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Review

Assessment and causes of stridor

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EDUCATIONAL AIMS

After reading this review readers will be able to:

- Understand the importance of medical history and physical examination in a child with stridor from birth to adolescence
- Discuss congenital and acquired causes of stridor according to the site of obstruction within different age groups
- Describe the principles of airway endoscopy, radiology and lung function in the assessment of stridor

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SUMMARY

Stridor is a variably pitched respiratory sound, caused by abnormal air passage during breathing and often is the most prominent sign of upper airway obstruction. It is usually heard on inspiration (typically resulting from supraglottic or glottic obstruction) but also can occur on expiration (originating from obstruction at or below glottic level and/or severe upper airway obstruction). Stridor due to congenital anomalies may exist from birth or may develop within days, weeks or months. Various congenital and acquired disorders prevail in neonates, infants, children, and adolescents, and have to be distinguished. History, age of the child and physical examination together often allow a presumptive diagnosis. Further investigations may be necessary to establish a definite diagnosis, and flexible airway endoscopy is the diagnostic procedure of choice in most circumstances (“stridor is visible”).

INTRODUCTION

Stridor, a variably high pitched respiratory sound, often is the most prominent sign of upper airway obstruction (UAO). It is usually heard on inspiration but it also can occur on expiration in severe UAO, and indicates substantial narrowing of the larynx and/or (extrathoracic) trachea. In minor degrees of narrowing there may be no stridor at rest; with increased activity (e.g. crying) and consequently increased velocity of airflow, however, stridor may develop. Biphasic stridor suggests severe, fixed airway obstruction at the level of the glottis, subglottis, or upper trachea. Loud stridor, especially when associated with retractions, occurs with significant narrowing of the airway; however, a sudden decrease in volume sometimes signifies worsening obstruction and decreasing air movement.

The character of the voice provides additional important information. Hoarseness suggests an abnormality of the vocal cords. A muffled voice with a low-pitched stridor may indicate a supraglottic process such as epiglottitis (supraglottitis).

Stertor, another form of noisy breathing, is a mainly inspiratory, low pitched, wet, grunting sound similar to snoring. Obstructing lesions of the nasopharynx (such as adenoid hypertrophy), oropharynx (such as micrognathia, macroglossia, and tonsil hypertrophy), and hypopharynx (such as tongue base mass and pharyngomalacia) typically produce stertor [1,2].

Stridor due to congenital pathologies may exist from birth or may develop within days, weeks or months after birth. Different congenital or acquired disorders prevail in different age groups (neonates, infants, children, adolescents) and have to be distinguished. Taking a careful history is mandatory. History, age of the child and physical examination together often allow a presumptive diagnosis. Further investigations may be necessary to establish a

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definite diagnosis, and flexible airway endoscopy is the diagnostic procedure of choice in most circumstances [3,4].

HISTORY AND PHYSICAL EXAMINATION

The age of the patient and the onset and duration of symptoms are the most important items for narrowing the differential diagnosis. The perinatal history is important and should include questioning regarding maternal condylomata, type of delivery (including shoulder dystocia), endotracheal intubation and its duration, and presence of congenital anomalies. A surgical history should be obtained; previous surgery, particularly neck or cardiothoracic procedures, puts the recurrent laryngeal nerve at risk for injury. Furthermore, a developmental history should be obtained.

Feeding and growth should be evaluated as significant airway obstruction can lead to increased "work of breathing" causing a "caloric wasting", resulting in a lack of weight gain and poor growth. Regurgitation and possetting could be signs of gastro-esophageal reflux (GER), which can cause laryngeal and tracheal mucosal irritation with subsequent oedema. The occurrence of cyanosis, and/or apnoea and increased respiratory effort have to be explored. Information about the circumstances (e.g. supine positioning, feeding, crying, sleep) in which stridor occurs, improves or deteriorates, may help to localize the obstruction. The most common symptoms and signs related to feeding include regurgitation, vomiting, cough, and choking.

During inspection and auscultation attention should be paid to retractions (suprasternal, intercostal, subcostal), nasal flaring, cyanosis, the patient's preferred body position, and possible syndromal deformities (especially craniofacial anomalies). Dysphagia and drooling may be associated. The skin should be assessed for haemangiomas. Assessment of the type of stridor (inspiratory, expiratory, biphasic) may provide information about severity and level of airway obstruction. Further information may be derived from the pitch and the character of the stridor, either voiced (a pure tone and overtones) or fricative (a noise like sound). A typical laryngeal stridor is inspiratory, high pitched and voiced, whereas a pharyngeal obstruction causes a bidirectional, low pitched and fricative sound. However, localization of stridor is poor with clinical observation [5].

