

Review article

Multi-disciplinary management of patients with benign airway strictures: A review



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ABSTRACT

Histologically benign airway strictures are frequently misdiagnosed as asthma or COPD and may present with severe symptoms including respiratory failure. A clear understanding of pathophysiology and existing classification systems is needed to determine the appropriate treatment options and predict clinical course. Clinically significant airway strictures can involve the upper and central airways extending from the subglottis to the lobar airways. Optimal evaluation includes a proper history and physical examination, neck and chest computed tomography, pulmonary function testing, endoscopy and serology. Available treatments include medical therapy, endoscopic procedures and open surgery which are based on the stricture's extent, location, etiology, morphology, severity of airway narrowing and patient's functional status. The acuity of the process, patient's comorbidities and operability at the time of evaluation determine the need for open surgical or endoscopic interventions. The optimal management of patients with benign airway strictures requires the availability, expertise and collaboration of otolaryngologists, thoracic surgeons and interventional pulmonologists. Multi-disciplinary airway teams can facilitate accurate diagnosis, guide management and avoid unnecessary procedures that could potentially worsen the extent of the disease or clinical course. Implementation of a complex airway program including multidisciplinary clinics and conferences ensures that such collaboration leads to timely, patient-centered and evidence-based interventions. In this article we outline algorithms of care and illustrate therapeutic techniques based on published evidence.

1. Classifications and physiology

In patients with benign airway strictures, clear definitions and classifications are needed to determine the appropriate treatment options and predict clinical course. Benign airway strictures can involve the upper and central airways extending from the supraglottis to the lobar airways. Irrespective of location, a physiologically abnormal obstruction is defined as narrowing of the airway by >50%. In patients with mild airway stenosis (i.e. <50% reduction in the cross-sectional area [CSA]), the airflow pressure drop along the stenotic segment which determines the work of breathing, is similar to the pressure gradient through the

normal glottic opening and thus is unlikely to cause significant dyspnea, even with exertion [1]. Moderate stenosis (51–70% reduction in CSA) could cause symptoms on exertion with a significant pressure drop occurring at higher flow rates. Severe stenosis (>71% reduction in CSA) results in significant pressure gradient even at a low flow rates leading to symptoms at rest or mild exertion. Objective quantification of the degree of narrowing determines whether a certain airway stricture contributes to patient's dyspnea. There are other symptoms, however, that impact the decision-making process pertinent to treatment. Patients with laryngotracheal stenosis (LTS) can have symptoms other than dyspnea such as dysphagia and dysphonia. In fact, some classification systems address

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these variables in addition to the extent, location and severity of airway narrowing. Table 1 summarizes and describes the pros and cons of each of the published classification systems [2–8]. While the ideal system in the classification of LTS remains questionable, a recent study assessed three classification systems to effectively stratify the risk of long term tracheostomy and demonstrated that the McCaffrey and Lano systems offer more precision than the Cotton-Myer scale [9]. We believe that regardless of which classification system one uses, a proper documentation of laryngeal or tracheal stenosis should be based on objective criteria and include: assessment of functional impairment (eg. Dyspnea scales, performance status); length of the stenotic airway; shape (circumferential, elliptical, crescent or triangular), complexity (with or without malacia) and precise location (centimeters or number of rings below or above a specific reference point-vocal cords, cricoid, main carina for laryngotracheal strictures or main carina, primary and secondary carinas for bronchial strictures) [10].

The optimal management of benign airway strictures requires the collaboration and availability of a multidisciplinary team, including otolaryngology, thoracic surgery and interventional pulmonology. A thorough history and physical exam is essential in identifying the etiology of the stricture and its possible association with other systemic diseases [Table 2]. This includes history of autoimmune disorders, airway infection, previous airway instrumentation, history of endotracheal intubation or tracheostomy, prior surgery or trauma. Objective evaluation includes computed tomography (CT) of the neck and chest with multiplanar reconstruction or 3D internal and external reconstruction (Fig. 1A) as well as serological tests for working up potential underlying connective tissue disorders (CTD). Pulmonary function testing with attention to the flow volume loops can help detect patterns of airflow obstruction and allow monitoring physiologic changes after interventions. Of note, the classic pattern of truncated inspiratory and expiratory limbs is not sensitive and may only be seen when the tracheal diameter is reduced to 6–8 mm [11] (Fig. 1B). Patients with unilateral bronchial stenosis may present with a biphasic flow-volume loop, but these findings are also not sensitive [12]. Once non-invasive assessment is completed, the next step is to evaluate the extent and severity of the narrowing and its impact on functional status, voice and swallowing. This involves performing a flexible laryngoscopy and/or a white light bronchoscopy. Biopsies could help narrow the differential diagnosis and rule out an underlying malignant process and may help in diagnosing a benign process. Depending on the disease extent, location, etiology and operability, the care of these patients requires the expertise of a multidisciplinary airway team. Endoscopic options include endoscopic resection, endoscopic dilation, intralesional injection of drugs, endoluminal stents and Montgomery T-tubes. Open surgical options include a chronic indwelling tracheostomy, cricotracheal/laryngotracheal resection with primary anastomosis reconstruction. Given the multitude of techniques learned through different training pathways, major academic centers have implemented such teams for management of patients with benign airway strictures. In this article we propose a multi-disciplinary algorithmic approach for the management of patients with benign airway strictures based on currently published evidence and available local expertise [Fig. 2].

2. Subglottic stenosis

2.1. Etiology, prevalence and symptomatology

Patients with subglottic stenosis (SGS) usually present with dyspnea on exertion, cough, wheezing and difficulty clearing secretions but may progress to dyspnea and stridor at rest. Other presenting symptoms include dysphagia, globus, and dysphonia [13]. A thorough history and physical examination is the key to a correct and timely diagnosis. Work up includes serological tests for anti-neutrophil cytoplasmic antibodies (ANCA) and angiotensin-converting enzyme (ACE), pulmonary function tests, CT scan of the neck and chest and an endoscopic examination.

Table 1
Classification system for laryngotracheal stenosis.

