Benign Tracheal Stenosis and Subglottic Stenosis

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KEYWORDS

• Subglottic stenosis • Tracheal stenosis • Rigid bronchoscopy • Interventional pulmonology

KEY POINTS

- Diagnosis and classification of benign tracheal and subglottic stenosis.
- Understand common etiologies and other systemic disease processes that contribute to tracheal and subglottic stenosis.
- Initial work up.
- Different management strategies.

INTRODUCTION

This article aims to explore the causes, diagnostic methods, and management strategies for benign tracheal and subglottic stenosis to enhance understanding and improve patient outcomes.

DEFINITIONS AND CLASSIFICATIONS

Laryngotracheal stenosis (LTS) is a broad term that describes narrowing of the proximal central airways which leads to obstructed airflow and subsequent respiratory distress. Subglottic stenosis is narrowing from below the vocal cords to the first tracheal ring, while tracheal stenosis describes the narrowing from the first tracheal ring down to the level of the main carina. Tracheal stenosis is often classified as simple versus complex. Simple stenosis is defined as lesions having occlusion of a short segment (<1 cm), with the absence of tracheomalacia, and no involvement of the cartilage. Whereas complex stenosis is defined as having extensive disease ($\geq$1 cm), multilevel stenosis, or varying degrees of cartilage involvement or circumferential contraction scarring, along with associated malacia.[1] Additionally, a commonly used system is the Meyer-Cotton classification for subglottic stenosis, which gives a grade based on severity of obstruction. A widely used classification system, created by Freitag and colleagues[2] classifies stenosis based on type, degree of stenosis, and location. This, however, may lead to variability among different proceduralists. Irrespective of which classification is used, it is paramount to document the length, location, and complexity of stenosis along with an assessment of their functional impairment (ie, performance status, dyspnea scales, inability to clear secretions etc).

CAUSES

The etiology of subglottic and tracheal stenosis is multifaceted, and understanding the underlying causes is crucial for appropriate management. Common causes include postintubation, posttracheostomy, and infections. Inflammatory conditions such as relapsing polychondritis, sarcoidosis, and granulomatous polyangiitis can contribute to both subglottic and tracheal stenosis. In a retrospective 10-year review of treatment outcomes of adult subglottic stenosis, 45% were related to granulomatosis with polyangiitis, 25% were postintubation, and 33% were idiopathic.[3] Additionally, there are other contributing factors such as diabetes mellitus, vascular disease, and gastroesophageal

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Abbreviations	
DES	drug-eluting stent
EC	electrocautery
GERD	gastroesophageal reflux disease
ICU	intensive care unit
MMC	mitomycin-c
PITS	postintubation tracheal stenosis
SCT	spray cryotherapy
α-SMA	α-smooth muscle actin
T2DM	type 2 diabetes mellitus

reflux disease (GERD). One common mechanism is fibrotic scarring in response to an insult, and in some cases without an apparent etiology.

Studies continue to show the relationship between GERD and subglottic or tracheal stenosis.[4] One study showed that 78% of the patients with laryngotracheal stenosis had GERD as verified by an abnormal 24-hour esophageal monitoring.[5] While the correlation between GERD and laryngotracheal stenosis is evident, the question then shifts to potential causality. Little and colleagues described successful improvement of laryngotracheal stenosis after treatment of GERD,[6] first as a case report, which led to animal models. In the experimental animals, mucosal lesions that were painted with gastric acid developed subglottic stenosis when compared with mucosal lesions in the control animals that were not exposed to gastric acid and did not develop subglottic stenosis. Multiple studies have shown the detrimental effects of intubation in relation to postintubation tracheal stenosis (PITS). Patients with PITS were more likely to develop web-like stenosis at the cuff site. Additionally, prolonged intubation has been related to an increased likelihood of developing PITS. Roushdy and colleagues[7] found that patients with longer duration of mechanical ventilation (16.6 $\pm$ 10.4 days) developed tracheal stenosis compared with patients with shorter duration of mechanical ventilation (12.1 $\pm$ 7.6 days) after 6 months of follow-up. It is important to recognize that during the coronarvirus disease 2019 (COVID19) pandemic, many patients had prolonged intubations due to initial scarcity of safety data for mitigating aerosol generation during tracheostomy.[8]