AIRWAY ENDOSCOPY

Flexible endoscopy allows one to examine the airways from the nose to the segmental bronchi. The investigation should be performed under light (or even without) anaesthesia to optimally visualize dynamic airway caliber changes. If during examination there is no respiratory noise and no airway pathology can be visualized, the level of anaesthesia should be altered so that airway obstruction will occur and can be documented. In children with stridor predominantly during sleep polysomnography may have already shown obstructive sleep apnoea (OSA). In this situation, so called sleep endoscopy may be the investigation of choice as it allows airway evaluation in a sleep-like state. [6] With flexible endoscopy the site and extent of airway obstruction and a possible cascade of various levels of obstruction can be documented. Flexible endoscopy is a very useful tool for diagnosing choanal pathologies and adenoid hyperplasia, and helps to estimate which anatomical structures participate in a pharyngeal and/or laryngeal collapse. A thorough inspection of the tongue base, supraglottis, glottis and subglottis followed by an inspection of the trachea and bronchi to gain information on possible associated airway pathologies in the lower airways is advisible in most circumstances. Exceptions from this rule are substantial subglottic stenosis from e.g. haemangiomas where the passage of the bronchoscope would possibly aggravate airway obstruction. Direct airway examination is indicated in virtually all infants with persistent stridor, especially when stridor is progressive or associated with cyanosis, apnoeas, difficulty in feeding, or failure to thrive. Documentation of laryngomalacia and the exclusion of other causes of stridor in an infant usually alleviates parental anxiety and may prevent further (unnecessary and potentially harmful) diagnostic evaluation. In infants and children with viral croup, endoscopy is rarely indicated unless there is no response to treatment or stridor persists for longer than two weeks [7].

A rigid endoscope approaches the larynx from a different angle; it elevates the hyoid and tongue base, lifting and distorting the larynx, while at the same time allowing a more detailed anatomic evaluation especially of the posterior aspects of larynx and trachea, as well as manipulation. When posterior laryngeal pathology (e.g. laryngeal cleft) is suspected, both flexible and rigid instruments may be needed to obtain a full understanding of the laryngeal anatomy and dynamics [8].

RADIOLOGY

Plain radiographs have a role in assessing the lungs and cardiac size, and may help to exclude a radiopaque foreign body. A normal frontal and lateral chest radiograph has been shown to exclude a vascular ring. The radiograph may show a right sided aortic arch, a poorly visualised distal trachea, or another cause for tracheal compression or deviation (e.g. a mediastinal mass) [9]. Fluoroscopy has lost importance because of the considerable amount of radiation even in short investigations and the availability of new imaging modalities. Upper gastrointestinal contrast studies may be helpful in diagnosing aspiration and be suggestive in conditions such as an H-type tracheo-oesophageal fistula or a posterior laryngeal cleft. A barium swallow remains an excellent technique for the diagnosis of a vascular ring, but the exact anatomy of a vascular malformation and its relation to adjacent structures has to be accurately defined by magnetic resonance imaging (MRI) and/or low dose multidetector computed tomography (MDCT). The latter techniques are most useful in confirming extrinsic compression of the airways (e.g. retropharyngeal soft tissue swelling), and provide information about the extent of masses such as haemangiomas in the surrounding soft tissue. Furthermore, virtual endoscopy by CT may be used in assessing fixed stenoses that cannot be passed during endoscopy. Ultrasonography may be of value in parapharyngeal and peritonsillar abscesses as well as lymphadenitis causing compression of laryngeal structures. Furthermore, laryngeal ultrasonography, although not seen as a substitute for flexible endoscopy, can give valuable information for differentiating cystic from solid masses and in the assessment of the vocal cords [7,10,11].

LUNG FUNCTION TESTING

Lung function testing can only be used in patients with minor UAO, because the measurement itself may disturb the patient and lead to deterioration. In infants and young children with persistent stridor, tidal breathing flow-volume loop analysis may be used as a first diagnostic approach, that may add useful information to physical examination. In these patients, it has been shown to be a rapid, non-invasive and accurate method for establishing the site of airway obstruction [7,12]. Visual inspection of maximal inspiratory and expiratory flow-volume loops, produced by patients able to co-operate, allows variable and fixed airway lesions to be distinguished. The flow-volume loop in a patient with variable extrathoracic airway obstruction is characterized by a plateau in the inspiratory limb (e.g. tracheomalacia of the extrathoraxic trachea), and the flow-volume loop in a patient

with fixed obstruction by plateaus in both the inspiratory and expiratory limbs (e.g. subglottic stenosis). For details, the reader is referred to a previous review [7].

Useful investigations for specific causes of stridor will be discussed below.

CAUSES OF STRIDOR

Causes of stridor can be classified according to the site of obstruction (nose and pharynx, larynx and trachea) and to the onset and duration of symptoms in different age groups. Typical diagnoses can be found in newborns, infants, toddlers, and schoolchildren and adolescents (Table 1) [13].

In this review we discuss congenital and acquired causes of stridor according to the site of obstruction within different age groups. Our aim is to point out typical clinical signs and historical data, and the most appropriate diagnostic approach.

