in diagnosis and treatment up to 4 years have been reported [7–11]. Given the multiple etiologies and recurrent nature of SGS, management may include repeated surgical intervention and hospital stays, as well as adjuvant therapies. Current treatment options vary in successful airway outcomes and need for reoperation. The ultimate goal is to reestablish a patent airway and avoid tracheotomy.

Etiology and Pathophysiology

Iatrogenic SGS

Iatrogenic SGS, caused by intubation or tracheostomy, was first theorized in 1969 to be the result of tissue ischemia due to endotracheal cuff pressures compromising mucosal blood flow, leading to subglottic scarring and fibrosis [12]. In patients undergoing prolonged intubation, about 57% may sustain acute laryngeal injury, with an increased risk of injury with endotracheal tubes (ETTs) larger than 7.0 [13]. Large ETTs and small airways have been implicated in the development of LTS and SGS. The use of large ETTs (size > 7.5), as well as obesity, is associated independently with the development of airway stenosis. Moreover, obese patients intubated with large ETTs have been shown to experience airway stenosis at a rate significantly higher than those intubated with small ETTs [14]. In the cohort of 150 patients studied by Gelbard et al., 18 healthy patients without diabetes or cardiovascular disease developed iatrogenic LTS, and the majority (83%) was female. The authors believe a smaller airway diameter in women relative to ETT size contributes to this sex bias [4].

In iatrogenic LTS, fibroblasts have been demonstrated as the predominant effector cell in fibrogenesis [15–17]. Recently, macrophages, specifically of the M2 phenotype, were found at high levels in iatrogenic LTS specimens and demonstrated to induce collagen production by fibroblasts [18]. By studying mice with severe combined immunodeficiency, Ghosh et al. were able to demonstrate that systemic circulating mediators, T cells, and B cells all play roles in initiating granulation tissue formation in response to tissue injury, as opposed to resident airway immune cells alone. In comparing immunocompromised to healthy mice, granulation tissue only formed in the injured airways of healthy mice [19].

Idiopathic SGS

Subglottic scarring in iSGS, believed to be an epithelial to mesenchymal transition (EMT), occurs without an obvious inciting cause. Recent research suggests the role of a dysregulated immune response leading to iSGS. Immune response dysregulation, specifically by T cells in the subglottic mucosa, has been shown to lead to collagen and extracellular matrix deposition by fibroblasts [20, 21, 22•]. In a study by Gelbard and colleagues, subglottic mucosal scar specimens demonstrated aberrant mucosal immune activation relative to healthy controls. The authors found upregulation of the IL-23/IL-17A inflammatory axis in iSGS, and they hypothesized that this may influence tissue fibrosis. Additionally, they found that among lymphocytes from iSGS scar, γδ T cells produce IL-17A [21]. IL-17A was later shown to drive fibroblast proliferation directly, leading to extracellular matrix production and further amplification of local inflammation in the subglottic scar tissue through chemokine and cytokine production [22•]. The propagation of inflammation associated with various protein expression profiles has been of interest to research teams. Schoeff et al. analyzed mucosal samples from iSGS patients and, as a proof of concept, found differential expression of 42 proteins. The authors identified patterns of hypermethylation found in iSGS patients that may be associated with differential protein expression and suggest the possibility of iSGS subgroups [23]. Liu et al. has demonstrated increased levels of CCL2, IFNγ, and IL-6 protein in iSGS specimen, although with marked heterogeneity [24]. Inflammation and cytokines (such as IL-17A) play an important role in stenosis [25].

