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Early View

Task Force Report

ERS Statement on Tracheomalacia and Bronchomalacia in Children

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ERS Statement on Tracheomalacia and Bronchomalacia in Children

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Abstract:

Tracheomalacia (TM) and tracheobronchomalacia (TBM) may be primary abnormalities of the large airways or associated with a wide variety of congenital and acquired conditions. The evidence on diagnosis, classification and management is scant. There is no universally accepted classification of severity. Clinical presentation includes early-onset stridor or fixed wheeze, recurrent infections, brassy cough and even near-death attacks, depending on the site and severity of the lesion. Diagnosis is usually made by flexible bronchoscopy in a free-breathing child but may also be shown by other dynamic imaging techniques such as low contrast volume bronchography, computed tomography or magnetic resonance imaging. Lung function testing can provide supportive evidence but is not diagnostic. Management may be medical or surgical, depending on the nature and severity of the lesions but the evidence base for any therapy is limited. While medical options that include bronchodilators, anti-muscarinic agents, mucolytics and antibiotics, (as well as treatment of co-morbidities and associated conditions) are used, there is currently little evidence for benefit. Chest physiotherapy is commonly prescribed, but the evidence base is poor. When symptoms are severe, surgical options include aortopexy or posterior tracheopexy, tracheal resection of short affected segments, internal stents and external airway splinting. If respiratory support is needed, CPAP is the most commonly used modality either via a facial mask or tracheostomy. Parents of children with TBM report diagnostic delays and anxieties about how to manage their child's condition, and want more information. There is a need for more research to establish an evidence base for malacia. This statement provides a review of the current literature to inform future study.

Introduction:

Tracheomalacia (TM) is a condition of excessive tracheal collapsibility, due either to disproportionate laxity of the posterior wall (pars membranacea) or compromised cartilage integrity. As a result, the anterior and posterior walls appose, reducing the tracheal lumen opening and creating a shape abnormality during bronchoscopy [1, 2]. TM may be localised or generalised [2, 3]. If the main bronchi are also affected the condition is called tracheobronchomalacia (TBM). The term bronchomalacia (BM) is used when the excessive collapsibility is restricted to one or both of the mainstem bronchi and/or their divisions at the lobar or segmental level [3, 4]. Cases of isolated BM as well as extrathoracic or cervical TM are relatively rare [5, 6].

Malacia is defined in this report as an arbitrary > 50% expiratory reduction in the cross-sectional luminal area during quiet respiration [7-13]. There is no universally agreed 'gold standard' diagnostic test although flexible bronchoscopy is the most commonly used modality by respiratory paediatricians. The degree of TM/TBM can be assessed either bronchoscopically or radiologically. There is also no universally accepted classification of severity. In clinical practice, the anatomical changes are arbitrarily described as mild (50 – 75% reduction), moderate (75 – 90% reduction), or severe (>90%) most often on the subjective visual inspection at bronchoscopy [14]. This is a purely descriptive system of classification that does not reflect clinical severity since the degree of lumen occlusion is not associated with disease morbidity (see clinical signs and symptoms below).

The expiratory recoil pressure of the chest wall leads to a dynamic increase in intrathoracic pressure, which is transmitted to the airways. If the large intrathoracic airways are normal, changes in calibre are negligible but occur, for example, with coughing. If there is malacia, the tracheal/bronchial walls collapse with partial or complete occlusion of the lumen [15, 16], in particular if expiratory efforts are increased due to airflow obstruction. The adult literature distinguishes between collapse of the pars membranacea and the cartilaginous wall. Some use the term hyperdynamic airway collapse (HDAC) to describe the excessive protrusion of the posterior trachealis muscle into the central airway lumen during expiration and reserve the terms TM and TBM for the collapsibility of central airways due to the loss of structural integrity of the affected cartilaginous rings [17-19]. Because of the intrinsic softness of the paediatric tracheal cartilages, this distinction is less clear in the newborn, infant, and young child. For the purposes of this report, TM and TBM will also encompass HDAC.

This ERS task force on paediatric TBM reviews the current literature in children describing the evidence for diagnosis, clinical impact and therapeutic options, and the impact on families and patients with suggestions for future research.

Methodology:

The ERS taskforce on tracheomalacia and bronchomalacia in children comprised a group of paediatric respiratory physicians, a paediatric chest surgeon, paediatric radiologists, a physiotherapist, an early career member of the ERS, a European Lung Foundation (ELF) representative, and an ERS methodologist providing expertise in statement development. ERS standardised procedures for conflict of interest declaration were followed.

The taskforce started with a teleconference in May 2017 to agree on the formulation of questions, and allocate work into twelve pairs. Each pair was allocated a key question and undertook their own literature search using relevant keywords in systematic reviews, randomised controlled trials, case series and reviews and observational studies, over the last twenty years (1997-2017), from SCOPUS and Medline (accessed via PubMed) databases, restricted to the English language. Details of the original questions, the allocated task force members, results of the searches and PRISMA diagrams are in the on-line supplement. There were face to face meetings during the ERS Congress in Milan in September 2017 and another two-day meeting in Athens in March 2018. Literature published subsequent to the final meetings were not included in this review.

Drafts were submitted to the task force chairs, integrated into a uniform manuscript, which was extensively discussed at the third face-to-face meeting during the ERS Congress in September 2018. All task force members further reviewed and contributed to the manuscript in its final form.

Conditions associated with TBM:

There is no generally accepted paediatric classification of the causes of airway malacia. The task force used a division into those conditions with an intrinsic alteration of airway cartilage (primary or congenital) and those where the cartilage was embryologically normal but developmentally malformed because of pressure on the airway wall from outside (secondary), or acquired from airway luminal disease such as chronic infection.

Pragmatically, it may also be helpful to distinguish conditions where TBM is clinically the main problem, and those in which, whilst still a factor, there are either more important complex extrapulmonary co-morbidities such as cardiovasular abnormalities, or pulmonary parenchymal disease. An example of the latter would be bronchopulmonary dysplasia, in which TBM worsens the prognosis but is far from the only abnormality [20].

The numerous causes of TBM are summarised in Table 1. Congenital airway malacia is part of many rare syndromes. TM can be found in association with chromosomal defect syndromes, mucopolysaccharidoses and inherited connective tissue disorders [21]. In addition, TM has been described in about 5% of children with achondroplasia [22]. Some conditions are associated with a discrete area of malacia. For example, children with trachea-oesophageal fistula typically have a short segment of TM post-operatively [18, 23, 24]; post-operative repair of vascular rings can leave a defined, short tracheomalacic defect.

One study[3] reported malacia (including laryngomalacia, a condition outwith the remit of this Task Force statement) in 299 of 885 bronchoscopies. Forty one had cardiovascular abnormalities, 29 had been treated for tracheo-oesophageal fistula (TOF), 9 had congenital lobar emphysema and 24 were syndromic. Boogaard et al. [25] found bronchomalacia in 160 of 512 paediatric flexible bronchoscopies, 136 cases being primary. Sixty seven of 86 children with primary malacia in whom bronchoalveolar lavage (BAL) was obtained had a positive bacterial culture; lavage neutrophil counts were not reported. Whether infection was secondary to malacia, or the converse, and the relationship between malacia and persistent bacterial bronchitis is also unclear.

It has been suggested that infant wheeze may be related to TBM [26] as a developmental phenomenon with spontaneous recovery, but the contribution of malacia is rarely determined in clinical practice.

Clinical Symptoms and Signs:

The type and onset of symptoms depend on length, site and severity of the malacic segment. The task force members were unable to find any consistent correlation between anatomical severity and clinical features in the literature.

Symptoms may be persistent or intermittent, and of varying severity [6, 27]. If the extrathoracic trachea is malacic there may be stridor; if intrathoracic, a monophonic expiratory wheeze is common [6, 28]. If the child develops a respiratory infection, there may be a barking cough, prolonged resolution of cough, expiratory wheeze or croup-like symptoms. Older patients often complain that complete exhalation is difficult [18].

In more symptomatic cases, stridor or wheezing are persistent, respiratory infections are frequent and respiratory distress may occur. Wheezing in children with malacia is typically centrally located, low pitched and monophonic [29] and distinct from the diffuse, high-pitched and musical wheezing in asthma. Moreover, in patients with malacia, wheezing remains unchanged or even worsens after bronchodilator inhalation [15]. Importantly, TM/BM should always be considered in the differential diagnosis of infants and preschool children with “atypical wheeze” (e.g. infants who are never completely symptom free or infants with frequently recurring wheeze). The “bagpipe sign”, an expiratory sibilant sound that persists after the end of visible expiration, may also be present [6]. Intermittent compression of a malacic trachea during bolus progression in the oesophagus can cause desaturation, leading to poor feeding and, consequently, poor weight gain.

In severe cases, airway obstruction with cyanosis, inspiratory and expiratory stridor during tidal breathing, apnoea and even cardiac arrest or sudden infant death may occur [6, 27, 30-32]. In the most severe cases, airway obstruction can only be resolved with intubation [6, 27], and successful extubation can be challenging [33].Tracheal obstruction can cause “dying spells” (also called “apnoeic spells”, “reflex apnoea”, “death attacks” or “blue spells”). These events are possibly elicited by a reflex triggered by secretions or when a bolus of food in the oesophagus compresses the trachea or the presence of increased intra-thoracic pressure from a Valsalva effect.

Severe malacia is typically evident clinically from birth, but many children with tracheomalacia or bronchomalacia do not show any symptoms before age 2-3 months [6, 27, 30]. Boogard et al. described symptoms in 96 outpatients with primary airway malacia and without comorbidities. Cough was found in 83% of children (night-time cough: 42%; productive cough: 60%; exercise-induced cough: 35%; characteristic barking cough: 43%), recurrent lower airway infections in 63%, dyspnoea in 59%, recurrent wheeze in 49%, recurrent rattling in 48%, reduced exercise-tolerance in 35%, symptoms of gastro-oesophageal reflux in 26%, retractions in 19%, stridor in 18% and funnel chest in 10% [25]. However, in many patients symptom onset is insidious, and for some the diagnosis is only made later in life [25], even in the elderly [34].

Table 2 summarises symptoms and signs of TM/BM. A barking or brassy cough is most commonly reported. Intra and inter-observer clinician agreement for brassy cough was very good [kappa=0.79, 95%CI 0.73–0.86) when undertaken by respiratory specialists, and the sensitivity and specificity of brassy cough (compared to tracheomalacia seen at flexible bronchoscopy) were 0.57 and 0.81 respectively [35]. The brassy cough is caused by vibration due to the mechanical juxtaposition of its anterior and posterior walls [27], which causes an irritable focus that stimulates further cough [36]. In a meta-analysis including five studies with 455 patients in whom bronchoscopy was performed because of recurrent croup-like symptoms, tracheomalacia was found in 4.6% of children [37].

In children with TM/BM, both airway closure during cough and ineffective cough due to an underlying condition can cause impaired clearance of secretion, leading to recurrent and/or

prolonged respiratory infections [6, 27]. Santiago-Burruchaga et al. demonstrated airway malacia in 52% of 62 children in whom bronchoscopy was performed because of recurrent lower respiratory tract infections [38]. Airway malacia is a frequent bronchoscopic finding in children with recurrent respiratory symptoms [3, 39, 40] and in children with protracted bacterial bronchitis [41], although which is causal and which is secondary, is often unclear.

In children with TM/BM, symptoms can be aggravated by any conditions requiring increased respiratory efforts, such as exercise, coughing, crying, feeding, Valsalva manoeuvres, forced expiration or lying supine. All these activities cause increased intrathoracic pressure which worsens airway collapse [6, 18]. Placing an infant in prone position may open the airway because gravity pulls the mediastinal structures anteriorly, thus alleviating symptoms [15, 42].

Natural history

In patients with primary non-syndromic TM/BM, symptoms may resolve. A greater tracheal diameter and increasing rigidity of the supporting cartilages with a more pronounced “C” shape of the cartilage rings with less protrusion of the pars membranacea (trachealis) often results in resolution of symptoms by age 1 or 2 years [27, 43, 44]. For some of these children, exercise intolerance or wheezing with exercise may persist into later childhood [21, 44].

The role of pulmonary function testing in diagnosing TBM:

Eleven studies address the role of pulmonary function testing (PFT) in diagnosing TM/TBM but all are small and only two [25, 45] reported ≥ 20 children. Many different PFTs were undertaken: spirometry, V'maxFRC (maximal flow at functional residual capacity), FRC (functional residual capacity), PEF (peak expiratory flow), MEF (mid expiratory flow), TEF (tidal expiratory flow), airway resistance, flow-volume loop description and airway hyper-responsiveness. None of the studies used newer techniques such as oscillometry and multiple-breath washout.

Many but not all studies showed that some children had expiratory airway obstruction. Lung function testing cannot be used to diagnose TBM but an obstructive airway pattern is supportive evidence [46, 47]. Early phase plateauing of the expiratory limb has been described. A plateau of both inspiratory and expiratory limbs of the flow volume loop is more likely due to fixed obstruction, unless there is both intra- and extra-thoracic TM [48]. Increased thoracic gas volume (TGV) was also documented in one study [49]. Flow limitation during VmaxFRC is neither sensitive nor specific for malacia, but flow limitation during tidal breathing is highly predictive and 100% specific [50].

One study [46] found airway hyper-reactivity to mannitol in 2 of 15 (7%) children, the significance of which is unclear. There was no significant effect of β-2 agonists on spirometry [25]. Indeed, beta2 agonist actually reduced V'maxFRC by 31.6% in 3 children [51].

The studies are for the most part small, and none related PFTs to severity of TBM, or even defined how the diagnosis was made. Hence, we could not calculate the sensitivity and specificity of any PFT abnormality for TBM. PFTs may or may not be abnormal in children with TBM. Limited data exist on whether or not currently available PFTs can be used to diagnose TBM. Until further data are available, we are unable to quantify a precision of an estimate.

The role of imaging to diagnose TBM:

The task force members could find no evidence to support the use of plain radiographs to diagnose TBM [52].

Fluoroscopy

Fluoroscopy is a quick, non-invasive dynamic study, with minimal radiation exposure (approximately 0.01mSv) and no requirement for sedation. Airway fluoroscopy is performed in the lateral position while the patient is free-breathing. [27, 53, 54]. The sensitivity is poor (20-24%), while the specificity is very high (93-100%) [55, 56]. Fluoroscopy is often combined with a barium swallow to rule out the presence of an external compression.

Multi-detector computed tomography (MDCT)

MDCT provides new diagnostic options [Figure 1]. Paired end-inspiratory and end-expiratory MDCT or paired end-inspiratory and dynamic expiratory MDCT are both reliable techniques[7-9, 57]. Children age <5 years generally require intubation and controlled ventilation technique [10, 58], which will influence airway dynamics. In some institutions a securely positioned face mask is used instead of intubation, especially when a tracheal stenosis is suspected above the thoracic inlet level. Intravenous contrast injection is only mandatory when looking for underlying compressive causes such as vascular abnormalities or mediastinal masses [10]. The reported overall diagnostic accuracy of paired airway MDCT compared to laryngoscopy/bronchoscopy is 91% [9]. However patients included in this study suffered from very severe TBM in whom surgery was required, so this is a biased population and the accuracy of the CT scan may have been over-estimated. Free breathing cine–MDCT is an alternative technique in young children as it does not require general anesthesia and controlled ventilation, and radiation exposure is low (mean effective dose less than 2mSv, with the minimum ever reported 0.19-0.8mSv) [11-13]. Reported sensitivity (96.3%) and specificity (97.2%) are high compared with bronchoscopic evaluation [11]. Virtual bronchoscopy is not very sensitive (sensitivity<75%) in detecting TM [59]. Only one study compared virtual bronchoscopy with flexible bronchoscopy reporting a sensitivity of 54.1% and specificity of 87.5% for TM and 45.2%, and 95.5% for BM [60].

MDCT has the advantage that it is a quick, less invasive technique which allows simultaneous assessment of any mediastinal, vascular and lung pathologies, as well as visualisation of airways distal to the obstruction [61]. The major disadvantage is the radiation exposure, which increases with the paired technique. This can be partially overcome by using reduced-dose techniques in the expiratory scan [62]. Another concern is the need for sedation and intubation in younger children, which can distort the airway and change the tracheal dynamics [7, 9, 11, 12, 28]. This problem can be partially solved by using free breathing cine –MDCT [11-13].

Dynamic MRI

There are very limited publications, with small numbers of children, describing dynamic MRI to diagnose TBM. The major advantage of dynamic-MRI is the lack of radiation exposure. Additionally MRI provides high-resolution imaging with excellent soft tissue imaging, which allow for identification of vascular and mediastinal structures without necessarily the need for contrast [63], but the technique is time consuming.