Nose and pharynx

Choanal atresia and stenosis

Choanal atresia is the most common congenital nasal anomaly (1:6,000-8,000 live births), followed by dermoid cyst, glioma, encephalocele and choanal stenosis, and represents a feature with a high index of suspicion for CHARGE syndrome [14,15]. It may be membranous or bony, bilateral or unilateral (right > left). While the origin of the anomaly is unknown, choanal atresia, oesophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis were common in methimazole- and carbimazole-exposed children in a nationwide Danish study [16]. Bilateral posterior choanal atresia (BPCA) is associated with increased neonatal mortality, especially if associated with major cardiac malformations and/or oesophageal atresia. Polyhydramnios is commonly seen in individuals with BPCA, but may also be present without BPCA, probably due to an insufficient swallowing mechanism. Newborns with BPCA will have significant difficulty in breathing and feeding, with stridor, cyanosis, and aspiration. The inability to pass a small catheter down either side of the nose is characteristic for BPCA. Unilateral atresia or stenosis can go unnoticed for years. Most commonly, children will have chronic thick drainage from one side of the nose. In an emergency, an oral airway or short tube along the top of the tongue can be placed so that the airway stays open. With other craniofacial anomalies present, intubation or rarely tracheostomy may be required. Once an airway is established, flexible endoscopy and CT (or MRI) confirm the diagnosis. Definitive treatment is surgical, through various techniques and surgical approaches. Transnasal repair has become the procedure of choice due to its safety and effectiveness, displacing the transpalatine approach [17,18].

Table 1
Differential diagnosis of stridor

Infectious causes
• Croup
• Supraglottitis (Epiglottitis)
• Bacterial tracheitis
• Retropharyngeal abscess
Noninfectious causes
Symptoms at birth
• Laryngomalacia
• Vocal fold paralysis
• Laryngeal web
• Laryngeal cleft
• Cystic hygroma
• Subglottic stenosis (congenital)
• Laryngeal atresia
• Choanal atresia
• Pierre Robin sequence
Symptoms manifesting during neonatal period or infancy
• Laryngomalacia
• Subglottic haemangioma
• Laryngeal papilloma
• Tracheomalacia
Acquired causes after neonatal period
• Foreign body (airway and oesophagus)
• Trauma (blunt and penetrating injury)
• Burn injury
• Anaphylaxis
• Hereditary angioedema
• Inducible laryngeal obstruction (vocal cord dysfunction)
• Damage from endotracheal intubation and tracheostomy
• Laryngospasm
• Spasmodic croup
• Subglottic stenosis in granulomatosis with polyangiitis (GPA)

Micrognathia, Pierre Robin sequence, macroglossia, craniofacial anomalies

Micrognathia is a small lower jaw which results in posterior displacement of the tongue leading to pharyngeal obstruction. It is predominantly seen in the supine position.

The Pierre Robin sequence (PRS) is characterized by micrognathia, glossoptosis, respiratory distress and often a cleft palate. More than 50% of patients have PRS in combination with other malformations, the most common of which are Stickler and 22q11.2 deletion syndromes. The dominant clinical problems are severe UAO, OSA, and failure to thrive. Various treatments have been developed to overcome UAO such as a palatal plate with a velar extension (the pre-epiglottic baton plate) pulling the tongue base forward, thereby widening the pharyngeal space [19]. In severe cases, endoscopic intubation may be needed especially with associated airway pathologies (e.g. laryngomalacia, tracheomalacia) [20]. At our centre, a skilled paediatric pulmonologist together with a neonatologist and a maxillo-facial surgeon are prepared to intervene immediately after birth in cases with expected severe PRS. Besides using a nasopharyngeal airway under endoscopic control, airway interventions in PRS patients with OSA include CPAP or non-invasive positive pressure ventilation, especially in more severe forms of OSA [21,22]. Even after surgical interventions (e.g. distraction osteogenesis and glossopexy) adjunct CPAP treatment will help to resolve OSA. In a recent evaluation of sleep apnoea, airway management, and feeding management in children with PRS 20% of infants with mild to moderate OSA and 55% with severe OSA required CPAP on discharge [23].

Macroglossia, an abnormally large tongue, can cause pharyngeal obstruction. It may be due to Beckwith-Wiedemann syndrome; affected infants typically present with neonatal onset hypoglycaemia and seldom require surgery to attain an appropriate airway [24–26]. Macroglossia also is a feature of Down syndrome, glycogen storage diseases, and congenital hypothyroidism. Children with Down syndrome have many phenotypic features that predispose to UAO including a flattened nasal bridge, shortened and narrowed ear canals, small mouth, and small hypopharynx. Together with the presence of decreased muscle tone (including pharyngeal muscles) the likelihood of proximal airway obstruction increases especially when physiological enlargement of tonsillar and adenoid tissues occurs during early childhood. Furthermore, children with Down syndrome have a higher incidence of laryngomalacia, tracheomalacia, and subglottic stenosis than control children [27,28].

Lingual thyroid and thyroglossal duct cyst

A lingual thyroid results from failure of descent of the thyroid gland from its embryological origin at the base of the tongue via the thyroglossal duct and a thyroglossal duct cyst arises from remnants of the thyroglossal duct. A cyst can fill with fluid or mucus and may enlarge if it becomes infected. If situated at the

base of the tongue and large enough, cysts can cause airway obstruction and swallowing difficulty. Symptoms can occur during infancy or later in childhood as well as adulthood. On examination a smooth discrete mass in the midline anywhere from just above the hyoid bone to the thyroid gland which moves up when the tongue is protruded may be palpated. It has been suggested to also palpate the posterior tongue [29]. Endoscopy reliably detects cysts at the tongue base. Further diagnostic steps like blood tests (thyroid function) and imaging (ultrasound, MRI, thyroid scan) will have to follow before operation [30,31].