With the well-known prominent role of inflammation in stenosis, it is important to identify homeostatic mechanisms of immune suppression. The immune checkpoint programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) regulates T-cell activation, self-tolerance, and immune-mediated tissue damage through an inhibitory function. Studies have implicated an upregulation of PD-1 and PD-L1 bleomycin-induced pulmonary fibrosis and idiopathic pulmonary fibrosis, respectively [26, 27]. Davis and colleagues found that PD-1 and CD4 + T-cells were upregulated in iSGS, while in iatrogenic LTS, PD-L1 was additionally upregulated, leading the authors to suggest the PD-1/PD-L1 axis may represent a potential target for immunotherapeutic inhibition of this pathway to prevent a profibrotic state [28•]. These recent studies have identified many key players in the chronic proliferation of scar tissue in iSGS; however, we still lack the understanding of what initiates this disease process. While studies primarily utilize tissue culture and have not yet translated to patient care, the evidence gathered supports immunologic factors

associated with iSGS and may lead to the identification of pharmacologic targets for treating iSGS.

The IL-23/IL-17A inflammatory axis activated in iSGS can be propagated by many types of immune cells. Among lymphocytes from iSGS, IL-17 was primarily produced by γδ T cells, a specific T cell subtype that recognizes microbial antigens [21]. Studies have examined the microbiota of larynges (primarily the glottis) in both benign and malignant pathologies, as well as in smokers and patients with reflux [29, 30]. However, tissue cultures for identification of infectious agents have failed to demonstrate any associations with iSGS [31, 32]. More recently, *Mycobacterium* proteins and nucleic acids have shown associations uniquely with iSGS samples, and host immune responses to these findings have been identified [31]. With culture-negative samples and the presence of mycobacterial species in iSGS specimens, it is possible that bacterial loads reside below identifiable histologic thresholds and the pathogenesis of iSGS may depend on the immunologic response to the organisms more so than the infectious agents themselves. While immune cell infiltrate is seen in multiple subtypes of SGS, recent evidence has demonstrated iSGS to have significantly higher levels of resident memory CD8 + T cells, a subset of T cells known to be important for immunity against viral and intracellular pathogens [33]. Swab samples of iSGS have also suggested specific microbial profiles, demonstrating strong associations with *Moraxella* and *Acinetobacter* genera, which may contribute to pathogenesis [31, 34]. Future studies will help determine whether these microbial species play a role in pathogenesis of iSGS or if the inflammatory milieu in iSGS promotes growth of these pathogens.

Reflux as a Causal Entity

Due to an incidence of reflux higher than that of the general population, many studies suggest associations between laryngopharyngeal reflux and the development of iSGS, as well as LTS with known causes [35–40]. Two recent translational studies have tested the hypothesis of this causality. In a challenge of bile acids on cultured primary tracheal epithelial cells from healthy volunteers, EMT markers, along with procollagen and fibronectin protein expression, were significantly upregulated. At the same time, expression of E-cadherin, an epithelial marker, was significantly reduced, supporting the potential role of bile acids in EMT [41]. However, the influence of pepsin on EMT was studied in vitro using epithelial cells from healthy patients and yielded no effects on gene or protein expression associated with EMT nor did the presence of pepsin induce fibroblast migration [42]. Further clinical investigation into a potential causal relationship is necessary.

Other Rare Causes

Less common causes of SGS include trauma, infection, and autoimmune disease. Granulomatosis with polyangiitis (GPA), formerly called Wegener's granulomatosis, is one of the autoimmune processes that can cause SGS. It is a systemic inflammatory disease that presents with necrotizing granulomas in conjunction with small or medium vasculitis throughout the entire respiratory tract, as well as kidneys, and patients are often positive for antineutrophil cytoplasmic antibody (ANCA) [43]. Autoimmune SGS is thought to develop from the degradation of extracellular matrix by subglottic inflammation, exposing the cricoid cartilage to the immune system, provoking autoantibodies and further inflammation [44]. The largest review to date of 46 GPA patients with SGS revealed no difference in sex distribution and that in about half of cases, SGS was the only active pathologic process related to GPA [45]. In patients who develop GPA at an age younger than 20 years, an increased incidence of SGS has been observed [45, 46]. Traumatic laryngeal injuries such as external blunt or penetrating with cartilaginous fractures or mucosal tears can lead to SGS [47–50]. Internal trauma leading to SGS can include chemical and thermal burns, laryngotracheal surgery, or radiotherapy. Infectious etiologies can include bacterial tracheitis, histoplasmosis, diphtheria, and papillomatosis [51]. Laryngeal tuberculosis should remain as a differential diagnosis for patients from an endemic area presenting with SGS [52].