Recent ultrafast sequences permit cine-MRI, which provides extremely rapid acquisition of images [63-65]. Another important advantage of cine-MRI, compared to bronchoscopy, is that in older

children (usually >8years) airways can be examined during static and dynamic breathing manoeuvres, such as forced expiration and cough, without any need for sedation or general anesthesia, which could obscure TBM [65]. For younger children sedation and/or general anesthesia is necessary [64, 66]. A disadvantage of cine-MRI is the relatively low spatial resolution, which may be a problem with smaller caliber airways [63-65].

A published protocol describes the combination of static and dynamic cine-MRI [64, 65].

Tracheobronchography

Tracheobronchography performed with low volumes of non-ionic water soluble contrast is safe [67], and useful in the evaluation of TBM because of its high spatial and temporal resolution [68] (Figure 2). Many centres continue to use tracheobronchography [12, 67, 69-71], often in combination with flexible bronchoscopy [68]. Free breathing, as with many of the imaging techniques, is required for diagnostic accuracy [72].

The role of bronchoscopy to diagnose and grade TBM:

We reviewed 27 papers on the role of bronchoscopy in the diagnostic work up of TBM[7, 55, 59, 60]. Task force members use flexible bronchoscopy in a spontaneous breathing child as a gold standard for the diagnosis of TM and BM. Rigid bronchoscopy plays a role but may splint the airway and is not as useful as flexible bronchoscopy in the evaluation of the airway dynamics. However, the limitations of flexible bronchoscopy must be appreciated. Firstly, the bronchoscope occludes a significant part of the airway, likely raising airway pressure and reducing the chances of detecting malacia. Secondly, even for experienced bronchoscopists, assessment of changes in the lumen is subjective[5, 6, 16, 27, 29, 53, 72-74]. Thirdly, there are also specific problems linked with the optical attributes of the instrument, namely, the distortion of the image due to curvature and orientation of the lens[75]. Furthermore, the bronchoscopic diagnosis of TM and BM can be difficult in children because of the small size of the bronchial tree and the rapid respiratory rate. There are no studies comparing flexible and rigid bronchoscopy.

Good anaesthetic technique is essential in order not to mask (too deep) or exaggerate (too light with severe coughing) TM and BM, but found a paucity of data in the literature on anaesthetic practice [76]. There are case reports [77-79] of airway collapse with anaesthesia in patients with either symptomatic or asymptomatic TM. Because general anaesthesia leads to increased collapsibility of the upper airways the same might be true of the lower airways [53, 80-82]. The topic of the most suitable drugs for anaesthesia in bronchoscopy remains an area for future research.

In their bronchoscopy practice, taskforce members divide the trachea into 3 arbitrary regions to describe the site and extent of TM: from the cricoid to the thoracic inlet, from the thoracic inlet to the mid portion of the intra-thoracic trachea, and from there to the carina.

Examples of malacia are portrayed in Figure 3.

Four papers attempt to refine the role of flexible bronchoscopy to quantify the degree of malacia. Masters et al. [75, 83] used digital video to capture and quantitate the images with high intra-observer and inter-observer agreement. The authors demonstrated that neither the site nor the severity of malacia correlate with the clinical symptoms or severity. Okazaki et al. quantitated the static pressure/area relationship of the trachea under general anaesthesia and paralysis[84]. Finally, Loring et al. evaluated central airway narrowing in adults by a “shape index” based on images taken during bronchoscopy and plotted against the transtracheal pressure[85].

Medical therapies in the management of TBM:

The following medical therapies for TBM are considered in the literature.

β2 agonists: Malacia causing bronchodilator unresponsive wheeze is not uncommon [26]. There are theoretical reasons why bronchodilators, by lowering airway smooth muscle tone may worsen airway obstruction. In one study, VmaxFRC was *below* normal in infants with wheeze and malacia at baseline and did not improve after inhalation of β2 agonists; infants with malacia were not more likely to worsen after β2 agonists than non-malacic, wheezy controls [86]. In older children with isolated TM, airways obstruction (reduced PEF and FEV_1, compatible with the increased central airway collapsibility during forced expiration) does not improve after bronchodilation [25]. Also, underlying bronchodilator responsiveness in a patient with severe TBM might only be detectable after optimal tracheal stabilisation [87].

Ipratropium Bromide: In a retrospective study, 32 out of 52 children diagnosed with TM and treated with ipratropium bromide showed improvement in symptoms [88] though it is not possible to say whether the improvement may be related to its effect on airways secretions and / or airways tone.

Muscarinic agonists: Anecdotally, muscarinic agonists (e.g. bethanechol, methacholine) reduce tracheal compliance probably by causing trachealis constriction [51]. This is not routine clinical practice.

Mucoactive agents: A Cochrane review [89] found one eligible study and concluded likely harm from recombinant human deoxyribonuclease (rhDNase) although this was not evident from the original data after adjusting for baseline factors. The single study included in the review [90]showed that 2 weeks treatment with nebulised rhDNase did not enhance recovery or reduce the need for antibiotics in children with airway malacia and a respiratory tract infection. Anecdotally, nebulised hypertonic saline may aid mucus clearance [27].

Antibiotic therapies: The relationship between airway malacia and protracted bacterial bronchitis (PBB) is unclear [38, 39, 41, 91]. The juxtaposition of the anterior and posterior walls of the trachea, results in recurrent vibrations and irritation of the airway, and reduced mucociliary clearance (MCC) as the compressed airway impedes clearance of secretions thus predisposing to distal infection [89]. Squamous metaplasia can develop over time, further impairing MCC [6]. Fourteen to 52 % of children with PBB had TBM. Treatment with >=2 weeks with antibiotics resolved symptoms in the majority [41] though recurrence was common[41, 89].
Task force members apply a lower threshold for using antibiotics in children with known TBM and an acute exacerbation. Prophylactic azithromycin is often prescribed with only anecdotal evidence of benefit.

Management of comorbidities / associations:

Gastro oesophageal reflux: In one study seventy percent of children aged 3-28 months with airway malacia had GOR (n=28) compared with 39% (n=16) in controls [92]. This association does not imply causation.

Eosinophilic Oesophagitis: These patients present with treatment non-responsive GOR. Children with eosinophilic oesophagitis and airway symptoms appear to have worse outcomes than their counterparts with purely GI symptoms [93]. Oesophageal eosinophilia is also seen after oesophageal atresia repair in 17% of children [94], many of whom have TM. This group have significantly greater

incidence of reflux symptoms, reactive airway disease, hypoxic spells (secondary to both TM and oesophageal dysfunction), and dysphagia when compared with the non-eosinophilic group.

General respiratory health All aspects of good respiratory health care should be emphasised such as immunisations, flu vaccinations, dry warm housing, exercise and passive smoke avoidance.

The role of respiratory physiotherapy:

Respiratory physiotherapy is commonly used in the treatment of children with TM or TBM, aiming to enhance mucociliary clearance [44, 89]. Our review of the literature did not identify any studies investigating the effectiveness of physiotherapy for patients with tracheomalacia. Moreover, we have not found any studies on the role of airway clearance techniques (ACT) in conjunction with mucolytics. Positive expiratory pressure (PEP) is often used for ACT in clinical practice. In infants with TM, continuous positive expiratory pressure (CPAP) increases maximal expiratory flow by raising functional residual capacity [47]. One study [95], reports that a PEP of 5-10cm H_2O increases the peak cough expiratory flow of children with clinically diagnosed TBM after tracheo-oesophageal fistula repair. However, they note that an increase of PEP above 15cm H_2O may have a negative effect, suggesting there should be close monitoring of PEP or use of a threshold expiratory pressure device. It is unclear if PEP devices for ACT prevent or reduce the impact of lower respiratory tract infections. Children with bronchomalacia may experience exercise limitation[44] but we did not find any studies on exercise rehabilitation.

Surgery including stenting for TBM:

Surgery may be necessary in severe TBM with acute life threatening events ("apnoeic spells"), cyanosis, feeding difficulties, inability to extubate the airway, and recurrent pneumonia [89]. A detailed diagnostic work-up informs planning for the most appropriate operative technique. Surgical and endoscopic options include tracheostomy, aortopexy, tracheal resection, tracheopexy (anterior or posterior), internal stenting and external airway splinting [27]. Intraoperative flexible bronchoscopy may be helpful in guiding the surgeon during some of these procedures [27, 96-98].

Tracheostomy

This technique was the mainstay of surgical treatment in the past, but is now used as a last resort [27, 99]. The tracheosotomy tube provides internal airway stenting and enables long-term mechanical ventilation if necessary

Aortopexy and tracheopexy

The main indication for anterior aortopexy is short segment TM secondary to congenital trachea-oesophageal fistula [27, 100, 101]. The ascending aorta or arch is pulled anteriorly to relieve pressure on the trachea. Aortopexy does not directly address airway malacia but creates more space around the mediastinal trachea so that the aorta, anteriorly, and the oesophagus, posteriorly, do not compress the airway [101]. Nevertheless, the evidence base for aortopexy is scant [102] with limited long term follow up data [103]. The approach may be a small left anterior thoracotomy, a partial upper sternotomy, or thoracoscopy [104, 105]. If bronchial collapse persists despite aortopexy, pulmonary artery suspension may be performed. Tracheal traction sutures can allow a more effective TM correction (anterior tracheopexy) [106-108]. A recent retrospective report [98] showed that partial upper sternotomy and open thoracotomy had the highest rate of symptom resolution. Reported overall effectiveness of aortopexy for TM, whatever surgical approach performed, is above 80% [101, 102].

More recently there has been interest in posterior tracheopexy, because in many cases the major contributor to airway collapse is the posterior tracheal membrane protruding into the tracheal lumen during exhalation [106, 109]. In this procedure the posterior tracheal membrane is sutured to the anterior longitudinal ligament of the spine through a posterior right thoracotomy. Preliminary results are encouraging [109]. Anterior and posterior tracheopexy may be combined but this approach is not used widely [110].

Tracheal resection

Tracheal resection is sometimes considered in highly selected patients with short segment TM in whom other surgical or endoscopic techniques have failed. Severe suprastomal collapse in tracheostomized patients, also called peristomal TM, can also be an indication for a limited tracheal resection with end to end anastomosis [99, 111].

Internal stenting for tracheobronchomalacia

Internal stenting is an attractive concept, but several practical problems limit the use of this technique in children [112]. The indications vary considerably, but in general a multidisciplinary team and an individualised approach to each patient are emphasised [113, 114]. Most centres reserve the use of internal stents for children who have no curative surgical options and where tracheostomy is not appropriate [113-116]. Other centres consider stent implantation to be a valid alternative to

tracheostomy [117]. Stent insertion is usually followed by an immediate improvement in the patient's clinical condition [118], although this may be transient.

Various stent types with different physical characteristics are available (Table 3) [114]. Silicone stents [119] and self-expanding plastic stents [120] have rarely been used in children with TBM. Encrustation with mucus, migration, and the development of granulation tissue or mucosal hyperplasia at the ends of the stent are problems [112, 116, 117, 119, 121]. Balloon-expandable metals stents may be difficult to retrieve after being *in situ* for longer than a few weeks, and may fracture or (rarely) cause vascular erosion [112-115, 117]. They may be dilated as the child grows [112, 114] (Figure 4). Uncovered self-expanding metal stents are less likely to fracture or cause vascular erosion, but cannot be dilated and are very difficult to remove [114, 116]. Covered self-expanding metal stents are retrievable, but suffer from the same problems as silicone stents [112, 114]. Recently, bioabsorbable airway stents have been used in selected children with malacia [117, 122] (Figure 5). Realistic goals for the use of absorbable stents include "proof of principle" that restoration of patency improves clinical status (for example by making the patient independent of invasive ventilation) before attempting surgery or permanent stenting [112, 113, 115], and stabilization of the airway to allow spontaneous resolution of malacia [115].

Extensive tracheobronchial stenting for diffuse TBM is not appropriate [112, 114] and it has been previously recommended to avoid a combination of stenting and tracheostomy [112, 113, 118]. Aortopexy is almost universally preferred over stenting for TM associated with oesophageal atresia [116, 123]. Metal stents [124], or serial stenting with absorbable stents [115], could be used as an alternative to aortopexy, but this concept has not been widely accepted.

Complications of metal stents include airway obstruction due to granulation tissue and mucus plugging, which is aggravated by the variable degree of impairment of mucociliary clearance caused by the stent [112, 116, 125]. Granulation tissue is usually managed by repeat bronchoscopic laser treatment, endoscopic removal or crushing with balloons [112, 126]. Fatal complications, including severe airway haemorrhage and pneumonia, may occur, but are uncommon when stents are used appropriately [118, 127]. Fully epithelialized metal stents are usually considered permanent, as they are difficult to remove safely and the long term results of permanent stenting are acceptable [112, 115, 117, 128].

External Splinting and tracheal reinforcement

Extraluminal splinting may offer effective airway support in highly selected, very severe and/or diffuse TM/TBM as an alternative to endoluminal stenting. Biocompatible ceramic rings, resorbable plates, or even 3D-printed biodegradable splints have all been used [129-131]. Possible erosion into surrounding structures, a strangulation effect after somatic growth in a small child, infection, and long-term tissue tolerance are concerns.

Ventilatory pressure support in TBM:

There is a pathophysiological rationale for pressure support in paediatric TBM. The variable dynamic deformity throughout the airway results in variable airflow velocities and time constants of respiration. Pressure support must overcome these forces and concomitantly allow enough downstream expiratory gas flow to ensure respiratory stability. Computer modeling reveals a complex relationship between length of malacia, diameter of the tracheal ring, site of malacia, and tissue type generally to predict the tipping point to airway collapse/closure or snap point[132-134]. These mathematical modeling studies provide some insight to the use of pressure support but greater insight might come from 3D modeling of the airway lesions[135].

TBM has been managed with all forms of non-invasive pressure support (CPAP, Bilevel airway pressure (BiPAP), high flow drivers, and full ventilation)[21, 136-140]. CPAP is the most widely used. BiPAP is rarely used because there is no advantage in the vast majority of patients (other perhaps than in those who require a very high distending CPAP pressure) and poor synchronization may be a problem[137]. Our literature search found no prospective or randomized studies that help inform decisions regarding when and how to use these approaches. Co-morbidities also may affect decision making.

Clinical studies[47, 141] have shown that CPAP improved gas flows at FRC without changing the appearance of the flow volume loop and most importantly flows were also still appreciably decreased compared to controls, particularly at lower lung volumes. Bronchoscopy or imaging can help titrate CPAP levels[138].

Currently there are no proven management algorithms. Pressure support should be considered in acute severe life threatening events though maintaining a child on NIV 24 hours a day without a tracheostomy is likely to prove impractical. Pressure support is usually considered in any patient with recurrent acute or chronic respiratory failure and sleep disordered breathing. Speculatively, it may also play a role in some patients with TBM associated with recurrent persistent bacterial bronchitis or recurrent pneumonia and poor growth where alternative surgical or medical therapies have failed[142].

Application of non-invasive pressures support is dependent on informed parental agreement for the intervention, the type of device, the interface interaction between device and patient, the operator experience and availability of sleep monitoring systems. These interventions may need to be established over a number of monitoring sessions with careful follow up. Protocols are usually determined on an individual basis. Weaning protocols take into account the possible natural history of improvement[2, 21, 47, 139, 140]. Just how long these modes of pressure support are required for on a daily basis or cumulatively over a longer time period is also not known and likely to be individualised.

A tracheostomy for the delivery of positive pressure is reserved for more severe cases in whom other approaches have failed or where pressure support is required for most of the 24 day[21, 43, 139, 140, 143].

Parent and patient perspective:

There are few published studies that specifically address this topic [144-146]. Grey literature searches identified discussion forums, blogs and news articles where parents, carers and patients

shared experiences and sought advice. Key concerns for parents and carers are described below with selected illustrative quotes from parents and carers in Box 1.

Getting a diagnosis

Parents express frustration at the length of time to get a diagnosis and a lack of understanding from health professionals. While some parents feel relief to have a diagnosis they have concerns about how to best support their child (Quote 1).

Specific symptoms and knowing when it's 'bad'

Parents and carers have concerns about specific symptoms, including laboured and noisy breathing, feeding, weaning and weight-loss (Quote 2). They seek advice to identify when symptoms are 'bad'.

Risk of interacting with other children and social impact

Some families express concern about their child with TM/BM catching colds and they avoid exposure (Quote 3). Families may experience the stigma associated with having a 'sick' or perceived contagious child (Quote 4).