Endotracheal intubation, and specifically the pressure related to the cuff results in tracheal ischemia and local necrosis, resulting in cellular dysfunction and injury which then leads to pathologic repair and subsequent fibrosis. Hypoxia-inducible factor-1 is a transcription factor shown to upregulate different profibrotic genes and cytokines. Under hypoxic conditions in vitro, normal laryngotracheal fibroblasts proliferated faster, and expression of profibrotic cytokine interleukin-6 (IL-6) which in turn increased expression of α-smooth muscle actin (α-SMA), collagen-1, and matrix metallopeptidase 13 (MMP13).[9] This increase led to a shift from normal laryngotracheal fibroblasts to a myofibroblast phenotype. Because of the local ischemia and pressure necrosis, it is important to understand that this may potentially be preventable with low-pressure cuffs and appropriate monitoring of cuff pressures.

This disease remains a burden on the health care system. Studies have suggested that tracheal stenosis develops in 20% to 30% of patients following tracheostomy and between 1% and 7% of these patients develop symptoms that require intervention.[10] The mortality rate in patients who developed post-tracheostomy tracheal stenosis was found to be 7.9%.[11]

There have been recent investigations to evaluate whether microbiome modulation can prevent subglottic stenosis. In 2017, Gelbard and colleagues[12] utilized culture-independent nucleic acid, protein, and immunologic approaches to profile laryngeal microbial flora. They found that 10 out of 10 patients with iatrogenic laryngotracheal stenosis showed PCR positivity for *Acinetobacter baumannii*, compared with only 1 of 10 patients with idiopathic subglottic stenosis. Interestingly, 10 of 10 idiopathic subglottic stenosis patients had detectable PCR products for *Mycobacterium tuberculosis complex*, compared with 2 of 10 iatrogenic laryngotracheal stenosis patients. While the correlation does not lead to causation, it is worth noting that these pathogens may promote a proinflammatory state and chronic inflammation with aberrant wound healing. A recent study showed that the use of a polymeric antimicrobial peptide eluting endotracheal tube in mice led to less infiltration of T cells and macrophages within the airway as well as reduces bacterial populations and decrease the thickness of the lamina propria in in vivo subglottic stenosis.[13] Further studies are warranted to evaluate the efficacy of such endotracheal tubes.

In recent years, diabetes has been the direct cause of 1.5 million deaths worldwide, and 48% of all deaths due to diabetes occurred before the age of 70 years.[14] Patients with diabetes mellitus are more likely to develop iatrogenic tracheal stenosis due to several reasons.

1. Impaired wound healing: Diabetes mellitus is characterized by impaired wound healing due to high blood sugar levels on blood vessels and immune function. Tracheal stenosis can result from aberrant healing after procedures like intubation or tracheostomy. In patients

with diabetes, the wound healing process may be further compromised, leading to a higher likelihood of scarring and subsequent tracheal stenosis. In a study published by Lina and colleagues, investigators evaluated scar fibroblasts in patients with type 2 diabetes mellitus (T2DM) compared with those without.[15] The findings showed that in patients with T2DM, the scar fibroblasts had increased α-SMA expression, increased contractility, and collagen-1 protein.

2. Vascular complications: It is widely known that diabetes is associated with microvascular and macrovascular complications throughout the body. These same vascular complications can occur to tracheal blood supply and in turn impair the healing process and contribute to tracheal stenosis.

