Review Article | Surgery: Lung Surgery

Benign airway obstruction: a clinical practice review of causes and managements principles

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Abstract: Benign airway obstruction occurs in a group of heterogeneous diseases with the potential for both high symptom burden and a challenging clinical course. The diverse pathophysiology causing benign obstruction includes not just a multitude of spontaneous diseases such as infections, autoimmune diseases, and benign tumors, but also the iatrogenic causes of intubation and tracheostomy, as well as the complications from lung transplantation. Despite the pathology, there is a tendency of both under diagnosis and delay in diagnosis, as well as variability in the predicted clinical course. Management of patients with benign airway obstruction requires an understanding of both the underlying process and the data supporting disease-specific interventions. New technology and studies in the fields of otolaryngology, pulmonology, and thoracic surgery have improved and diversified available treatments and treating providers can consider endoscopic intervention, surgical options, and systemic medical therapies. The objectives of this review include describing the commonalities and differences in the presentation and treatment of common causes of benign airway obstruction, as well as an up-to-date literature review of the current management strategies. We aim to highlight recent updates to diagnosis and management, as well as the need for a multidisciplinary approach for both management and further study of this diverse and challenging group of diseases.

Keywords: Airway obstruction; airway stenosis; bronchoscopy; interventional pulmonology

Received: 04 July 2023; Accepted: 07 December 2023; Published online: 01 March 2024.

doi: 10.21037/amj-23-103

View this article at: https://dx.doi.org/10.21037/amj-23-103

Introduction

Central airway obstruction (CAO) is defined as narrowing of the central airways: the subglottic space, trachea, right and left mainstem bronchi, and right bronchus intermedius. Obstruction in more distal airways, lobar bronchi and beyond, is peripheral airway obstruction. In addition to airway location, airway obstruction is classified by pathology as malignant or non-malignant, with malignant causes being more common and associated with worse outcomes (1). In this review, we will discuss the causes and management strategies for non-malignant airway obstruction, also referred to as benign airway obstruction. Though benign, this group of diseases can have potentially devastating consequences and consists of diverse pathology and clinical presentations. In contrast with malignant airway obstruction, the diseases leading to benign CAO are often not life-limiting and the assessment and management of airway obstruction for these patients must account for this.

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Table 1 Causes of benign airway obstruction grouped by stenosis pattern

Type of stenosis	Examples
Intraluminal	Inflammatory and autoimmune (granulomatosis with polyangiitis, relapsing polychondritis, sarcoidosis, amyloidosis)
	Infections (tuberculosis, fungal infections including aspergillosis and blastomycosis, HPV-related respiratory papillomatosis)
	Benign tumor (hemangioma, hamartoma, tracheopathia osteoplastica, granulation tissue)
	Endogenous (mucus plug, blood clot, broncholith)
	Exogenous foreign body
Extrinsic compression	Lymphadenopathy, goiter
Scar/stricture	Post intubation/tracheostomy tracheal stenosis, idiopathic subglottic stenosis
Distortion	Vascular sling, post-pneumonectomy distortion
Post surgical complications	Post lung transplant, post sleeve resection, post airway stenting
Dynamic airway obstruction	TBM, EDAC

HPV, human papillomavirus; TBM, tracheobronchomalacia; EDAC, excessive dynamic airway collapse.

Despite the lack of large, randomized clinical trials, there have been advancements in treatment, both procedural and nonprocedural, available for benign CAO. Multiple types of specialists, including pulmonologists, otolaryngologists, and thoracic surgeons, may manage patients with benign airway obstruction and have contributed to the growing body of research and literature available to understand and manage these patients. This review will focus on unifying knowledge across these diverse fields and identifying areas for collaborative management and further study.

Causes and classification

Numerous diseases cause benign airway obstruction via varying mechanisms (*Table 1*) and it is paramount to identify the distinct cause and pathophysiology of airway stenosis in each patient. Several classification systems have been used to describe CAO in general or for specific diseases. These systems include both structural descriptors of the stenosis as well as functional or symptomatic scores. For example, the original and expanded Myer-Cotton grading systems, developed by laryngologists for subglottic stenosis, utilizes the percentage of obstruction, the extent of disease, based on number of sites involved, as well as comorbidities with higher scores correlating with worse surgical or functional outcomes (2,3). A classification schema for any etiology of tracheobronchial stenosis proposed by Freitag and colleagues proposed simple and reproducible classification by the type, degree, and location of stenos(es) (4). However, no classification systems have yet been widely adopted.

Presentation

Patient presentation and symptoms depend on the location, acuity, and extent of obstruction as well as patient's underlying cardiopulmonary reserve. For example, acute airway obstruction, such as foreign body aspiration, is more symptomatic than the typical gradual onset of idiopathic subglottic stenosis. Acuity also influences time to diagnosis: it is not uncommon for patients with gradual onset of symptoms from a chronic, mild, or slowly progressive disease process to be misdiagnosed with asthma or chronic obstructive pulmonary disease (COPD) for months or even years (5,6). It is therefore imperative to maintain a high degree of suspicion, especially if history is suggestive of an alternative diagnosis or there is no response to disease-targeted therapy.

Severity of symptoms, often dyspnea, correlates with diameter and length of the affected airway. Exercise tolerance is affected first, as the pressure gradient across the obstruction increases with the increase of airflow required to increase minute ventilation. In the simplest example, of single site fixed tracheal stenosis, patients typically become dyspneic with exertion when the diameter has narrowed to less than 8 mm (50% stenosis) and experience dyspnea at rest or stridor when the diameter is less than 5 mm

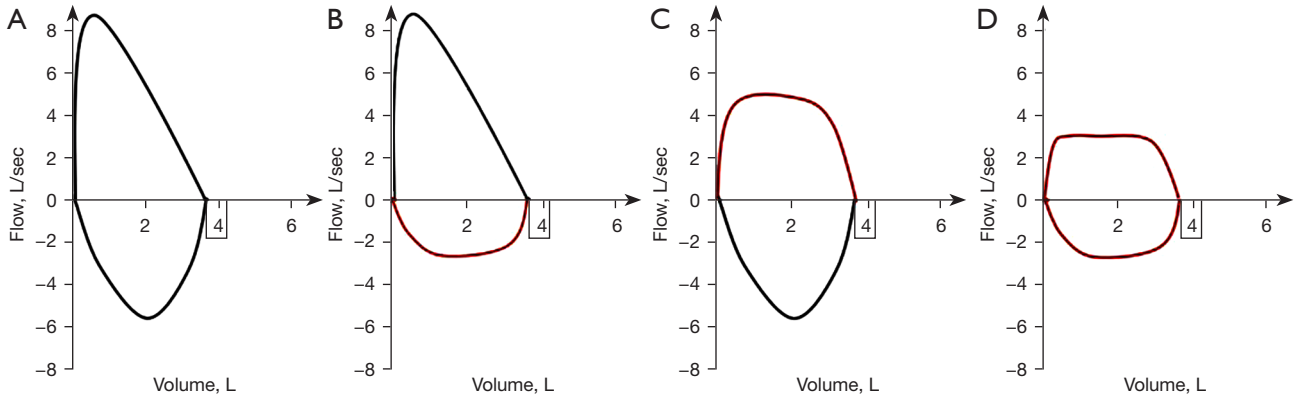

Figure 1 Idealized examples of: (A) normal flow-volume loop, (B) variable extra-thoracic airway obstruction with a flattened inspiratory limb, (C) variable intra-thoracic obstruction resulting in a flattened expiratory limb, and (D) fixed airway obstruction resulting in a flattening of both inspiratory and expiratory limbs (box shaped loop). Red denotes abnormal limbs or loops and black denotes normal limbs or loops.