Information and support

Parents and carers recognise the importance of being well-informed. The need for timely, high quality information, delivered in a variety of formats is well recognised [144-146].

Families also seek support and reassurance from peers both face-to-face and online [146] to gain practical information about their child's condition and likely outcomes.

Information should be timed carefully and sensitively, particularly in severe cases. Some parents find it difficult to handle too much information in the early stages or find stories of other children's treatment frightening [146].

Long-term outcomes

Parents and carers express concern about long-term TM/BM outcomes but reassure each other that improvement can occur in certain cases. Nevertheless, some parents note that their child has not fully recovered or improved as quickly as expected, making it difficult to reconcile their expectations (Quote 5). In some adolescents, mental health issues may arise. Parents also have concerns about the impact of long-term treatment. Understanding which symptoms require intervention and the long -term outcomes for their child are key concerns for families.

Box: Illustrative quotes from parents and carers

1. "I am glad that he has been diagnosed after seeing 3 doctors who all fobbed me off with 'it's wind, give him infacol'... but feel disappointed that there is nothing I can do for him!" (Mumsnet thread "floppy windpipe", 2005)
2. "I was so worried about all the noises she was making especially at night. I used to be up and down all night checking up on her as she sounded like she was choking." (Mumsnet thread "floppy windpipe", 2005)
3. "I have always visited friends even when they had kids with a cold but feel now I may be a bit more cautious" (Mumsnet thread "My 4 month old diagnosed with laryngeal or trachea malacia - anyone got any experience?", 2009 - 2011)
4. "I know what it's like to feel the glares and hear the negative comments from others who think I've brought a sick child to a public place when I know nothing about him is contagious" (Horwath, 2015).
5. "My son is now 6 years old the condition has not gone away as they said it would […]. We were told he would grow out of the condition by the age of two" (Mumsnet thread "My 4 month old diagnosed with laryngeal or trachea malacia - anyone got any experience?", 2009 - 2011)

Areas for future endeavour:

For any future research into this topic of malacia, it is important to have a working definition of TM, BM and TBM. All TF members perform flexible bronchoscopy under carefully regulated anaesthetic conditions with airways undistorted by endotracheal tubes or laryngeal masks, where ever possible, in order to get the best anatomical assessment of malacia during free breathing and forced expiratory manoeuvres such as coughing. In experienced hands, tracheobronchography provides invaluable information.

Taskforce members grade the degree of malacia as:

1 Normal: collapse up to 50% of the lumen

2. Mild: loss of cross sectional area (which may be asymmetrical) between 50 and 75%

3. Moderate: loss of cross sectional area between 75 and 90%

4. Severe: Greater than 90% loss of cross sectional area.

The reliance of subjective visualisation may be replaced by enhanced digital quantification in the future.

The site and length of the affected area can also be assessed bronchoscopically. Contrast enhanced trachea-bronchography provides useful dynamic information as airway collapse is dependent on the properties of the airway and transmural airway pressure.

Using these defined criteria, standardised data collection in a prospective manner by a network of interested parties could establish much needed information on a number of key areas:

1. The natural history of this condition from premature infancy to mature adolescents;
2. The role and impact of current surgical interventions such as the anterior and posterior pexy procedures and the impact of these procedures on long term growth and outcomes;
3. Studies into the use of antibiotic therapy in the prevention and treatment of infection in TBM;
4. Increasing awareness and establishing markers for the role of malacia in refractory respiratory illness thereby reducing delay in the diagnosis and unnecessary therapies;
5. Registry data to establish the role of biodegradable stents in the management of TBM and the histological changes that may happen in the tracheal wall as part of the reabsorption process;
6. Clarity on the apparent disconnect between the extent and degree of malacia and the clinical presentation;
7. Long term outcomes, including the management of realistic expectations around full recovery.

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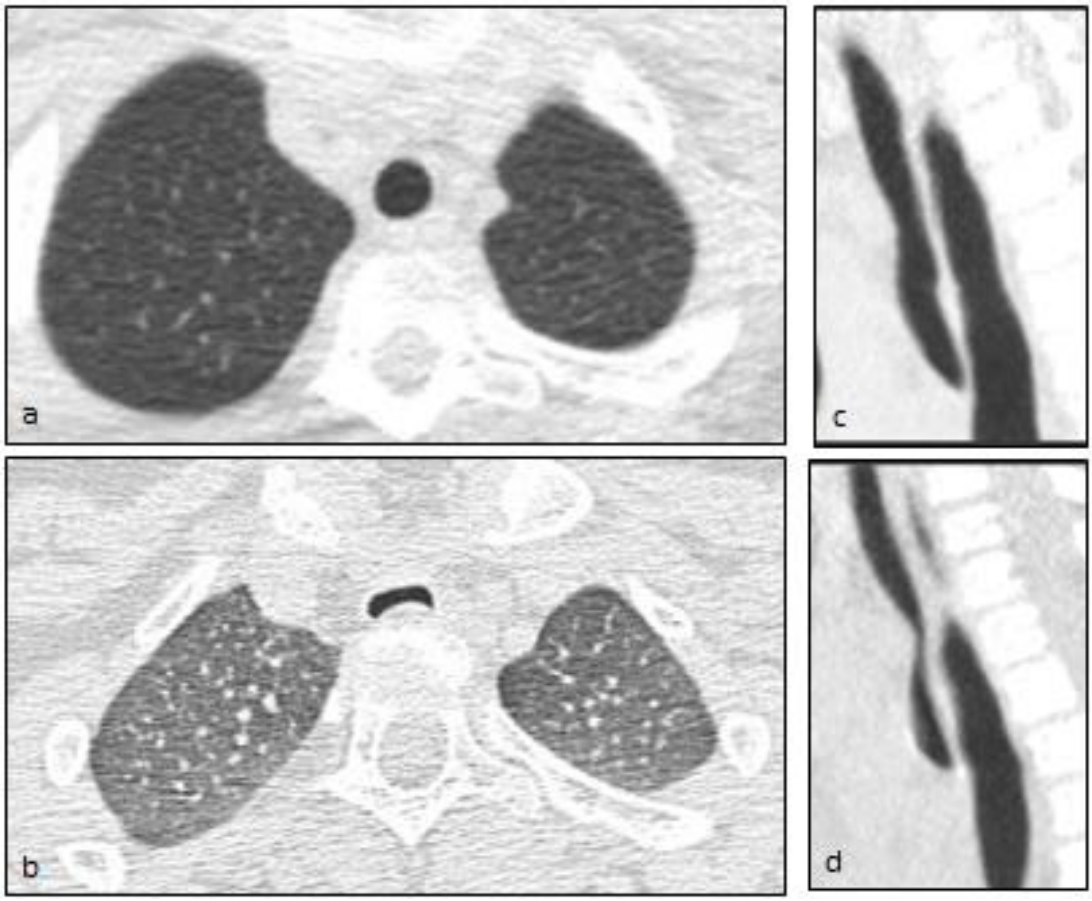
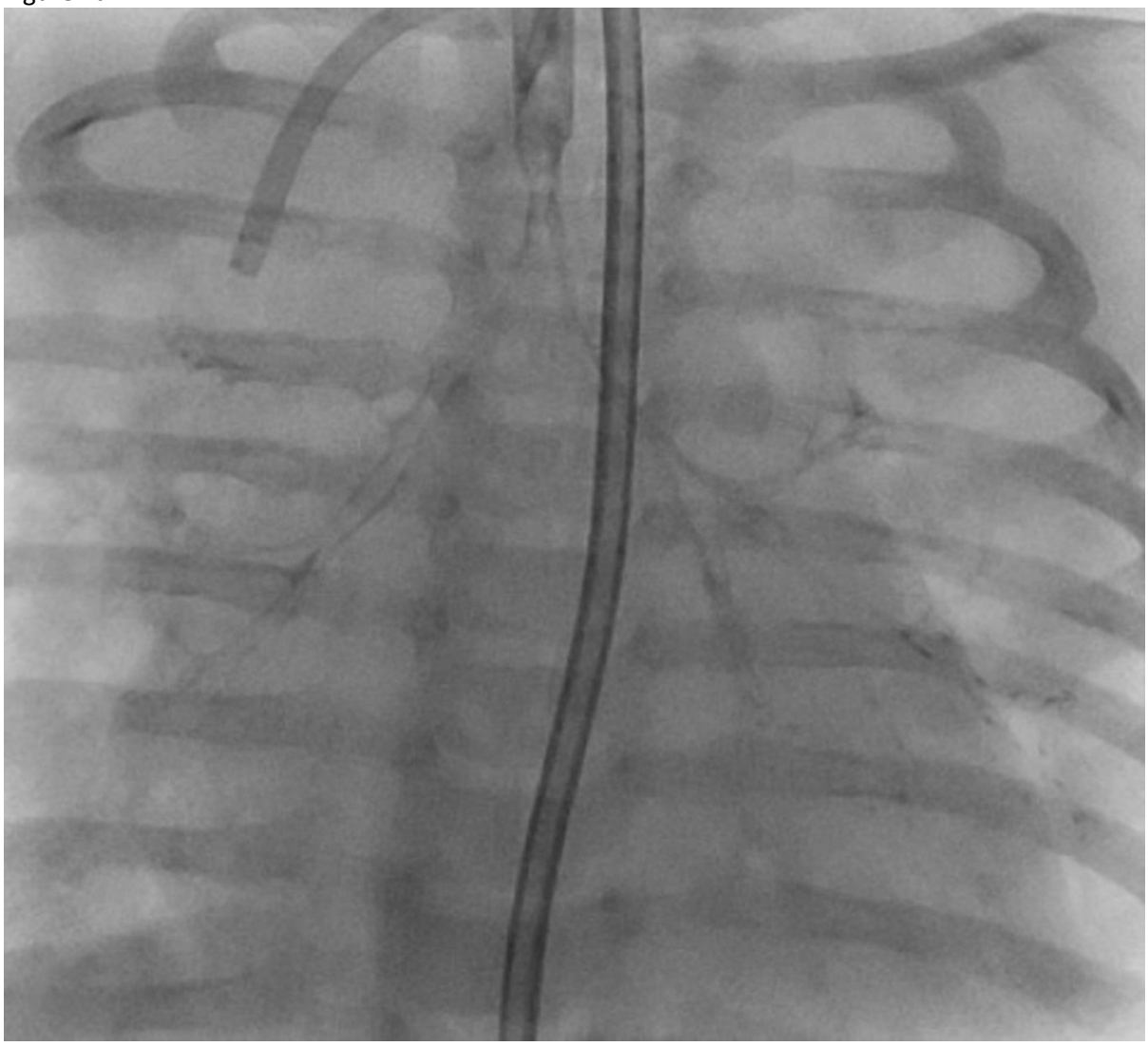
Figure 1



Paired end-inspiratory and end–expiratory MDCT scan of the chest: axial scan at end-inspiration (a) and end-expiration (b) phase and sagittal MPR at end-inspiration (c) and end-expiration (d) phase shows significant expiratory reduction in the cross-sectional luminal area of the trachea. The appearance is consistent with tracheomalacia.

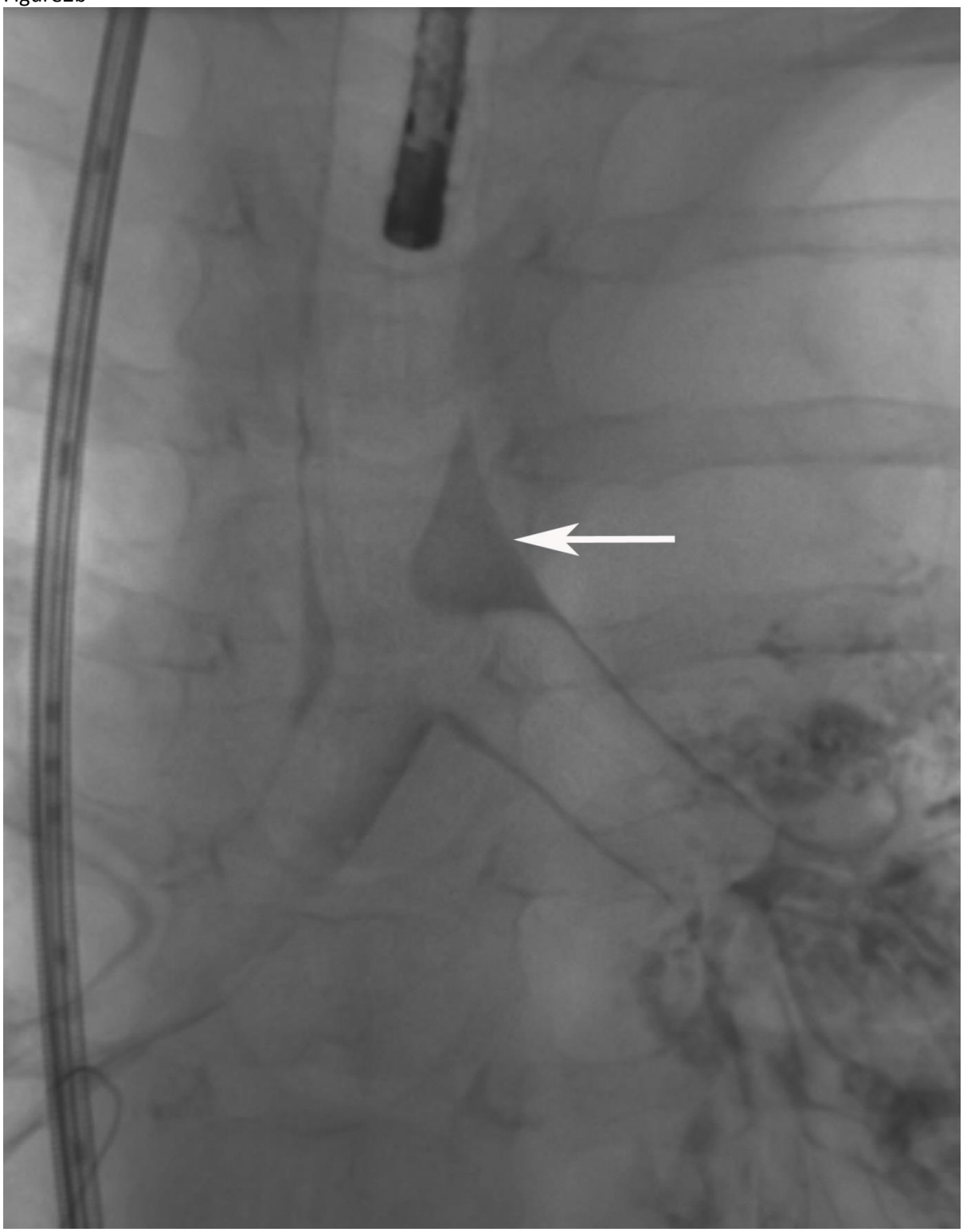
FIGURE 2

Figure 2a



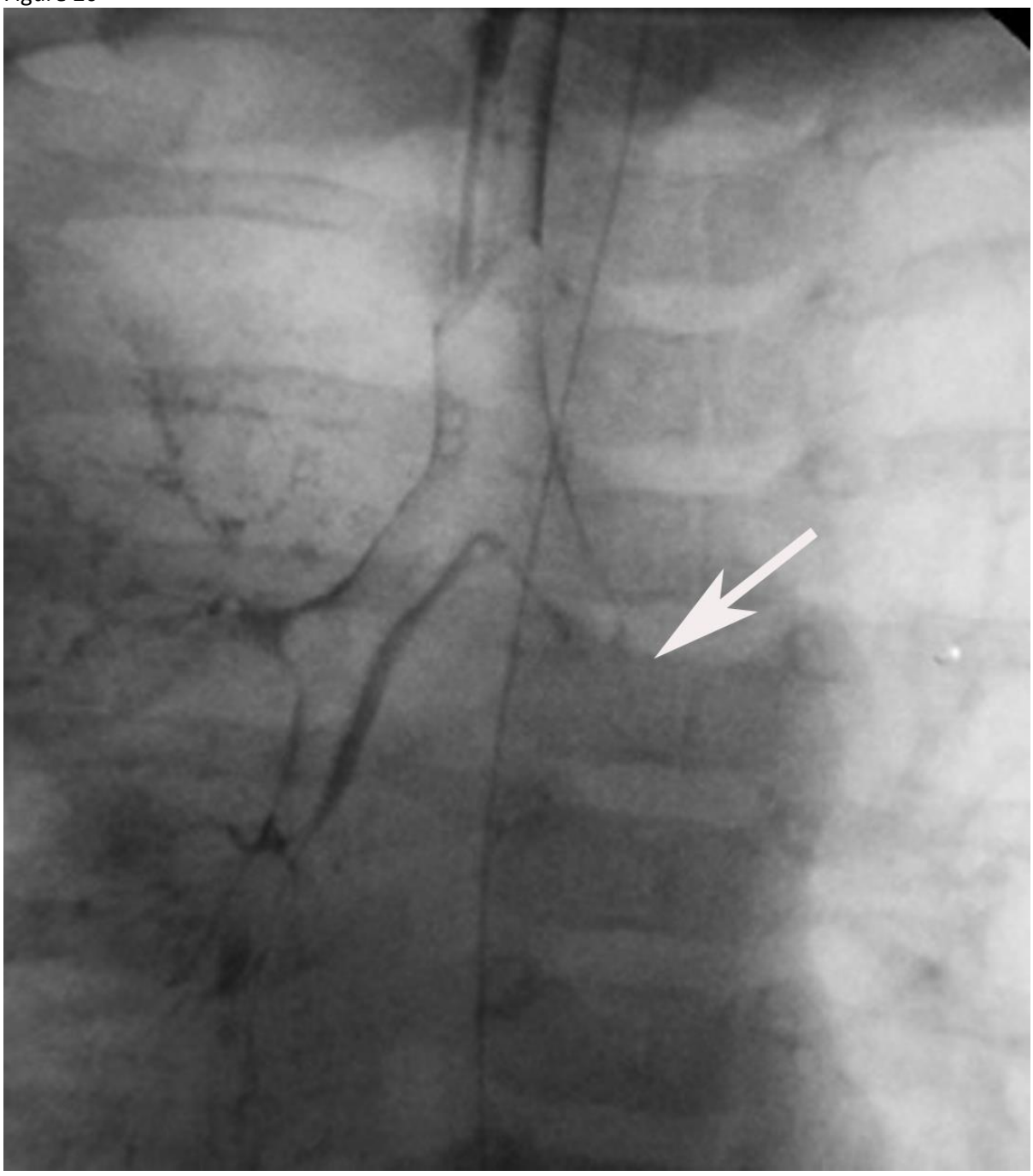
Bronchography image showing diffuse TBM in a 7 month old girl with 22q11 deletion, right aortic arch and an aberrant left subclavian artery. The tracheostomy tube has been withdrawn into the upper trachea.

