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REVIEW

The "forgotten zone": Acquired disorders of the trachea in adults

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Summary
The upper airway is generally defined as the air passage segment that extends between the naso- or oropharynx and the carina. The longest segment of the upper airway—the trachea—begins at the inferior portion of the larynx and extends to the branch point of the main carina. The trachea has the potential to be a "forgotten zone" in differential diagnoses, as pathological processes involving this portion may not receive prominent clinical consideration in disorders presenting with respiratory symptoms and signs. Unlike the oropharynx, this anatomical area is beyond visualization on routine inspection; unlike the mediastinum and lung fields, it is a potential "blind spot" on initial, plain radiographic examination of the chest. Nonetheless, the adult trachea is affected by a number of primary disorders and is also a target organ of a variety of systemic diseases. This review will focus on both primary and systemic diseases involving the adult trachea with specific attention to their clinical manifestations and diagnostic hallmarks.

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Introduction

The upper airway extends between the naso- or oropharynx and the carina. The longest segment of the upper airway—the trachea—begins at the inferior portion of the larynx and extends to the branch point of the main carina, a length of 10—16 cm. Its inner diameter is 21—27 mm and is supported anteriorly and laterally by 15—20 C-shaped, cartilaginous rings that protect the integrity of the airway[1] (Fig. 1, panel A). It lies anterior to the esophagus; the non-reinforced, posterior wall of the trachea is appropriately compressible during swallowing. The trachea has the potential to be a "forgotten zone" in differential diagnoses, as pathological processes may not receive prominent clinical consideration as other more common disorders presenting with similar respiratory symptoms.[2] Unlike the oropharynx, this anatomical area is beyond visualization on routine inspection; unlike the mediastinum and lung fields, it is a potential "blind spot" on the routine, plain radiographic examination of the chest.[3] Nonetheless, the adult trachea is affected by a number of primary disorders and is also a target organ of a variety of systemic diseases. If this anatomic area is not considered in the differential diagnosis the results can be disastrous because unlike the lower airways, the upper airway has no collateral ventilation and airflow obstruction can be life threatening. This review will focus on primary and systemic diseases involving the adult trachea. Specific attention will be paid to their clinical manifestations and diagnostic hallmarks.

Physiology of airflow in the upper airway

The shape and function of the larynx and trachea are of great importance from a physiologic and clinical point of

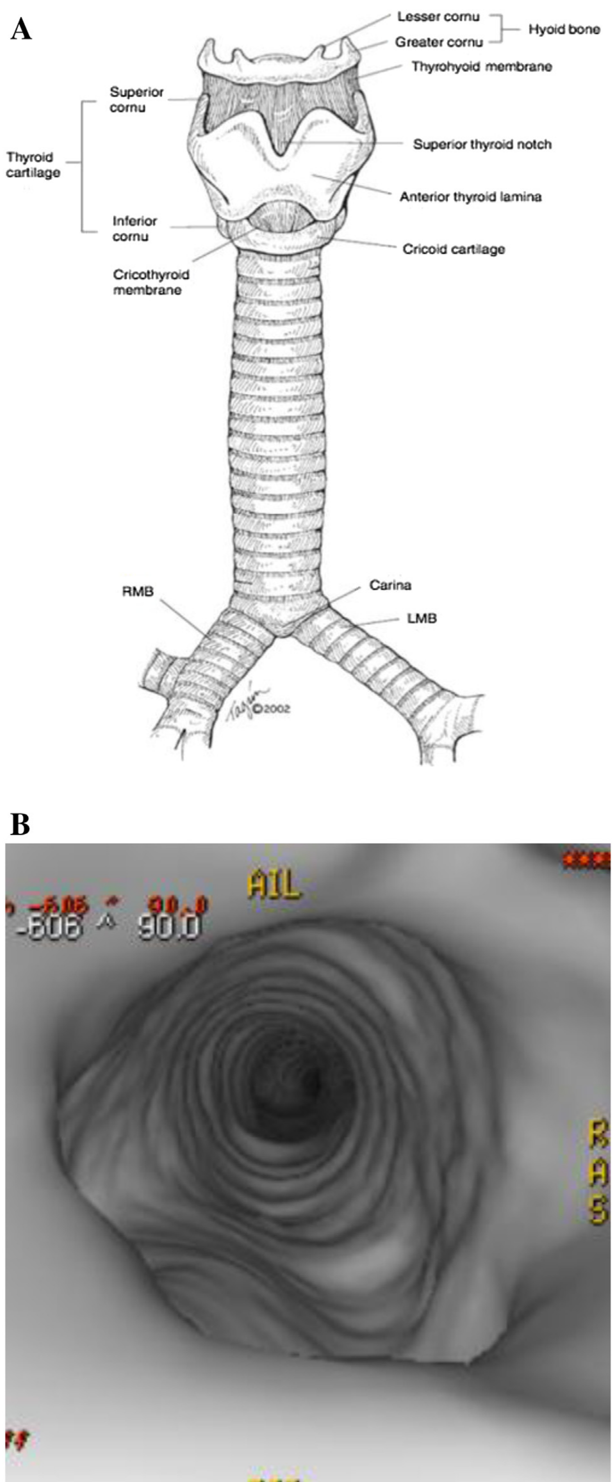

Figure 1 Panel A: Anatomy of upper airway (adapted from Surgery of the Trachea and Bronchi, by H. Grillo. Copyright 2004, PMPH-USA. Reprinted with permission) panel B: virtual bronchoscopy using CT scan reconstruction shows appearance of tracheal rings and intact mucosa.

view. Depending on the density of gas molecules, flow rate, and airway diameter; the pattern of airflow may be laminar or turbulent.[4,5] Laminar flow usually occurs in the very small airways where flow is reduced. In the larynx and trachea where air velocity is high, airflow is usually turbulent. The driving pressure for turbulent flow is proportional to the square of the flow rate and inversely related to the fifth power of the radius. Thus, a minor decrease in the radius of the upper airway results in a significant increase in the driving pressure necessary to achieve the same airflow. The inhalation of a low-density gas such as helium-oxygen mixture has been successfully used with acute upper airway obstruction as it increases the proportion of laminar flow.[6] This decreases the density-dependent driving pressure required for airflow.