Hypertrophy of adenoids and/or tonsils, retropharyngeal or peritonsillar abscess

Large adenoid and tonsillar tissue may cause supraglottic airway obstruction, particularly in supine position and during sleep. A blocked nose causing breathing through the mouth is typical; restlessness and pauses in breathing for a few seconds during sleep may be noticed by caretakers. Snoring or stertor, and sometimes stridor are typical noises [1,2]. A bidirectional, low pitched and fricative sound is characteristic for pharyngeal obstruction [5].

While fever, odynophagia, neck stiffness, swelling and torticollis prevail as typical signs and symptoms of a retropharyngeal abscess, stridor is a rare finding [32]. The disease is most commonly seen in infants and children up to 4 years of age, whereas a peritonsillar abscess is typically seen in adolescents with pharyngitis. Data from the US between 2000 and 2009 showed an increase of the incidence of retropharyngeal abscess from 0.1 to 0.22 cases per 10,000. Beside physical examination and ultrasonography of the neck a CT with contrast potentially shows the precise anatomical extension of the lesion in differentiating a true abscess from cellulitis [33].

Larynx

Laryngomalacia

Laryngomalacia (LM) is the most common cause of stridor in newborns affecting 45-75% of all infants with congenital stridor [34–36]. The exact aetiology of LM is unknown; theories include anatomic, cartilaginous, and neurologic ones. The neurologic theory, best supported in the literature, states "that LM may be a consequence of an underdeveloped or abnormally integrated CNS system, particularly the peripheral nerves and brainstem nuclei responsible for breathing and airway patency" [36]. It has been demonstrated that the sensory stimulus needed to elicit the typical laryngeal motor response is elevated in infants with moderate-to-severe disease compared to those with mild disease [37].

Laryngomalacia typically presents with inspiratory stridor that increases with feeding, crying, agitation, supine positioning, and upper respiratory tract infections; and decreases with extended neck and in the prone position. Symptoms begin at birth or within the first 4 to 6 weeks of life, peak at 6 to 8 months and typically resolve by 12 to 24 months. The most common associated symptoms are related to feeding, including regurgitation, emesis, cough, and choking. The disease spectrum is mostly mild to moderate. Infants with severe LM (up to 10%) present with recurrent cyanosis, apnoeic pauses, feeding difficulty, aspiration, and failure to thrive. Suprasternal and subcostal retractions can lead to pectus excavatum. The avarage resting baseline SpO_2 in severe disease is below 90% [37,38].

Diagnosis is suspected by the history and confirmed by flexible endoscopy, which should be performed by an experienced bronchoscopist [7,39]. It is important to examine the movements of the laryngeal structures during spontaneous respiration and differentiate LM from other causes of inspiratory stridor. Supraglottic tissue collapse and obstruction during inspiration are the hallmarks of LM. Characteristic abnormalities include elongation and lateral extension of the epiglottis (omega shape) that falls posteriorinferiorly on inspiration; redundant bulky arytenoids that prolapse into the airway on inspiration; shortening of the aryepiglottic folds, resulting in tethering of the arytenoids to the epiglottis thereby narrowing the airway during inspiration; and inward collapse of the cuneiforme cartilages on inspiration. Expiration results in expulsion of supraglottic structures with largely unimpeded airflow. In an individual patient, different combinations of these abnormalities may be seen. Endoscopic investigation of the subglottic area, trachea and mainstem bronchi informs about possible associated pathologies and may help in managing future respiratory complications [36]. Comorbidities impact upon symptoms and disease course; gastrointestinal reflux disease (GERD) and neurologic disease are the most common, with GERD in 65-100% of infants with LM [37]. GERD should always be treated, and 24-hour pH and impedance studies may be useful in determining management strategies for infants with severe reflux despite acid suppression therapy. In some infants fundoplication surgery may be warranted for reflux control. Associated neurologic diseases may further decrease laryngeal tone or result in collapse of the supporting pharyngeal muscles. Supraglottoplasty, accessory routes for feeding and sometimes, in extreme cases, even tracheostomy may be required. Patients with secondary airway lesions (e.g. tracheomalacia), congenital heart disease, congenital anomalies or genetic disorders (e.g. Down syndrome) will more likely need surgical interventions (supraglottoplasty, tracheostomy) [40–44]. Non-invasive positive pressure ventilation (continuous and bilevel positive pressure) has been used successfully in some children with severe laryngomalacia and respiratory distress or OSA. Careful monitoring and comparison of risk/benefit ratio to surgery is recommended as facial side effects (mid face retrusion) are associated with non-invasive positive pressure ventilation. For the interested reader we recommend a recent detailed review of current clinical practice in laryngomalacia [45].