CLINICAL PRESENTATION

The most common presenting symptoms are progressive dyspnea, cough, hoarseness, and retained secretions. As the disease progresses, patients will present with dyspnea on exertion, dyspnea at rest, and even wheezing and stridor. Many times, these patients are misdiagnosed with asthma. Initial evaluation starts with good history taking, as this may lead to the etiology of their stenosis. Diagnostic testing involves pulmonary function tests, specifically to look at the flow/volume loops on spirometry. The classic finding is fixed obstruction on flow/volume loop. The Expiratory Disproportion Index obtained by spirometry is both a sensitive and specific parameter to distinguish between laryngotracheal stenosis and asthma.[16,17] Additional work up can include a CT trachea and flexible bronchoscopy. The advantage of CT trachea is that no sedation is necessary for the study to be completed, compared with sedation to tolerate bronchoscopy. Flexible bronchoscopy should only be done by skilled bronchoscopists, as even minimal trauma to the airway by the bronchoscope can lead to a critical airway in an already compromised lumen.

The physiology of symptoms is based on the limitation of air flow. Flow is equal to velocity × sectional area. Poiseuille's law states that flow rate is proportional to the radius to the fourth power. Based on this, a 50% reduction in radius results in a 16-fold increase in airflow resistance. Therefore, when the sectional area is decreased by stenosis, the resistance increases and leads to low air flow, followed by dyspnea and tachypnea, which in turn leads to turbulent flow and subsequent respiratory failure.

MANAGEMENT

The initial management is based on presentation, severity of symptoms, and their underlying cause. Based on the author's practice, for clinically unstable stenosis, initial optimization in an intensive care unit (ICU) setting is preferred. This allows close monitoring while more definitive management options are being coordinated. A plan for intubation and rescue airway should be discussed and coordinated among all parties involved, including discussion with the ICU, Anesthesia services, Interventional Pulmonology, Otolaryngology, and Acute Care Surgery in the event a surgical airway is necessary. Additional stabilization of symptoms includes the use of Heliox, a combination of helium and oxygen, which has been used in this setting for a long time.[18] The physiochemical property of helium being less dense allows for improved airflow because it increases laminar flow, which reduces the work of breathing and improves alveolar ventilation.

Definitive management involves surgical intervention and management of the primary etiology (ie, autoimmune disorder, GERD, etc). However, bronchoscopic management with the goal of restoring airway patency is most often the first-line therapy given that it is less invasive, carries less risk, and more often available when compared with surgical interventions. The simultaneous use of 2 or more bronchoscopic techniques is very common and has been reported.

Bronchoscopic management varies based on the evaluation of the stenosis, which we will review.

1. *Mechanical dilatation*: This technique involves an endoscopic balloon via bronchoscope to slowly widen the endoluminal component of the airway. Mechanical dilatation can also be performed with the use of a rigid tracheoscope.
   a. *Advantages*: Balloon dilatation via bronchoscopy is more readily available than other modalities. While the rigid tracheoscope maintains the airway and allows additional tools to be advanced through the barrel to aid in restoring airway patency, rigid bronchoscopy does require general anesthesia availability.
   b. *Disadvantages:* Success rates are modest (around 40%), especially in complex stenosis, and often require multiple procedures.[19] The use of rigid bronchoscopy requires additional training and general anesthesia.
   c. *Risks:* Mucosal abrasions, lacerations, and full thickness tears. Unfortunately, a tear will lead to scarring and further stenosis.