Classification System Study/year	Classification Criteria	Comments
McCaffrey et al.,/ 1992	Stage I: Lesions are confined to the subglottis or trachea and <1 cm long Stage II: Lesions are isolated to the subglottis and >1 cm long Stage III: Subglottic/tracheal lesions not involving the glottis Stage IV: Lesions involve the glottis Grade 1: 0%–50% Obstruction Grade 2: 51%–70% obstruction Grade 3: 71%–99% obstruction Grade 4: No detectable lumen	- It is based only on the vertical extent - It can predict tracheal decannulation on the basis of anatomic location and extent of stenosis 90% of stages I and II, 70% of stage III, and 40% of stage IV patients undergo decannulation successfully
Myer et al.,/1994	Grade 1: 0%–50% Obstruction Grade 2: 51%–70% obstruction Grade 3: 71%–99% obstruction Grade 4: No detectable lumen	- It is based only on the degree of reduction in airway cross surface area (CSA).
Lano et al.,/1998	Stage I: One subsite involved Stage II: Two subsites involved Stage III: Three subsites involved	- It is based on sites involved (glottis, subglottis, trachea) - The following is the correlation between this staging and likelihood for successful decannulation Stage I: 94%, stage II: 78%, stage III: 20%
Nouraei et al.,/ 2007	Airway status 1 No airway prosthesis 2 Intraluminal airway prosthesis (stent) 3 Tracheostomy or tracheostomy-tube dependent, patient voices 4 Tracheostomy dependent, patient does not voice 5 Death as a result of a direct complication of airway disease Dyspnea Grade 1: "I only get breathless with strenuous exercise." Grade 2: "I get short of breath when hurrying on level ground or walking up a slight hill." Grade 3: "On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace." Grade 4: "I stop for breath after walking about 100 yards or after a few minutes on level ground." Grade 5: "I am too breathless to leave the house or I am breathless when dressing." Voice 1 No problems with voice	- This is a comprehensive system used by otorhinolaryngologists - It does not include extent and severity criteria (ie, reduction in CSA) - It is primarily designed for documenting functional outcomes of adult laryngotracheal stenosis

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Table 1 (continued)

Classification System Study/year	Classification Criteria	Comments
Freitag et al.,/2007	2 Some problems with my voice 3 Making voice is effortful and significant difficulties being heard or understood 4 Can only produce a weak voice or whisper 5 No voice Swallowing 1 Eat and drink normally 2 Normal diet but with some difficulty swallowing 3 Significant swallowing difficulties 4 Serious problem swallowing (ie, diet consists almost entirely of liquidized foods) 5 Unable to swallow	- It is primarily designed for grading tracheal stenosis from pulmonologists' perspective - The degree of severity criterion is not justified physiologically. - The structural types are not mutually exclusive thus leading to overlap in classification.
Ghorbani et al.,/2012	Type: Structural Type 1: Exophytic or intraluminal Type 2: Extrinsic Type 3: Distortion Type 4: Scar or stricture Dynamic or functional Type 1: Damaged cartilage or malacia Type 2: Floppy membrane Degree of stenosis: Code 0: No stenosis Code 1: <25% Code 2: 26%–50% Code 3: 51%–75% Code 4: 76%–90% Code 5: 91%–100% Location: I Upper one-third of the trachea II Middle one-third of the trachea III Lower one-third of the trachea IV Right main bronchus V Left main bronchus	Diameter of structure Score 0: Stenosis rate between 0% and 25% Score 1: Stenosis rate between 26% and 50% Score 2: Stenosis rate between 51% and 75% Score 3: Stenosis rate between 76% and 90% Score 4: Stenosis rate 91% or higher Type of stenosis Score 1: Granulation tissue Score 2: Granulation tissue, fibrosis, and inflammation Score 3: Fibrosis Score 4: Malacia Clinical symptoms Score 1: Dyspnea only during intense activity Score 2: Dyspnea during normal activity but

Table 1 (continued)

Classification System Study/year	Classification Criteria	Comments
Monnier et al. (European Laryngological Society)/2015	Grade of Stenosis I ≤ 50% Obstruction II 51%–70% obstruction III 71%–99% obstruction IV No lumen a = Only one site involved (supraglottic/glottis/subglottis/tracheal) b = two sites involved c = three sites involved d = all four sites involved + is added to any final score to indicate an additional severe comorbidity or congenital anomaly	physical examination results are normal Score 3: Long inhalation and exhalation but with no stridor or retraction Score 4: Stridor and retraction - Combination of three parameters, instead of just using severity or extent of stenosis may be able to better predict the post-operative course in these patients.

Table 2

Etiology of benign airway stenosis.

Etiology of Benign Airway Strictures

Subglottic Stenosis

Idiopathic Subglottic Stenosis

Congenital (Membranous web, Deformed Cartilage, Closed First Ring)
Connective Tissue Disorders (Granulomatosis with Polyangiitis, Sarcoidosis, Amyloidosis, Relapsing polychondritis, Ulcerative colitis, Scleroderma)
Post Intubation Tracheal Stenosis
Post Tracheostomy Tracheal Stenosis

Infectious (Tuberculosis, Respiratory Papillomatosis, Bacterial Laryngitis)
Radiation injury
Inhalational Injury

Benign Tracheal Stenosis

Post Intubation Tracheal Stenosis

Post Tracheostomy Tracheal Stenosis
Connective Tissue Disorders (Granulomatosis with Polyangiitis, Sarcoidosis, Amyloidosis, Relapsing polychondritis, scleroderma)
Infectious (Tuberculosis, Respiratory Papillomatosis, Bacterial Tracheitis)

Radiation injury
Inhalational Injury
Foreign Body Aspiration

Benign Bronchial Stenosis

Tuberculosis

Endobronchial Fungal Infections
Connective Tissue Disorders (Granulomatosis with Polyangiitis, Sarcoidosis, Amyloidosis, Relapsing polychondritis, scleroderma)
Lung Transplantation
Post Foreign Body removal (including post stent removal)
Radiation or photodynamic therapy Injury
Inhalational Injury
Stent Related Stenosis

While a causative role has not been clearly established in adults, gastroesophageal reflux disease (GERD) is noted to be more prevalent in patients with this condition [14]. One study noted the presence of pepsin in 59% of the patients with Idiopathic SGS (iSGS) in biopsy specimens from the posterior commissure and subglottic airway mucosa, but none in the matched controls [14]. SGS is also seen in 16–23% patients with granulomatosis with polyangiitis (GPA) and accounts for 10–23% of all patients with SGS [15–17]. While a large number of these patients (~95%) can be ANCA positive on serology at some point in their disease