Classification of tracheal disorders

Tracheal disorders result from intrinsic disorders (infections, inflammatory disorders, trauma, and malignancy) or extrinsic compression from adjacent structures (Table 1). These disorders manifest mainly as obstruction of the upper airway (narrowing or stenosis). However, when the integrity of tracheal wall is lost, tracheal dilatation (tracheomegaly) may develop and can be associated with tracheal scalloping or diverticulosis. Such deformities may predispose the trachea to dynamic collapse during inspiration or expiration in extrathoracic and intrathoracic central airway involvement respectively.

Clinical manifestations

The clinical manifestations of tracheal disorders are determined by the extent and location of the abnormalities. Tracheal obstruction can be life-threatening acutely as, unlike the lower airways, it has no collateral ventilation. Acute obstruction is a life-threatening condition and typically presents with inspiratory stridor that is best heard in the neck, and with cough, and dyspnea. Most primary and systemic diseases involving the adult trachea are more insidious. Patients with extrathoracic stenosis may have hoarseness, inspiratory wheezing, stridor, and nonproductive cough. However, intrathoracic stenosis may cause more difficulty with expiration and worsening dyspnea in the recumbent position. In addition, patients with normal cardiopulmonary reserve may present with dyspnea only on exertion. In general, dyspnea at rest develops when the upper airway diameter is decreased by 75% (<5 mm). The presence of preexisting pulmonary disease may result in significant dyspnea at lesser degrees of airway narrowing. Furthermore, tracheobronchial stenosis may impair clearance of secretions and increase the risk of respiratory infections. Patients with tracheal disorders may have dyspnea and wheezing that mimic asthma but with no response to bronchodilators.

Intrinsic disorders

Infections

Diffuse swelling of the larynx and trachea associated with signs of upper airway obstruction is not uncommon in children in the setting of certain acute upper respiratory viral diseases, such as those caused by parainfluenza types 1–3, the most common causes of the croup syndrome; influenza A and B viruses; adenoviruses; coronavirus NL63; and

Table 1 Classification of tracheal disorders.

A) Intrinsic
1. Infectious
Viral
Bacterial
Fungal
2. Inflammatory/Infiltrative
Relapsing polychondritis
Granulomatosis with polyangiitis (Wegener's granulomatosis)
Sarcoidosis
Amyloidosis
Rheumatoid arthritis
Miscellaneous: inflammatory bowel diseases
3. Non-inflammatory
Tracheomalacia (and Mounier-Kuhn syndrome, Saber-Sheath deformity)
Excessive dynamic airway collapse
Tracheopathia osteochondroplastica
Idiopathic tracheal stenosis
4. Iatrogenic
Post-intubation tracheal stenosis
5. Neoplastic
Primary neoplasm (squamous carcinoma, adenoid cystic carcinoma)
Secondary neoplasm (metastasis)
B) Extrinsic
Extrinsic compression (lymph node, carcinoma, vascular anomalies)
Extrinsic diseases infiltrating the trachea
Fibrosing mediastinitis
Mediastinal granuloma
Tracheobroncholithiasis

respiratory syncytial virus.[7] In adults, such clinical manifestations are less likely because of their cumulative immunologic experience with environmental respiratory viruses and the relatively large diameter of the adult trachea. However, several, severe, viral-associated acute infections of the upper airways are described in adults. Tracheal involvement, manifested as focal or diffuse necrotizing tracheitis was frequently observed in autopsy analyses of 34 decedents from the 2009 H1N1 influenza A outbreak in New York City[8]; concurrent lower respiratory tract involvement was also nearly universally identified in this study.[8,9]

A variety of pathogens have been described as etiologic agents of acute or chronic upper airway diseases in adults (Table 2). Nearly all reported cases are associated with epidemiologic predispositions in the host. Risks include immunocompromised states, local damage to the tracheal mucosa from a variety of sources, and upper airway involvement with systemic infections. For some infectious diseases, only isolated case reports are available; others are more commonly associated with diseases of the upper airways in adults.

Tracheal papillomatosis is a benign condition caused by human papilloma virus (most commonly HPV-6 and HPV-11) characterized by papillomatous growth of the laryngeotracheal epithelium. The disease is more common in early childhood before the age of 5 years and affects male more than female.[31] The larynx is involved in most cases and is rarely limited to the trachea. Longstanding laryngotracheal papillomatosis may transform to squamous cell carcinoma.

Invasive *Aspergillus* tracheobronchitis is an uncommon but well described syndrome that generally has been reported in the same profoundly immunocompromised patient populations at risk for disseminated aspergillosis.[32] It has been described with several different species of *Aspergillus*. With less severe infection mucosal inflammation or intraluminal obstruction may occur, the latter due to exuberant growth of exophytic fungal collections. Both generally occur in settings of local tracheal injury, such as prolonged endotracheal intubation or previous nonfungal infection.[33] *Aspergillus* tracheobronchitis may also cause more severe disease with pseudomembranous and ulcerative lesions, generally in more profoundly immunocompromised individuals.[33] The prognosis associated with severe disease is typically poor, in large part related to the underlying severity of immune suppression in the host. Ulcerative disease tends to have a slightly better outcome, as it is usually associated with limited involvement of the respiratory tree. Many cases have occurred in the setting of organ transplantation. They are more likely to be diagnosed early and thus respond to early antifungal therapy.[34] Pseudomembranous invasive *Aspergillus* tracheobronchitis typically affects individuals with profound immunosuppressed states and is nearly universally fatal.[34]

Laryngeotracheal histoplasmosis is extremely rare and typically associated with disseminated disease in immunocompromised patients. In immunocompetent individuals, primary infections are asymptomatic or present as a flu-like illness. The disease is endemic in the river valleys in the central United States. Mucosal lesions begin as painless flat plaques. Later, these lesions ulcerate and may resemble squamous cell carcinoma.[35] Histoplasmosis may cause external compression of central airways due to granulomatous lesions or calcified massive mediastinal lymph nodes, which may erode into adjacent airways.