Vocal cord paralysis (vocal fold paralysis)

Vocal cord paralysis (VCP) or vocal fold paralysis (VFP) is the absence of movements of the vocal folds following dysfunction of the second motor nerve supply to the larynx, and the second most common congenital anomaly of the larynx. According to a retrospective review of 102 cases (48% bilateral) of paediatric VCP, the aetiology is mostly iatrogenic (43%), followed by idiopathic (35%), neurologic (16%), and birth trauma (5%). Concomitant airway disease was reported in 46/102 cases, with laryngomalacia, tracheo-bronchomalacia, and subglottic stenosis as prevailing diagnoses [46]. In a recent review of 404 paediatric cases (so far the largest reported series) with a mean follow up of 26.5 months similar data were presented. Associated airway disease was reported in 162 patients (40%), with laryngomalacia and subglottic stenosis being the most common. Tracheostomy and gastrostomy were significantly more likely in patients with bilateral vocal fold paralysis (BVFP) and those with comcomitant airway disease [47].

Bilateral vocal fold paralysis (BVFP) typically presents with inspiratory stridor at rest that worsens upon agitation, near normal phonation (most cases are abductor palsies) but a weak voice, and progressive airway obstruction which may require airway intervention (endotracheal intubation, tracheostomy). In a clinically stable patient flexible endoscopy should be performed to demonstrate the paralysis. In contrast to BVFP, dysphonia (a hoarse, breathy cry) aggravated by agitation is a common sign of unilateral VFP. Stridor is present in most patients; feeding difficulties and aspiration may occur, but unilateral VFP may also go unnoticed.

Rarely, VFP is secondary to a neuromuscular disorder such as congenital myasthenic syndromes (CMS) [48,49], in particular

DOK7 CMS which typically present with stridor and feeding difficulties [50–52] but also CMS caused by other mutations [53,54]. Thus, in a patient with BVFP which appears to be idiopathic, a CMS should be considered and excluded, especially if there is concurrent feeding difficulty. A careful neurologic examination looking for subtle signs such as ptosis and limb weakness should be undertaken. Molecular analysis and stimulation single fibre electromyography in the hands of an experienced neurophysiologist will help in establishing the diagnosis. Appropriate treatment may ameliorate weakness, feeding difficulties and life-threatening respiratory complications of CMS. Pharmacological treatment may allow earlier decannulation and might even avoid tracheostomy [50].

It was suggested that within the first year after diagnosis children with VFP should be followed up 4-monthly. If their condition has resolved clinically, they should undergo flexible laryngoscopy to ensure true resolution; if VFP has not resolved at one year, they should undergo endoscopy as needed for worsening symptoms or yearly if ongoing immobility is noted. If they remain asymptomatic for several years repeat endoscopy is suggested every 5 to 6 years into adulthood. This schedule would allow subtle effects of vocal fold immobility to be identified earlier, and the patient to then be offered appropriate therapies and interventions to reduce morbidity [47].

Subglottic stenosis

Acquired subglottic stenosis (SGS) is caused by either infection or trauma; the most common cause is endotracheal intubation, especially in low birth weight infants who require prolonged intubation and ventilation.

Congenital SGS is part of a continuum of embryologic failures including laryngeal atresia, stenosis, and webs; and is the third most common congenital laryngeal anomaly, and the most common requiring tracheotomy in infants. Membranous congenital SGS is the most common form, resulting from circumferential submucosal hypertrophy with excess fibrous connective tissue and mucus glands. Cartilaginous congenital SGS is characterized by an abnormal shape of the cricoid cartilage [34,55]. Children with Down syndrome [27] and other congenital and neck lesions are at increased risk of having congenital SGS [55]. Subglottic and tracheobronchial stenosis represent airway involvement in children with granulomatosis with polyangiitis (GPA) [56]. In a recent review of data of two paediatric cohorts with GPA the incidences of SGS were 11 of 56 (20%) and 9 of 65 (14%) [57]. A classification scheme describes stenoses in percent of obstructed area: grade 1 (0-50%), grade 2 (51-70%), grade 3 (71-99%), grade 4 (no detectable lumen) [58]. Infants may not be symptomatic for weeks or months even with grade 3 stenosis. Biphasic stridor with or without respiratory distress is the most common presenting symptom. Upper respiratory tract infections lead to a clinical presentation not different from that in infectious laryngotracheobronchitis. Children with recurrent and/or prolonged croup symptoms especially when <6 months of age as well as children with a history of prolonged intubation should always raise suspicion and require endoscopic assessment. Treatment options range from endoscopic interventions to more extensive surgical procedures such as open laryngeal surgery [59–61].

Laryngeal cyst

Supraglottic cysts are usually congenital, whereas subglottic cysts are usually acquired as a result of airway trauma (e.g. endotracheal intubation). Congenital cysts typically present in the first few days of life, with signs of airway obstruction, a muffled cry, and dysphagia. In infants, stridor, hoarseness, weak cry or aphonia, and sometimes feeding difficulties are common. Endoscopy confirms the diagnosis. The appearance of cysts varies widely; while some are covered by thin mucosa and are easy to recognise, others appear as a submucosal mass. The treatment of choice is resection of the cyst [55,62,63].