Diagnosis and Preoperative Evaluation

The diagnostic work-up of SGS includes a thorough history, including intubation, tracheostomy, laryngotracheal surgery, trauma, infection, autoimmune disease, reflux, and radiation. Common presenting symptoms include shortness of breath, dyspnea on exertion, stridor, wheezing, and dysphonia [11, 53]. In a 263 patient cohort with iSGS, the median time from symptom onset to diagnosis was 36 months, and nearly half (42%) had delays in treatment due to a misdiagnosis of asthma [53]. The NoAAC group recently published an inquiry on social determinants of health associated with iSGS and found that in this relatively homogeneous population, there were no associations of education, income, or social support with time to diagnosis or time to disease recurrence [54].

Endoscopic evaluation is the foremost important aspect of diagnosis and preoperative evaluation. This can be done as flexible laryngoscopy and flexible tracheobronchoscopy in either the awake or asleep patient or suspension microlaryngoscopy and bronchoscopy with a rigid telescope. Flexible laryngoscopy allows for evaluation of vocal fold mobility, and flexible tracheobronchoscopy in awake patients enables

further airway assessment in the clinic. These modalities offer the ability to record video, with suspension microlaryngoscopy allowing for easy instrumentation of the larynx and trachea for palpation, measurement, and operative planning. As most iSGS lesions are recognized to have maximal stenosis located between the superior border of the cricoid cartilage and the first tracheal ring, it is important to characterize the superior and inferior borders of stenosis and the narrowest lumen diameter [55]. Sizing and measuring length can be achieved by passing various sized telescopes, bougies, ETTs, or Kirschner wires into the airway [56–58]. One must also note the presence of other subsite involvement, fresh, incipient granulation versus mature, cicatricial stenosis, and atypical features or nasal passage abnormalities concerning for autoimmune or infectious etiologies described above, which could be an indication for biopsy.

The grading system used most commonly, developed in 1994, is the Myer-Cotton system, which utilized ETTs initially to classify mature, firm, circumferential stenosis based on cross-sectional percent stenosis. Grading as I–IV corresponds with 0–50%, 51–70%, 71–99%, and no detectable lumen, respectively [59]. Since this system was developed for the pediatric patient but has been used in adults, a system to complement the Myer-Cotton grade has been proposed to incorporate a letter (a–d) according to one, two, three, or four laryngeal subsites involved in stenosis, respectively, and an addition sign (+) to indicate the presence of severe comorbidities or congenital abnormalities [56, 60].

Diagnosis and management of SGS are aided by radiographic, serologic, and reflux testing. Spiral computed tomography (CT) with multiplanar reformatting and virtual endoscopy has proven comparable to rigid bronchoscopy with a 100% sensitivity and 100% specificity of detecting SGS. The length and grade of stenosis as well as measurements of proximal and distal airway are accurate on CT [61]. Dynamic expiratory CT is another imaging modality that can help detect airway collapse due to tracheomalacia, which can be associated with SGS [62]. Serologic testing can help determine the etiology of stenosis in GPA patients with positive ANCA only [63]. While the causal relationship of reflux with iSGS is continually being investigated, evaluation of reflux through 24-h pH-impedance testing using upper and lower esophageal probes can determine characteristics and severity [35].