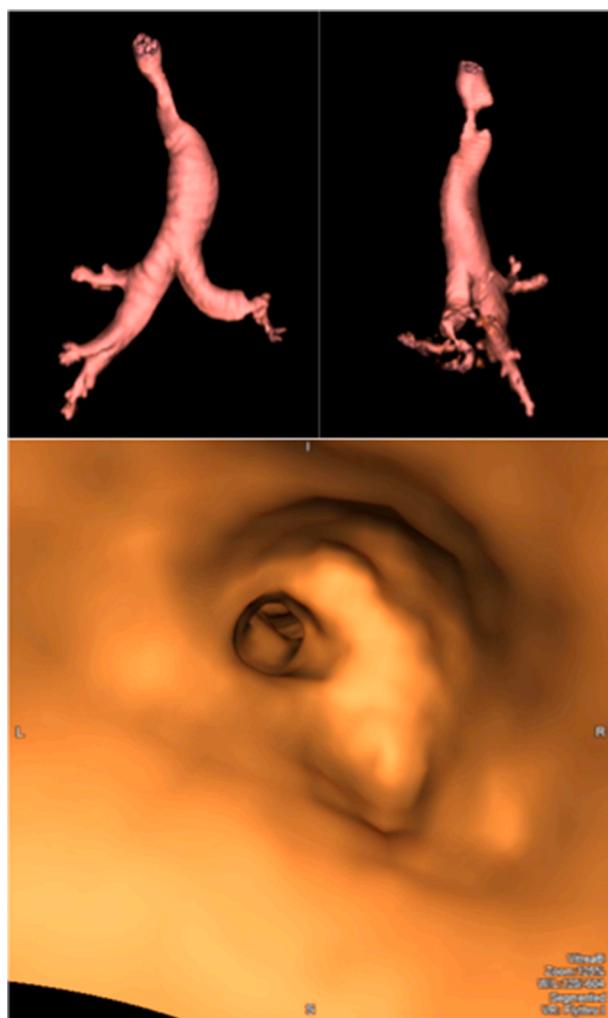


Fig. 1A. 3D Reconstruction of the CT Scan of the Neck and Chest in a patient with complex benign airway stenosis.

course [17], a negative ANCA does not permit exclusion of GPA. In fact, only 56–60% of the patients may be ANCA positive at the time of diagnosis or relapse of SGS related to GPA [18,19]. Serologic testing, however, should be performed in all patients with SGS, as there is about 1 in 4 chance of identifying an underlying connective tissue disease (CTD). In a study of 92 patients with non-traumatic LTS, 75% were found to be idiopathic LTS, but 25% were due to autoimmune disease. In fact, this study showed that ANCA antibodies were only positive in patients with GPA with all other serological testing being equivocal between the two cohorts [20]. The histopathologic assessment in SGS often demonstrates nonspecific fibrosis and infiltration by neutrophils and epithelioid histiocytes and rarely shows overt vasculitis or granulomatous disease [17–19]. SGS can also be seen with other CTDs, such as Relapsing Polychondritis (RP). In a large case series of patients with RP, SGS was noted in 5.5% (8/145) of patients [21]. This is often associated with malacia extending to trachea and mainstem bronchi. Other possible etiologies of SGS are listed in Table 2. Despite a thorough work up, in cases when no etiology is identified, a diagnosis of iSGS is established [22–24]. Idiopathic SGS is primarily seen in females, often in the 5th decade of life [25]. GERD can be seen in up to 65% of the patients with iSGS. There is some evidence demonstrating an imbalance between estrogen receptor-alpha, estrogen receptor-beta, and progesterone receptors in surgical specimens from female idiopathic subglottic stenosis patients, possibly indicating a role in inappropriate inflammation and increased stenosis susceptibility in these patients [26].

2.2. Management of idiopathic subglottic stenosis

A variety of treatment modalities are used for the management of idiopathic subglottic stenosis (iSGS). This includes medical therapy (oral steroids, inhaled steroids, anti-reflux medications and oral antibacterial medications), endoscopic dilation, endoscopic resection and open surgery [27].

The open surgical approach in patients with iSGS involves a single-staged laryngotracheal resection and reconstruction (LTRR). A meta-analysis showed a success rate of 95% in patients undergoing LTRR [28]. In a large series, Wang et al. reported outcomes of 263 patients that underwent LTRR with 93.5% (243/261) patients extubated in the operating room and 6.1% (16/261) patients requiring a temporary tracheostomy at the end of the surgery [25]. Anastomotic complications such as granulation, subcutaneous emphysema or early stenosis were noted in 11.7% (31/261) patients at the 30-days post op. On long-term follow-up (median – 66 months), delayed recurrence occurred in 8.7% (23/261) patients with 3.4% (9/261) patients requiring repeat laser assisted mechanical dilation (LAMD) every 6 months. A further follow-up survey in 180 of these patients showed that normal voice was present in 45% patients (82/180), while a change in voice occurred in 54% (96/180) patients with 67% (121/180) having a difficulty in projective voice. This is consistent with the data from a recent systematic review that also showed significantly worse voice quality in patients who underwent open resection [29].

There is lack of data on the role of medical therapy alone for patients with iSGS. However, studies have demonstrated a benefit from synergistic use of a combination of anti-reflux medications, oral trimethoprim-sulfamethaxazole and inhaled corticosteroids along with endoscopic therapies with a possible reduction in the rate of recurrence [27,30]. For patients with iSGS, endoscopic resection with adjuvant medical therapy (ERMT) has been suggested as the first line of management. Endoscopy has the advantage of being a less invasive and outpatient approach. It also has fewer complications than the open surgical approach in regards to voice-related outcomes. In a large prospective cohort study by Gelbard et al., patients who underwent ERMT were noted to have a lower recurrence rate (12.4%) compared to patients who underwent endoscopic dilation (either with a rigid instrument or balloon dilation) alone (28%) [30,31]. Patients who underwent crico-tracheal resection (CTR) were noted to have the lowest recurrence (1.2%) but the open surgery was associated with the higher peri-operative risk and worse postoperative patient-related voice outcomes. However patients who underwent CTR had the most surgical procedures performed (mean = 5) before open reconstruction [30]. Endoscopic resection entails removal of a significant portion of the scar using CO₂ laser [31] or knife with a “mucosal sparing technique”. Topical Mitomycin C has been used as an adjuvant treatment following mucosal sparing interventions and has been shown to reduce time to re-intervention. There is no consensus, however, on its routine use given possible complications and association with anastomotic complications in patients who underwent surgical resection [25,32,33]. When used, two applications of 0.5 mg/ml of topical mitomycin C can be considered at a 3–4 week interval [33]. Intralesional injection of steroids can be performed as part of the ERMT procedure to potentially decrease scar tissue formation [34]. A few recent studies have shown that serial in-office intralesional steroids with triamcinolone 40 mg/ml using topical anesthesia 3–6 weeks apart resulted in decreased recurrence of stenosis and increased the endoscopy free interval [35,36]. If symptomatic recurrence occurs after endoscopic intervention, surgical candidacy for an open surgical intervention for these patients should be considered.