(70% stenosis) (5-7). Concomitant other airway or lung diseases, such as asthma, COPD, or indolent infection, should also be considered and can contribute to earlier or atypical symptoms. Key information obtained from patient interviews includes not only their dyspnea symptoms and the course over time, but evaluation of cough symptoms, exercise/activity tolerance, orthopnea, paroxysmal nocturnal dyspnea as well as signs and symptoms of suspected systemic diseases. Key components of the physical exam include auscultation over both the lungs and the airways, oropharynx exam, neck extension, overall functional status, and sequalae of infection or connective tissue disease.

Diagnostic tests

Pulmonary function test with flow volume loops

Flow volume loops can categorize CAO into two major groups: fixed and variable obstruction as well as localize disease to intra- or extra-thoracic involvement. Fixed obstruction will have blunting of both inspiratory and expiratory limbs with a box-shaped loop. Variable obstruction can be seen with intrathoracic obstruction presenting with a blunted or flattened expiratory limb and extrathoracic obstruction with blunted or flattened inspiratory limb (*Figure 1*) (8). Notably, spirometry and flow volume loops have low sensitivity for detection of mild to moderate CAO; the classic blunting of flow volume loops often does not occur until diameter is reduced to 8–10 millimeters (9). Given this, pulmonary function testing should not be used to rule out CAO. Instead, it can be helpful as an adjunctive diagnostic tool. It has also been proven useful in follow up after therapeutic intervention to assess for response or recurrence of obstruction (10).

Imaging

Computed tomography (CT) of the chest is valuable in both diagnosis and treatment planning for benign airway obstruction. Critical information obtained from CT includes site(s), length(s), and severity of stenosis as well as patency of distal airways and identification of non-airway disease. Post-processing of CT imaging can include multiplanar reformation, 3D reconstruction, volume rendering, and creation of virtual bronchoscopy (11-13). For dynamic airway obstruction, comparison of inspiratory and expiratory CT images can utilized to assess degree of expiratory collapse and air-trapping (14). Most recently, CT has allowed for planning for patient-specific, customized airway stenting (15,16).

Bronchoscopy

Bronchoscopy has a potential dual role in benign CAO: diagnostic and therapeutic. Direct visualization of the sites and severity of obstruction along with tissue sampling with needles, brushes, or forceps can be obtained for diagnosis, as well as prognostication and treatment planning. Therapeutically, multiple interventions can be considered including electrosurgery, cryotherapy, light amplification by stimulated emission of radiation (LASER) therapy, mechanical dilation with rigid scopes or balloons, and medication injection or application (17-21). Stenting can

also be considered as a second line intervention (22-24) and the therapeutic endoscopy toolkit will be discussed further later in this review.

However, even diagnostic bronchoscopy in CAO is not without risk. At minimum, the bronchoscope further occludes an already narrowed airway with the potential complications of bleeding or mucosal edema causing further obstruction. In patients with CAO, bronchoscopy should be performed by experienced and skilled operators in appropriate facilities with personnel and equipment allowing for complex maneuvers, including rigid bronchoscopy and difficult airway management. The advantages of rigid bronchoscopy include the ability to quickly bypass a critical stenosis as well as rigidly dilate, ventilation via side ports of the rigid barrel, and use of the rigid barrel to secure the airway or enable tamponade when sampling vascular lesions (25).

Management of benign CAO

Management of benign CAO is based on the underlying disease as well as the individual patient, but a few general principles apply to all benign disease involving the central airways. There is no data demonstrating improved survival following endoscopic management of benign CAO. Thus, clinical observation is indicated for mild (less than 50% reduction of lumen) and asymptomatic patients, as well as for patients with severe comorbidities or limitations in functional status that would not improve with intervention (25). For symptomatic patients who are procedural and/or surgical candidates, the clinical scenario must guide the involvement of specialists or subspecialists including otolaryngologists, pulmonologists, interventional pulmonologists, and/or thoracic surgeons. Algorithms developed for tertiary care/academic medical centers have been developed to provide guidance for multidisciplinary approaches for these patients (26,27).

Next, we discuss some common causes of benign airway obstruction and their management, highlighting the available data around management strategies. We have used examples from our practice for illustration.

Post intubation tracheal stenosis and post tracheostomy tracheal stenosis (PITS and PTTS)

Stenosis after an oral, nasal, or surgical airway is the most common cause of acquired benign tracheal stenosis, with an estimated incidence of 4.9 cases per million people per year in the general population (28). PITS has been reported to occurs in anywhere from 1–21% of intubated patients, but with only 1–2% of cases severe enough to warrant intervention (29,30). There is data to suggest this is an under-recognized disease, with as many as four out of five patients with severe PITS having a delayed or missed diagnosis (31). Patient risk factors for both PITS and PTTS have varied between studies, but most frequently include advanced age, female sex, obesity, sleep apnea, use of corticosteroids, acid reflux disease, and history of neck radiation (31-33). Though airway injury can occur after any duration of intubation, risk of PITS increases with higher duration of intubation and use of high endotracheal cuff pressures with cuff pressures exceeding 20 cmH_2O lead to trachea ischemia, necrosis, and granulation or scar tissue (34,35). In tracheostomy, abnormal wound healing, including wound infection and cartilaginous damage, are also associated higher incidence of PTTS (34). One study found PTTS to appear to originate from the tracheal stoma 85% of the time, versus the site of the tracheostomy tube cuff seen in PITS (30).

Both PITS and PTTS can be divided into two major categories: simple and complex stenosis. Simple stenosis is defined as a web-like, membranous concentric stenosis without damage to the cartilage and less than one centimeter in length. By comparison, complex stenoses are lesions more than one centimeter in length and/or with destruction of a cartilaginous structure or structures (27). In a single-center retrospective review, PTTS patients were found to have more complex stenoses, lower success rates with nonsurgical interventions, and lower rates of stent or tracheostomy tube removal (36). Recent data suggests a separate dichotomy into keloid and non-keloid lesions, either of which can occur in PITS or PTTS. PTTS keloid patients were noted to have earlier stenosis, poorer treatment outcomes, and increased recurrence when compared to PITS or non-keloid PTTS (37). It is well established complex lesions more require surgical intervention such as tracheal resection (27,36).