2. *Laser therapy*: Laser allows the proceduralist to make radial incisions and to ablate or remove the scar tissue leading to stenosis. It is usually followed by dilatation.
   a. *Advantages:* Ability to use Nd:YAG, Holmium, or CO_2 laser. Laser incision works well for simple web-like stenosis and allows for incision prior to mechanical dilation via endoscopic balloon and/or rigid bronchoscope.[20] The energy from the laser is noncontact and can be localized to the area of interest while minimizing further dissipation to surrounding tissue. A particular advantage to the use of laser in idiopathic subglottic stenosis is the ability to make large wedge excisions to remove stenotic tissue with preservation of small bridges to allow for remucosalization (**Figs. 1** and **2**).[21] This technique, along with maximum medical therapy allowed for a decrease in recurrence rates of stenosis. Further studies are addressing effectiveness of laser resection versus dilatation.[22]
   b. *Disadvantages*: Laser may not be readily available, FiO_2 must be decreased to 0.40 due to risk of airway fire. Cartilage destruction can promote restenosis.
   c. *Risks*: Due to its properties, it can penetrate through the airway. To minimize the risk of airway perforation, the laser beam must always be parallel to the wall of the airway.
3. *Electrocautery*: Electrocautery (EC) uses heat energy to ablate tissue, and using an EC knife for radial incision. This technique could also be followed by mechanical dilatation of the stenotic area.
   a. *Advantages:* The EC knife allows for very precise radial incision, prior to mechanical dilation.
   b. *Disadvantages*: Given that EC is a contact mode of thermal ablation, this can lead to distribution of energy to the surrounding tissues, and in turn lead to scarring and subsequent stenosis. Like the laser, EC also requires FiO_2 to be decreased to 0.40 due to risk of airway fire. Further limitations include the ability to use EC in patients with pacemaker or Automatic Implantable Cardioverter-Defibrillator (AICD).
   c. *Risk:* The high energy through a contact mode can also lead to excessive cutting and lead to airway perforation.
4. *Cryotherapy*: Cryotherapy uses extreme freeze and thaw cycles to cause cryogenic destruction of tissue that leads to stenosis.[23]
   a. *Advantages:* Cryotherapy is used as an adjunct to balloon dilatation. Does not require a decrease in FiO_2 like laser and EC, so it can be used safely in patients who are severely hypoxemic. Can be performed via contact method with a cryoprobe versus noncontact modality such as a Cryospray. Cryotherapy is less likely to affect

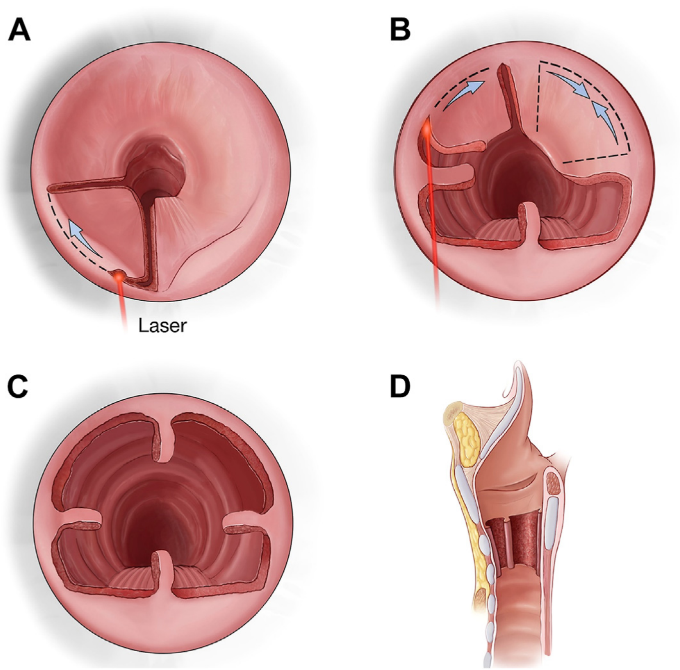

Fig. 1. Endoscopic wedge excisions with CO_2 laser for subglottic stenosis. (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