Laryngeal (laryngo-tracheo-oesophageal) cleft

A congenital posterior laryngeal cleft (LC) is a rare lesion, and may be associated with other anomalies including tracheomalacia (>80%) and tracheo-oesophageal fistula (TEF) (20%). The most common associated syndrome is Opitz-Frias (Opitz B/GGG) syndrome (hypertelorism, anogenital anomalies, posterior laryngeal cleft). Four types can be distinguished: *Type 1*: supraglottic interarytenoid cleft present to, but not below, the level of the true vocal folds; *type 2*: partial cricoid cleft extending into, but not through, the posterior cricoid cartilage; *type 3*: total cricoid cleft with or without extension into the cervical trachea; *type 4*: cleft extending to the thoracic trachea (may extend as far as to the carina) [64]. The most common cleft, type 1 (50%) should be suspected in infants with laryngomalacia.

Symptoms are not necessarily indicative of a specific cleft type. Stridor results from laryngeal collapse. Aspiration of saliva and food is most likely, and causes coughing, choking, cyanosis, respiratory distress and recurrent chest infections. Tracheomalacia may significantly compromise the airway, especially in children with an associated TEF. While infants with type 1 cleft may be asymptomatic, newborns with a more extensive cleft may show severe respiratory distress. Diagnostic tools include flexible airway endoscopy, endoscopic evaluation of swallowing, and video fluoroscopy-barium swallow; the diagnostic gold standard is rigid bronchoscopy and oesophagoscopy. Given that a cleft is often hidden by redundant mucosa, it is not uncommon for it to be undiagnosed or misdiagnosed on initial evaluation with flexible or rigid bronchoscopy. [55] As flexible and rigid bronchoscoy are complementary techniques, children suspected of aspiration should be evaluated with both flexible and rigid endoscopy to definitively ensure that there is no laryngo-oesophageal cleft or "H-type" TEF [8]. Minor clefts (type 1 and some type 2 forms) may be corrected endoscopically, whereas longer clefts require open repair [55].

Laryngeal web

Laryngeal webs comprise only 5% of laryngeal anomalies. They are usually located at the level of the glottis (95% anterior); supraglottic and subglottic webs may also occur. Webs may be complete or incomplete and vary in thickness. Most are thick and usually associated with a subglottic "sail" compromising the subglottic lumen; they may therefore be considered as a form of partial laryngeal atresia.

Neonates may present with an abnormal cry or respiratory distress at birth, and an emergent airway intervention may be required. Nonetheless, clinicians should be well aware of the fact that infants are remarkably tolerant of airway compromise and even those with a moderate to severe glottic web may initially show only subtle airway symptoms. Symptoms typically exacerbate over the first few months of life, and biphasic stridor and retractions become increasingly evident, particularly with feeding. With a significant association between webs and chromosome 22q11.2 deletion syndrome (velocardiofacial syndrome) it may be prudent to refer patients for genetic evaluation [65,66]. A definitive diagnosis requires flexible or rigid endoscopy to evaluate both the severity of the web and its subglottic extension. Whereas flexible endoscopy provides an excellent view of the anterior commissure, rigid endoscopy is more advantageous in evaluating the degree of associated SGS. Management strategies depend on the extent and thickness of the web. Thin glottic webs may never be diagnosed, as in a child with neonatal respiratory distress intubation may actually tear the web and resolve the problem. Thick glottic webs

may be repaired in the neonatal period or in later childhood, with a tracheostomy placed first. Late repair is usually performed by age 4, to improve the quality of a child's voice prior to school age [55].

Subglottic haemangioma

The larynx, particularly the subglottis is the most common site of airway haemangiomas. More than 50% of patients with a subglottic haemangioma (SH) also have cutaneous haemangiomas. Patients with haemangiomas in a beard distribution (i.e. chin, jawline, and praeauricular areas) are at the highest risk of SH. [67] The natural history of airway haemangiomas is similar to cutaneous lesions, with an initial proliferative phase until 6-10 months of age and a phase of involution usually beginning at about 18 months of age; however, SHs expand and involute more rapidly.

Infants may become symptomatic between two weeks and six months of age, with progressive deterioration as the haemangioma increases in size. Symptoms include biphasic stridor with retractions, especially when the child is upset or feeding, and a barking cough similar to that seen with croup. With severe airway obstruction, apnoea, cyanosis, and "dying spells" may occur. Flexible endoscopy is the investigation of choice, not only allowing for visualization of the compromised subglottis but also for ruling out other causes of stridor such as VFP or laryngomalacia. In infants with suspected extralaryngeal involvement MRI with T2-weighted gadolinium contrast should be performed. It is important to diagnose PHACE syndrome (posterior fossa brain malformations, haemangiomas, arterial lesions, cardiac anomalies and coarctation of the aorta, eye anomalies, with or without sternal clefts) as in these children treatment with propranolol might pose a risk due to cardiac and central nervous system arterial anomalies [68]. For SHs, many reports have documented dramatic results achieved with propranolol, which has replaced both open and endoscopic resection and obviated the need for tracheostomy placement. Treatment is typically maintained for a minimum of six months; careful monitoring during the weaning process is essential, as cessation may result in regrowth of the SH [69–74]. A recent review of 41 propranolol studies revealed a low rate of serious adverse events [75].