For simple stenosis, a therapeutic bronchoscopy is often the initial intervention, with therapies including thermo-ablative tissue destruction, dilation, and application of anti-inflammatory or antifibrotic agents. Mucosal-sparing radial incisions can be performed using either electrocautery knife/needle or LASER prior to dilation. Dilation can be done using the rigid bronchoscope barrel or continuous radial expansion balloons under direct visualization. In a single center study, the combination of radial incisions with an electrocautery knife with balloon dilation resulted

in greater improvement in the degree of stenosis and decreased recurrence rates compared to balloon dilation alone (38). Cryospray has also demonstrated benefit in reducing symptoms and severity of airway stenosis in PITS and PTTS (39,40).

Endoscopic application of medications have been evaluated for benefit in the management of PITS and PTTS. Localized corticosteroid injection, to suppress inflammation and prevent further airway scarring, has been conjectured to prevent disease recurrence, but there has been little success with animal studies (41-44). There is some evidence of benefit for injection in the office setting, as well as some evidence for systemic steroids in those with recurrent disease to diminish need for repeated dilation or surgical management (45,46). Mitomycin C, a DNA-crosslinking agent, has antineoplastic and anti-fibroblastic properties and has also been theorized to prevent recurrence. Mitomycin C has demonstrated efficacy in animal studies (47), but use in humans has demonstrated to mixed results, with some signal of potential benefit of increasing interval to repeat procedures (48-50).

For complex stenosis, bronchoscopic intervention can be utilized to stabilize patients with critical narrowing or severe symptoms, but definitive therapy should be discussed within a multi-disciplinary team given the high risk of recurrence (26,27). Definitive surgical management is resection with primary tracheal anastomosis and should be considered based on time to recurrence or for those without symptom or disease control after nonsurgical intervention. For non-surgical candidates, tube stents, tracheostomy tube, or Montgomery T-tubes can be placed for safety or symptom control. Based on limited case series, placement of silicone stents within the first 6 months of presentation have been showed to allow for remodeling and eventually stent removal (51). Data suggests silicone stenting has an acceptable safety and tolerance (22,52). There is limited data for other stents, with one case series of fully covered metal stents in a mixed population of nonoperative tracheal stenosis patients demonstrating high complication rates, including need for stent removal (53).

The coronavirus disease 2019 (COVID-19) pandemic resulted in record numbers of patients requiring intubation and mechanical ventilation with higher mean duration of ventilation days, and increased rates of reintubation and tracheostomy reported at some centers (54,55). The aftermath of the pandemic is predicted by experts to increase the overall incidence of PITS and PTTS, but population data has yet to be published (56). Initial proposed management strategies are comparable to non-COVID-19 patients, include bronchoscopic and surgical interventions and initial case series suggest good success rates (57,58).

Case 1

A 30-year-old morbidly obese female with prior COVID-19 infection requiring prolonged mechanical ventilation and complicated by cardiomyopathy requiring left ventricular assist device (LVAD) placement, presented two months post tracheostomy decannulation with inspiratory stridor. A CT showed mid-tracheal stenosis (*Figure 2A*) and bronchoscopy revealed concentric complex stenosis, four centimeters below the vocal cords and five centimeters above the main carina. The stenotic segment was two and a half centimeters in length and the lumen diameter was 4–5 millimeters (*Figure 2B*). Combined rigid and flexible bronchoscopy was used for initial radial cuts using rigid scissors and an electrocautery knife, followed by balloon and rigid barrel dilation to 10 mm diameter (*Figure 2C*). The patient had subjective improvement after the procedure. However, she re-presented within one month following initial dilation with similar symptoms and repeat dilation was done in similar manner. Thoracic surgery evaluated the patient at the time of the second dilation and she was deemed a high-risk surgical candidate for tracheal resection given morbid obesity and LVAD-dependence; surgery was deferred. Given the complex nature of her stenosis, along with rapid recurrence, decision was made to proceed with tracheal silicone stent placement (not shown). Patient had good control of respiratory symptoms in the 3 months post-stent placement and required no further airway procedures.

Idiopathic subglottic stenosis

Idiopathic subglottic stenosis most often effects females, typically presenting in the fourth or fifth decade of life (59). Surgical specimens have suggested a potential role for hormone receptor imbalance; recent genomic data suggests a role for several genes involved with epithelial-mesenchymal transition (60,61). There is also data supporting genetic risks, with reports of familial clustering (62). Delays in diagnosis are common, with more than 30% of patients in one case series diagnosed with asthma and another with average time to diagnosis of greater than 18 months (63,64). It is a diagnosis of exclusion and other pathologies, such as systemic autoimmune diseases and infections, must be ruled out. Idiopathic subglottic stenosis is usually a short