Rhinoscleroma is a slowly progressive granulomatous disease caused by *Klebsiella rhinoscleromatis*. This gram-negative bacterium is endemic in tropical and subtropical areas.[36] The disease typically involves the nose, paranasal sinuses, and central airways; and progresses slowly over years. Granulomatous nodules may cause partial obstruction of the involved airways and may progress to fibrosis with stenosis in later stages. Treatment consists of prolonged antibiotic therapy.

Nosocomial tracheobronchitis occurs in 1–3% of individuals in ICUs.[37,38] One study found 201 cases over a 6.5-year period in non-immunocompromised, critically ill individuals intubated for more than 48 h; gram-negative organisms, most commonly *Pseudomonas aeruginosa*, account for 75% of isolates.[37] This entity, also known as ventilator-associated tracheobronchitis (VAT), has been associated with increased duration of mechanical ventilation and length of stays in the ICU.[37,38] VAT is probably part of a continuum between respiratory tract microbial colonization and ventilator-associated pneumonia (VAP); nearly one-third of VAT patients progressed to VAP in one study.[38] Antimicrobials appear to lower ICU-associated mortality in VAT.[39]

Tuberculosis tracheitis is a rare clinical manifestation of tuberculosis that is considered one of the most

Table 2 Infectious etiologies of acute tracheitis in adults.

Microbial etiology	Epidemiology	Tracheal lesions	Refs
Herpes simplex virus	Immunocompromised host; prolonged intubation; corticosteroids; AIDS	Necrotic ulcerations with squamous metaplasia; reversible cause of tracheal stenosis	10—13
Corynebacterium pseudodiphtheriticum	Mucosal damage from antecedent viral URI; endotracheal intubation	Necrotizing tracheitis	14
Aspergillus spp.	AIDS; acute or chronic leukemias associated with neutropenia; solid organ transplantation (lung, kidney, heart); tracheal injury due to chronic infection	Necrotizing tracheobronchitis with ulcers, pseudomembranes, hyphae; mycetoma formation; no fungal invasion of lungs; transmural extension with possible bronchoarterial fistula	15—21
Candida albicans	Prolonged endotracheal intubation, tracheostomy	Intraluminal fibrinoid membrane comprising fungal elements	22
Pasteurella multocida	CLL, anti-TNF monoclonal antibody treatment	Symptoms and sputum culture only; no bronchoscopy	23
Microsporidiosis	AIDS	Tracheal involvement as part of disseminated infection; squamous metaplasia; parasites in macrophages and in lamina propria	24
CMV	AIDS	Necrotizing tracheitis	24
Mycobacterium tuberculosis		Diffuse tracheal stenosis; usually associated with pulmonary disease	
Klebsiella rhinoscleromatis	Rhinoscleroma affects nose and paranasal sinuses but may affect nasopharynx, larynx, trachea. Chronic, progressive, granulomatous infection endemic in Africa, South America, and other parts of the developing world. Rare in developed world.	Diffuse tracheal stenosis	25
Staphylococcus aureus	Antecedent tracheal mucosal injury	Acute membranous tracheitis	
Pseudomonas aeruginosa	Prolonged mechanical ventilation, tracheostomy	Not described	26
Bacillus cereus	Aplastic anemia, antilymphocyte globulin	Pseudomembranous tracheobronchitis	27
Aeromonas veronii	Near-drowning	Non-occlusive tracheobronchitis	28
Actinomycosis	Congenital tracheal bronchus	Not described	29
Sporothrix schenckii	Cirrhosis, tracheal involvement as part of extracutaneous sporotrichosis	Yeast forms in tracheal tissue	30

communicable forms of the disease due to the high burden of mycobacteria expelled by coughing.[40] It typically results from contiguous spread from peribronchial lymphatics or mediastinal lymph nodes. Sequelae include obstruction due to mucosal necrosis and edema and secondary fibrosis and airflow obstruction upon healing. Chronic tuberculosis may also cause fibrosing mediastinitis, associated with secondary involvement of the trachea and central airways through contiguous encroachment by the mediastinal infection. However, this clinical presentation is more commonly observed in relation to chronic histoplasmosis (see below).[41]

Inflammatory and infiltrative disorders

Relapsing polychondritis

Relapsing polychondritis is a rare episodic and progressive multisystem inflammatory disease of the proteoglycan-rich structures. The exact etiology of the disease remains unknown. However, the presence of fibrocartilagenous infiltration with CD4+ lymphocytes, immune deposits in tissue lesions, and elevated levels of autoantibodies against type II collagen suggest an immunologic mechanism.[42] Patients with relapsing polychondritis may have an associated connective tissue disease, systemic vasculitis, myelodysplastic syndrome, or lymphoproliferative disorder. The disease primarily affects cartilages of external ears, larynx and tracheobronchial tree, sparing the posterior membranous part of the trachea. The disease occurs in all age groups and affects males and females equally. Upper airway complications develop in up to 55% of patients and may include subglottic stenosis, tracheal wall thickening with subsequent stenosis, and tracheobronchomalacia.[43] Large airway disease can be subtle in the early stages of the disease. Respiratory symptoms such as cough, wheezing, hoarseness, stridor and dyspnea are present in up to 50% of patients.[44] These symptoms should be taken seriously as the severity of symptoms poorly correlates with the extent of the disease and may herald life-threatening collapse of central airway. Dynamic CT may reveal expiratory collapse of central airways.[45]