Figure2b



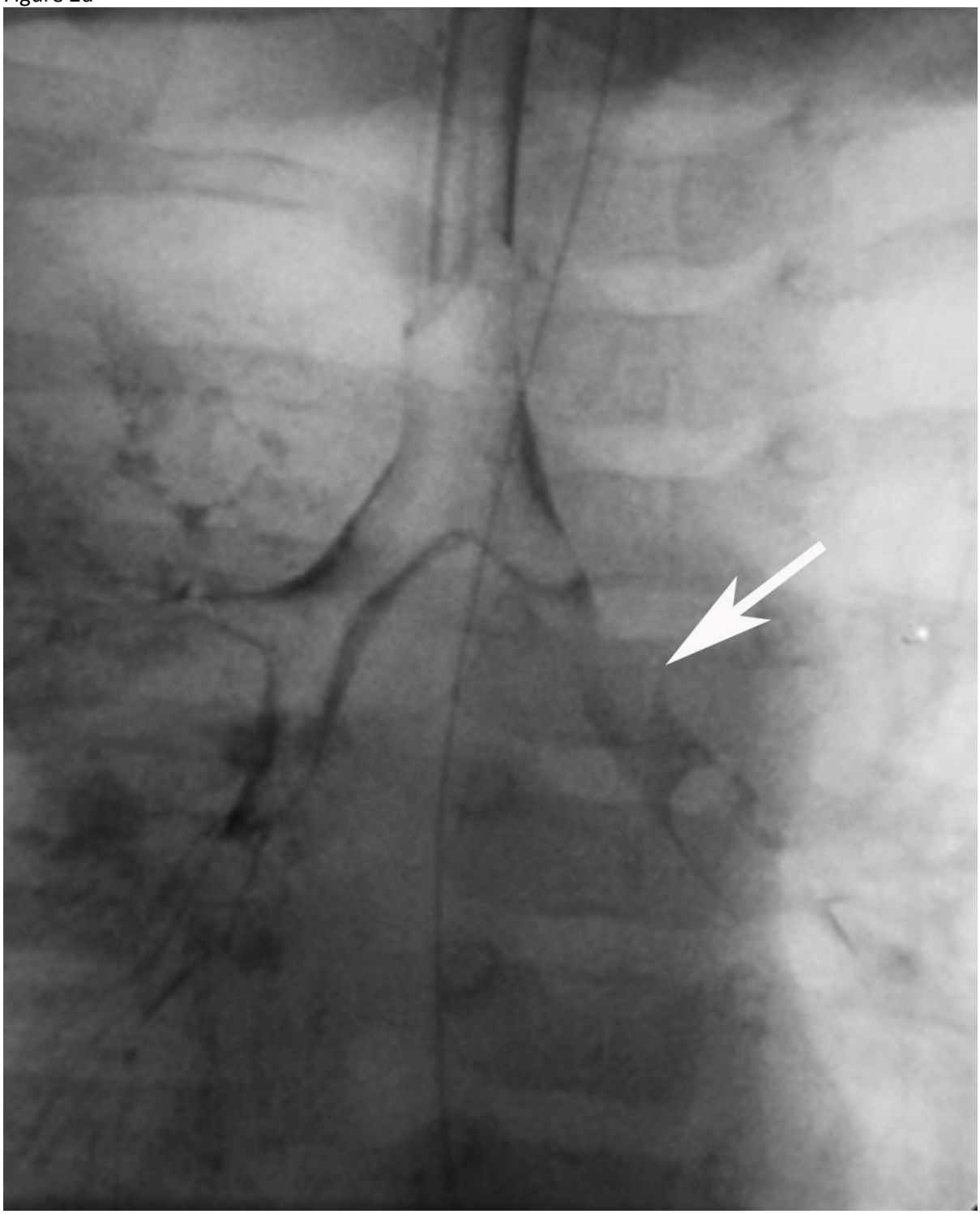
Bronchography image showing apposition of the anterior and posterior wall of the trachea (white arrow highlighting darker 2smudge" effect) in a one year old girl with TM related to vascular compression.

Figure 2c



5 month old girl with left pulmonary artery and vein hypoplasia with severe BM of the left main bronchus. Bronchography image showing complete collapse of the left main bronchus (white arrow).

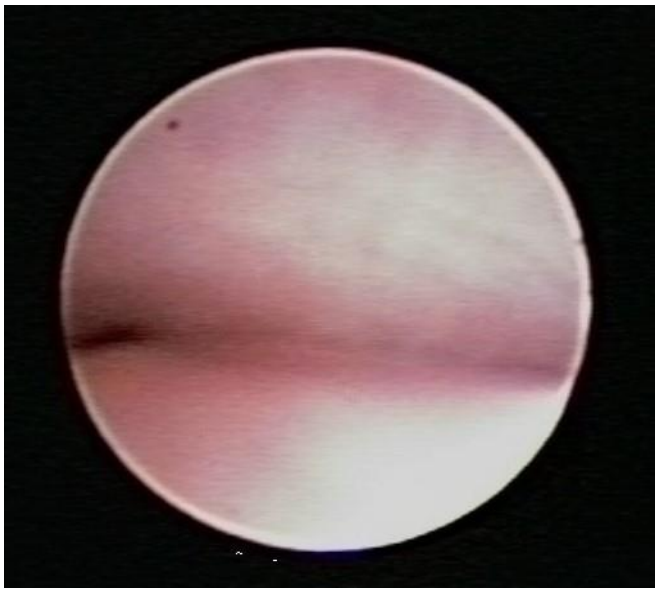
Figure 2d



Patient in Figure 2c where CPAP is now applied. Bronchography image showing some opening of the left main bronchus with additional CPAP (white arrow).

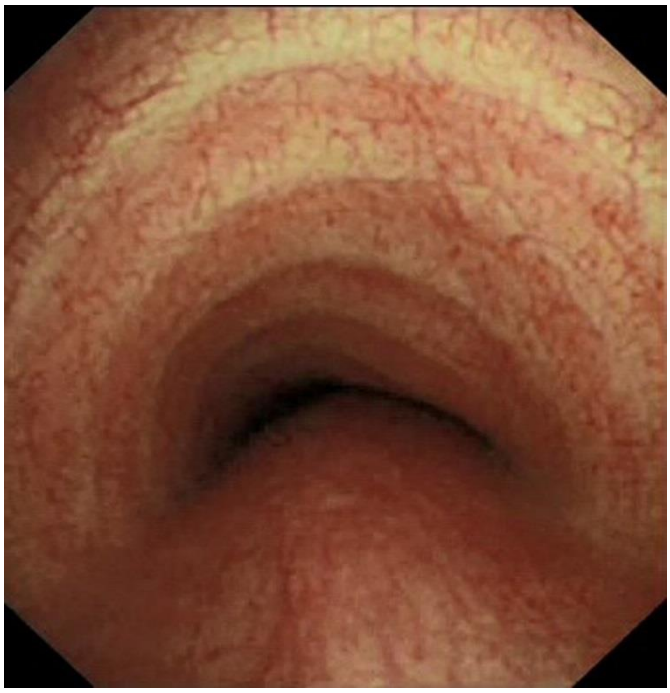
Figure 3 Bronchoscopic images

3a: Severe malacia affecting the carina and opening of both right and left bronchi



3b

Bronchoscopy image showing focal TM and predominantly posterior membrane collapse in a 15 year old boy with tracheo-oesophageal fistula and oesophageal atresia repaired at birth



3c. Severe malacia affecting the left main bonchus

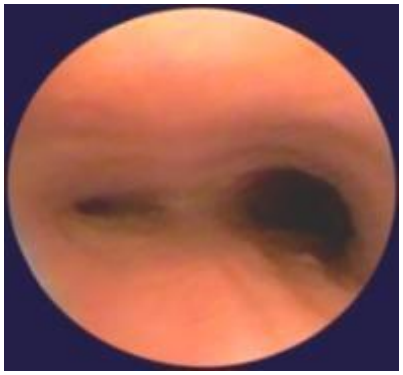


Figure 4

A self expanding stent inserted into the left main bronchus of the same child illustrated in Figure 2c and 2d with immediate relief of symptoms

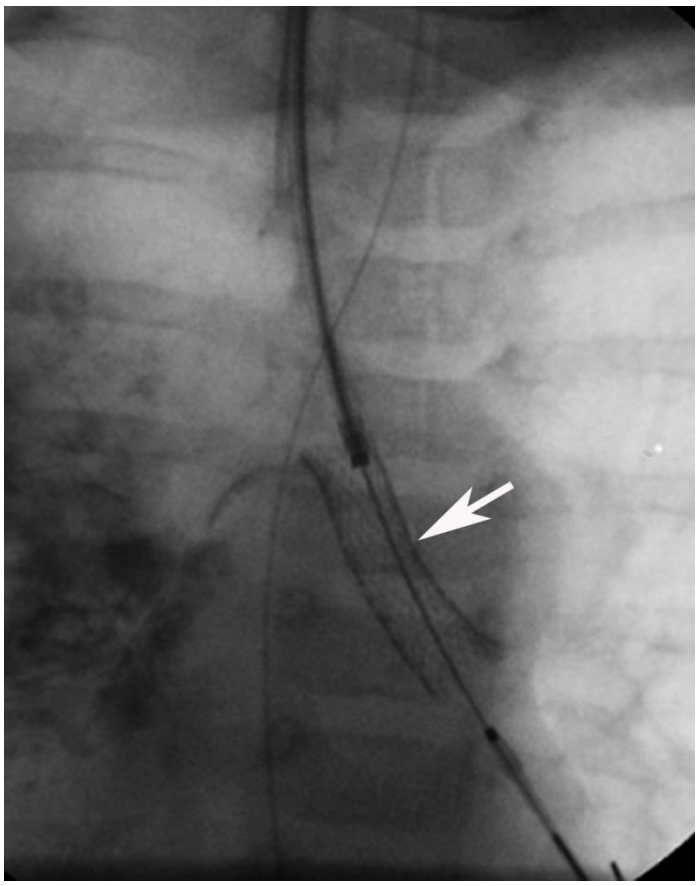
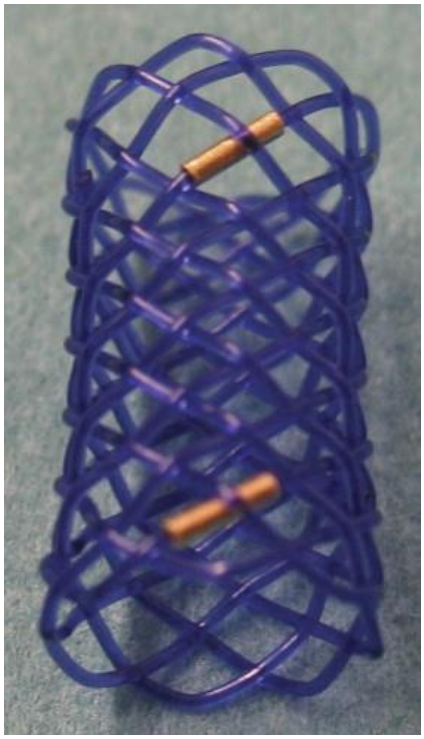


Figure 5: Biodegradable stents

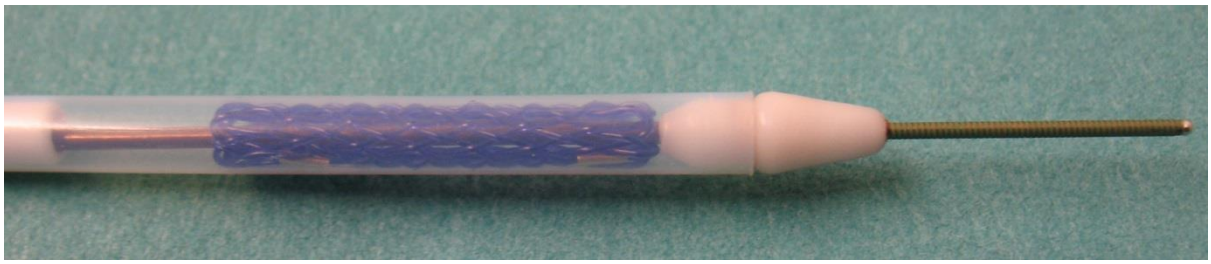
5a

A biodegradable stent



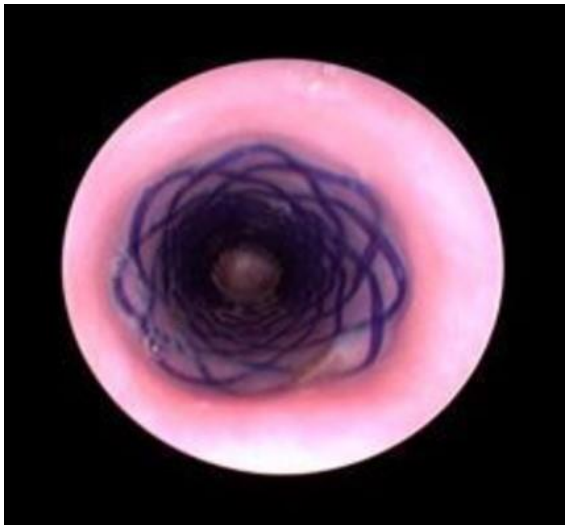
5b

Stent within introducer



5c

Bronchoscopic image of stent recently deployed



5d

Bronchoscopic image of biodegradable stent after 8 weeks placement with evidence of partial reabsorption showing an open lumen and mild granulation tissue formation.