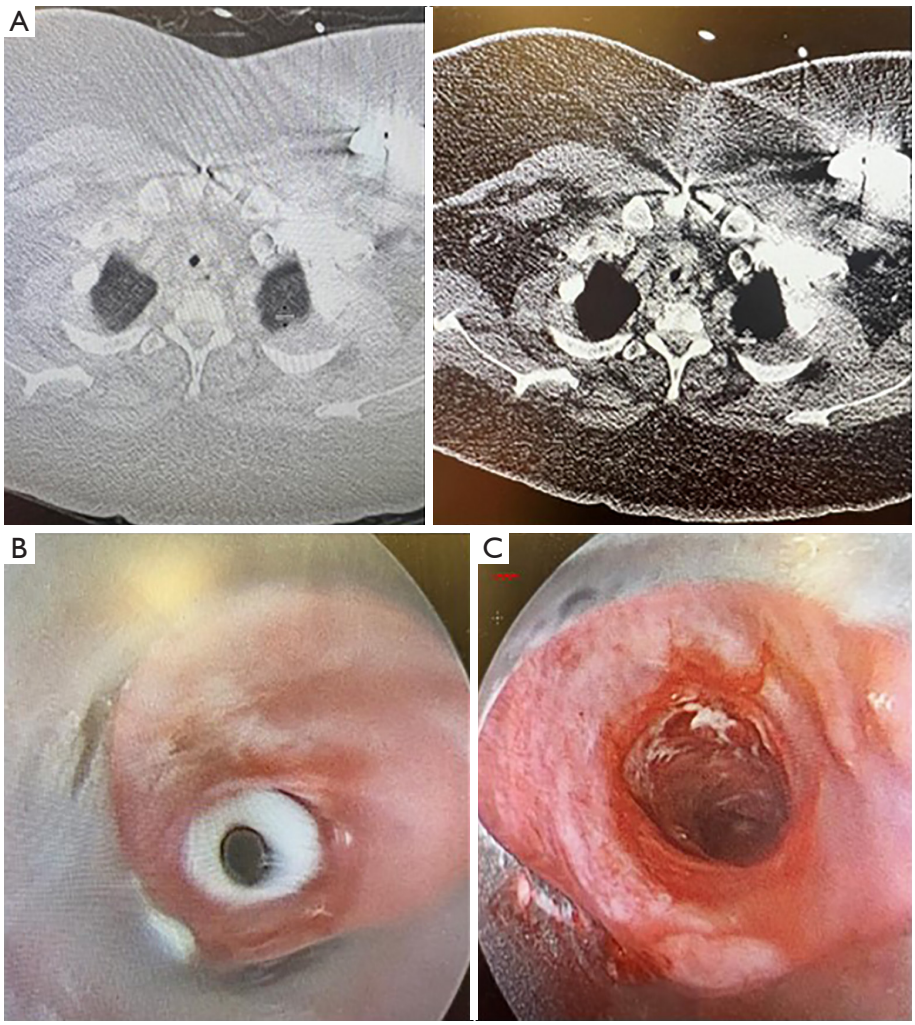

Figure 2 Radiographic and bronchoscopic images and patient with post tracheostomy tracheal stenosis. (A) Axial CT images demonstrating severe stenosis of the proximal trachea. (B) Initial inspection with rigid bronchoscopy. (C) Post radial incisions and initial dilation. CT, computed tomography.

length and circumferential lesion involving the cricoid ring, with histology showing keloid-like fibrosis and epithelial squamous metaplasia with sparing of the cartilage (59).

Like PITS and PTTS, a simple stenosis is often treated endoscopically with radial incision and dilation, but recurrent or complex disease is more challenging to manage. Both otolaryngologists and pulmonologists have published studies of different endoscopic modalities leading to successful management. A single center study of 132 patients showed successful bronchoscopic treatment in 100% of simple stenoses, but only 69.8% in complex disease (65). A separate single center study supported utilizing endoscopic laryngotracheoplasty via suspension laryngoscopy with multiple modalities including CO_2 laser dissection, steroid injection, and balloon dilation to increase success. This study of 54 patients revealed an overall 5-year success rate of 87.5% in a population of both simple and complex stenosis, in which 78% of patients were managed only endoscopically (66). The use of radiofrequency coblation, utilizing bipolar energy to ablate and coagulate soft tissues at low temperatures via suspension laryngoscopy has also been described as successful (67,68). Recurrent disease is common, with one study showing a mean of 3.8 dilations required, albeit separated by long average inter-dilation interval of 90.7 weeks (69). There is also some conflicting data regarding different treatment modalities, including

one recent study demonstrating CO_2 laser treatment being associated with an increased risk of recurrence over balloon dilation alone, a difference from prior studies (18). Upcoming multicenter trials are planned to attempt to answer this question more definitively (70).

For non-procedural management, while idiopathic subglottic stenosis is often associated with gastroesophageal reflux, there is mixed data on the utility of proton-pump inhibitors, as well as conflicting data around the support of Bactrim, other antibiotics, or inhaled corticosteroids (64,71,72). Studies of steroid injection, known to be helpful in keloids, has had mixed results in studies (73,74). Mitomycin C has not been studied in idiopathic subglottic stenosis populations alone, but in mixed populations with mixed results (20,75)

Patients with disease recurrence or disease nonamenable to endoscopic management subglottic stenosis should be evaluated by an ear, nose, and throat (ENT) or thoracic surgeon for resection (66). If surgery is not an option, stenting, tracheostomy tube, or silicone T-tube placement can be used in cases with critical narrowing or rapid recurrence (52).

Systemic inflammatory diseases with airway manifestations

Many systemic inflammatory disorders can manifest with airway complications, including sarcoidosis, amyloidosis, relapsing polychondritis, granulomatosis with polyangiitis (GPA), inflammatory bowel disease, and other autoimmune connective tissue diseases (76). Treatment of the underlying systemic disorder in these cases often results in control of the airway disorder. However, when inflammatory airway obstruction has already occurred, reversal of the obstruction with systemic therapy is variable, and bronchoscopic intervention may be required to alleviate symptoms.

Granulomatous inflammation of the submucosal vasculature and airway mucosa in GPA can result in subglottic stenosis, thought to occur in up to 20% of GPA patients (77,78). More distal bronchial stenosis is also common, associated with higher recurrence than subglottic disease only, and can result in disabling multilevel stenosis (79). There is limited evidence for the best practice for airway stenosis management in patients with GPA. Radial incision with lasers or electrocautery; radiofrequency coblation; balloon dilation; and local steroid injection have all demonstrated efficacy in small studies (68,80-83). High dose systemic steroids and other systemic immunosuppressants such as cyclophosphamide and rituximab have been proven beneficial (79,84). Availability of effective systemic therapy, frequency of multi-level stenosis, and the risk of restenosis limits the role of surgery for these patients.

In contrast, benign relapsing polychondritis is characterized by inflammatory destruction of cartilage and sparing of the posterior membrane, with airway involvement occurring in up to 20–50% of patients and contributing to both morbidity and mortality (85-89). Initial obstruction due to cartilaginous edema is often followed by malacia from cartilaginous damage, which can lead to a combined fixed and dynamic obstruction. In a recent large case series, respiratory failure or infection from airway obstruction accounted for 65.4% of deaths (89). Airway stenosis in this population may be under-recognized, with up to 94% of patients having abnormal CT expiratory imaging in one case series (90). There is limited data on the management of airway involvement outside of systemic immunosuppression, though proximal airway malacia may necessitate placement of a tracheostomy to prevent death from airway collapse (91). A single center series demonstrated self-expanding metal stents (SEMS) improved dyspnea as well as facilitated weaning from mechanical ventilation (92).

In the common inflammatory disease sarcoidosis, airway involvement in any form is observed in approximately two-thirds of patients (93). Multiple pathophysiologies can result in obstruction, including extrinsic compression from lymphadenopathy, endobronchial granulomatous disease or scarring, or airway distortion from fibrosis. Airway obstruction can also be difficult to differentiate from sarcoid-induced hyperreactive airway disease, and treatment with systemic corticosteroids or other immunosuppressants improves obstruction from either cause (94). The deeper submucosal involvement of endobronchial disease may limit the utility of laser, electrocautery, topical mitomycin C, and cryotherapy, but each has been described as successful in small studies (95-99). Balloon dilatation and stenting can be utilized for patients without adequate response to systemic treatment (95,96,100).