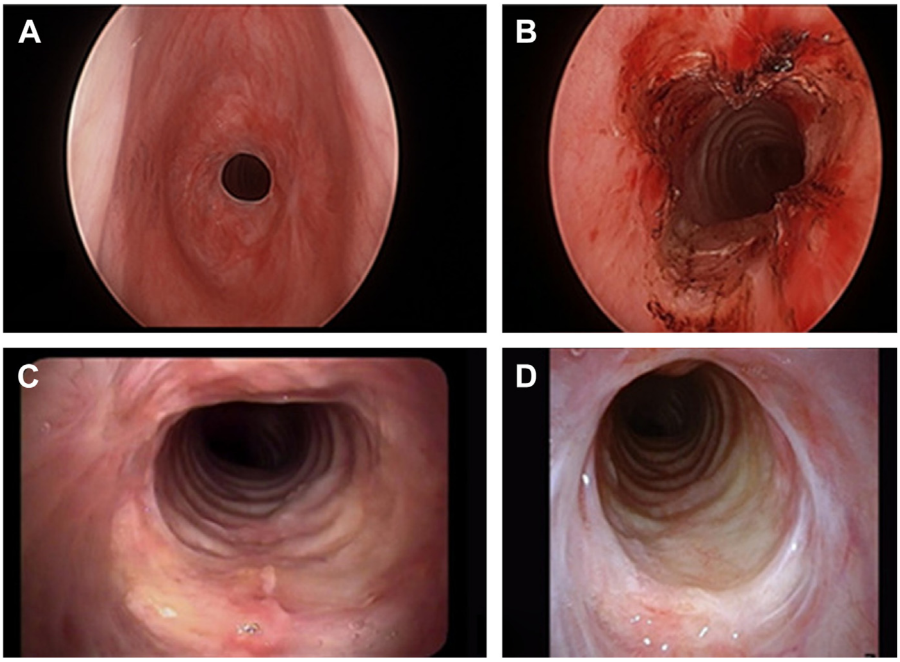

Fig. 2. (*A*) Intraoperative image pre-excision, (*B*) intraoperative after 3 wedge excision, (*C*) 7 weeks postop in clinic, and (*D*) 5 years postop in clinic. (Ekbom, D.C., Bayan, S.L., Goates, A.J. and Kasperbauer, J.L. (2021), Endoscopic Wedge Excisions with CO2 Laser for Subglottic Stenosis. The Laryngoscope, 131: E1062-E1066. https://doi.org/10.1002/lary.29013.)

the cartilage, collagen, or fat tissues in the airway and thus less likely to lead to airway perforation.

b. *Disadvantages*: Cryotherapy has a delayed effect, and thus may not be the initial modality for critical stenosis. Large studies are lacking, but from smaller studies, complex stenosis requires more procedures.[24]

c. *Risks:* Spray cryotherapy (SCT) using liquid nitrogen leads to expansion of the gas as the temperature rises, and this can lead to barotrauma and pneumothorax. SCT should be used with open/passive ventilation.

5. *Pharmacologic approaches*: There have been investigations into the use of medications such as topical mitomycin-c (MMC) application, intralesional steroid injection, application of rapamycin, and even the use of oral antifibrotic medications Nintedanib and Pirfenidone. These agents are considered to prevent recurrence of stenosis and not as a primary management.

   a. *Topical MMC application*: Mitomycin C is an alkylating antitumor antibiotic that works by inhibition of DNA and protein synthesis. MMC is applied topically in the immediate postdilation period, aimed at preventing restenosis. A study by Sun and colleagues showed that MMC regulated microRNAs involved in fibroblast apoptosis, overall leading to reduced fibrosis.[25] This mechanism is favorable to minimize restenosis in the setting of LTS. A small prospective randomized double-blind trial suggests that 2 applications of MMC reduced stenosis rates for 2 to 3 years when compared with a single application. However, at the 5-year follow-up period, relapse rates were the same between the 2 groups.[26] A meta-analysis was conducted to evaluate the efficacy of MMC in the endoscopic management of LTS.[27] Overall, it suggested that MMC is an effective and safe option, with studies showing a longer symptom-free time and increased length of time between repeat procedures. One major limitation is that most of the included studies were observational, and thereby a lower quality of evidence. Topical use of MMC was suggested not to provide a significant difference in stenosis relapse compared with placebo in a randomized, double blind, placebo-controlled trial, however, the enrollment target was not achieved.[28] Ultimately, large high quality, prospective, randomized trials are still needed to evaluate the use of MMC in LTS, but it provides potential adjunctive opportunities.