Granulomatosis with polyangiitis (Wegener's granulomatosis)

Wegener's represents a small-vessel vasculitis characterized by necrotizing granulomatous inflammation that mainly involves the upper airway, lungs and the kidneys. It has a peak incidence in the fourth and fifth decades of life. Most patients have upper airway involvement and the trachea (typically the subglottic area) is affected in 10–20% of patients. Although the disease affects males and females equally, more than 90% of patients with tracheal stenosis are females.[46] Subglottic stenosis is more frequent in patients with early age of onset.[47] Patients usually present with symptoms such as hoarseness, sore throat, stridor, cough, hemoptysis, or dyspnea. Bronchoscopy may reveal laryngeal stenosis, focal subglottic eccentric or concentric tracheal stenosis, tracheal ulceration, calcification of tracheal rings, and inflammatory pseudo-polyps. Transbronchial lung biopsy can be used to confirm the diagnosis and may be evident for vasculitis, necrosis, or granulomatous inflammation. Approximately half of patients who have bronchoscopic abnormalities demonstrate histopathologic features consistent with the disease.[48] However, the full spectrum of histologic features on individual biopsy is only present in 16% of specimens. Approximately, ninety percent of patients have elevated anti-neutrophilic cytoplasmic antibodies (c-ANCA).[49]

Sarcoidosis

A multisystemic granulomatous disease of unclear etiology, the disease is characterized by activation of CD4+ T-lymphocytes and macrophages that leads to the formation of epithelioid non-caseating granulomas in the affected organs. Sarcoidosis usually affects individuals in the 25- to 50-year-old age group. Although the respiratory system is involved in more than 90% of patients, central airway involvement is uncommon and is often overlooked.[50] The trachea and main bronchi can be affected by intrinsic granulomatous infiltration or by extrinsic compression of enlarged mediastinal and hilar lymph nodes. The upper part of the trachea is affected in 1%–3% of patients, while distal trachea and lower airways are less frequently involved. Patients with upper airway involvement may be asymptomatic or may present with unexplained cough, dyspnea, or wheezing. These symptoms are more related to airway hyperresponsiveness due to tracheal mucosal involvement rather than mechanical obstruction.[51] Airway involvement in sarcoidosis is also associated with increased morbidity and mortality.

Amyloidosis

Amyloidosis is caused by deposition of abnormal hetrogenous fibrillary misfolded proteins that form from immunoglobulins produced by clonal plasma cells. Systemic amyloidosis may result in functional upper airway dysfunction because of macroglossia. Tracheobronchial amyloidosis is the commonest pulmonary pattern seen in patients with primary (AL) amyloidosis and is more common in males.[52] The disease has predilection to the larynx and can result in laryngeal stenosis.[53] Patients may have tracheal diffuse multifocal plaques within the sub-mucosa and is usually associated with poor prognosis. Tumor-like "amyloidomas" may be seen in localized amyloidosis confined to the tracheobronchial tree and is usually more benign although it may result in mechanical obstruction. These endoscopic abnormalities are sometimes confused with other intrinsic tracheobronchial disorders, especially tracheopathia osteochondroplastica.

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease characterized by chronic symmetric inflammatory arthritis, with various extraarticular manifestations. The disease is characterized by tissue infiltration with T lymphocytes and plasma cells, hyperplasia and hypertrophy of synovial lining cells. The laryngeal structures are involved in 26%–53% of patients.[54,55] Patients may have arthritis of the cricoarytenoid joint, rheumatoid nodules of the vocal cords, and vocal cords paralysis secondary to ischemic atrophy of the recurrent laryngeal nerves. The most common symptoms are hoarseness, sore throat and fullness, and dyspnea. In addition, isolated tracheal involvement has been reported and usually presents with of cough. Chest radiographs and pulmonary function studies are usually necessary to exclude the presence of parenchymal lung disease.

Inflammatory bowel diseases

Tracheobronchial manifestations of inflammatory bowel diseases are uncommon. These include ulcerative tracheitis, bronchiectasis, and obliterative bronchiolitis.[56] Tracheobronchial involvement is more common with ulcerative colitis than Crohn's disease and rarely precedes the intestinal manifestations.[57] Concentric ulceration, calcification of the tracheal cartilages, and irregular luminal narrowing may be evident by bronchoscopy.[58] Histopathologic examination may reveal submucosal fibrosis with chronic inflammation. Patients may present with stridor, dyspnea, and dry cough.

Non-inflammatory

Tracheomalacia (TM)

TM is a weakness of the tracheal wall due to loss of the cartilage integrity. This can be localized to a tracheal segment or diffuse extending to one or both main bronchi (ie. tracheobronchomalacia). TM can be classified according to the morphologic appearance of the trachea. The anterioposterior wall narrowing is called "crescent type" or "scabbard shape" and lateral wall narrowing is referred to as "saber-sheath type".[59]

TM predisposes the trachea to dynamic collapse during expiration (intrathoracic trachea) or inspiration (extrathoracic trachea) with 10–20% narrowing of the tracheal lumen.[60] TM can be idiopathic with significant tracheal dilatation (tracheomegaly) as in "Mounier-Kuhn syndrome" and the diagnosis is usually established when the diameter of the trachea, right main bronchus and left main bronchus exceed 3.0, 2.4, and 2.3 cm respectively on standard radiograph.[61] Mounier-Kuhn syndrome can be associated with tracheal scalloping or diverticulosis. Secondary TM can result from damage to tracheal wall from external compression, pressure and ischemia of the internal tracheal wall (eg. post-intubation), or chronic inflammation of the bronchi (chronic bronchitis) or tracheal cartilages (eg.

relapsing polychondritis). Post-intubation TM is usually segmental and typically <3.0 cm in length. TM may present with nonspecific symptoms like dyspnea, cough or hemoptysis often attributed to a coexisting pulmonary disease such as chronic bronchitis. In addition, patients may develop recurrent infections and bronchiectasis due to poor clearance of secretions.[62] Dynamic tracheal collapse visualized by bronchoscopy is considered the gold standard for the diagnosis of tracheomalacia.[63] The presence of an anterior bulging posterior tracheal wall, narrowed anteroposterior tracheal luminal diameter, and widened posterior membranous tracheal wall is very suggestive of TM.