Amyloidosis is a systemic disease involving extracellular amyloid fibril deposition and can affect many organ systems. Parenchymal nodules and pleural effusions are the most common pulmonary manifestations (101). Multifocal infiltration of amyloid plaques into airways is a rarer presentation, accounting for an estimated 1.1% of all amyloid cases, and not usually associated with detectable peripheral lymphoplasmacytic clonal proliferation (102). Bronchoscopy typically demonstrates irregular white

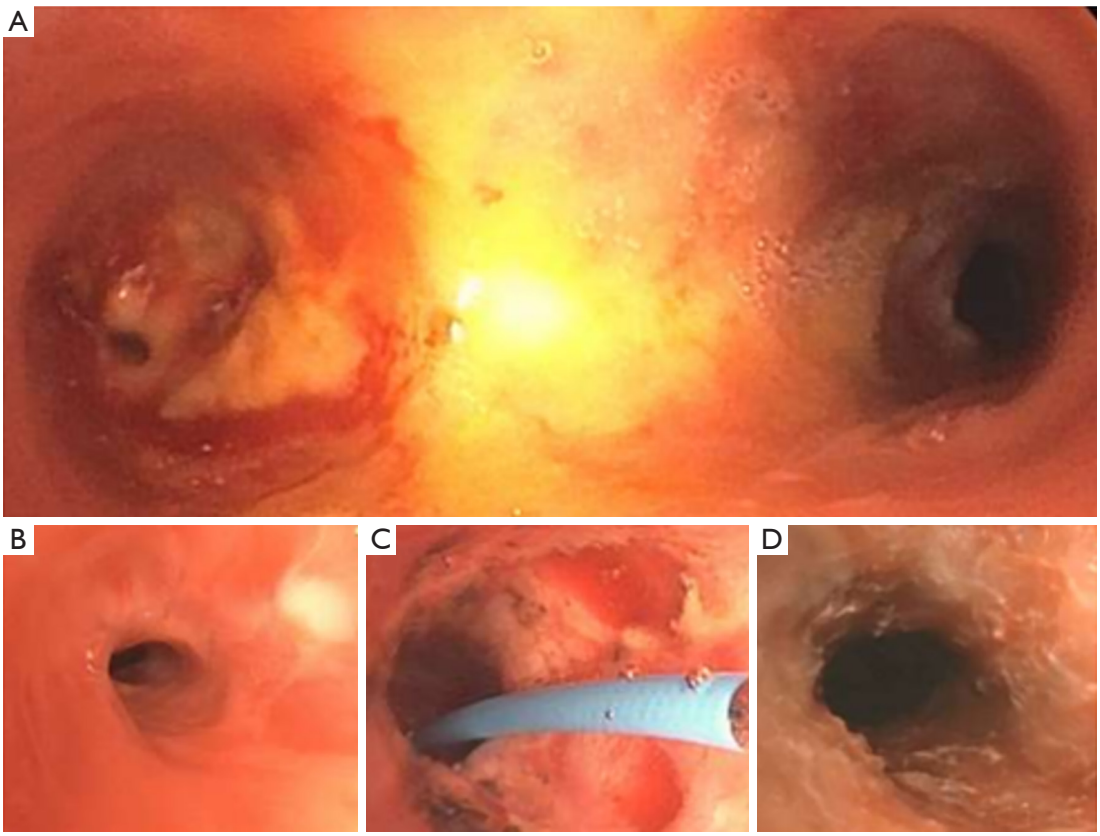

Figure 3 Severe left mainstem stenosis in GPA. (A) Bronchoscopic view from the distal trachea of cicatricial stenosis in the left mainstem. (B) Pre-intervention from the proximal left mainstem. (C) Balloon dilation after radial electrocautery incisions. (D) Final result after dilation and injection of triamcinolone. GPA, granulomatosis with polyangiitis.

deposits, often arising from the posterior wall, which may completely occlude the airway. Systemic therapy has been trialed with some success and there is no evidence to guide the choice of bronchoscopic therapy modalities, which can be necessary in central disease or more peripheral disease with near complete occlusion leading to infection or symptoms. Bronchoscopic treatment with laser or forceps resection, balloon dilation, as well as treatment with external radiation is described, but data is limited (103-108).

Case 2

A 61-year-old female with GPA on systemic immunosuppression presented with shortness of breath and wheezing. She had required several bronchoscopies for dilation and stenting more than 2 years prior for left mainstem stenosis, but this had become quiescent after initiation of rituximab. CT revealed multi-level tracheobronchial stenosis with stenosis in the subglottic area as well as the left mainstem. On bronchoscopic exam, there was mild subglottic stenosis with estimated reduction of diameter to 30% and no intervention was done at that level. There was severe stenosis with a luminal diameter of <3 mm at the left mainstem (*Figure 3A*,*3B*), radial cuts using electrocautery knife followed by balloon dilation and steroid injection was performed (*Figure 3C*,*3D*). Recurrence of the stenosis required further dilations in the 18 months of follow-up, but patency was able to be maintained.

Infectious causes of central airway stenosis

Viral, bacteria, mycobacterial, and fungal infections can affect the airways with varying presentation and severity. Infectious obstruction can take the form of severe airway inflammation, endobronchial lesion(s), or airway stenosis. Treatment of underlying infection will often result in resolution of airway disease. However, some infections, such as tuberculosis (TB), can result in chronic, fibrotic airway stenosis, while others,

like recurrent respiratory papillomatosis (RRP), have a recurrent and progressive nature.

RRP, caused by human papillomavirus (HPV) types 6 and 11, results in debilitating chronic disease in both adult and pediatric patients with a current estimated incidence of two cases per 100,000 adults (109). However, the overall incidence is declining in multiple first-world countries due to increased utilization of HPV vaccinations (110,111). Papillomas typically appear as white, polypoid lesions with smooth surfaces and can affect any part of tracheobronchial tree, from vocal cords down to and including the lung parenchyma, and there is potential for malignant transformation (112). Endoscopic removal of obstructing papillomas is the primary treatment modality, and recurrence rate approaches 100% as the HPV virus is thought to be dormant even in non-papillomatous epithelial cells (113,114). Both laryngologists' and bronchoscopists' skillsets are needed in these complex patients with laryngoscopy and microsurgery for supraglottic vocal cord, subglottic, and proximal tracheal papillomas, and flexible and rigid bronchoscopy for more distal tracheal and bronchial papillomas. Given the recurrence rates, procedural goals are noncurative, but focus on maintaining adequate voice quality and airway patency. Studies have shown success with lasers, including potassium titanyl phosphate (KTP), pulsed dye and CO_2 lasers as well as microdebriders, rigid mechanical debridement, or cryotherapy (115,116). Tracheostomy placement is reserved for impending airway compromise, with consider of early decannulation given a risk of development or spreading of trachea papillomas (117). Though transmission is unproven, there is potential to aerosolize viral particles in procedures for RRP and personal protective equipment is paramount, with airborne precautions, including eye protection, a necessity for all entering or cleaning the room prior to air turnover (118).

Multiple medications have been studied in RRP and data is promising. Endoscopic intralesional injection of cidofovir, a cytosine analog, is well described with a systematic review of fourteen smaller studies showing an overall remission rate of 73.6% (119). In a case series of five patients treated with systemic bevacizumab, an antiangiogenic, all patients had a rapid and sustained response with a reduction in the number of bronchoscopic interventions required; there is also limited data for bevacizumab use intra-lesionally (119,120). Treatment with immunotherapy agents, including avelumab and bintrafusp alfa, has also demonstrated improvement in outcomes (121,122). There is now also evidence for use of HPV vaccination even after disease occurrence, with efficacy in decreasing the frequency of procedures (123,124).