Thus, the published data seem to justify the following approach: ERMT first and consider LTRR in cases of frequent recurrence. The definition of frequent recurrence is not clear from the literature, with investigators performing surgery after 3–7 endoscopic interventions [30]. If a patient is noted to be a poor candidate for open surgery, then

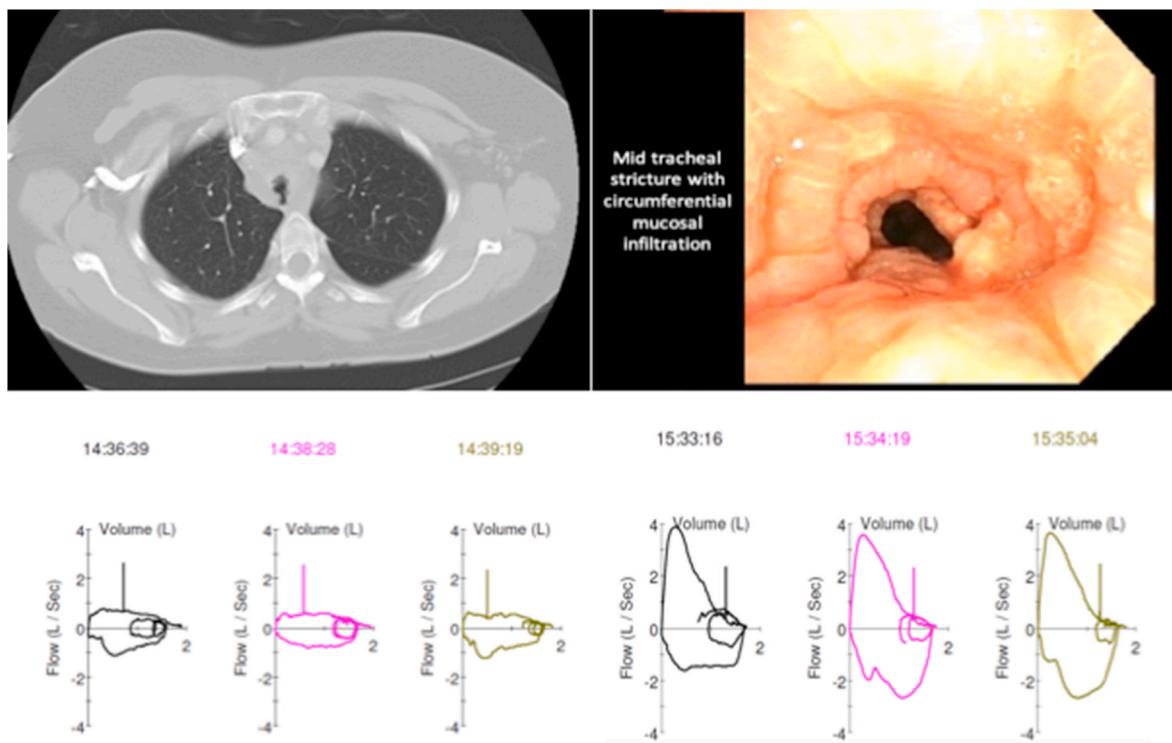


Fig. 1B. Flow volume loop demonstrating tracheal stenosis with flattened inspiratory and expiratory flow loop, with resolution post systemic treatment. Top Left: CT of the Chest (Axial Cut) demonstrating mid tracheal stenosis. Top Right: Bronchoscopy demonstrating mid tracheal stenosis with circumferential mucosal infiltration due to blastomycosis. Bottom Left: Flow volume loop prior to treatment demonstrating flattened inspiratory and expiratory loop consistent with tracheal stenosis. Bottom Right: Post treatment (Systemic anti-fungal therapy) flow volume loop demonstrating normal pattern and resolution of the stenosis. Pictures courtesy: Dr. Steve Pearson, MD. University of Chicago.

repeated endoscopic interventions with adjuvant local and medical therapy should be the mainstay of treatment and based on symptoms. A T-tube placement could be considered in refractory patients with need for repeat frequent interventions.

2.3. Management of subglottic stenosis associated with connective tissue disorders

Endoscopic interventions and systemic immunosuppressive therapy remains the cornerstone of management of symptomatic SGS in patients with connective tissue disorders such as GPA. While clinical remission rates have improved with newer pharmacologic therapies in these patients, studies suggest that SGS can prove refractory to pharmacologic therapy alone with up to 62% patient experiencing a relapse on conventional GPA therapy [18]. A recent study demonstrated that Rituximab may be more effective than other conventional GPA therapy (methotrexate, cyclophosphamide, azathioprine or TMP/SMX) in management of otolaryngologic manifestations of GPA including SGS [37]. LTRR in patients with GPA and SGS has been associated with disease relapse even in a highly selective group with 55–75% patients requiring additional tracheal dilation and 9–13% patients requiring a permanent tracheostomy [38,39]. In addition, patients with a systemic autoimmune disease causing SGS may also be susceptible to lower airway stenosis (mainstem bronchial or lobar) that may need repeated endoscopic procedures [40]. These include LAMD or electrocautery knife-assisted radial incisions with mechanical dilation using a rigid bronchoscope or balloon dilation along with intralesional steroids injection [15,18, 41]. Given the high risk of recurrence and risk of developing lower airway disease, close clinical and bronchoscopic follow up is recommended in these patients to ensure early diagnosis and management. Indeed, these patients will likely require multiple bronchoscopic dilations during the course of their illness. In a study with 47 patients,

after the first endoscopic procedure, the cumulative incidence of endoscopic treatment failure was 50% at 1 year, 70% at 2 years and 80% at 5 years [42].

Similarly, the primary treatment of patients with SGS in patients with RP includes management of the underlying disease with immunosuppressive therapy. Patients with refractory disease may require endoscopic interventions or tracheostomy [21].