"Saber-Sheath" deformity is a rare deformity of the intrathoracic trachea characterized by marked decrease in the transverse diameter of the trachea associated with an increase in its sagittal diameter. Saber-sheath trachea develops almost exclusively in men with chronic obstructive pulmonary disease (COPD) with a specificity of 92.9%.[65] This deformity results from mechanical forces of hyperinflated lungs that cause narrowing of the coronal diameter of the intrathoracic trachea and elongation of the sagittal diameter with abrupt widening of the tracheal lumen above the thoracic inlet. The diagnosis is made when the coronal to the sagittal diameter (measured 1 cm above the aortic arch) is equal to or less than 0.5 as this condition is not thought to cause symptoms.[66]

Excessive dynamic airway collapse (EDAC)

Excessive dynamic airway collapse represents collapse of the posterior membranous tracheal wall with 50% or more reduction of the sagittal diameter during expiration or coughing.[64] In contrast to tracheomalacia, EDAC is not related to a structural or functional cartilage pathology. However, tracheomalacia and EDAC may coexist.

Tracheobronchopathia osteochondroplastica (TPO)

A rare disorder characterized by the presence of submucosal cartilaginous nodules and ossified lesions. The disease affects the cartilaginous part of the trachea and spares the posterior membranous wall.[67,68] These lesions usually form a semicircular endotracheal structure that may vary in shape. It is usually diagnosed in individuals older than 50 and is slightly more common in males. Although TPO was thought to be a form of primary localized amyloidosis with ossification, the exact etiology remains unknown. Some studies have shown possible association between TPO and atrophic rhinitis.[69] Bone morphogenetic protein 2 (BMP-2) may have a role in the pathogenesis of TPO.[70] The disease typically affects the lower two thirds of the trachea and proximal bronchi. Patients can be asymptomatic or may present with cough, dyspnea, hemoptysis, and recurrent pneumonia. Chest radiographs may show calcified tracheal wall and/or narrowing of the tracheal lumen. Nodular irregularity of the anterior and lateral walls seen at bronchoscopy and punctate calcification evident on the CT scan can be diagnostic.[71]

Idiopathic laryngotracheal stenosis

A rare condition characterized by stenosis at the level of the cricoid cartilage and upper trachea with no apparent clinical or pathologic etiology. Most patients are diagnosed in their fourth and fifth decade of life. The disease has strong female predominance suggesting a possible hormonal role in the pathogenesis. Some studies of estrogen receptors (ER) and progesterone receptors (PR) have shown positive staining of fibroblasts in most cases.[72] However, the clinical significance of this is unclear. Several pathologic mechanisms have been postulated with a possible role of gastroesophageal reflux disease (GERD).[73] A study of ambulatory 24-h pH monitoring in patients with idiopathic tracheal stenosis showed significant pharyngeal acid reflux compared to the control group.[74]

Iatrogenic

Post-intubation tracheal stenosis

Ischemic injury of tracheal mucosa may complicate trauma and several therapeutic interventions such as endotracheal intubation, tracheostomy, and radiation therapy.[75] The incidence of post-intubation tracheal stenosis (PITS) is estimated up to 21% and is more common in females. PITS can present as concentric web-like membranous stenosis without cartilage damage. Furthermore, "A" shaped stenosis that resembles the vocal cords may result when the lateral tracheal wall is damaged, hence called pseudoglottic stenosis. A more extensive "complex" stenosis with circumferential hourglass-like contraction can also develop when the tracheal cartilage is damaged. High-pressure cuff in addition to low capillary pressure (eg. hypotension) result in tracheal mucosal ischemia and chondritis with subsequent fibrosis anywhere from the site of cuff down to the distal end of the tube. The stoma of the tracheostomy is another potential site for stenosis in patients with tracheostomy.

Neoplastic

Tracheal tumors represent only 2% of all upper airway tumors.[76] In adults, tracheal tumors are most commonly malignant and occur between the third and fifth decades of life.[77] These tumors commonly arise from the distal third of the trachea. Squamous cell carcinoma and adenoid cystic carcinoma account for up to 85% of all malignant adult tracheal tumors.[78] Secondary tracheal tumors are usually caused by direct invasion from the lung, thyroid, or esophagus. Metastasis to the trachea is rare but may be seen in breast, gastrointestinal, or renal cell carcinoma.[79]

Extrinsic disorders

External compression

The trachea can be compressed extrinsically by benign and malignant tumors of the surrounding structures (eg. thyroid, esophagus) as well as adjacent lymph nodes and vascular structures. Distinct pathologies that may cause external compression are reviewed here.

Fibrosing (sclerosing) mediastinitis

A rare disorder that results from exaggerated granulomatous inflammatory response to different pathogens. The disease is characterized by excessive proliferation of fibrous tissue invading major mediastinal structures (blood vessels, esophagus, trachea, and bronchi). 50%–70% of cases are related to *Histoplasma capsulatum*. Leakage of fungal antigens from lymph nodes into the mediastinal space leads to a hypersensitivity reaction that progress slowly over months to years. Cases attributable to *Mycobacterium tuberculosis* and fungi such as *Coccidioides immitis*, *Aspergillus flavus*, in addition to methylsergide have been also reported. Airways are involved in approximately 20% of cases with tracheal narrowing or compression in 15%–30% of cases. Chest radiographs usually reveal widened mediastinum due to massive adenopathy and fibrosis.