TB most commonly involves the lobar bronchi, affecting up to 50% of patients with active TB and can persist even after antituberculosis treatment has been completed. Endobronchial TB is classified into one of seven subtypes: active caseating, edematous-hyperemic, fibro-stenotic, tumorous, granular, ulcerative, and nonspecific bronchitic (125). Success with balloon dilation, mitomycin-C application, CO_2 and Nd:YAG laser therapy, cryotherapy, electrocautery, and stent placement have each been described (126-128). One recent retrospective analysis of stenosis in TB patients suggested both disease recurrence and development of malacia were increased in patients who underwent airway intervention, recommending patients diagnosed with TB early should be managed conservatively (129).

Fungal infections can present with airway involvement in both immunocompetent and immunocompromised hosts. Immunocompromised hosts are susceptible to invasive opportunistic fungal infections including mucormycosis, *Fusarium* infection and cryptococcal infections, while endemic fungal infections such as blastomycosis or coccidioidomycosis can present with airway disease even in patients with intact immune systems (130). Aspergillosis, the most common endobronchial fungal disease, is more common in immunocompromised hosts, but can occasionally occur in healthy individuals. There are four patterns identified for airway aspergillosis: pseudomembranous, ulcerative, obstructive, and invasive (131,132). Targeted antifungal antibiotics are the mainstay of treatment and multi-modality bronchoscopy has been described for both diagnosis and treatment (130).

Case 3

A 29-year-old male with a history of HPV infection since infancy presented with worsening dyspnea as well as vocal changes; he was previously managed with suspension laryngoscopy for papilloma removal from the vocal cords and proximal trachea once to twice a year. CT imaging revealed more distal polyps (*Figure 4A*). A joint procedure with a laryngologist and interventional pulmonologist was performed; suspension laryngoscopy revealed obstructing polyps both above and below the vocal cords that were removed with a microdebrider (*Figure 4B-4D*). Rigid bronchoscopy with mechanical debulking with the rigid barrel was then performed in the trachea and right and left mainstems with good result (*Figure 4E,4F*). Papillomas removed from the right mainstem revealed malignant

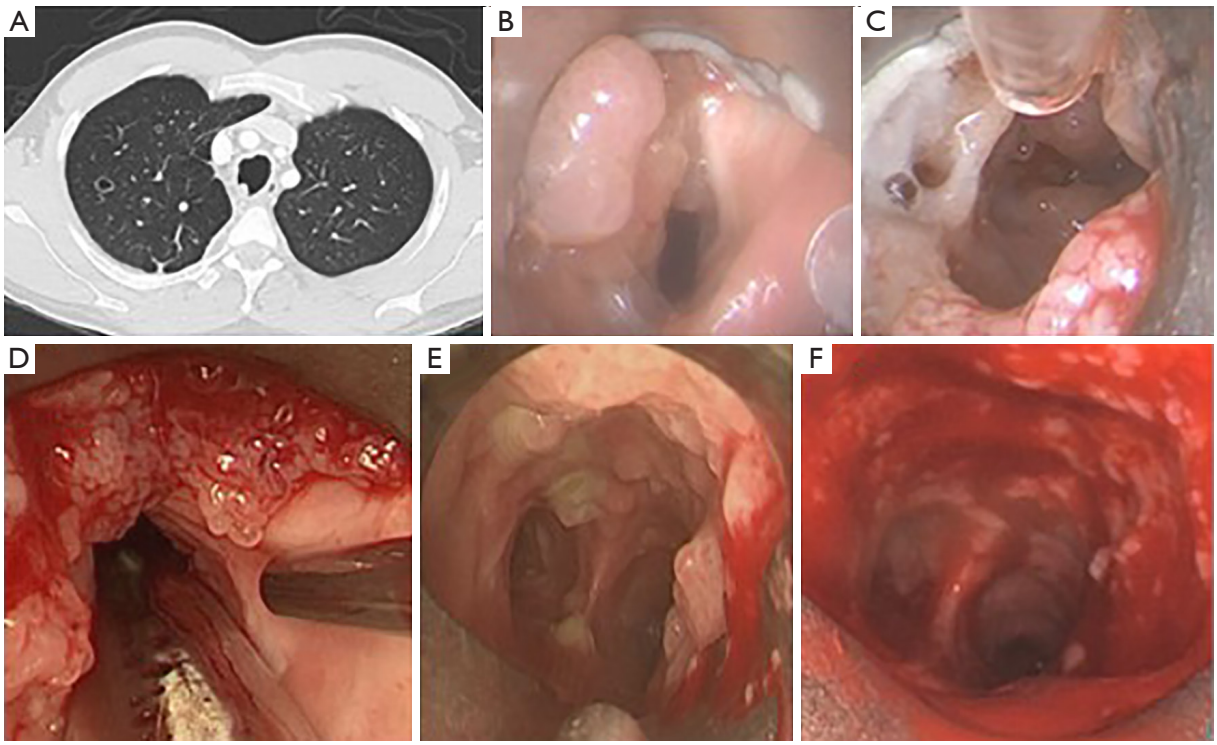

Figure 4 Radiographic and endoscopic images for a patient with severe recurrent respiratory polyposis. (A) Axial CT image of the mid-trachea with non-obstructing papillomas. (B) Supraglottic space with papillomas. (C) Obstructing papillomas of the subglottic space and proximal trachea. (D) Micro debridement with improvement of the subglottic space. (E) Mid-trachea with non-obstructing papillomas. (F) Improvement after rigid debulking of the mid and distal trachea. CT, computed tomography.

transformation. He required a repeat procedure within 10 weeks, but after initiation of immunotherapy for his malignancy, all papilloma regrowth slowed, and procedure interval was able to be lengthened.

Central airway disease caused by benign tumors

Tracheobronchopathia osteochondroplastica (TO) is a rare disorder wherein multiple osseocartilaginous nodules are distributed over the cartilaginous rings of the tracheobronchial tree, with sparing of posterior membrane and the spaces between rings (133). These lesions are very firm, limiting biopsy and making effective dilation challenging. Fortunately, most TO patients are asymptomatic with lesions discovered incidentally, and can be managed conservatively with observation. TO can rarely cause severe tracheal stenosis requiring therapeutic bronchoscopy to maintain patency and limit symptoms. Use of vaporizing therapy, such as laser, combined with or without a rigid bronchoscopy mechanical coring technique has been described with good success, though data is limited (134,135).

Endobronchial hamartomas are benign lung malformations and can include a mixture of tissues including cartilage, fat, muscle and epithelium (136). Though more common in the pulmonary parenchyma, hamartomas are the most common benign airway tumor with 1.4% of cases presenting in an endobronchial location (137). Bronchoscopic treatment modalities include mechanical dissection, laser, cryotherapy, and argon plasma coagulation have been described with good result (138-140). Surgical resection should be reserved for those with symptoms from disease not amenable to bronchoscopic resection (138).