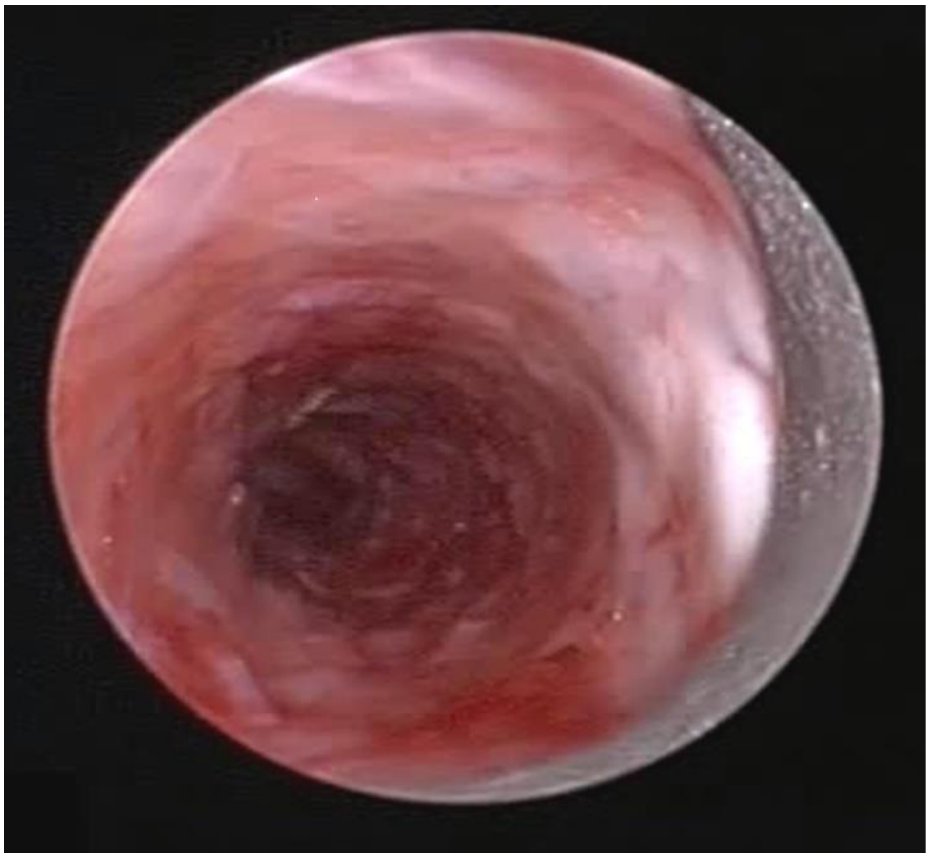


Table 1: Summary of causes of TM and BM and TBM

PRIMARY or CONGENITAL

CONGENITAL IDIOPATHIC
Idiopathic TM/BM (may be genetic factors)

CONGENITAL ABNORMALITIES OF THE CARTILAGE
Dyschondroplasia/chondromalacia/achondroplasia
Ehlers-Danlos syndrome
Marfan syndrome
Left bronchial isomerism with normal atrial arrangement

CONGENITAL ANOMALIES OF AERODIGESTIVE TRACT
Tracheoesophageal fistula
Esophageal atresia (with or without laryngeal cleft)

ANOMALIES OF RESPIRATORY TRACT DEVELOPMENT
Prematurity
Bronchopulmonary dysplasia

CONGENITAL SYNDROMES ASSOCIATED WITH TM/TBM
Mucopolysaccharidosis (Hurler syndrome, Hunter syndrome)
CHARGE syndrome
VATER anomaly
Trisomy 9
Trisomy 21
Cri du chat syndrome
Smith's syndrome
Opitz syndrome
Goldenhaar syndrome
Cotello's syndrome
Neurofibromatosis
Allagille's syndrome
Arthrogryposis
Atelosteogenesis type 1
Antley-Bixler syndrome; 11p13 deletion; 16p13.3 deletion; 22q11 deletion
18–22 translocation
Partial trisomy of long arms of chromosomes 11 and 22
Hallermann-Streiff syndrome
Pfeiffer syndrome
Blackfan-Diamond syndrome
Williams-Campbell syndrome
Kniest dysplasia
Diastrophic dysplasia
DiGeorge syndrome
Deletion of 12 q
Larsen syndrome and Larsen-like syndromes
Fryn's syndrome
Brachmann-de Lange syndrome
Camptomelic dysplasia
De la Chapelle dysplasia
Pierre-Robin syndrome
Crouzon syndrome
Noonans syndrome
Chitayat syndrome
Spondyloepiphyseal dysplasia congenital
Spondylocostal dysostosis
Late onset Pompe's disease
Loeys-Dietz syndrome
Filamin A mutation
Osteogenesis imperfect
Cariofaciocutaneous syndrome

SECONDARY OR ACQUIRED

CARDIOVASCULAR ANOMALIES ASSOCIATED WITH TM/BM

Double aortic arch
Abnormal take-off of the innominate artery
Pulmonary arterial sling
Right aortic arch
Aberrant right subclavian
Enlarged pulmonary veins
Left atrial hypertrophy
Enlarged left atrium
Tetralogy of Fallot with absent pulmonary valve syndrome
Left to right shunting leading to enlarged pulmonary arteries
Severe pulmonary artery hypertension
Dilated cardiomyopathy

SKELETAL ANOMALIES ASSOCIATED WITH TM/BM

Scoliosis
Pectus excavatum

INFECTIONS AND INFLAMMATORY PROCESSES ASSOCIATED WITH TM/TBM

Severe tracheobronchitis
Protracted bacterial bronchitis
Chronic suppurative lung disease, including cystic fibrosis, primary ciliary dyskinesia, other causes of bronchiectasis
Stevens-Johnson syndrome
Relapsing polychondritis

TRACHEOBRONCHIAL INJURY ASSOCIATED WITH TM/TBM

Button battery ingestion injury
Delayed removal of inhaled foreign body
Trauma

MEDICAL PROCEDURES AND SURGERY ASSOCIATED WITH TM/TBM

Prolonged intubation
Tracheostomy
Tracheo-oesophageal fistula repair
Laryngotracheal reconstruction
Tracheoplasty
Heart transplant
Fetal balloon insertion for congenital diaphragmatic hernia

TUMORS AND CYSTS ASSOCIATED WITH TM/TBM

Primary tracheal tumor
Teratomas
Thymoma
Goiter
Lymphatic malformation
Lymphoma
Neuroblastoma
Hemangiomas
Bronchogenic cysts
Enterogenous cysts
Cystic hygromas

Table 2. Common symptoms and signs of TM/BM in children.

Brassy or barking cough
Stridor
Wheezing
Noisy breathing
Recurrent and/or prolonged respiratory infections
Dying spells
Feeding difficulties
Dyspnoea

Table 3: Internal airway stents commonly used in children

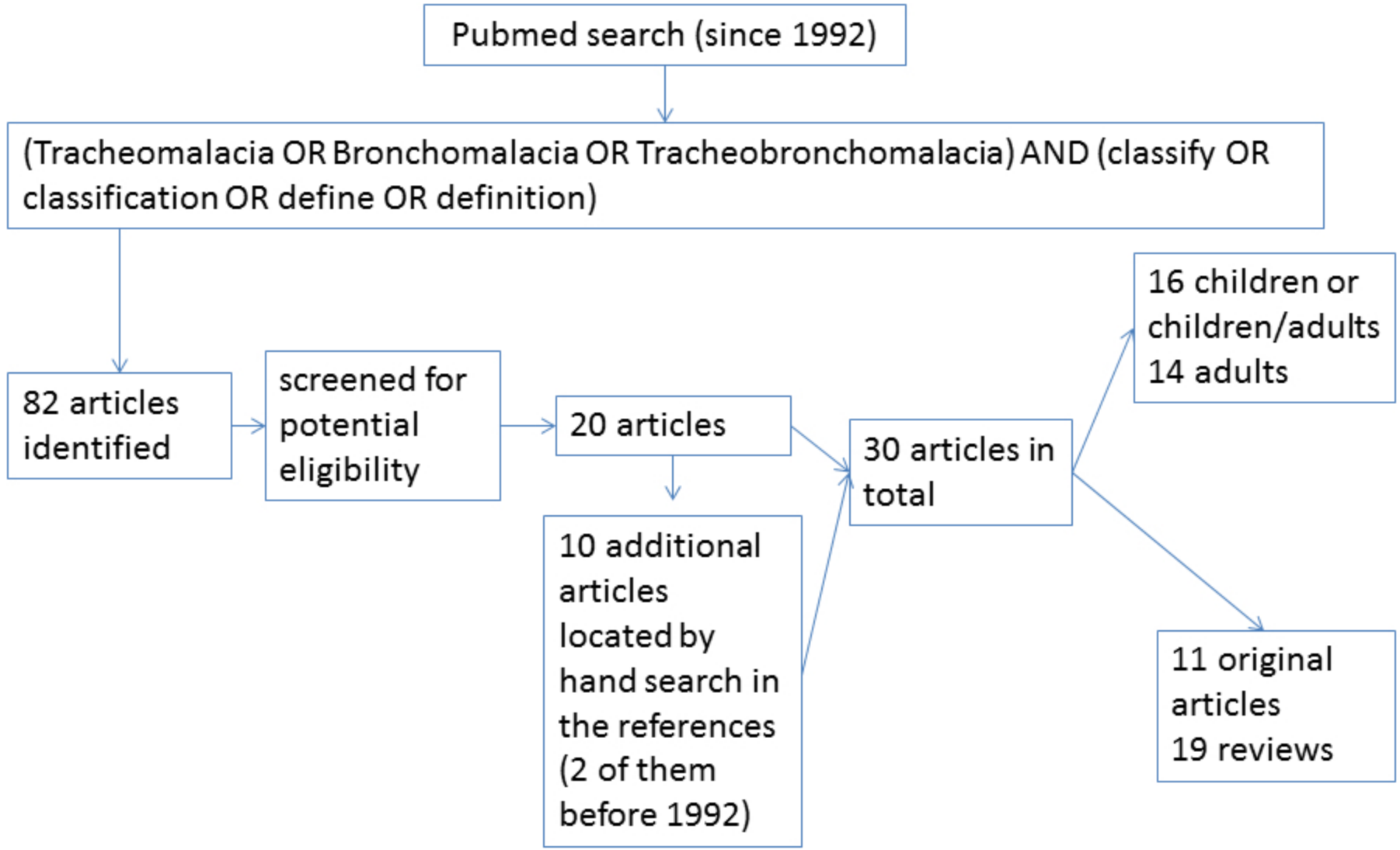
Stent type	**Characteristics**	**Advantages**	**Disadvantages**	**Typical indications**
Silicone (Dumon™)	Semi-rigid	Easier to remove	Prone to migration and/or blockage	Short duration use Palliative care
Silicone (Polyflex™) self-expanding	Flexible	Relatively easier to remove	Large delivery device Difficult to insert Prone to migration	Rarely used
Metal balloon-expandable	Rigid	Easy to insert Can be dilated with growth Much less prone to migration	Difficult to remove Prone to granulation May cause vascular erosion	Malacia secondary to tracheal surgery Isolated segment of malacia
Metal self-expanding	Flexible	Easy to insert May be safer if vascular compression is present	Very difficult to remove Cannot be dilated with growth	In nearly fully-grown child Vascular compression
Bioabsorbable self-expanding stent	Will reabsorb over 3 – 4 months	Can be custom-made for individual child Offers a temporary treatment option	May require serial stenting Expensive	"Proof of principle" before more definitive treatment Short-term support following tracheal surgery

Tracheomalacia and bronchomalacia in children (TF-2016-21)

TOPIC ALLOCATION July 2017. Key question numbers and final section headings

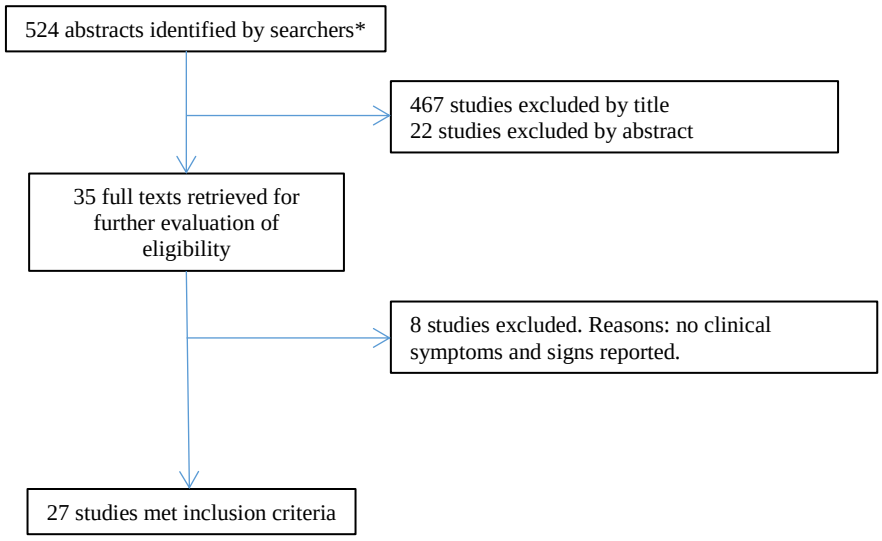
QUESTION AND FINAL TOPIC HEADING	RESPONSIBLE TF MEMBERS
1. What is the definition of tracheal (TM) and major bronchial malacia (BM) and what classifications of severity exist? INTRODUCTION	Deborah Snijders Kostas Douros
2. What are the causes of tracheo-bronchomalacia (TBM)? CONDITIONS ASSOCIATYED WITH TBM	Ahmad Kantar Andrew Bush
3. What is the spectrum of clinical presentation, severity and clinical course – to include any studies on the untreated natural history of this condition? CLINICAL SYMPTOMS AND SIGNS	Ernst Eber Rafaella Nenna
4a.In children suspected of having TBM, can pulmonary function tests be used to diagnose TBM 4b. In children with known TBM, what are the pulmonary function abnormalities ROLE OF LUNG FUNCTION	Ann Chang Ahmad Kantar
5. How do we use Imaging to diagnose TM & BM? [To include tracheobronchography] ROLE OF IMAGING	Efthymia Alexopoulou Derek Roebuck
6a. How do we use Bronchoscopy [rigid and flexible] to diagnose TM & BM? 6b. What influence does a general anaesthetic have on the diagnostic testing for TBM ROLE OF BRONCHOSCOPY	Fabio Midulla Kostas Douros
7. Which medical therapies have been suggested for the management of TBM and co-morbidities [e.g. wheezing, endobronchial infection, atelectasis?] MEDICAL THERAPIES	Jayesh Bhatt Andrew Bush
8. What is the role for respiratory physiotherapy? PHYSIOTHERAPY	Anna-Maria Charatsi Julie Depiazzi
9. How and when should we treat TM & BM by internal stenting? SURGERY INCLUDING STENTING	Derek Roebuck Juan Anton-Pacheco
10. What surgical strategies have been suggested for the management of TBM – eg aortopexy, tracheopexy, external splints, tracheal resection, tracheostomy. SURGERY INCLUDING STENTING	Juan Anton-Pacheco
11. What is the indication for long term ventilatory support either by tracheostomy or non-invasive interface and what ventilator strategies have been trialled? VENTILATORY SUPPORT	Mark Everard Ian Brent Masters
12. What is the parent and patient perspective? PARENT AND PATIENT PERSPECTIVE	Courtney Coleman Barbara Johnson

PRISMA for question 1 and 2



PRISMA: QUESTION 3

Clinical Symptoms and Signs



***Keywords:**

(tracheomalacia or bronchomalacia) and (symptoms or "clinical presentation" or "severity" or "clinical course" or “natural history”)

Limited to:

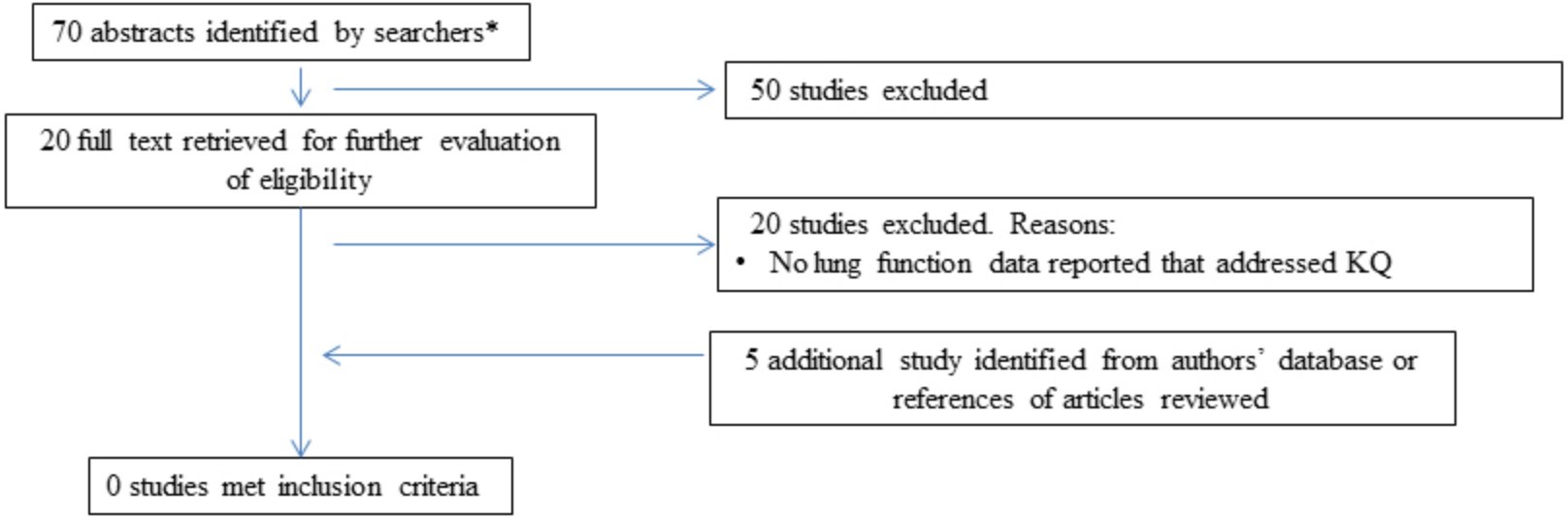
Publication dates: from 01/01/1997 to 01/06/2017