Lymphangioma

A lymphangioma can involve pharynx and larynx and lead to airway compromise. It may cause stridor in a neonate, but may also manifest later in childhood when swelling occurs due to infections or when bleeding into the lymphangioma occurs. Endoscopy may show an obstructing mass with a typical multicystic appearance. MRI will delineate the extension into adjacent tissues. Various therapeutic options exist; the most promising treatment modality in complicated refractory lymphangiomas seems to be sirolimus, an immunosuppressant agent [76,77].

Croup (viral laryngotracheobronchitis)

The acute onset of a typical seal-like barking cough, associated with hoarseness and varying degrees of stridor are characteristic of the most frequent cause of acute UAO in children: croup or viral laryngotracheobronchitis. In most cases, croup develops over several days with concurrent coryzal illness, symptoms of UAO disappear over 3-5 days. It mainly affects children aged 6-36 months with a peak incidence at 12-24 months. A number of viruses may cause this disorder resulting in inflammation of pharynx, larynx, trachea and bronchi. However, it is specifically subglottic inflammation that compromises the airway [78,79].

Risk factors such as preexisting congenital airway malformations and differential diagnoses including foreign body aspiration, supraglottitis, bacterial tracheitis, angio-neurotic oedema, and diphteria should be considered. Assessment of severity is done clinically. Mild UAO can be assumed when the child appears happy and is prepared to drink, eat, and play; moderate UAO is indicated by persisting stridor at rest, retractions, use of accessory respiratory muscles, and increased heart rate. Treatment with oral steroids (dexamethasone 0.15-0.3 mg/kg or prednisolone 1-2 mg/kg) or nebulised budesonide 2 mg if oral corticosteroids are not tolerated should follow immediately [78,79]. Despite the lack of controlled studies, rectal steroids (prednisolone prefered over prednisone because of an earlier and stronger anti-inflammatory effect) are a widely used treatment option in Germany and Austria (2 mg/kg prednisolone) [80,81]. If a child with moderate UAO begins to be worried or starts to sleep for short periods hospitalisation and close observation are indicated. Nebulized adrenaline (epinephrine) is effective for temporary relief of symptoms and may be used until corticosteroids take effect, or as additional therapy when steroids alone fail to relieve symptoms of UAO. Oximetry is no substitute for good clinical assessment as oxygen saturation may be close to normal even in severe croup or may be lowered in mild cases due to associated lower airway disease. A radiograph is generally not advisable in acute croup. Flexible bronchoscopy should be considered in children presenting with atypical, prolonged or frequently recurrent symptoms, and in children not responding to medical treatment or outside the typical age range for croup (<6 months and >6 years). For the interested reader we recommend the above mentioned excellent reviews [78,79].

Spasmodic (recurrent) croup may mimic laryngotracheobronchitis, but is usually not preceded by an upper respiratory tract infection and occurs in older children. While initial studies in the 1970s and 1980s suggested a correlation between recurrent croup and reactive airway disease together with other allergic diseases, [82–86] studies between 1992 and 2000 have shifted the focus to the association between GERD, subglottic stenosis, and other airway narrowing diseases [87–90]. A more recent study suggested that flexible bronchoscopy should be performed in recurrent croup as a high incidence of endoscopic evidence for GER and subglottic stenosis ranging from 15% to 70% airway narrowing was found [91].

Supraglottitis

With vaccination against *Haemophilus influenzae* type B, supraglottitis has beome a rare disease in developed countries. The classic presentation is with high fever, irritability, and the "4Ds" – drooling, dysphagia, dysphonia, and dyspnoea. Cough is usually absent, and stridor a late finding indicating impending complete airway obstruction. A recent study of 606 patients with acute stridor demonstrated that if a stridulous child has cough and no drooling the diagnosis is likely to be croup, whereas if the child has drooling and no coughing the diagnosis is likely to be supraglottitis [92]. On examination the child is anxious, remarkably still, with a preference to assume a sitting position, refusal of food and drink, inability to swallow, and a muffled voice. Lateral chest x-ray or sonographic investigation ("thumb sign") for supraglottitis or the antero-posterior x-ray for the "steeple sign" in croup have a poor to moderate reliability [93]. Occasionally, direct inspection under controlled circumstances (PICU) to confirm or exclude a condition, with the possibility to immediately intubate if the patient deteriorates, may be necessary.

Respiratory papillomatosis

Respiratory papillomatosis is the most common laryngeal neoplasm in children, and involvement of the lower airways does occur. It is caused by human papilloma viruses (HPV) types 6 and 11; however, there are more than 100 types of HPV. A vertical transmission from an infected mother during vaginal delivery or in utero has been documented, but only very few children born to mothers with genital HPV infection later develop airway

papillomatosis. The recent introduction of HPV vaccines is expected to reduce the incidence of this condition.

Respiratory papillomatosis is rarely a cause of neonatal stridor, sometimes presents with progressive biphasic stridor and loss of voice in infants, but typically presents with hoarseness, stridor and progressive dyspnoea at 3-4 years of age. Airway endoscopy shows the typical cauliflower-like appearance, usually above the vocal folds; a biopsy will allow identification of the virus type. At present, the condition is most commonly treated with repeat debulking using a microdebrider, cold steel, a CO_2 laser, or cidofovir injections. Future treatment possibilities include angiolytic lasers, bevacizumab and clecoxib [76,94,95].