Pulmonary function tests (PFTs) have proven reliable for diagnosis and differentiation of LTS from other pulmonary diseases through the use of the expiratory disproportion index (EDI), which is based on the ratio of forced expiratory volume in 1 s to peak expiratory flow rate [64]. The diagnostic utility of EDI in obese patients is reliable, albeit with a lower sensitivity than nonobese patients, making it less useful to rule out airway stenosis in this cohort [65]. This diagnostic test could potentially prevent delays in diagnosis. One study found endoscopic grading of stenosis may have poor reliability compared to PFTs, and another found no correlation between grading of stenosis and PFTs [66, 67]. However, peak expiratory flow has been shown to be a simple measurement to monitor iSGS progression with a sensitivity and specificity of 84.4% and 82.0%, respectively [68].

Providers should be vigilant assessing for LTS and SGS in patients with a history of hospitalization for novel coronavirus disease 2019 (COVID-19), as the rates of iatrogenic airway complications have been theorized to increase. New respiratory symptoms may commence at least 3 weeks following extubation and resolution of COVID-19 symptoms [69, 70]. Many authors recommend that all patients who have been intubated for COVID-19 pneumonia maintain close follow-up with an otolaryngologist or airway specialist after discharge for early diagnosis of any complications [69, 71].

Management

Optimal management for SGS is still debated, and there is no standardized treatment algorithm. Patients are managed collaboratively by otolaryngologists, interventional pulmonologists, and thoracic surgeons, which includes surgical management with either endoscopic or open surgical procedures, with or without adjuvant medical therapy. While treatment protocols vary by institution, they have been described as singular and homogeneous within individual institutions [6, 72]. Reoperation and surgery-free interval (SFI) are primary outcome measures for treatment of SGS. In 2005, Monnier et al. suggested the guideline that endoscopic CO2 laser resection with or without dilation be used in grade I, some grade II, and mild grade III SGS with lengths less than 1.5 cm, and open surgery should be considered for grades II, III, and IV SGS or stenosis greater than 1.5 cm [73].

Endoscopic procedures usually involve excision of subglottic scar using CO2 laser but can be done with KTP laser, Nd:YAG laser, electrocautery, microdebrider, or radiofrequency coblation and can be followed with mechanical dilation of the airway using firm bougies, endotracheal tubes, or a radial-expansion balloon catheter [1]. Feinstein et al. assessed optimal endoscopic dilation (ED) management of SGS from various etiologies by comparing retrospectively the use of balloon dilation, resection with CO2 laser or cold knife, and combinations of techniques, finding no significant differences in mean SFI among interventions nor were there significant associations with advanced grade of stenosis or adjuvant corticosteroid injection [74].

Open surgical approaches present the alternative to ED and include laryngotracheal resection (LTR) with reanastomosis and laryngotracheoplasty (LTP) using expansion grafting with or without stent placement. A systematic

review by Lewis et al. encompassing 39 studies and 834 patients aimed to assess outcomes of open surgical procedures compared with endoscopic procedures for SGS patients of various etiologies with or without tracheal extension examined need for additional procedures and rate of decannulation for tracheotomized patients [75•]. Overall, 32% of patients who underwent LTR received additional surgery, and 89% were decannulated. For patients who underwent LTP, 38% received additional surgery, and 83% were decannulated. Patients undergoing ED received additional surgery and were decannulated at an incidence of 44% and 63%, respectively. Regardless of approach, iSGS has been shown to have the lowest rate of requiring additional surgery (25%) compared with iatrogenic (35%) and traumatic (54%) etiologies. There was reporting bias in various studies and a lack of multivariate meta-analysis considering additional factors such as stenosis grade, length, and comorbidities. Additionally, based on their experience, the authors of this systematic review reported that there was likely underreporting of endoscopic procedures for granulation tissue removal after open procedures [75•]. When the decision to perform endoscopic or open surgery is being considered, one must discuss options with the patient regarding the safest procedure that will yield the greatest results.

Tracheotomy is an option for relieving acute respiratory distress or securing the airway prior to surgical intervention; rates of tracheotomy and decannulation vary. Incidence of tracheotomy is associated directly with higher grades, longer stenosis, or stenosis of multiple subsites for SGS patients with the exception of iSGS, which usually does not need a tracheostomy.