   b. *Intralesional steroid injection*: Intralesional steroid injection is known to decrease collagen synthesis and fibrosis. Corticosteroids were used to decrease postdilation fibrotic healing in benign esophageal strictures[29] following caustic injury, and these data were then applied to endoscopic management of LTS. Another mechanism of action is the ability for triamcinolone to prevent the cross-linking of collagen that results in scar contracture.[30] There are multiple small retrospective studies of serial intralesional steroid injections for subglottic stenosis that can be performed in the outpatient setting.[31] This provides a potential alternative for managing stenosis, while mitigating the use of resources such as operating room time and general anesthesia (which carries its own risk) and potentially obviate the need for future airway procedures. Note that this is after initial endoscopic management with dilatation.

c. *Inhaled corticosteroids*: Inhaled budesonide is a potential adjunct in the multimodal management of laryngotracheal stenosis. Given its strong local anti-inflammatory effect, budesonide deposits on the respiratory mucosa and increases the local drug concentration and inhibits the inflammatory response in the airway.[32] Potential use for this includes following radial incision with thermal energy and balloon dilatation to decrease the inflammatory response and granulation tissue associated with stent placement.

d. *Drug-eluting stents (DESs):* Local sirolimus delivery via DES was shown to reduce fibrosis in LTS in a murine model.[33] The ability to deliver sirolimus locally is advantageous given its potential systemic side effects. This study showed proof of concept for the use of DES in the management of LTS.

e. *Antifibrotics*: While antifibrotics have become a mainstay in the treatment of interstitial lung disease, there is ongoing research for the use of Nintedanib and Pirfenidone in the use of tracheal stenosis. Nintedanib is a triple tyrosine kinase inhibitor and an antagonist to TGF, which can simultaneously block the expression of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and fibroblast growth factor receptors. Animal studies have shown that Nintedanib can reduce stenosis by leading to reduced fibrosis and tissue hyperplasia.[34] Pirfenidone inhibits TGF-β1-induced differentiation of fibroblasts into myofibroblasts, thereby preventing excess collagen synthesis and extracellular matrix production. Small case reports have shown that the use of Pirfenidone along with bronchoscopic interventions can prolong the time to repeat bronchoscopic interventions.[35]

6. *Stent placement:* In cases where stenosis cannot be managed conservatively, a stent can be considered. It is wise to ensure the patient has the appropriate support and insight before placing a tracheal stent. Airway stents come in many different sizes and varieties (eg, metallic-uncovered, metallic-covered, silicone, 3-dimensional printed silicone).
   a. *Advantages*: Tracheal stents allow for the stabilization of the airway and maintain airway patency, while offering a less invasive approach when compared with surgical interventions. **Figs. 3** and **4** provide an example of a young patient with post-intubation tracheal stenosis who required laser incision, balloon dilation, and stent placement.
   b. *Disadvantages*: Requires close follow-up and stent maintenance. Not recommended for subglottic stenosis. Oversizing a stent to avoid migration poses the risk of further ischemia and pressure necrosis due to the radial force exhibited by the stent.
   c. *Risk*: Stent migration can lead to a potential airway emergency, as it could migrate and obstruct a more distal main stem bronchus. The bronchoscopist can suture the stent to help prevent migration,[36] however, this carries a small risk of infection at the suture site. Additionally, stent migration leaves the previous area of stenosis compromised. Mucus plugging of stent can be a life-threatening emergency and should be discussed with all patients if a stent is being considered. The coating of a tracheal stent (whether silicone or covered metallic stent) is vulnerable to mucostasis, and subsequent mucus plugging which can acutely narrow the lumen patency and even completely occlude it. Furthermore, there is an up to 58% risk of restenosis within 1 year following stent removal.[37] Risk factors for restenosis include diabetes mellitus and morbid obesity.
7. *Surgical resection*: Considered the gold standard treatment for tracheal and subglottic stenosis. It is important to note the difference of cricotracheal resection for subglottic stenosis when compared with tracheal resection.
   a. *Advantages*: High success rate, with long-term effects.[38] In the results published by Grillo and colleagues, over 93% of patients