Anaphylaxis

Anaphylactic and anaphylactoid reactions may involve the larynx and cause hoarseness and stridor due to mucosal oedema. A barking cough, swallowing difficulty, dyspnoea, wheezing, and respiratory arrest can develop rapidly. Skin, gastrointestinal, cardiovascular, or neurologic symptoms are often associated but not necessarily present. In children, the most common triggers are food allergens (cow's milk, egg, peanuts, tree nuts, and seafood). Immediate adrenaline is the therapy of choice [96].

Hereditary angioedema

Laryngeal oedemas occur in approximately 50% of patients with hereditary angioedema (HAE) at some time point, and tooth extractions and oral surgery are common triggers. HAE should be suspected with a history of recurrent angioedema (especially if hives are absent), a positive family history, onset of symptoms in childhood/adolescence, and recurrent abdominal pain. Diagnosis is via blood tests, checking C1 esterase inhibitor level and function, and C4 levels. With the delayed therapeutic effect of specific medication, treatment with inhaled adrenaline may be an alternative to intubation or tracheostomy in severe UAO [97,98].

Inducible laryngeal obstruction

The term inducible laryngeal obstruction (ILO) includes both glottic (typically the anterior two thirds of the vocal folds) and supraglottic (aryepiglottic folds, arytenoids) obstruction during episodes of unintentional paradoxical adduction, causing acute stridor and dyspnoea. If this happens during exercise (e.g. in elite athletes) it is called EILO (E for exercise). Flow-volume loops immediately after the attack will not show expiratory flow limitation, but may in some cases show truncated inspiratory flow-volume curves [99,100]. The diagnostic gold standard is laryngoscopic visualization of inappropriate glottic or supraglottic movements resulting in airway narrowing during a spontaneous event or provocation challenge. A number of different behavioural techniques, including speech therapy, biofeedback, and cognitive-behavioural psychotherapy may be appropriate for treatment of individual patients [101,102].

Foreign body aspiration

Foreign body (usually food or small objects) aspiration is most common in children 1-3 years of age. Most aspirated objects lodge in the bronchi, but rarely they can cause complete or significant partial obstruction of larynx or trachea. A history of aspiration or choking can be obtained in the majority of cases; cough and stridor are typical signs. Oesophageal foreign bodies may also cause stridor; in addition, children often complain of dysphagia and avoid swallowing. Some objects, such as coins, can be visualized on plain imaging. A coin in the trachea will be seen on its edge in an anterior-posterior view; in the oesophagus, it will appear as a full circle [103]. For further reading, we refer to our recent review [3].

Trachea

Tracheomalacia

Congenital tracheomalacia (TM) is caused by congenital absence, deficiency, malformation, or softness of tracheal cartilage. Acquired forms may develop as a result of prolonged intubation and mechanical ventilation, tracheostomy or severe tracheobronchitis. TM can be primary or secondary, and may be localized or generalized. Primary TM is found in association with oesophageal atresia, Down syndrome, Ehlers-Danlos syndrome, and with laryngomalacia or bronchomalacia. Its incidence has been reported to be at least 1 in 2,100. Localized secondary TM may occur as a consequence of compression from a vascular malformation (e.g. double aortic arch, pulmonary artery sling). Intrathoracic TM leads to excessive dynamic collapse during expiration or periods of increased intrathoracic pressure such as crying and coughing or during respiratory infections. Tracheal collapse may result in retention of secretions from the lower airways, which in turn may cause bronchopulmonary infections. In contrast, malacia of the extrathoracic part of the trachea may result in partial or complete airway collapse on inspiration.

Signs and symptoms include a "barking cough", tachy- and dyspnoea, retractions, cyanosis, localised monophonic (expiratory) wheezing in intrathoracic TM and inspiratory or biphasic stridor in extrathoraxic TM. Flexible airway endoscopy is the diagnostic procedure of choice; it is mandatory that evaluation of airway dynamics is performed during spontaneous breathing [8]. A pulsatile compression of the trachea can be suggestive of vascular malformations. Chest radiograph can arouse suspicion of the presence of a major vascular malformation, and barium swallow remains an excellent technique for the diagnosis of a vascular ring, but the exact anatomy of vascular malformations and its relation to adjacent structures has to be accurately defined by MRI and/or CT [104–107].

Bacterial tracheitis

Bacterial tracheitis may follow viral croup or start resembling viral croup with fever, cough, and stridor, but typically less responsive to treatment with steroids and/or adrenaline. On average, children with bacterial tracheitis are 4-6 years of age. Flexible endoscopy shows a typically fibrinous (pseudomembraneous) swelling of the mucosa of the subglottic region extending into the trachea. Antibiotic treatment against causative organisms (*H. influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *S. pyogenes*, *Moraxella catarrhalis*) should be started [3,108,109].

CONCLUSION

In children with stridor, a detailed history and thorough physical examination are mandatory for further diagnostic steps and subsequent therapeutic interventions. Knowledge of age specific aetiologies and their principles of treatment are important prerequisites to guide adequate assessment. Airway endoscopy is the most important diagnostic technique in the majority of cases.

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