3. Benign tracheal stenosis: post intubation and post tracheostomy

3.1. Etiology, prevalence and symptomatology

Benign tracheal stenosis is the end result of an altered inflammatory response to injury and excessive scar formation and possibly cartilage destruction leading to malacia. Post-intubation stenosis (PITS) and post tracheostomy tracheal stenosis (PTTS) appear to be the most common benign LTS followed by idiopathic and autoimmune causes [43]. PITS can be seen in 1–21% of intubated patients with 1–2% patients developing severe stenosis [44,45]. The risk factors of PITS include duration of intubation, size of endotracheal tube, cuff pressure (≥ 30 mm H₂O), trauma during intubation and need for reintubation, infection, previous radiation and diabetes mellitus. Symptomatic PTTS can be seen in 1.5–1.7% patients undergoing tracheostomy [46–48]. The risk factors for post-tracheostomy tracheal stenosis includes obesity, delayed tracheostomy after orotracheal intubation, endotracheal tube cuff pressure ≥ 30 mm H₂O, percutaneous dilatational tracheostomy and an initial tracheostomy tube size of >6 [48,49]. We also believe that excessive force during a percutaneous dilatational tracheostomy with subsequent cartilage fracture or compression will result in PTTS, often of a complex morphology and more difficult to manage given higher location and chondritis [50]. Other causes of benign tracheal stenosis are listed in

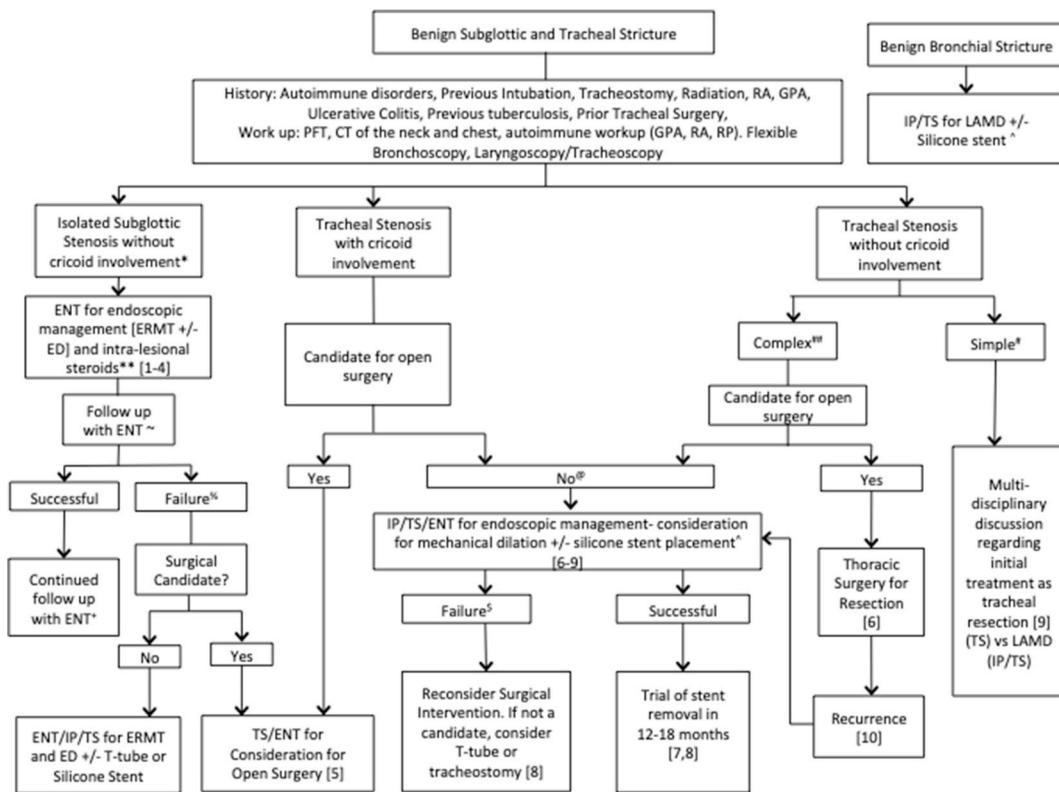


Fig. 2. A Multi-disciplinary Management Algorithm in Patients with Benign Airway Strictures Mechanical Dilation: LAMD (Laser Assisted Mechanical Dilation) or Cold Knife Assisted Mechanical Dilation. ERMT: Endoscopic resection (+/- Wedge Approach) with adjuvant medical therapy (PPI, ICS and TMP/SMX). ED: Endoscopic Dilatation, ENT: Ear, Nose & Throat Surgery, IP: Interventional Pulmonology, TS: Thoracic Surgery. *This algorithm applies only to idiopathic subglottic stenosis (iSGS). For patients with connective tissue disorders, first treatment option will be endoscopic management due to high recurrence rate post surgical resection. ** Endoscopic management depending on severity of symptoms. Patient will undergo radial incision with or without mechanical dilation. ~ Outpatient follow up with ENT including outpatient laryngoscopy and in-office injection of intra-lesional steroids. % Failure defined as patients requiring more than 3 interventions over 2–3 years with symptomatic recurrence and >50% stenotic index, despite office-based intra-lesional corticosteroid injection. + Consider use of office based intralesional steroid injection to maintain patency and reduce time to re-intervention. ## Complex: Longer > 1 cm, with or without chondritis. # Simple: Less than 1 cm in size, without chondritis. ¶ Factors affecting surgical candidacy include multiple comorbidities, prolonged steroid use, stricture location, or long vertical extent (>4–6 cm). § Failure defined as repeated procedures including recurrent stent migration, followed by symptomatic recurrence of stenosis. ^ All patients with airway stent will follow the stent protocol defined below. Stent Follow-up Protocol: Flexible Bronchoscopy with moderate sedation 4–6 weeks post stent placement. Follow up bronchoscopy every 2–3 months or based on clinical symptoms. 0.9% Normal saline nebulizer 5–10 ml TID. Stent card & Stent education.

Table 2. These patients are often misdiagnosed with asthma or COPD exacerbations as their symptoms include dyspnea, wheezing, cough, and inability to mobilize secretions. Stridor, negative pressure pulmonary edema, syncope and hypercapnic respiratory failure can occur in severe cases.

We propose that the approach to these patients with tracheal stenosis should be based upon the extent, complexity of the stenotic segment and the presence or absence of cricoid involvement.

3.2. Management of tracheal stenosis with cricoid involvement (laryngotracheal stenosis)

Patients with a tracheal stenosis with cricoid involvement who are not in acute respiratory distress should be evaluated for tracheal resection of the hypertrophic stenotic segment with end-to-end anastomosis. This may include LTRR based on the extent of the stenotic segment. Endoscopic interventions such as LAMD are considered as a bridge to surgery in patients with acute respiratory distress or performed in patients who are not surgical candidates (Fig. 3A). The role of endoluminal silicone stenting in these patients is discussed above. However, given the high location of the stenosis and involvement of the cricoid, a T-tube can be considered in patients who develop recurrent silicone stent migration or in those who already have a tracheostomy [51]. Complications of a T-tube include granulation at the stomal site,

subglottic edema and retention of secretions. There are life-threatening complications due to obstruction of the T tube by thick gluey secretions [52] and mucus plugging. The inherent disadvantage of a T-tube is the need for a tracheostomy as compared to a dedicated endoluminal stent. It also requires patient compliance with pulmonary hygiene measures including but not limited to saline nebulization, deep breathing exercises and self-suctioning. It thus can significantly compromise the quality of life. In our opinion, T-tubes should be reserved for patients who are not surgical candidates for open resection and endoluminal stent placement that is associated with recurrent stent-related complications.