Idiopathic SGS

The recurrence rates of restenosis of iSGS are around 40% for open surgery and up to 80% for ED; stenosis recurs at a median of 8 months [5, 72]. A systematic review of 15 studies published between 2001 and 2018 including 862 total patients with iSGS ranging from 40 to 100% stenosis evaluated ED techniques [76]. Patients from the studies underwent a mean of 3.7 procedures. Treatment techniques varied in almost every study reviewed, and all but one study utilized multimodal techniques, making meta-analysis difficult. The study that used a single modality CO2 laser had the highest recurrence rate (100%) [77]. The lowest recurrence rate (40%) was found in the study by Bertelsen et al. that utilized rigid dilation with corticosteroid injections [78]. Tracheotomy and open surgery were eventually required in 7% and 10.9% of all patients, respectively, and the highest rate of open surgery (28%) was found in a study utilizing a combination of CO2 laser, rigid dilation, balloon dilation, mitomycin C (MMC), and corticosteroids [79]. A large retrospective multicenter NoAAC study of 479 iSGS patients found that a majority (80.2%) of patients were managed exclusively endoscopically throughout the mean follow-up period of 54.2 months, without a significant association with stenosis grade [5]. Regardless of approach, iSGS has been shown to have the lowest rate of requiring additional surgery (25%) compared with iatrogenic (35%) and traumatic (54%) etiologies [75•].

As perhaps the most informative study to date, NoAAC recently reported on an international, prospective, 3-year multicenter cohort of 810 patients with iSGS to compare mean SFI associated with ED, endoscopic resection with adjuvant medical therapy (ERMT; anti-reflux, antibacterial, and ICS), and LTR with anastomosis [72, 80••]. Overall, 22.8% of patients recurred, most commonly in the ED group (28%), followed by ERMT (12.4%) and LTR (1.2%). Using weighted, propensity score-matched, Cox proportional hazards regression models, ED was found to be inferior to ERMT (hazard ratio 3.16). The LTR group had only 1 case of recurrence, and among patients without recurrence, patients in this group had the best quality of life scores and worst Voice Handicap Index-10 (VHI-10) scores. Interestingly, ED was the procedure performed most commonly (74.4%). Even though these patients had the shortest median stenosis length, ED was associated with the highest recurrence rate and worst quality of life. This further raises the question of advantages and trade-offs associated with different approaches, as complications were reported similarly in the ED and ERMT groups, but LTR is usually associated with the most severe complications and the worst permanent voice outcomes. However, 3 deaths were reported in the ED and ERMT groups secondary to airway obstruction more than 30 days postoperatively [80••].

iSGS patients rarely require tracheotomy, with an incidence of 3% in one cohort of 479 patients [5]. In comparing iSGS and GPA with SGS, the former has been shown to have higher Myer-Cotton grades, while the latter is more likely to require tracheotomy [81]. Patients who are tracheotomized due to iSGS have the lowest rate of decannulation (63%) [75•]. Recent research has built upon our knowledge of fibrogenesis in iSGS, but studies have yet to identify biomarkers to monitor disease progression and prognosis [24]. The IL-23/IL-17A inflammatory axis appears to be a potential therapeutic target [21]. A number of studies that elucidate inhibitory actions of this pathway pose potential drug interventions for iSGS [82–84].

Iatrogenic SGS

Irrespective of surgical approach, the pooled recurrence rate of iatrogenic SGS requiring additional surgery in a systematic review was estimated to be 25–47%, which was significantly higher than that of iSGS [75•]. Iatrogenic SGS usually requires tracheotomy at the highest rate compared

to other etiologies [4]. Systematic review also demonstrated that patients tracheotomized due to iatrogenic SGS had the highest rate of decannulation (88%) compared with idiopathic (63%) and traumatic (78%) etiologies [75•].