Many other less common benign tumors can occur in the airways, including chondroma, epitheliomas, lipomas, hemangiomas (141).

Case 4

A 65-year-old-female presented with recurrent left lower

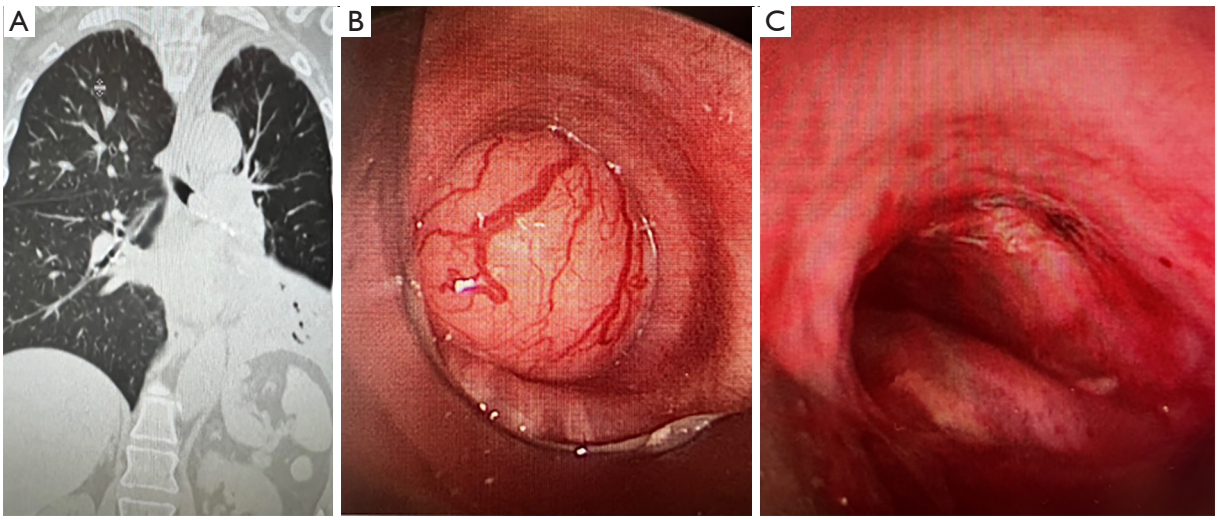

Figure 5 Radiographic and bronchoscopic images for a patient with benign airway tumor. (A) Coronal CT image with left lower lobe endobronchial disease and distal obstruction. (B) Vascular, well demarcated tumor occluding the left lower lobe. (C) After snare resection and removal *en bloc*, no residual tumor was seen in the airway. CT, computed tomography.

lobe pneumonias. A CT was performed and revealed a large left mainstem endobronchial tumor (*Figure 5A*), complicated by left lower lobe obstructive pneumonia. Rigid bronchoscopy revealed a large mid left mainstem tumor completely occluding the left mainstem; the surface of mass was vascular and glistening (*Figure 5B*). Given the predominant endobronchial component of the tumor with narrow pedunculated base, it was resected with electrocautery snare and then removed *en bloc* using cryo-adhesion with no residual tumor seen and restoration of 100% patency of the left lower lobe bronchus (*Figure 5C*). Histopathology was consistent with a pleomorphic adenoma, a benign tumor commonly originating in a salivary gland, but rarely described as arising from the airway. Follow up CT and bronchoscopy after 6 months showed no recurrence.

Dynamic airway obstruction

Excessive central airway collapse (ECAC) is disproportionate (>50%) narrowing of the airway lumen during all or part of expiration leading to symptoms of dyspnea, barking cough, mucus production, recurrent infections, and/or low quality of life. Excessive dynamic airway collapse (EDAC) and tracheobronchomalacia (TBM) are two separate pathologies within ECAC (142,143). EDAC is the excessive bowing the posterior membrane and TBM is the softening or loss of strength of the cartilaginous airway. EDAC and TBM can also co-exist. Spirometry can be suggestive of and expiratory CT is very sensitive for both EDAC and TBM components (144,145). Multiple co-pathologies, including COPD, asthma, chronic infections, gastroesophageal reflux disease (GERD), autoimmune disease, and obesity can contribute to ECAC and treatment of each should be medically optimized in symptomatic patients (143). The diagnosis of symptomatic ECAC should be suspected when usual treatment of other disease pathologies does not result in improvement.

Procedural management in ECAC is uniquely, compared to other causes of benign airway obstruction, distinctly divided into diagnostic and therapeutic maneuvers. Diagnostic bronchoscopy under minimal sedation is key to evaluate the severity of collapse and identify which airways are involved. Therapeutically, continuous positive airway pressure (CPAP) can be used as a pneumatic stent, and titration bronchoscopy to visual CPAP effect has been described as both a bridge to therapy and definitive management (143,146). In patients with a predominant central airway pattern and limited peripheral involvement, tracheal and bronchial stenting can visually and symptomatically improve ECAC. However, the long-term side effects of granulation tissue formation, stent migration, mucus plugging, and need for repeat procedures outweigh the benefits of definitive stenting in most patients with ECAC. Surgical tracheoplasty is an option in ECAC patients with symptomatic central disease.

For potential surgical candidates, a role for stent trials to evaluate for symptomatic and physiologic benefit has been described (147,148). Both robotic and open surgical approaches have been described with good symptomatic success (149,150).

A word on airway stenting in non-transplant benign airway obstruction

Airway stenting is utilized in malignant airway obstruction to maintain luminal patency and provide structural support as a bridge to cancer-targeted therapy or for palliation. In benign airway obstruction, consideration of stenting must often account for a longer life expectancy, as well as lower morbidity of the disease process itself. Currently available airway stents include various sizes and shapes of both silicone stents and metallic stents; metallic stents are available as uncovered, partially covered, and fully covered (24). Patient specific customization via silicone 3D-printed stents, have also recently available and deserve further study (15,16,151,152). Metallic stents can be deployed using a combination of flexible or rigid bronchoscopy, airway guidewires, and fluoroscopy, while silicone stents require rigid bronchoscopy. Stent selection is based on length, diameter, and shape of the stenosis as well as stent material, deployment methods, and procedural skillset and tools available. Stent complications are common and include migration, mucus plugging, and granulation tissue formation with reported complication rates of up to 50%, often requiring permanent removal or removal and revision (22,53,153-155). Indeed, granulation tissue formation from uncovered metallic stents is a particular challenge and high complication rates and difficulty with removal were reported in the early 2000s (153,154). The U.S. FDA applied a black box warning on the use of metallic stents in central benign airway stenosis in 2005 (156). Additional covered or partially covered metallic stents have come to market since this warning. Studies of the use of covered metallic stents and silicone in benign airway stenosis suggest fewer complications (22,53,155). Our practice is to use airway stents as a last resort in benign disease, with anticipatory discussions with the patient, close monitoring post placement including planned repeat bronchoscopy, and anticipation and optimization for timely removal if possible.