3.3. Management of tracheal stenosis without cricoid involvement

The management of isolated tracheal stenosis depends upon the complexity of the stricture, associated co-morbidities and patient's ability to undergo open surgical resection. A multi-disciplinary discussion must thus occur in the beginning of managing such patients to determine the most optimal first management strategy. Endoscopic management as an initial approach can be considered in patients with a simple web-like stenosis (<1 cm) with only mucosal involvement without cartilage destruction (Fig. 3B) [53]. The endoscopic techniques involve laser- or electrocautery-assisted assisted radial incisions of the scar/web followed by mechanical dilation using a rigid bronchoscope or

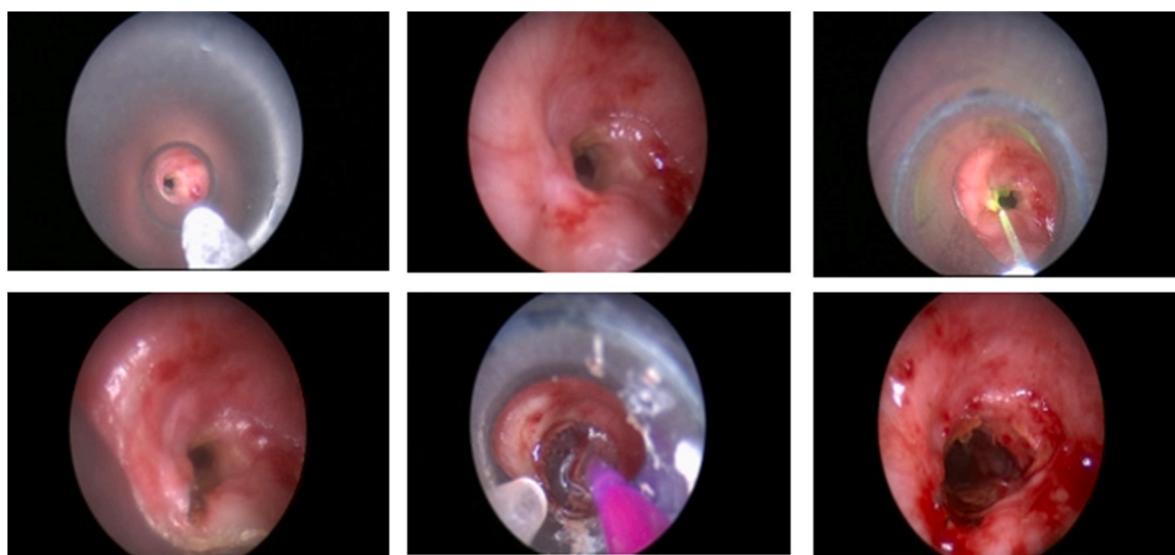


Fig. 3A. Critical tracheal stenosis in a patient with respiratory failure with rigid bronchoscopy and KTP-laser assisted mechanical dilation. Top Left/Top Center: Complex Benign Tracheal Stenosis with diameter of 4 mm. Top Right: Use of KTP laser to make incision. Bottom Left: Incision made at 7 o'clock position using KTP Laser. Bottom Center: Balloon dilation of the stenotic segment after incision. Bottom Right: Post KTP-laser assisted mechanical dilation with airway diameter of 14 mm.

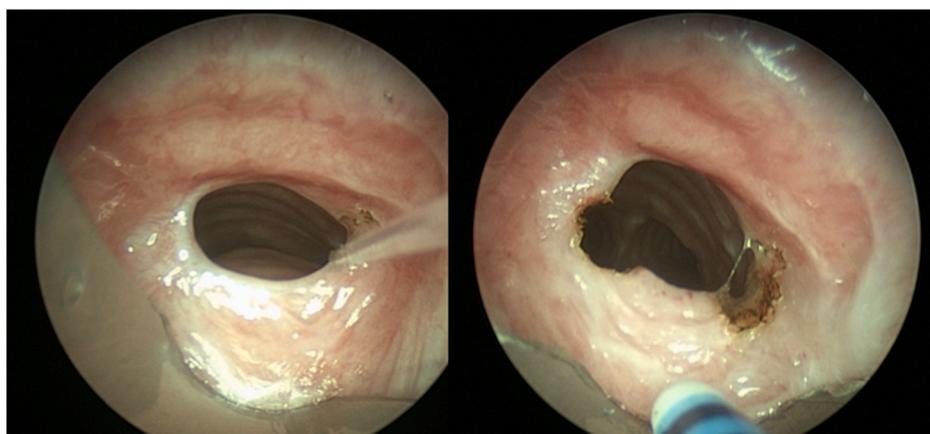


Fig. 3B. Simple tracheal stenosis treated with KTP laser and electrocautery (EC). Left – Simple Web Like Tracheal Stenosis with the use of KTP Laser. Right – Simple Web Like Tracheal Stenosis with electrocautery knife assisted radial incision at 4 o'clock and 8 o'clock position.

balloon tracheoplasty [54,55]. For patients with a complex stenosis with a long segment lesion (>1 cm) or associated cartilage involvement, surgical resection of the involved airway segment is the preferred modality and should be offered before any endoscopic attempts. In fact, some endoscopic procedures (i.e. stenting) may lengthen the extent of the narrow segment potentially precluding a curative-intent surgical resection [56].

Tracheal resection and reconstruction (TRR) is the surgical intervention of choice and is considered a relatively safe procedure with the overall success rate reported to be $>95\%$ [57,58] (Fig. 4). Patient selection is paramount since both modifiable and non-modifiable factors such as diabetes mellitus, prior tracheostomy, stricture location (high subglottic), or length of resection ($>4\text{--}5$ cm) may lead to anastomotic complications [59]. Patients are weaned off steroids before open surgery if possible to avoid deleterious effects on wound healing [57].