Tracheobroncholithiasis

Tracheobroncholithiasis is caused by erosion of calcified peribronchial lymph node into the tracheobronchial tree.[80] It usually complicates granulomatous lymphadenitis caused by mycobacterial or fungal infections. Patients typically present with cough and expectoration of fragments of calcified material. The identification of a calcified lymph node on chest CT and presence of calcified material in combination with acute inflammation or granulation tissue on histopathology are suggestive of the diagnosis.

Diagnostic evaluation

When tracheal disorder is suspected, securing an airway should start simultaneously with the diagnostic workup. Evaluation of the trachea involves several non-invasive imaging and physiologic modalities. These studies are complementary to more invasive procedures such as bronchoscopy.

Radiographic assessment

The aim of imaging is to localize the pathology, describe the nature of the disease (diffuse or focal, intrinsic or extrinsic), and if present determine if the obstruction is dynamic or fixed. Plain AP and lateral soft tissue radiographs of the neck can be helpful in diagnosing acute extrathoracic upper airway obstruction. However, the trachea and central airways are best evaluated by computed tomography (CT). With the recent advances in imaging, more sensitive modalities such as multi-detector computed tomography (MDCT) and magnetic resonance imaging (MRI) have replaced conventional imaging modalities.[81] MDCT provides high-resolution images that can be used to generate multiplanar reformations, 3D volume-rendered images, and virtual bronchoscopic images.

Chest roentgenogram and lateral films of the neck

Evaluation of the larynx and extrathoracic trachea is composed of anteroposterior (AP) and lateral films of the neck and oblique views of the trachea with the head slightly hyperextended. This lateral view provides useful information about diseases that involve the sagittal plane, including the anterior and posterior tracheal wall.[82] The intrathoracic trachea can be visualized on routine chest radiograph. However, abnormalities may be obscured by overlying mediastinal and bony structures.

Fluoroscopy of the trachea

Fluoroscopy of the trachea is used to assess the compliance of tracheal wall.[83] In addition, weakness of the tracheal wall can be visualized during breathing. Extrathoracic tracheal weakness results in bulging (eg. laryngocele or pharyngocele) during the Valsalva maneuver. However, during forced inspiration, collapse may occur as the pressure around the extrathoracic trachea exceeds the intratracheal pressure. In contrast, weakness of the intrathoracic trachea (eg. tracheobronchomalacia) results in expiratory collapse.

Computed tomography (CT)

CT scan has become the modality of choice in the evaluation of upper airway disease. Helical CT scanning (HCT) provides imaging of the whole thorax during a single breath hold. This technique minimizes artifacts due to respiratory motion and allows detection of intra- and extra-luminal tracheobronchial lesions. The use of multidetector CT (MDCT) provides greater speed of image acquisition, improved resolution and better contrast enhancement.[84] The addition of multiplanar and three-dimensional reconstruction can provide virtual images that precisely delineate local and diffuse lesions and demonstrate the degree of airways involvement. Evaluation of the longitudinal extent of abnormalities, tracheal wall thickness, and extraluminal pathologies is also possible with this technique. The use of dynamic CT can be helpful for the diagnosis of tracheomalacia. Dynamic CT provides imaging of the entire central airways in a few seconds and has a comparable accuracy to that of bronchoscopy for diagnosing TM[85] and greater sensitivity compared to end-expiratory CT.[86]

Virtual bronchoscopy using three-dimensional reconstruction from helical computed tomography images is another novel CT-based imaging technique that offers a noninvasive technique for visualization of the tracheobronchial tree (Fig. 1, panel B). This modality provides accurate assessment of fixed intraluminal lesions. However, it does not replace the need for actual bronchoscopy.

Magnetic resonance imaging (MRI)

MRI is used mainly for the evaluation of the larynx and trachea. The major advantage of MRI over CT is that it provides excellent visualization of the larynx and entire length of the trachea in coronal, transverse, and sagittal plans without the need for contrast.[87]

Bronchoscopic evaluation

Bronchoscopy is very useful in the evaluation of tracheal disorders. It can precisely determine the extent of the lesion. Moreover, lesions can be biopsied for accurate pathologic diagnosis. Another advantage of bronchoscopy is to treat obstruction, if present, in order to provide an airway adequate for further studies or therapeutic interventions such as resection, stenting or irradiation. Rigid bronchoscopy can provide a magnified image and accurately delineate the extent of lesions. It can be used to control bleeding and for removal of foreign bodies. Different interventional bronchoscopic techniques can also be applied through bronchoscopy such as electrocautery and laser therapy (Fig. 2, panel A and B).

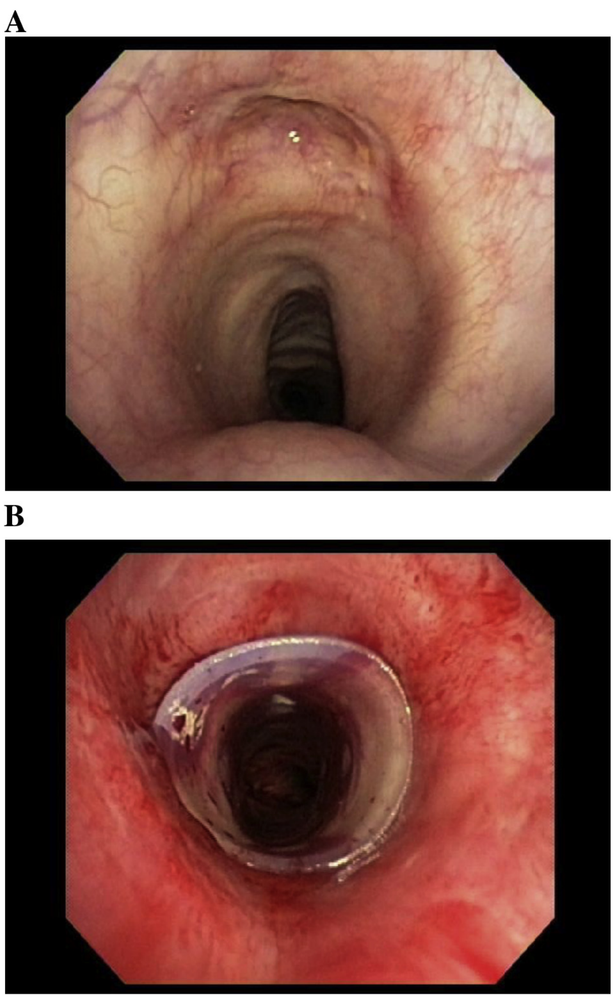

Figure 2 Panel A: post-traumatic tracheal stenosis, panel B: post-traumatic tracheal stenosis, after stent placement.