Species: Humans

Languages: English

Figure 4a: Selection of studies that addressed key question (KQ) 4

4a.In children suspected of having TBM, can pulmonary function tests be used to diagnose TBM

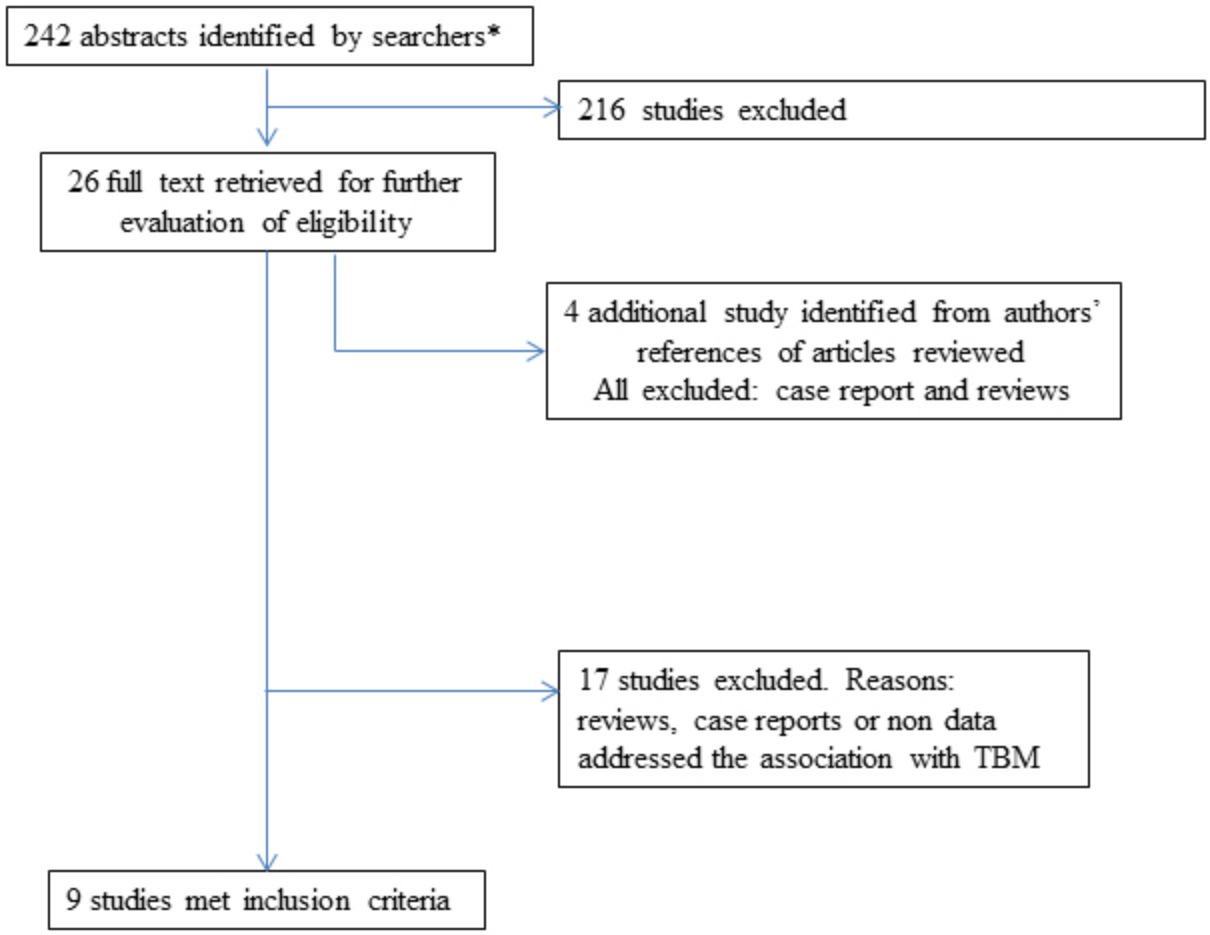


Search on Pubmed (3rd Aug 2017)

("tracheomalacia"[MeSH Terms] OR "tracheomalacia"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) AND ("respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields])

PRISMA FOR QUESTION 4B

In children with known TBM, what are the pulmonary function abnormalities

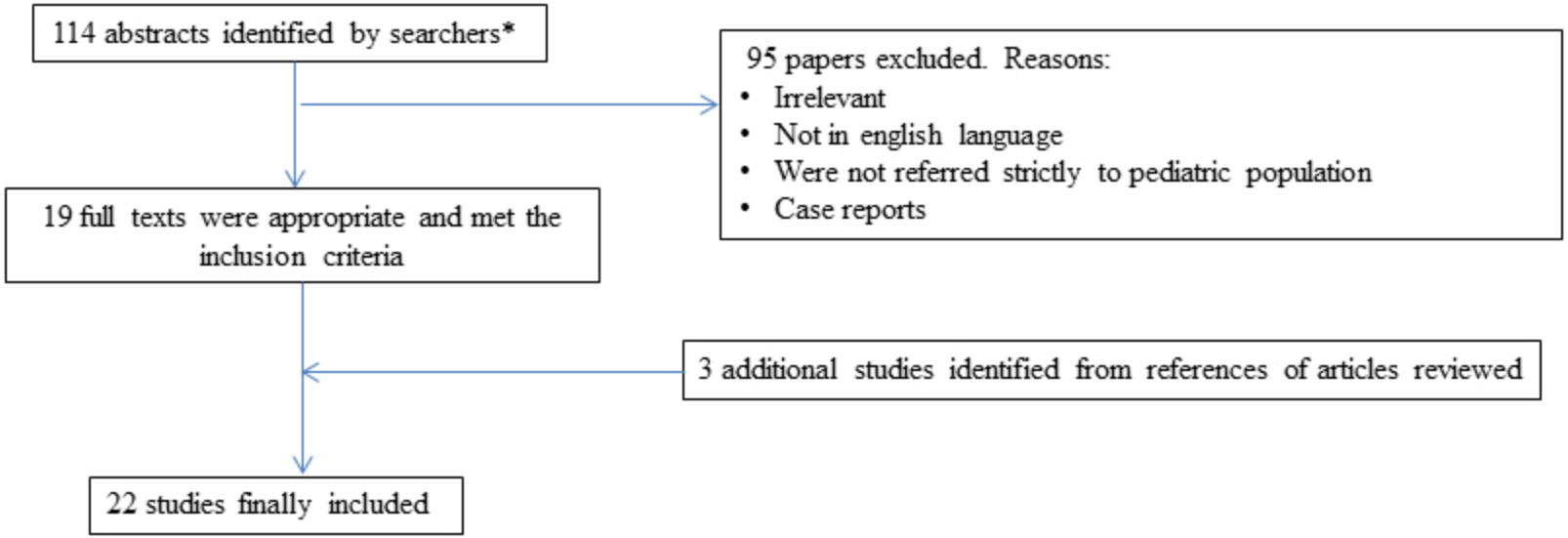


Search on Pubmed (3rd Aug 2017)

("tracheomalacia"[MeSH Terms] OR "tracheomalacia"[All Fields]) OR ("bronchomalacia"[MeSH Terms] OR "bronchomalacia"[All Fields]) OR ("tracheobronchomalacia"[MeSH Terms] OR "tracheobronchomalacia"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) AND "infant"[MeSH Terms] OR ("infant"[All Fields]

Selection of studies that addressed key question (KQ) 5

5.How do we use Imaging to diagnose TM & BM? [To include tracheobronchography]



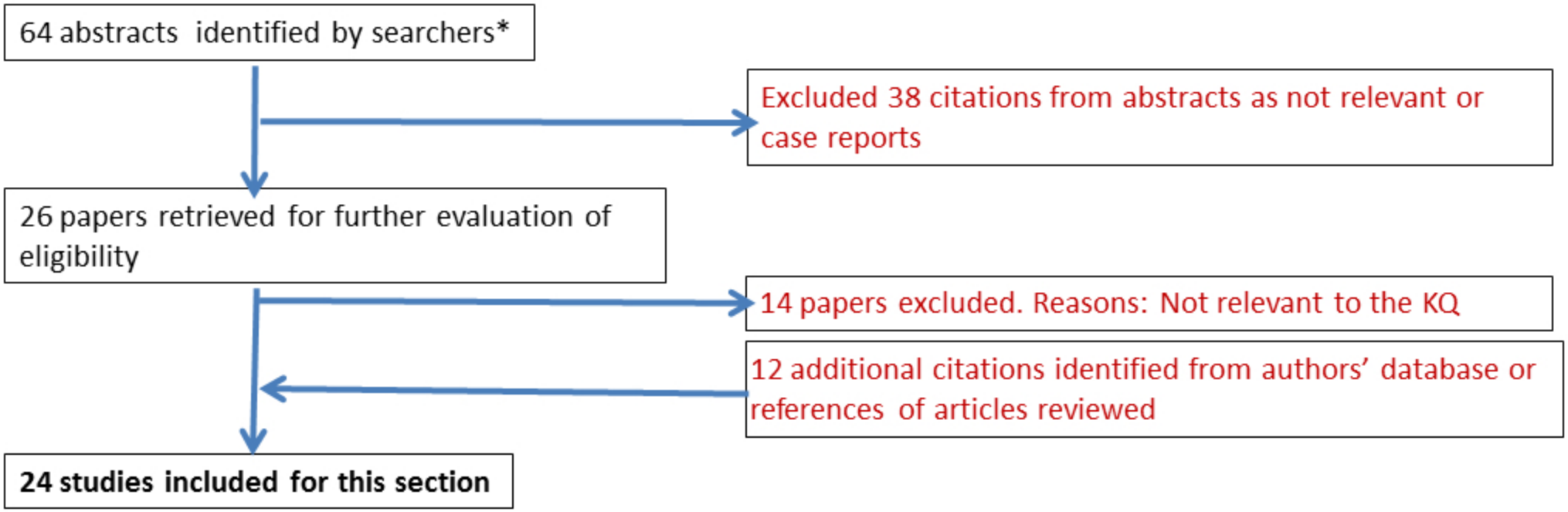
*Search on PubMed (1/1/1997 – 26/8/2017), all the type of articles:

Keywords:

All the possible combinations of: TRACHEOMALACIA, BRONCHOMALACIA, IMAGING, CHILDREN, PEDIATRIC, CT, CT SCAN, MRI, FLUOROSCOPY, RADIOLOGY, BRONCHOGRAPHY

PRISMA QUESTION 7

Which **medical therapies** have been suggested for the management of **TBM and co-morbidities** [e.g. wheezing, endobronchial infection, atelectasis?]



Search on Pubmed (10th August 2017)

("tracheomalacia"[MeSH Terms] OR "tracheomalacia"[All Fields]) ("tracheobronchomalacia [MeSH Terms] OR "tracheobronchomalacia"[All Fields])" AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields]) AND ("symptoms"[MeSH Terms] OR ("treatment"[All Fields]

=320 items

Filters activated: Publication date from 1997/01/01 to 2017/12/31, Humans, English.

= 241 items

Excluded:

Diagnosis

Respiratory physiotherapy

Internal stenting

Surgical strategies eg aortopexy, tracheopexy, external splints, tracheal resection, tracheostomy

Long term ventilatory support either by tracheostomy or non-invasive interface

Adults

= 177 excluded

PRISMA QUESTION 8 - PHYSIOTHERAPY

Search terms

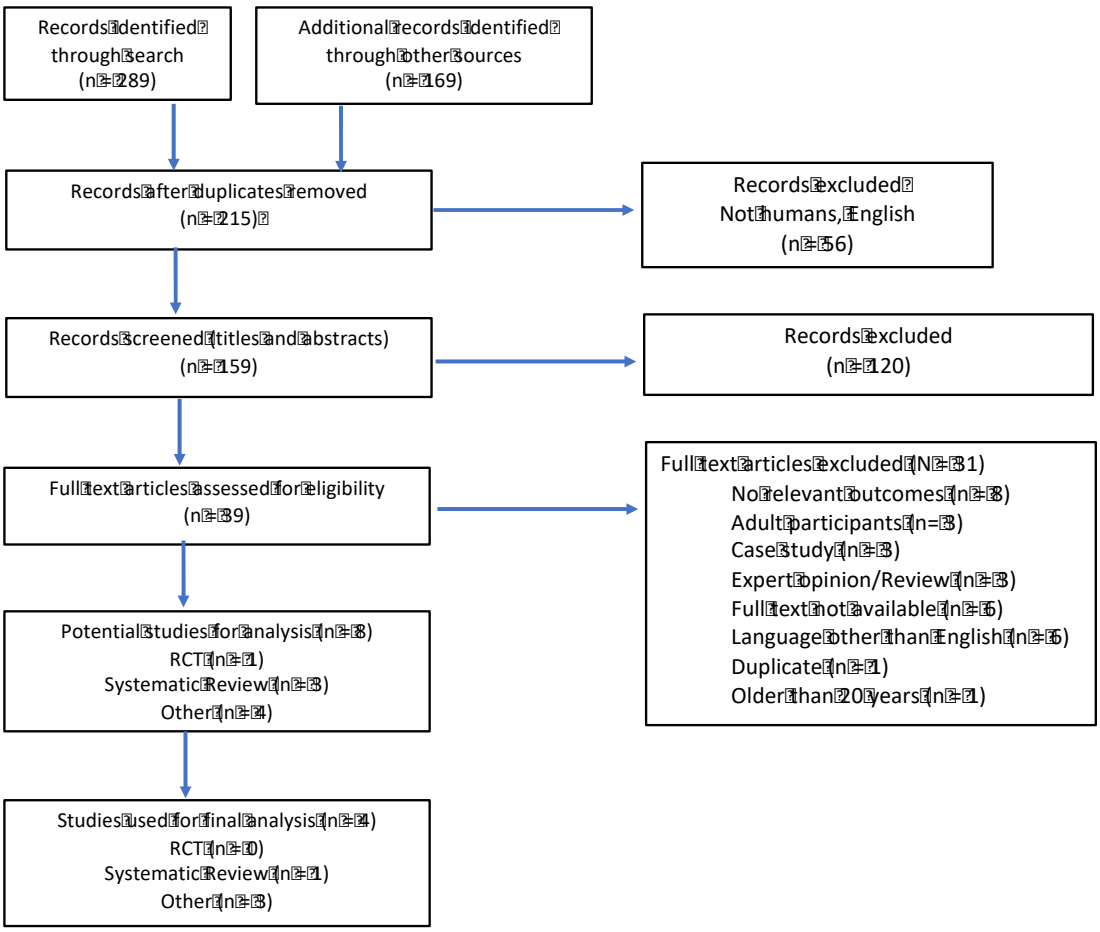
Tracheomalacia OR bronchomalacia OR tracheobronchomalacia OR malacia OR tracheal abnormalities OR tracheal diseases