Transplant airway complications

Airway complications of lung transplant include anastomotic necrosis and/or dehiscence, endobronchial infection, granulation tissue formation, fistula formation, anastomotic stenosis, stenosis at airways distal to anastomoses, and malacia. The reported incidence of airway complication post-transplant varies widely between 2% and 18% but has decreased over time (157-159). Time since transplant is associated with complication type, with dehiscence being most common in the immediate post operative period and stenosis later in the course.

Bronchial anastomoses are particularly susceptible to ischemia, due to the severing of the bronchial artery during transplant. The remaining perfusion via retrograde pulmonary arterial flow is restored intraoperative at time of pulmonary arterial anastomosis and revascularization occurs 2–4 weeks post-transplant, though a small study of perfusion scans in patients post-transplant demonstrated persistent distal airway hypoxemia even at 3 and 12 months (160). Risks factors for ischemia and airway complications have been identified and include the length of the donor bronchus, donor-recipient height mismatch, surgical techniques, donor ventilation time, and extracorporeal membrane oxygenation (ECMO) in the recipient (161-163).

In 2018, the International Society for Heart and Lung Transplant (ISHLT) published a consensus statement on airway complication including definitions, grading system, and recommended therapeutic interventions (164). The gradation system developed by the ISHLT accounts for the pathophysiologic change(s), the location, and the severity or extent of each abnormality. A summary of the therapeutic recommendations for complication type are noted in *Table 2*, with evaluation and treatment of infection also playing a critical role in management. Overall, combined data for all complications would suggest, similar to non-transplant benign disease, stenting in particular has a high complication rate and need for repeat procedures (165,166). It does have demonstrated efficacy in symptom management but no data on overall survival has yet been demonstrated (167).

The management of the early complication anastomotic necrosis or dehiscence is driven by the severity and presence of complications such as abscess or fistula. Necrosis without dehiscence can be managed conservatively with frequent surveillance bronchoscopy to assess for progression or complications (164). Extensive necrosis or dehiscence can be treated with self-expanding metallic stent placement. Uncovered stents are favored to promote neo-epithelization are favored by some studies, while

Table 2 Management of post-transplant airway complications, adapted from the ISHLT 2018 Guideline (164)

Airway complication	ISHLT recommendation
Dehiscence	Partial airway thickness: conservative management with antibiotics and frequent surveillance bronchoscopy
	Full thickness: placement of a covered or uncovered self-expanding metallic stent to induce granulation and healing prior to consideration of surgical repair
Stenosis	Initial step: balloon dilation at regular intervals
	If requiring >2 dilations/month with symptomatic benefit, stent placement
	Airway debridement if stenosis is due to granulation tissue or webbing
Malacia	If critical ill and ventilatory support cannot be weaned, consider airway stenting
	If not critically ill, consider noninvasive positive pressure prior to a stenting or surgical correction

ISHLT, International Society for Heart and Lung Transplantation.

utilizing covered stents to seal airway defects by other (168,169). Silicone stents are generally avoided due to the force required for placement (170). Overall, the practice remains controversial due to high rates of complications. Salvage surgical maneuvers are challenging, and most case reports note the requirement for tissue grafting to reinforce the necrotic anastomosis (171-173).

Bronchial stenosis is the most common airway complication post transplantation and can occur anytime from months to years post-transplant. Airway stenosis is classified as central if occurring within 2 cm of the anastomosis and distal if greater than 2 cm from the anastomosis (164). The vanishing bronchus syndrome is stenosis of the bronchus intermedius distal to the right anastomosis and occurs in approximately 2% of right lung transplants. It is associated with increased morbidity and mortality with a mean survival of 25 months (174). Like non-transplant benign stenosis, if a stenosis is less than 50% of the normal lumen diameter and the patient is asymptomatic a watchful waiting approach is recommended; while if greater than 50%, bronchoscopic therapeutic intervention has to be considered. Balloon dilation alone is often the first treatment modality, but may need to be repeated to be effective, with an average of four balloon dilations to obtain good result in the largest case series (175). If balloon dilation is ineffective, limited data exists to support ablative therapies, stenting, brachytherapy, and topical therapy (176-181). Surgery is described by the ISHLT as the nonpreferred approach, but multiple surgical maneuvers have been described in case reports or series (182-184). The ISHLT highlight the importance of noting if malacia is resulting in airway narrowing and recommends treating malacia conservatively in the absence of critical illness, severe symptoms, or functional impairment (164).

Strengths and limitations

The range of subspecialists, procedures, surgeries, medications, and other therapies available to manage the varied pathologies making up benign airway obstruction are both a strength and weakness for these complex patients. The number of case series demonstrating high rates of success is heartening, but the frequent lack of multi-center or prospective data challenges interpretation. The delay to diagnosis in many patients certainly influences outcomes and conflicting data likely also represents practice preference, local expertise, and differences in patient populations. The investment of providers from multiple specialties and subspecialties widens the cumulative cognitive and technical skillset but can lead to fractures in ongoing progress in improving our understanding and management. The next years will be particularly revealing as more data becomes available from the challenging post-COVID 19 population and additional insight from electronic medical record (EMR) based artificial intelligence (AI) and genomics improves diagnostic acumen. The suggestion for a multi-disciplinary approach for benign airway stenosis should not just apply to patient management, but also for ongoing research. With the universal availability of electronic health records, virtual work platforms, and, soon, AI, there is no reason accurate and high-impact data, including prospective clinical trials, could not be forthcoming.

Conclusions

In summary, diagnosis and management of benign

airway obstruction must include a high clinical suspicion, fastidious triage and stabilization, understanding and assessment of each patient's pathology and physiology, and meticulous procedural planning. Treating providers must be realistic with each patient about expected outcomes from procedures, the need for frequent reassessment, and the potential for repeat procedures and referrals to other specialists. While the field of interventional bronchoscopy continues to expand in both availability and toolkit, we cannot underemphasize the role of a surgical subspecialists and a multidisciplinary approach to achieving patients' goals safely, consistently, and for meaningful durations of time. We must remember evidence-based data in these diseases is often limited and personalizing the approach to management in a thoughtful manner is critical for success.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Jonathan Kurman and Bryan S. Benn) for the series "Diagnostic & Therapeutic Bronchoscopy" published in *AME Medical Journal*. The article has undergone external peer review.

Peer Review File: Available at https://amj.amegroups.com/article/view/10.21037/amj-23-103/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-23-103/coif). The series "Diagnostic & Therapeutic Bronchoscopy" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All clinical procedures described in this study were performed in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for the publication of this article and accompanying images.

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doi: 10.21037/amj-23-103
Cite this article as: Hattab Y, de Salmeron SP, Malsin E. Benign airway obstruction: a clinical practice review of causes and managements principles. AME Med J 2024;9:4.