Physiological assessment

Spirometry is an essential test for the evaluation of causes of shortness of breath. Maximum forced expiratory and inspiratory maneuvers are done, and flow and volume are simultaneous measured and depicted as the flow volume loop (Fig. 3, panel A). Thus, abnormal airflow pattern can give clues to the diagnosis of upper airway obstruction and prompt further evaluation. However, a normal spirometry should not preclude upper airway disorder from the differential diagnosis.[88] Since evidence of expiratory airflow obstruction is usually caused by asthma or COPD, the less common conditions of the upper airways often are not considered in the differential diagnosis. The diagnosis may be further delayed because upper airway obstruction must be quite advanced before symptoms occur and lung function testing becomes abnormal. Studies suggest that an upper airway obstruction must narrow the lumen of the airway to less than 8 mm in diameter to produce abnormalities on the flow-volume loop.[89,90] When an artificial obstruction is imposed, the 1 s forced expiratory volume (FEV_1), remains above 90 percent of control until the orifice is reduced to 6 mm. Peak expiratory flow may be affected with less obstruction. Although spirometry may not be a sensitive way to detect upper airway abnormalities, certain patterns suggest the diagnosis and should prompt further investigation, especially if careful efforts were taken to assure maximum effort during the testing.

Typical patterns of the flow-volume loop may be seen, depending on whether the obstruction to flow is "fixed" or "variable" and whether the site of the obstruction is above or below the thoracic outlet or suprasternal notch. Fixed obstructions of the upper airway are those whose cross-sectional area does not change in response to transmural pressure differences during inspiration or expiration. A fixed obstruction may occur in either the intrathoracic or extrathoracic airways. A variable obstruction is one that responds to transmural pressure changes, eliciting varying degrees of obstruction during the respiratory cycle. The configuration of the flow volume curve may give clues to the presence and site of obstruction.

Upper-airway obstruction should be suspected when a plateau is seen suggesting a fixed point of obstruction. Oscillations in the inspiratory or expiratory curves have also been described, probably representing a mechanical instability of the airway wall. A plateau of forced inspiratory flow alone suggests an extrathoracic upper airway obstruction. (Fig. 3, panel B). With extrathoracic upper airway obstruction, flow is limited only during inspiration. Intraluminal pressure is subatmospheric during inspiration for both the extrathoracic and intrathoracic trachea. However, the transmural pressure of the extrathoracic trachea is negative during inspiration whereas that of the intrathoracic trachea is positive because the pressure surrounding the extrathoracic trachea is atmospheric and the pressure surrounding the intrathoracic trachea is subatmospheric. Thus the extrathoracic trachea will then be more prone to collapse during inspiration and an extrathoracic upper airway lesion would cause airflow limitation during inspiration. The opposite would be true for expiration. Poor effort may result in abnormal inspiratory curve and thus, a single inspiratory curve limitation should be confirmed by looking at all the flow-volume loops.[91]

A plateau in the forced expiratory curve alone is seen with a central obstruction in the intrathoracic airway as the airways are influenced by the surrounding positive pleural pressure during exhalation (Fig. 3, panel C). A pattern that shows similar flow in both forced inspiratory and expiratory flows suggests a fixed upper airway obstruction that may be located in the extra or intrathoracic airway (Fig. 3, panel D).

Physiologic evaluation by spirometry and flow-volume loop can be a simple and noninvasive method to assess for improvement in upper airway obstruction following intervention.

Management

Management of acute upper airway obstruction

The primary goal in management patients with upper airway obstruction is maintain adequate oxygenation and ventilation. General therapeutic measures for acute obstruction may include elevation of the head of bed, administration of humidified oxygen, inhaled racemic