AND

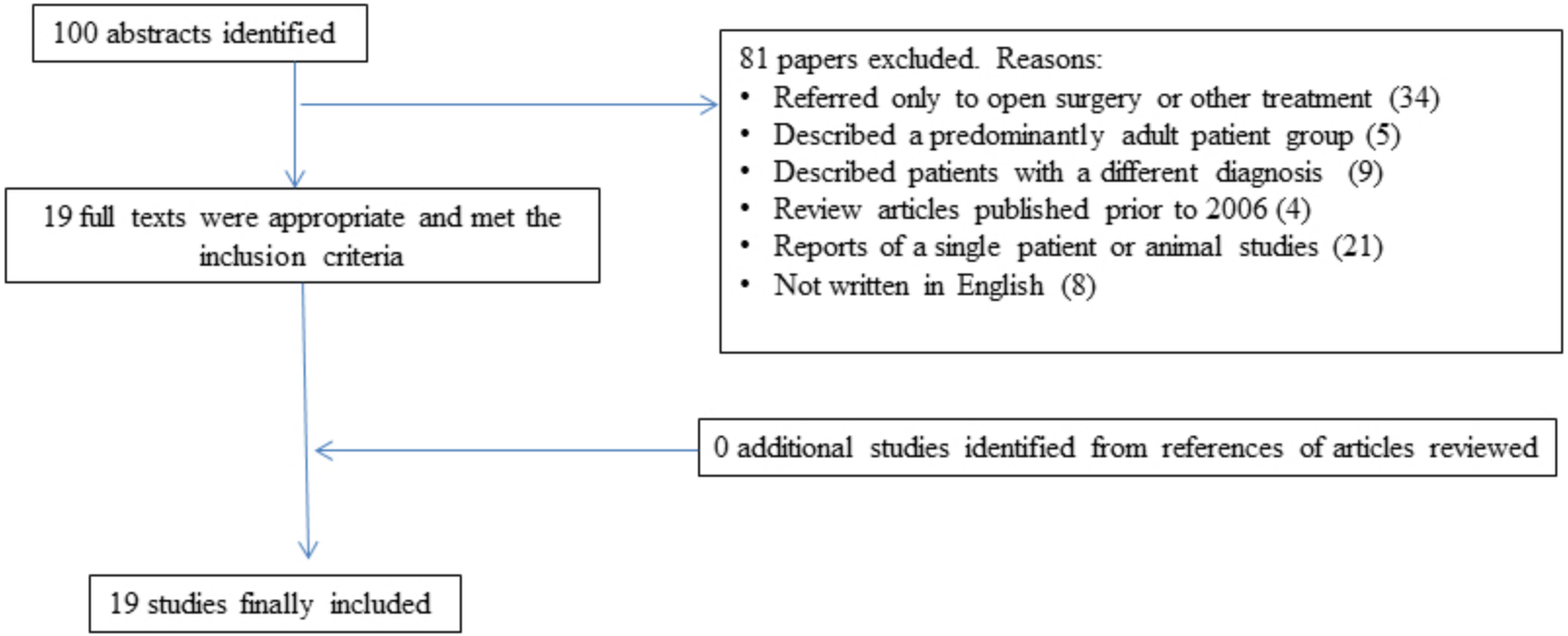
Physiotherapy OR physical therapy OR physical therapy modalities OR airway clearance OR positive pressure and physiotherapy

Exercise tolerance OR exercise therapy

Administration inhalation OR nebulisation OR saline solution hypertonic OR deoxyribonuclease I OR nebulised dornase alfa OR nebulised hypertonic saline



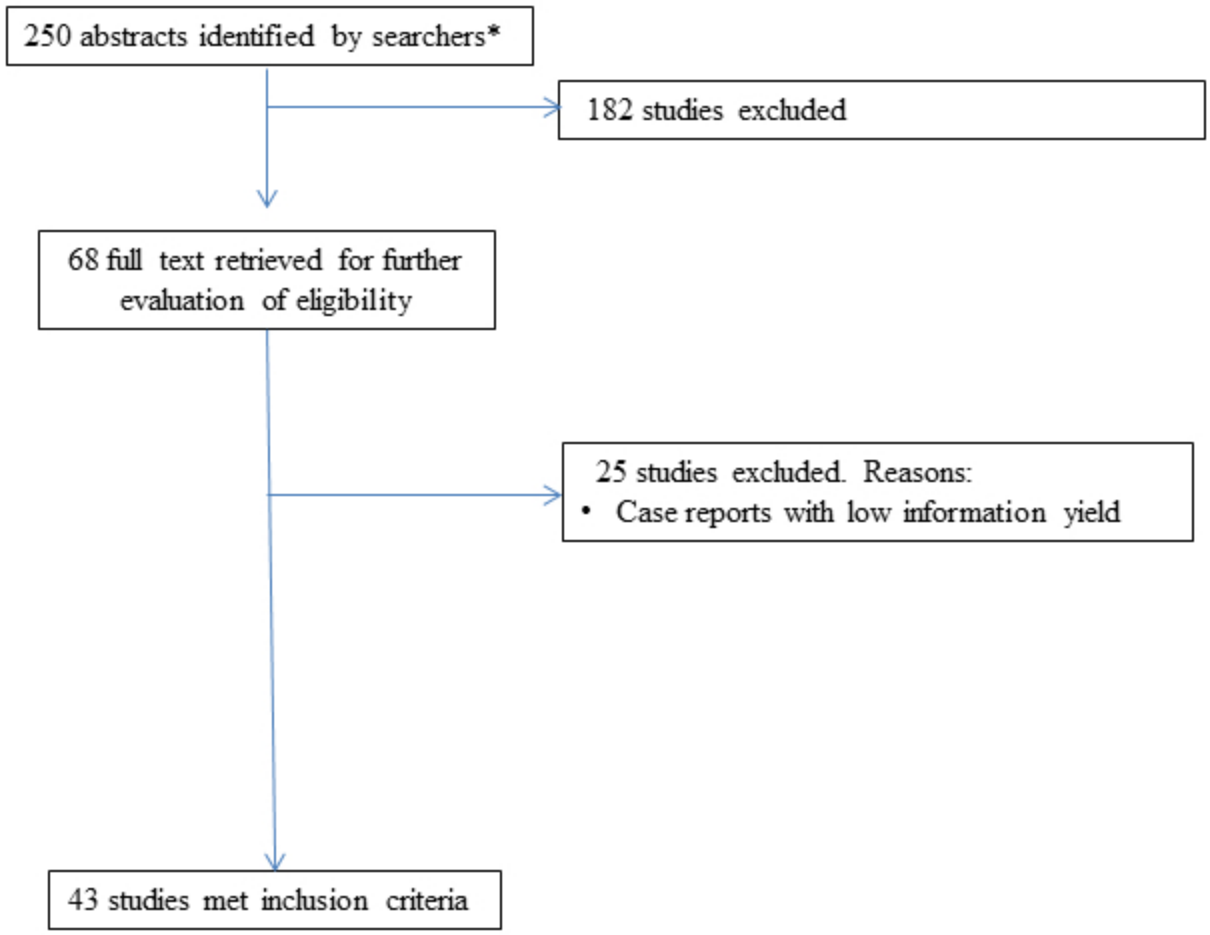
PRISMA. QUESTION 9: STENTS



Search on PubMed 30-06-2018

PubMed search: (tracheomalacia OR tracheobronchomalacia OR bronchomalacia) AND stent
limits: age 0-18 years

PRISMA for question 10:
What surgical strategies have been suggested for the management of TBM



Search on Pubmed and Embase (September 2017)

"tracheomalacia/surgery"[MeSH Terms] OR "bronchomalacia/surgery"[MeSH) AND ("child"[MeSH Terms] OR "infant" (MeSH) OR "adolescent"[MeSH] OR "children"[All Fields]) AND ("aortopexy OR tracheopexy OR external splint OR tracheal resection OR Tracheostomy" [MeSH Terms] OR the combination of the above items.

Question 3: Clinical Symptoms and Signs

1st author, publication year	Setting; Study design	Inclusion criteria; Exclusion or definitions	Description of cohort	Main aim(s) of study	Primary findings relating to KQ	Main study limitation	Method of confirmation of TBM and type
Adil 2012	Tertiary referral centre; retro-spective	130 consecutive preterm and term infants with laryngomalacia, as diagnosed by airway endoscopy between June 2004 and August 2009	TM: 25 infants	1 "to identify the most common area(s) of supraglottic collapse" 2 "to compare airway findings in term and preterm infants" 3 "to evaluate the incidence of secondary airway lesions"	19% of infants with laryngomalacia had TM	Retrospective study; different methods of confirmation of TM	Fluoroscopy and/or direct laryngoscopy and bronchoscopy under general anaesthesia
Boogaard 2005	Tertiary referral centre; retro-spective	All flexible bronchoscopies performed between 1997 and 2004 (n=512); malacia defined as collapse of at least 50% of the airway lumen, during expiration, cough or spontaneous breathing, or a ratio of cartilage to membranous wall area of < 3:1.	TM: 63 children; TBM: 49 children; BM: 24 children	1 "to estimate the incidence of primary airway malacia in the general population" 2 "to estimate the predictive value of clinical diagnosis of malacia by paediatric pulmonologists" 3 "to characterise the presenting symptoms and findings in patients diagnosed with primary airway malacia"	Types of symptoms and clinical features	Retrospective study	Flexible bronchoscopy under general anaesthesia; airway malacia was diagnosed by visual inspection of airway shape and dynamics during spontaneous breathing without positive endexpiratory pressure, or during coughing.
Carden 2005	Review	TM and TBM in children and adults	NA	"a comprehensive review of both the adult and paediatric forms of the disease" and "review of the various modalities that are used for diagnosis as well as the state	Types of symptoms, severity, natural history	NA	NA

				of the art of treatment"			
Choo 2013	Review	Tracheomalacia/ Tracheobroncho-malacia and hyperdynamic airway collapse	NA	NA	Types of symptoms, severity, natural history	Adult literature	NA
Dessoffy 2013	Retro-spective	236 children with achondroplasia, who were initially assessed between 1985 and 2012	9 children with TM or TBM	1 "to establish the frequency of airway malacia in a cohort of children with achondroplasia" 2 "to assess its interactions with other known breathing abnormalities in these individuals"	4% of children with achondroplasia had TM or TBM	Retrospective study; different methods of confirmation of TM or TBM	Airway endoscopy or clinical examination
Doshi 2007	Case report	NA	NA	To describe symptoms of TM in an infant	Types of symptoms	Case report	Bronchoscopy
Finder 1996	Retro-spective	Patients with primary BM	17 children (age at diagnosis of BM: 3 months-17 years)	"to determine the natural history of primary BM in infants and children"	Natural history	Retrospective study	Bronchoscopy under light sedation?
Fraga 2016	Review	Primary (congenital) and secondary (acquired) TM and TBM	NA	NA	Time of onset and types of symptoms, severity	NA	NA
Hiebert 2016	Systematic review and meta-analysis	Articles addressing bronchoscopy in children with recurrent croup	11 articles reviewed; 5 articles (455 patients) included in meta-analysis	1. "to identify risk factors that may predict clinically significant findings on bronchoscopy in children with recurrent croup" 2. "to note the frequency of bronchoscopy findings in general"	TBM in 4.6% of children with recurrent croup	Heterogeneity between studies and lack of specificity in patient reporting. Selection bias of the patients.	Bronchoscopy
Hysinger	Review	Focus on TM	NA	1. "to distinguish congenital	Types of symptoms, natural	NA	NA

2015				TM from acquired TM"; 2. "to define respiratory mechanics that affect airway compliance"; 3. "to describe the formation and maturation of the paediatric central airway"; 4. "to describe advantages and disadvantages of the various methods of diagnosing paediatric TM"; 5. "to understand the current available treatment strategies for paediatric TM"	history, associated diseases		
Javia 2016	Review	Congenital/primary and acquired/secondary TM	Neonates	NA	Types of symptoms and clinical features, associated conditions	NA	NA
Keng 2017	Case report	NA	83-year-old woman	NA	Delayed onset of symptoms	Case report, adult patient	NA
Kompare 2012	Retro-spective, specialty clinic	Incl: <60 months of age with cough, wheeze, and/or noisy breathing present for at least 1 month without other diagnoses for whom BAL cultures grew at least 10^4 cfu/mL of a specific organism Excl: asthma, CF, and other chronic diseases TM or BM	70 children	"to examine associated findings and clinical outcome in young children with prolonged cough, wheeze, and/or noisy breathing in whom high colony counts of potentially pathogenic bacteria were cultured from bronchoalveolar lavage (BAL) during diagnostic flexible fibreoptic bronchoscopy"	TM in 20%, BM in 43% and TBM in 11% of patients with protracted bacterial bronchitis	Retrospective study, no control group	Flexible bronchoscopy using topical lidocaine and intravenous procedural sedation

		diagnosed when segmental collapse such that the airway narrowed to a slit during expiration in the absence of suction through the bronchoscope's channel.					
Kugler 2013	Review	TM in children and adults	NA	NA	Types of symptoms	NA	NA
Maeda 2017	Review	TM in children	NA	"to present the technical aspects of diagnosis and treatment of the most common paediatric airway disorders"	Types of symptoms	NA	NA
Masters 2002	Tertiary referral centre; observational study	Children with the endoscopic diagnosis of laryngomalacia, TM or TBM; TM defined as "a membranosa deformity in the trachea" BM defined as "an appearance of deformity in the large right or left main-stem bronchi, and/or their respective divisions at the lobar or segmental	299 children with malacia disorders	1. "to describe an extensive experience of various forms of laryngomalacia, tracheomalacia, and bronchomalacia" 2. "to explore some of the interrelationships that exist between these conditions with respect to their anatomical sites and associations"	Types of symptoms and clinical features, associated conditions	No detailed description of symptoms and signs	Flexible bronchoscopy during spontaneous breathing under gaseous general anaesthesia

		level.					
Masters 2008	Tertiary referral centre; case-control study	Children with chronic respiratory symptoms of cough, stridor, or wheeze present for >3 weeks that underwent bronchoscopy Malacia defined as a deformity of the airway recorded at the end-expiratory point	Cases: 81 children (0.2-12.4 years) Controls: 35 children (0.2-17.3 years)	"to prospectively examine the relationship between site and size of lesions with their respiratory symptoms and illness frequency"	Children with malacia have an increased likelihood of respiratory illness frequency, severity, significant cough, and tendency for delayed recovery. Neither the site nor the severity of malacia exhibited any significant dose effect on respiratory illness profiles.	Sample size	Bronchoscopy with spontaneously breathing oxygen and sevoflurane general anaesthesia
McNamara 2004	Review	Primary and secondary TM	NA	NA	Types of symptoms and clinical features, natural history	NA	NA
Peh 2006	Case report	NA	4-week-old infant	NA	Delayed onset of symptoms	Case report	Bronchoscopy
Peters 2005	Case report and review	NA	20-month-old boy	"to discuss the differential diagnosis and clinical evaluation, and propose a new pathophysiological mechanism by which obstructive sleep apnea causes TM"	Types of symptoms and clinical features	Case report	Bronchoscopy
Rohde 2005	Case report	NA	15-month-old boy	"to stress the importance of considering laryngo-tracheo-bronchomalacia as a cause of death in infancy and early childhood"	Types of symptoms	Case report	Autopsy
Santiago-Burruchaga 2014	Retro-spective case-control	Incl: Children with recurrent pneumonia, chronic wet or	Cases: 62 children (12-144 months) Controls: 29	1. "to describe the bronchoscopic changes in children with recurrent lower airways infection"	Airway malacia in 52% of children with recurrent lower airway infection	Retrospective study; control group not normal healthy	Bronchoscopy on spontaneous breathing under sedation-analgesia

	cohorts study	productive cough, persistent atelectasis, or bronchiectasis Excl: Bronchopulmonary dysplasia, prematurity, difficult to control asthma, CF, immunodeficiency, genetic syndromes, neuromuscular, CNS or heart disease, airways or digestive tract malformations, severe scoliosis, protracted endotracheal intubation, tracheotomia or endobronchial aspiration syndrome Airway malacia considered to be present when >50% dynamic collapse of the airways lumen during expiration on spontaneous breathing or during cough,	children (5-168 months)	2. “to investigate the prevalence of lower airway malacia” 3. “to assess their prevalence in a control group without recurrent lower airways infection”		children	and local anaesthesia

		without suctioning					
Snijders 2015	Review	Congenital and acquired TM	NA	"to provide an update on diagnosis of TM in children"	Types of symptoms and clinical features	NA	NA
Vicencio 2006	Short review	TM	NA	NA	Types of symptoms and clinical features	NA	NA
Weinberger 2007	Review	TM	NA	"to increase awareness of common and uncommon entities that have resulted in inappropriate diagnoses of asthma"	Causes of cough in children with TM	NA	NA
Yalcin 2005	Tertiary referral centre; retro-spective	Incl: Patients with chronic respiratory symptoms who underwent bronchoscopy between February 1999 and November 2003. Excl: Asthma, cystic fibrosis TM defined as an appearance of deformity and narrowing of the trachea's cross-sectional area by, at least, more than 25% on expiration; BM defined as an appearance of deformity in the right or left main	34 children with TM and/or BM	1. "to review experience with flexible bronchoscopy for the assessment of TM and BM in children who presented with chronic respiratory problems" 2. "to evaluate their clinical and radiological characteristics and their association with other disorders"	Clinical presentation, associated disorders	Retrospective study	Bronchoscopy under mild sedation and topical anaesthesia

		bronchi, and/or their divisions at the lobar and segmental levels, and narrowing of their cross-sectional areas by, at least, more than 25% on expiration					
Zgherea 2012	Tertiary referral centre; retro-spective	Incl: Children with wet cough of more than 4 weeks' duration, unresponsive to therapy, referred for bronchoscopy Excl: Cystic fibrosis, primary ciliary dyskinesia, immunodeficiency syndromes, genetic syndromes, major airway abnormalities, muscle weakness, neurologic disorders, aspiration, asthma TM defined as collapse of at least 50% of the tracheal lumen during expiration	197 children	1. "to determine the frequency of lower respiratory tract bacterial infections in children with wet cough" 2. "to analyse the bronchoscopic findings in these children"	9 (14.1%) of children with purulent bronchitis and 6 (13.3%) of children with nonpurulent bronchitis had TM	Retrospective study; no reliable data on the prevalence of certain comorbidities; symptoms of children with TM not provided	Flexible bronchoscopy under light sedation

NA, not applicable;

LITERATURE REVIEW: QUESTION 4B

KQ 4b: In children with known TBM, what are the pulmonary function abnormalities?