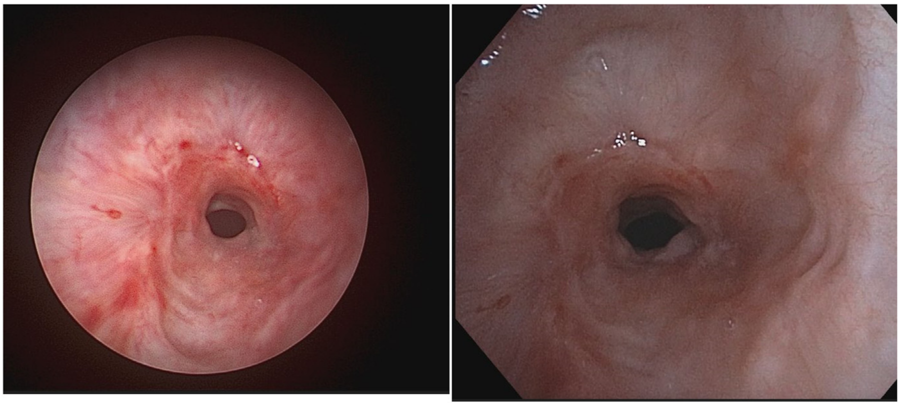

Fig. 3. A 33-year-old female with motor vehicle accident and prolonged intubation and tracheostomy who developed tracheal stenosis. 5-mm airway. Severe complex stenosis. About 3.0 cm distal to the cricoid, and about 7.0 cm proximal to the main carina. Total length: 1 cm (picture from Henry Ford Health).

undergoing tracheal resection for PITS were found to have good or satisfactory results.

b. *Disadvantages*: Should not be considered in a critical or unstable airway. Requires a high level of expertise and limited patient comorbidities. Recurrence of stenosis is around 40% after surgery in patients with idiopathic subglottic stenosis.[39]

c. *Risk*: Restenosis, wound infection, glottic dysfunction. Suture line granulations occurred in nearly 10% of patients early on, and almost completely resolved with the use of absorbable sutures (after 1978).[38]

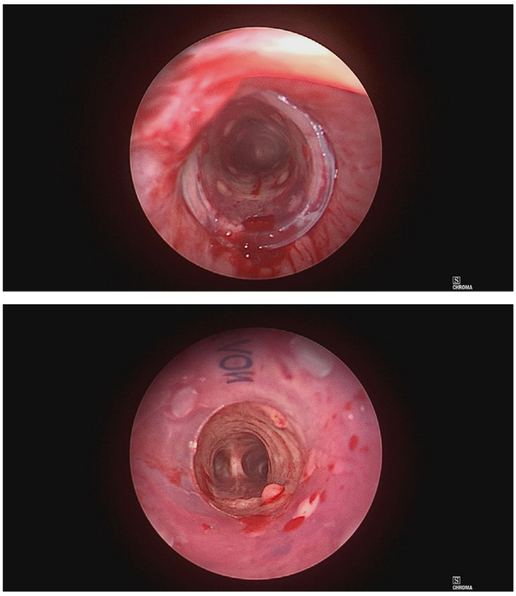

Fig. 4. Status postlaser incision, balloon dilatation, straight silicone stent placement (picture from Henry Ford Health).

FUTURE ADVANCES FOR MANAGEMENT

The potential role of novel therapies, such as tissue engineering and regenerative medicine,[40,41] are in the early stages of research and provide a promising alternative for the near future.

SUMMARY

Tracheal and subglottic stenosis are complex and challenging conditions that require a multidisciplinary approach for effective management. Early diagnosis and prompt intervention can improve the quality of life for patients and prevent further complications. Further research and advancements in diagnostic techniques, bronchoscopic and surgical interventions, and postoperative care are essential to enhance the understanding and treatment of laryngotracheal stenosis.

CLINICS CARE POINTS

- Diabetes mellitus is a strong risk factor for development and recurrence of laryngotracheal stenosis.
- Tracheal stenosis treated with airway stenting recurs after stent removal in approximately 50% of the cases.
- Surgical resection is the gold standard treatment of tracheal stenosis.
- Idiopathic subglottic stenosis has a high recurrence rate (approximately 40%) after surgical resection.

DISCLOSURE

None.

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