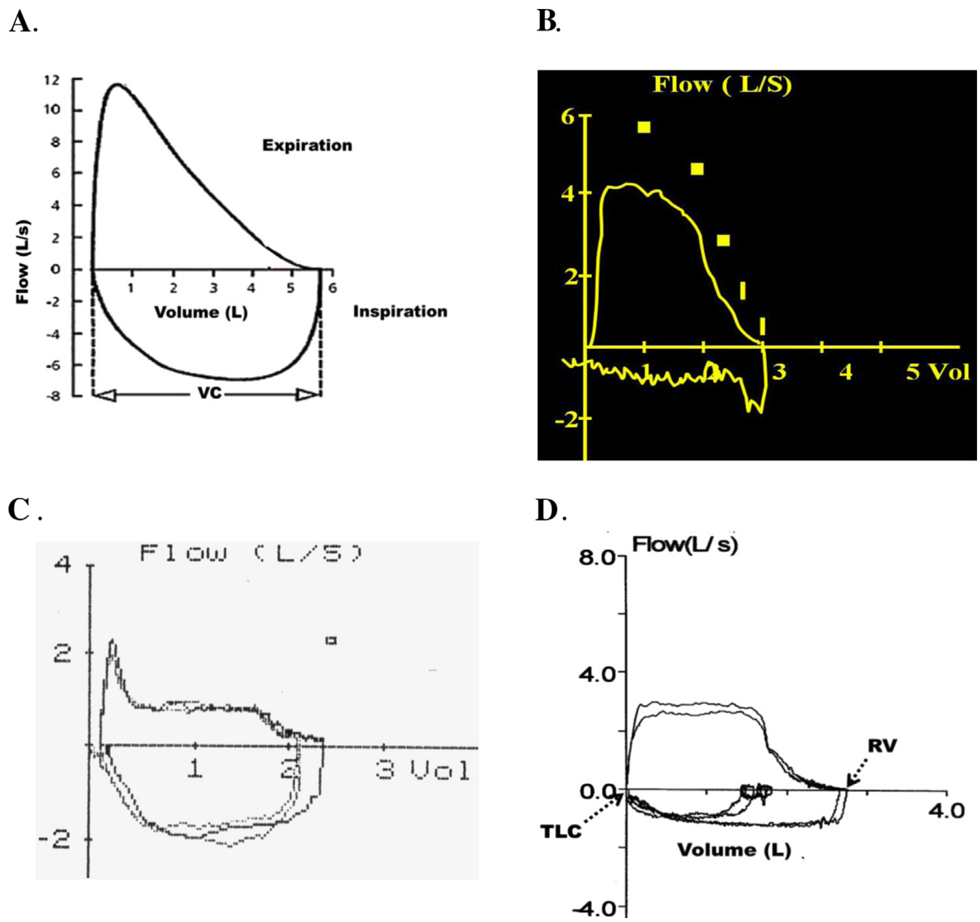

Figure 3 Flow-volume loop. Normal pattern (panel A), variable extrathoracic obstruction (panel B), variable intrathoracic obstruction (panel C), fixed upper airway obstruction (panel D).

epinephrine, and systemic corticosteroids. A helium—oxygen gas mixture (Heliox) is a low-density gas, commonly delivered as 80% helium/20% oxygen, that can be used in management of reversible upper airway obstruction. This gas mixture has a low density because the helium is replacing nitrogen. This results in conversion of the predominantly turbulent flow at the site of obstruction to a more laminar pattern. Laminar flow requires less pressure gradient than turbulent flow to achieve the same flow rate, thus it reduces the work of breathing. Oxygen can be titrated to raise the FiO_2. However, the benefit of the mixture is lost as the FiO_2 of the heliox mixture increases.

Maintaining airway adequate for oxygenation and ventilation can be challenging in patients with upper airway disease since they may deteriorate quickly. The most experienced physician available should try to secure airway in those patients. A variety of noninvasive and invasive tools are available as alternatives to standard intubation. Invasive methods include percutaneous needle cricothyrotomy, tracheostomy, fiberoptic endotracheal intubation, and use of a rigid ventilating bronchoscope.

Management of chronic upper airway disorders

Therapies applied for chronic upper airway disorders vary according to the underlying pathology, severity of symptoms, nature of the disease (ie. fixed stenosis resulting in obstruction or dynamic with variable airway collapsibility), duration of expected survival, and ultimate goals of care.

Benign asymptomatic lesions generally do not require specific therapies. Symptomatic patients may require bronchial hygiene measures (to optimize secretion clearance), and bronchodilators. In addition, immunosuppressant therapy is required in patients with systemic diseases (eg. relapsing polychondritis, sarcoidosis) affecting upper airways.

Stenotic lesions can be treated by various surgical interventions (eg. surgical excision, tracheostomy) depending on the underlying etiology. In addition, a variety of less invasive techniques can be applied through the bronchoscope such as bronchoscopic dilatation, intralesional corticosteroids injection, laser therapy, photodynamic therapy, cryotherapy, external beam radiation and brachytherapy. Airway stents are used primarily as a palliative measure of airway obstruction. Attention should be paid to the rare but potentially fatal negative-pressure pulmonary edema that may develop after relieving the obstruction.

Patients with dynamic central airway collapsibility (ie. tracheomalacia and EDAC) can be managed by continuous positive airway pressure (CPAP) device to reduce expiratory airway collapse. Airway stenting and tracheoplasty can be used in selected patients.[92] Membranous wall tracheoplasty implies plication of the membranous wall to a mesh to restore the normal airway configuration.

Advances in the management of tracheal obstruction

Several types of stents are currently available and are highly effective in alleviating symptoms of tracheal obstruction. The most commonly used stents are silicone stents, metal stents, and stents that combine a silicone or synthetic coating with metal mesh (ie. hybrid stents).[93] Metallic stents may be difficult to remove and may fragment or penetrate into adjacent structures, although newer models have avoided these complications. Self-expanding metal stents are usually made of nitinol, which has a high elasticity similar to cartilage. These stents can be 'covered' with a plastic membrane to prevent tumor growth inside the lumen. Silicon stents are inexpensive and can be easily removed or exchanged if needed. However, migration and adherence of secretions are the major disadvantages.[94] More recently, a novel bioabsorbable drug-eluting stents have been introduced with promising results. These stents allow sustained drug elution to minimize or delay tracheal restenosis.

Patients who require surgical repair or resection of long tracheal segment (more than one-half of the tracheal length) usually need a repair tissue. Since the 1950's, different materials have been used for tracheal reconstruction, including foreign materials, nonviable tissues, autogenous tissues and tissue engineering.

Moreover, a new field of tracheal reconstructive surgery has emerged in the last few years focusing on tracheal replacement using tissue-engineering techniques. The first tissue-engineered tracheal reconstruction was performed in 2008, using a decellularized cadaveric tracheal segment and the recipient's own stem cells.[95] In 2011, the first stem cell-based bioartificial tracheal replacement surgery was performed successfully.[96] However, long-term outcomes of these methods are yet to be determined.

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Significance

This paper provides a comprehensive review of acquired non-traumatic diseases of the trachea in adults. Both primary disorders of the trachea but more commonly its secondary involvement in systemic disease are important problems in medicine; their appropriate management depends on accurate differential diagnostic sorting.

Author contributions

All of the authors performed the literature searches, wrote the manuscript, and prepared the tables and figures.

Conflict of interest

None declared.

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