Adjuvant Therapy

There is a rapidly expanding body of literature on serial intralesional steroid injections (SILSI) as a treatment for SGS of multiple etiologies. SILSI is performed in-office as primary or adjuvant therapy with the goal of preventing surgery or increasing SFI (Fig. 1). Pan and Rosow examined a retrospective cohort of SGS patients of various etiologies who underwent a mean of 4.2 injections following ED and demonstrated a significantly increased SFI following SILSI [85]. A study of 24 SGS patients of various etiologies who underwent a mean of 4.08 injections (88% had undergone ED prior to SILSI) showed that 71% of patients did not require further surgery after SILSI. This study demonstrated a longer mean SFI for autoimmune compared with iSGS and iatrogenic etiologies, as well as marginally longer SFI for iSGS compared with iatrogenic [78]. Hoffman et al. demonstrated that the procedure is well tolerated with significant improvements in percent stenosis after the first two injections for patients with iSGS [86]. Patient-reported outcomes from the same institution describe significant improvements in Dyspnea Index and Modified Medical Research Council dyspnea scale without change in VHI-10 or serious side effects [87]. A systematic review evaluated these four retrospective studies and found that overall, patients underwent a mean of 3.6 injections; for 35 patients with multiple etiologies, the mean SFI was about 219 days longer after SILSI. Forty-one out of 55 included patients (74.5%) did not require return to the operating room after SILSI throughout the duration of these studies [88•]. A retrospective review of side effects found about half of patients (55%) reported minimal tolerable side effects (the most common being menstrual irregularities), all of which resolved after completion of treatment [89]. SILSI was also shown to have a small but significant improvement in voice-related quality of life, as well as a weak correlation with spirometry data [90]. Preliminary retrospective data is promising for SILSI reducing the need for surgical intervention in SGS, but prospective studies with adequate power and length of follow-up may help define a role for this treatment.

The goal of medical management is to quell the propagation of inflammation in the subglottis and is employed generally as adjuvant treatment to surgery. In an attempt to limit scar formation, some authors advocate for aggressive reflux management [40, 91]. Maldonado et al. have shared their regimen of anti-reflux management, high-dose inhaled corticosteroids (ICS), and daily trimethoprim-sulfamethoxazole in conjunction with endoscopic CO2 laser with intralesional injection of corticosteroids and application of mitomycin C treatment for iSGS [6]. Although retrospective, addition of triple therapy showed a trend toward reduction in recurrence rate; prospective studies are needed to further determine the effect of adjuvant therapies. The use of ICS has been attractive to airway specialists as a method of treating the stenosing subglottis directly. Some case reports and retrospective series argue for the efficacy of ICS in treating airway stenosis, but there is a paucity of prospective data on the therapy [92, 93]. In a small prospective randomized controlled trial ($n=14$), the use of ICS in LTS after balloon dilation showed no short-term benefits of treatment [94]. These findings may be explained by a computational analysis using 3-dimensional larynx models that suggests in ideal conditions, only 2.48% of inhaled drug particles may deposit at the site of stenosis [95]. The role of systemic corticosteroids has been assessed prospectively in a randomized placebo-controlled trial for patients with iatrogenic tracheal stenosis after ED, which demonstrated no significant difference in mean SFI