In patients with symptomatic tracheal stenosis who are not candidates for open surgery, endoscopic interventions such as LAMD with or without silicone stent placement are performed given reproducible evidence on improving lung function and on quality of life (QOL) [10,60]. Of note, while self-expandable metallic stent (SEMS) may provide ease

of placement via flexible bronchoscopy, the US Food and Drug Administration has recommended against the use of SEMS for benign airway stenosis due to excessive granulation formation, airway injury and stent fracture [10,61]. Silicone stents, however, may be used for long-term palliation in non-surgical candidates [54,60,62–64]. Silicone stenting in patients with benign tracheal stenosis does not have to be a life-long intervention. Some patients may become operable in which case the stent will be removed allowing for tracheal healing and then proceeding with surgical resection. In addition in some patients tracheal remodeling can occur after long term indwelling stenting and the stent could be removed without the need for further intervention. For example, in a large study by Dumon et al., 263 patients underwent 419 silicone stent placements for tracheal stenosis [64]. Of the 117 patients in whom the stent was removed, no recurrence was noted in 64 (25% of all cases). Overall complications included migration (9.5%), granuloma (7.9%) and obstruction by secretions (3.6%) justifying the practice of routine surveillance bronchoscopy. Similarly, in another 2 studies where 47 and 55 patients underwent stent placement for PITS, successful stent removal was possible in 47% (22/47) and 40% (22/55) patients, respectively, without need for further interventions [54,62].

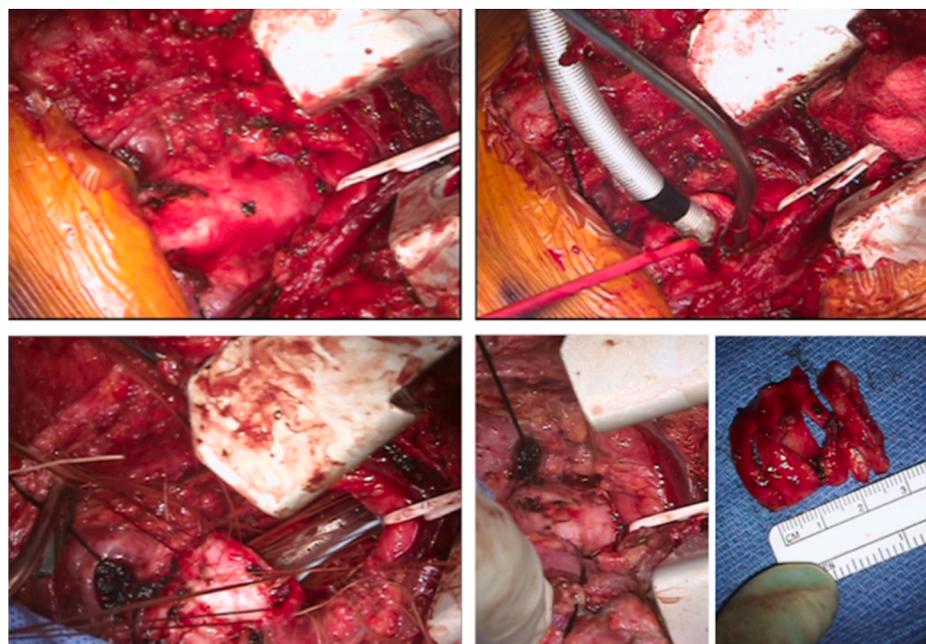


Fig. 4. Intraoperative images from tracheal resection and reconstruction via cervical collar incision and partial sternotomy in a patient with post-intubation tracheal stenosis. Top Left: Exposure anterior trachea: affected segment marked by silk stitches. Top Right: Trachea is opened and cross-field ventilation applied to facilitate resection and placement of anastomotic sutures. Bottom Left: Tying down anastomotic sutures. Ventilation from oral endotracheal tube. Bottom Right: Anastomosis completed, final pathologic specimen.

Therefore, we believe that a stent removal should be attempted to evaluate airway patency as regeneration of the tracheal cartilage is possible and patency may be restored (Fig. 5A). While the optimal time frame for a trial of stent removal is unknown, a higher rate of success (46.8%) was described when stents remained in place for a longer time (mean of ~12 months) [54]. We thus propose a trial of stent removal at 1-year post insertion understanding that patients with recurrence may need to be reconsidered for open surgical intervention or need long term indwelling airway silicone stents.

A chronic indwelling tracheostomy may be warranted in certain situations where patients have failed an endoscopic intervention (dilation, resection, endoluminal stent or T-tube) and are not surgical candidates for open surgery. The presence of an indwelling tracheostomy at the time of open surgery has shown worse outcomes [57] and therefore, a multi-disciplinary discussion should be ensued prior to pursuing a tracheostomy in patients with laryngeal or tracheal strictures.

4. Benign bronchial stenosis

4.1. Etiology, prevalence and symptomatology

Benign bronchial stenosis can be isolated or associated with tracheal or laryngeal involvement. Such multifocal disease can be seen in patients as a sequelae of endobronchial tuberculosis (TB). Around 59–65% of patients with endobronchial tuberculosis can progress to the fibrostenotic type with up to 23% of patients presenting with severe airway narrowing [65,66]. Bronchial stenosis is also seen post lung transplantation secondary to tissue ischemia and altered immune response and can occur anywhere from months to years after transplantation. Risk factors include surgical technique, anastomotic necrosis, dehiscence and infection [67]. While older studies showed an incidence of 80% in post-transplant bronchial stenosis [68], improved surgical techniques, immunosuppressive agents and peri-operative management has led to a reduced incidence (5–30%) [69,70]. This can be severe, however, and may require stent insertion.

Similarly, in patients with GPA, in addition to subglottic stenosis, tracheobronchial involvement may be noted in 11–18% of the patients [40]. As highlighted in this paper, these patients are better served by

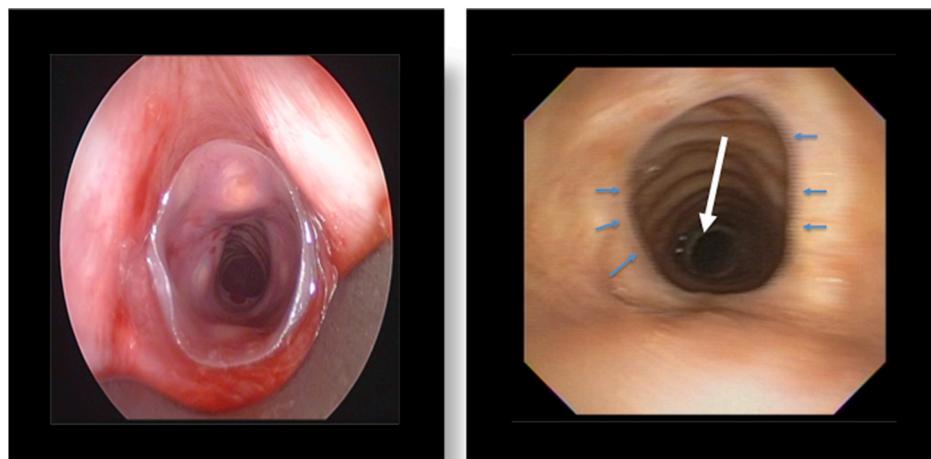


Fig. 5A. Patent airway due to remodeling after long term indwelling silicone airway stenting. Left panel-post intubation tracheal stenosis palliated with an indwelling silicone stent. Right panel-approximately one year after insertion, stent has migrated down to the main carina (white arrow); the airway cartilage re-modelled at the level of the stenosis and there was only minimal airway narrowing (blue arrows), not requiring intervention. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

endoscopic management and optimization of the immunosuppressive therapy. Bronchial stenosis has also been reported in patients with sarcoidosis with the incidence ranging from 1 to 18% [71,72], but this is often due to compression from large mediastinal, hilar or interlobar adenopathy, rather than a true airway stricture. The various etiologies of bronchial stenosis are listed in Table 2.