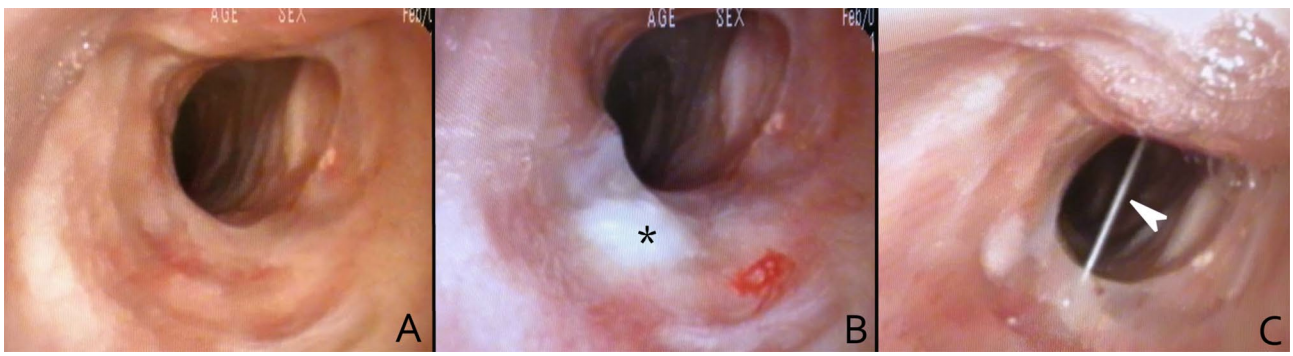

Fig. 1 Mild residual cricotracheal stenosis is seen in a patient following prolonged intubation (**A**). After appropriate topical anesthesia is achieved, corticosteroid is injected in submucosal fashion (**B**) through the cricothyroid space or anterior tracheal wall directly into the scar tissue, with blanching indicating proper placement (black asterisk). Avoidance of perforating the mucosa allows the injected material to remain in place without leakage. If additional posterior areas require treatment, the needle (white arrowhead) may also be passed transluminally into posterior scar tissue (**C**)

following surgery or number of dilations required. Patients on prednisolone who eventually underwent airway resection required a statistically significant shorter length of resection (5.3 mm), although the clinical significance of this difference is not well understood [96].

Topical MMC, first used in airway stenosis in 1998, is possibly the most utilized and heavily investigated adjuvant therapy in the treatment of LTS and SGS [97]. MMC is an alkylating agent derived from *Streptomyces caespitosus* that inhibits DNA and RNA synthesis and fibroblast proliferation when applied topically, without damaging respiratory epithelium [98]. A literature review focusing on representative studies assessing efficacy of MMC in airway stenosis argues that its off-label use is supported and the associated risk of airway obstruction from exudate should be discussed with patients [99]. While timing, dosage, and duration of application are not standardized, randomized controlled trials may help elucidate the role of MMC in LTS. The retrospective study by Feinstein et al. found that MMC application was associated independently with an increase in mean SFI of 157 days regardless of etiology [74]. In an attempt to determine whether 2 applications of MMC are superior to 1, Smith et al. conducted a randomized placebo-controlled trial for patients with various etiologies of SGS in which 26 patients received adjuvant MMC after ED. One month later, patients were randomized to receive a second application of MMC or placebo following a second endoscopic procedure. The study found that for two applications, recurrence rates decreased at both 1- and 3-year follow-up, but there was no significant difference at 5-year follow-up, suggesting that MMC may delay, but not prevent recurrence [100]. Further prospective investigation is encouraged. Other potential adjuvant therapies include the use of methotrexate, an immunomodulatory agent, which may increase the mean SFI in patients with recurrent nonvasculitic LTS [101].

Conclusions

SGS arises from various etiologies, and further understanding of its pathogenesis can aid in the development of novel therapies for this disease. Role of inflammation in the development of iatrogenic and idiopathic SGS is continuing to be studied. The IL-23/IL-17A inflammatory axis appears to be a potential mechanism for development of iSGS. Additionally, recent findings demonstrating upregulation of PD-1/PD-L1 expression in SGS may lead to a potential target for immunotherapeutic inhibition for development of SGS. It is imperative to obtain a thorough history for each patient presenting with respiratory complaints, as misdiagnosis can delay proper treatment. Endoscopic and surgical techniques continue to be investigated to determine optimal treatment protocols. In-office corticosteroid injections continue to show promise in the treatment of SGS.

Compliance with Ethical Standards

Conflict of Interest No disclosures relevant to the subject matter. Dr. Rosow reports a one-time payment from Springer for co-editing a published book.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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