4.2. Management of benign bronchial stenosis: post infectious, post-transplant, idiopathic or due to autoimmune disorders

Endoscopic interventions are the mainstay of management of patients with bronchial stenosis, regardless of etiology. Treatment options include LAMD or electrocautery knife with or without stent insertion depending upon symptoms, flow limitation, extent of stenosis and the presence or absence of bronchomalacia. While the use of stents in lung transplant patients (Silicone vs SEMS) is dependent on local expertise and practice and the presence of bronchial dehiscence, we advocate for the use of endoscopic interventions with LAMD (with or without silicone stents) in patients with benign bronchial stenosis related to lung transplantation if clinically indicated [73,74]. We prefer either silicone or fully covered SEMS rather than uncovered SEMS in patients with post-transplant stenosis and/or symptomatic bronchomalacia. A close follow up within weeks is warranted as studies of SEMS show a potentially worsened outcomes during the long term follow up in patients with such indwelling airway stents [75]. In a study by Dutau et al., 17 patients with post-transplant bronchial strictures had 23 silicone stents inserted for anastomotic airway stenosis. Successful stent removal was achieved in 16/23 (69.5%) cases without recurrence of stenosis with a median stent duration of 266 days [76]. Patients with post-TB-fibrotic

strictures have also been treated with endoscopic interventions such as LAMD or balloon dilation after a electrocautery knife-assisted incision but often need long-term stenting (>12 months) to maintain airway patency [10,77,78]. In patients with bronchial stenosis with connective tissue disorders such as GPA, pharmacologic therapy remains the mainstay of treatment. Endoscopic interventions with LAMD or electrocautery assisted mechanical dilation may be used in refractory patients with clinical symptoms (Fig. 5B). Long-term bronchoscopy surveillance is required in these patients due to the risk of recurrence and thus close outpatient follow-up is recommended.

5. Conclusion

Patients with histologically benign airway strictures are often misdiagnosed as suffering from asthma or COPD and may present with severe symptoms including respiratory failure. The acuity of the process, location, extent, morphology, degree of airway narrowing, comorbidities and patient functional status are all factors that determine the need for open surgical or endoscopic interventions in these patients. Therefore, a multi-disciplinary team approach with the involvement of otolaryngology, thoracic surgery and interventional pulmonology is essential for the optimal management of these patients. Implementation of a complex airway program including multi-disciplinary clinics and conferences ensures that such collaboration leads to timely, patient-centered and evidence-based interventions.

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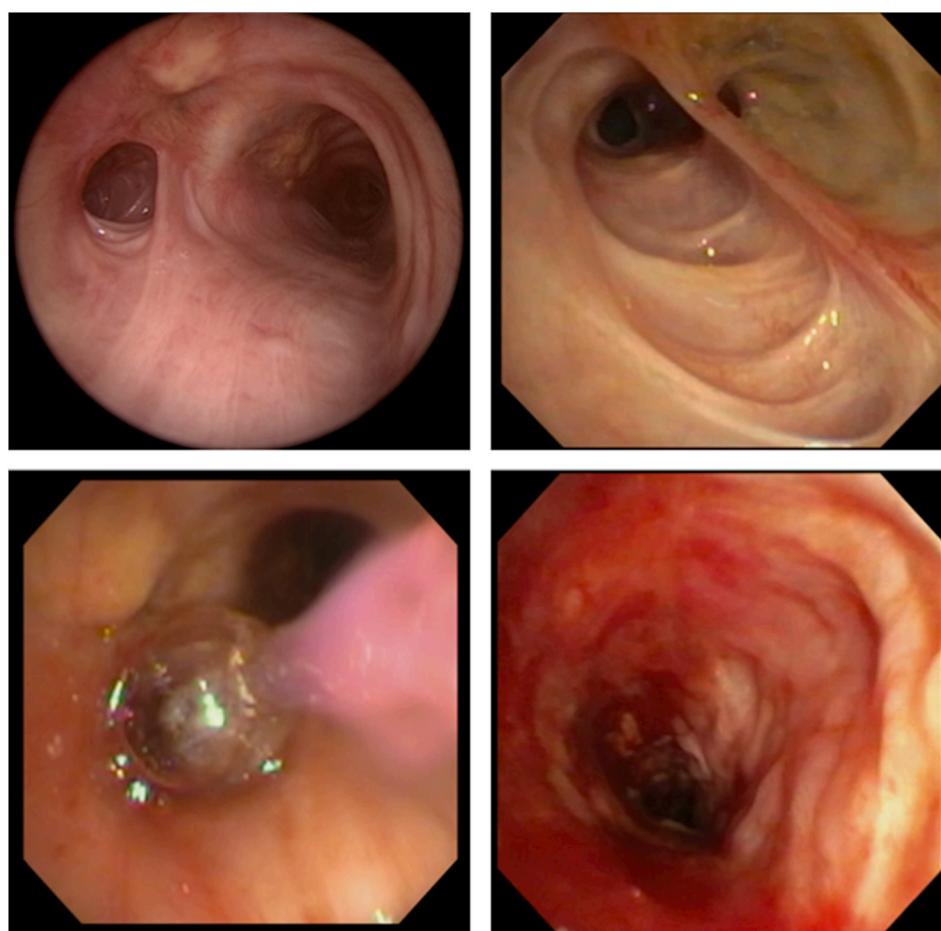


Fig. 5B. Endoscopic intervention in a patient benign bronchial stenosis of the left mainstem bronchus in a patient with granulomatosis with polyangiitis.

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Author contributions

All authors have contributed equally to the entire manuscript.

Declaration of competing interest

AA has no conflict of interest related to this manuscript. BB has no conflict of interest related to this manuscript. MLM has no conflict of interest related to this manuscript. EB has no conflict of interest related to this manuscript. SM has no conflict of interest related to this manuscript.

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