1st author, publication year	Setting; Study design	Inclusion criteria; Exclusion or definitions	Description of cohort	Main aim(s) of study	Primary findings relating to KQ	Main study limitation	Method of confirmation of TBM and type
Abdel 2007	Retro-spective	Incl: children with TM who had aortopexy Excl: aortic arch anomalies; TM not defined	N=20 mean age=29-mo (range 0.25, 11 years)	"Assess the efficacy of aortopexy in the long term, the clinical results and respiratory function…"	Tidal expiratory flow values (TEF25%); median of cohort estimated at 66.5 %pred (range 15, 103)	Data was estimated from the graph provided. No other PFT data provided	Flexible bronchoscopy, spontaneous breathing
Beardsmore 1994	Cohort	Incl; children with esophageal atresia-tracheoesophageal fistula presenting to surgical service; TM not defined	16 children in cohort but only 3 had TM confirmed	1. "Assess the relationship between clinical findings and respiratory function in infants following repairs of esophageal atresia-tracheoesophageal fistula; 2. Determine the value of respiratory function tests in elucidating mechanisms of respiratory disturbances and in predicting clinical outcome"	Increased (>2 z-score) total gas volume in 2 of the 3 children; Increased total airway resistance in 2 of the 3 children	TM undefined	In one child, endoscopic confirmation mentioned; other 2 method not described
Boogaard 2005	Cross section	TM="collapse of at least 50% of the airway lumen, during expiration, cough or spontaneous breathing, or a ratio of cartilage to membranous wall area of < 3:1"	45 of the 115 children with TM had PFT. Mean age of this group not described	1. Estimate the incidence of primary TBM 2. Estimate the predictive value of a clinical diagnosis of TBM by pediatric pulmonologists 3. Characterize symptoms and findings in patients with primary TBM	Mean % pred (SD) FVC=99.3 (15.9) FEV_1=91.5 (19.9) FEV_1/FVC=87.7 (14.2) PEF=74.7 (19.4) MEF_{25}=62.2 (31.3) Pre and post broncho-dilation undertaken in 35, all values showed increased in mean values but no significant change	Proportion with FVC and FEV_1 abnormality not provided	Flexible bronchoscopy; primary TM

Davis 1998	Cross section	TM=50% tracheal narrowing at bronchoscopy	6 infants (3-10 mo old) with moderate to severe TM; Controls: 2-12 mo old	In children with TM, to determine whether the increase in V'max FRC with CPAP could be explained by the increase in FRC with CPAP (0, 4, 8 cm H_20)	<u>Children with TM</u> Mean FVC=104%pred (SD 10) Mean V'50=56%pred (SD 18) Mean V'75=53%pred (SD 17) <u>Controls</u> Mean FVC=93%pred (SD 21) Mean V'50=112%pred (28) Mean V'75=108%pred (23)		Bronchoscopy (type undefined)
Johnston 1980	Pre, post Sx, Case study	NA; TM undefined	Child with R ligamentum arteriosum, L aortic arch, R descending aorta	To study animal model of tracheomalacia and describe 2 children with symptomatic TM	After stenting- expiratory total pulmonary resistance decreased by 104%; inspiratory equivalent changed by 1% (PFT at ~18 mo)	2 children but only 1 with PFT data. Child also had VSD and tracheostomy decannulated after TM stented	Bronchoscopy (type unspecified); vascular ring divided at 3-mo followed by external rib stent over TM at 12 mo
Moore 2012	Cross section	Incl: Children with TBM (21 of 66 invited participated Excl: laryngomalacia; TM undefined	19 children; median age 9.4 years (range 7.6–14.3)	To determine "whether children with TBM have persisting respiratory symptoms and/or definable abnormalities of lung function on long-term follow-up"	Mean %pred (95%CI), no abnormal in cohort FEV_1=81% (72, 91), 7 FVC=96% (87, 105), 4 FEV_1/FVC%=73 (67, 78), 13 FEF_{25-75}=54% (43, 64), 15 PEF=60% (49, 70), 14 Classical TBM flow-volume loop seen in 4 (22%) Mannitol challenge negative in 13 of 15 (93%); 1 of 2 had significant bronchodilator responsiveness		Flexible bronchoscopy
Olbers 2015	Cross section	Inclusion: children born with esophageal atresia who have reached aged 7 years; TM undefined	Group of 13 of 26 children who had TM	1. Assess the prevalence of respiratory morbidity in children born with esophageal atresia 2. Examine the cause this morbidity using pulmonary and esophageal function tests.	Of those with known TM (n=13), 3 had FEV_1/FVC below 2 SD, 10 had FEV_1/PEF ratio of >8	Other PFTs in TM group not described and TM undefined	Authors stated "diagnosis of TM requires X-ray findings or bronchoscopy"; that was not routinely but done in many

Panitch 1990	Case study	3 children in series but only 1 included as 2 had other concurrent significant lung disease and tracheostomy; TM undefined	Child with repaired laryngo-trachea-esophageal cleft repaired at 1-mo	To study pulmonary mechanics of 3 children with intrinsic TM after bronchoconstrictor and bronchodilator	Reduced (V'maxFRC) c.f. published norms; Methacholine improved V'maxFRC by 14.4%, Albuterol reduced V'maxFRC by 31.6%; saline did not alter VmaxFRC.	Changes described may not be specific to TM{57}	Rigid bronchoscopy
Shell 2001	Case study		Child with TM related to innominate artery compression		Sx to rotate aorta anteriorly and to the left; Pre Sx FEF25-75=28%, post=69%; Pre Sx V'maxFRC=19%, post=57%; Pre Sx FVC 114%, post 116%		Fluoroscopy followed by MRI
Uchida 2009	Case series	NA; TM undefined	3 children with double aortic arch	Description of 3 children mistreated as poorly controlled asthma whereby analysis of flow-volume curve suggested diagnosis	Flow-volume curves #1: plateau of expiratory limb #2: plateau of inspiratory and expiratory limbs #3: plateau of expiratory limb	TM undefined	Chest CT with angiogram showing airway compression (undefined)
Weber 2002	Retro-spective	Children with life-threatening TM who had aortopexy; TM undefined	8 of the 32 in cohort had PFT done (not specifically described)	To report on children with life-threatening TM treated with aortopexy	FEV_1 pre-aortapexy=52% pred, SD 4% post=82% ± 3% post PFT undertaken 2 weeks to 3-mo post aortopexy		Rigid or flexible bronchoscopy spontaneous breathing

CPAP= continuous positive airway pressure; Excl=exclusion; Incl=inclusion; mo=months; NA=not applicable; PFT=pulmonary function test; pred=predicted; Sx=Surgery; TBM=trachea-broncho-malacia; TM=tracheomalacia; V'maxFRC=maximal flow at functional residual capacity

Summary of data

- Lung function cannot be used to diagnose TBM but provides supportive diagnosis
- Sensitivity and specificity of any PFT cannot be determined
- Although many studies show some have a degree of expiratory airway obstruction; not all have.
- Obstruction pattern defined by reduction in FEV1, V'max FRC, PEF, MEF, TEF, airway resistance, abnormality in flow-volume loops
- FVC not affected or may be elevated, TGV elevated
- AHR present in some children

Limitation of data

- Need PFT related to TBM severity;
- Limited studies- many small number; only 2 cohorts

LITERATURE REVIEW ON QUESTION 5 - RADIOLOGY

How do we use imaging to diagnose TM & BM? [to include tracheobronchography]

1st author, publication year	Setting; study design	Inclusion criteria; exclusion or definition	Description of cohort	Main aim(s) of study	Primary findings relating to KQ	Main study limitation	Method of confirmation of TBM and type
Austin J, 2003	Review	Do not describe papers search					
Berrocal T, 2004	Review	Do not describe papers search					
Fraga JC, 2016	Review	Do not describe papers search					
Sanchez MO, 2012	Prospective study	Children with a suspected airway abnormality and with clinical symptoms including stridor, chronic cough, recurrent pneumonia, persistent pulmonary infiltrates or atelectasis.	22 children underwent fluoroscopy and Flexible Bronchoscopy (FB). TM was found in 21 children by FB.	To study sensitivity, specificity and predictive ratios of airway fluoroscopy compared with FB.	Fluoroscopy detected TM in 5/21 children. Airway fluoroscopy was poorly sensitive (23.8%) but highly specific (100%) and positive likelihood ratio was 8.6	Small cohort of children	Flexible Bronchoscopy
Berg E, 2008	Retrospective study	Children with stridor who underwent both endoscopy and fluoroscopy within a 5y time period.	39 children, endoscopic findings: 13 with airway stenosis, 11 with laryngomalacia, 7 with airway mass lesion, 5 with tracheomalacia.	To determine the sensitivity and specificity of airway fluoroscopy in the diagnosis of pediatric laryngotracheal abnormalities.	The sensitivity of fluoroscopy in the diagnosis of laryngomalacia, TM, airway stenosis, and an airway mass was 27%, 20%, 69%, and 43%, respectively. The specificity	Small cohort of children. The sample sizes within each diagnostic subgroup were even smaller (eg, there were only 5 patients in the tracheomalacia group).	Endoscopy

					for the same diagnoses was 100%, 94%, 100%, and 100%, respectively. Airway fluoroscopy appeared to have low sensitivity but high specificity in detecting airway abnormalities.		
Lee EY, 2008	Case series (Retrospective review and analysis of radiologic and clinical data)	Infants with mediastinal aortic vascular anomalies referred for paired inspiratory-expiratory MDCT.	5 symptomatic infants underwent paired inspiratory – expiratory MDCT, while 4 underwent bronchoscopy as well.	To assess the feasibility of paired inspiratory – expiratory MDCT for evaluating TM among symptomatic infants with mediastinal aortic vascular anomalies.	TM was confirmed in 3 out of 5 infants at the level of mediastinal aortic vascular anomaly. The CT results were concordant with the results of bronchoscopy in all patients who underwent bronchoscopy.	Limited cohort	Bronchoscopy
Lee EY, 2008	Retrospective study	Pediatric patients with respiratory symptoms who underwent paired inspiratory- expiratory MDCT and were diagnosed with	15 children, underwent paired inspiratory-expiratory MDCT, while 9	To determine the prevalence of TM associated with different types of mediastinal	8 of 15 patients diagnosed with TM, results concordant with Bronchoscopy. Symptomatic	1. Small cohort. 2. Not equal number of cases from each type of vascular	Bronchoscopy and/or paired inspiratory-expiratory MDCT

		mediastinal aortic vascular anomalies.	underwent bronchoscopy as well.	aortic vascular anomalies in symptomatic children using paired inspiratory-expiratory MDCT.	pediatric patients with mediastinal aortic vascular anomalies have a relatively high prevalence of TM. Paired inspiratory-expiratory MDCT should be considered part of the routine preoperative evaluation of TM.	anomaly. 3. Retrospective study.	
Ngerncham M, 2015	Retrospective study	Infants who had esophageal atresia (EA) and underwent MDCT as preoperative evaluation of TBM prior to aortopexy.	18 patients underwent paired inspiratory-expiratory MDCT.	To compare paired inspiratory-expiratory MDCT with intraoperative Diagnostic Laryngoscopy and Bronchoscopy (DLB) in the assessment of TBM in symptomatic pediatric patients with EA.	Overall diagnostic accuracy of dynamic airway MDCT compared to DLB was 91%. MDCT is highly accurate and reliable non-invasive modality for evaluating TBM.	1. Small population size. 2. Retrospective nature of study. 3. No normal control group to be compared.	Intraoperative Diagnostic Laryngoscopy and Bronchoscopy
Lee EY, 2009	Review	Do not describe papers search					
Long FR,	Retrospective	Pediatric patients,	87 children	To describe the	Full inflation	1. Retrospective	Controlled-ventilation

2001	study	who underwent conscious sedation and controlled-ventilation CT (CVCT) of the chest over a 2-year period, because they could not cooperate with breath holding.	underwent conscious sedation and CVCT of the chest.	technique and utility of a non-invasive method called controlled-ventilation CT (CVCT) for obtaining motion-free full-inflation and end-exhalation images of the lung in infants and young children.	CVCT was useful in evaluating tracheal and bronchial stenosis, bronchial wall thickening, early bronchiectasis, bronchial fistula, extend of interstitial fibrosis and lung nodules. End exhalation CVCT was useful in evaluating TM and air trapping.	study, which did not compare prospectively the CVCT with the quiet breathing technique. 2. CVCT requires the use of sedation.	CT
Goo HW, 2013	Retrospective study	Pediatric patients with TM who underwent free-breathing cine-CT.	27 children with bronchoscopic evidence of TM, and a control group (n=320) underwent free breathing cine-CT.	To investigate the accuracy of free breathing cine-CT for diagnosis of TM in young children with bronchoscopy as reference standard.	If a cross sectional area change of the trachea of 31.6% was used as a cut-off value for the diagnosis of TM the sensitivity, specificity and accuracy of cine-CT were 96.3% (26/27), 97.2% (311/320) and 97.1% (337/347), respectively.	1. Bronchoscopy not performed in controls. 2. Only a few slices of the entire trachea were evaluated. 3. A reproducibility study of the measurements was not performed. 4. Sedation might influence tracheal collapse on	Bronchoscopy

					Free-breathing cine-CT has potential to provide the diagnosis of TM in young children.	cine-CT.	
Tan JZ, 2013	Case series (Retrospective study)	Pediatric patients with complex clinical respiratory presentation who were referred for dynamic assessment of their airways, at a tertiary paediatric centre.	8 infants: 4 with TM, 4 without tracheobronchial abnormalities (proved with bronchoscopy or bronchography). All underwent dynamic volumetric CT (four-dimensional technique).	To evaluate the dynamic volumetric CT (four-dimensional technique) in the assessment of the paediatric airway.	Volumetric CT enables four-dimensional assessment for paediatric TBM without intubation or patient cooperation and at low radiation dose.	Retrospective study with a small sample group.	Bronchoscopy or Bronchography
Greenberg SB, 2014	Retrospective study	Infants with congenital heart disease who underwent Dynamic Pulmonary CTA (DP-CTA) for evaluation of unexplained persistent respiratory distress.	23 infants with congenital heart disease and persistent respiratory distress: 17 with TBM proved by DP-CTA (cine-CT).	To evaluate the efficacy of DP-CTA to provide unique information for patient care in newborns and infants with congenital heart disease and persistent respiratory distress.	DP-CTA is uniquely suited for comprehensive and simultaneous evaluation of airway and vascular abnormalities in infants.	1. Small cohort. 2. Comparative bronchoscopies not performed in enough patients. 3. No long term follow up available.	Dynamic Pulmonary CTA (Cine-CT)
Lee S, 2014	Retrospective study	Infants who underwent both chest CT and bronchoscopy within 1 week.	17 infants who underwent both bronchoscopy and 3D-CT-bronchoscopy:	To evaluate the use of a non-breath held 3D-CT bronchoscopy	In 10 children TM was confirmed. Sensitivity was<75% in	1. 11/17 bronchoscopies were performed after CT and	Flexible Bronchoscopy

				in detecting TBM in infants.	detecting laryngomalacia, TM and BM. Specificity and PPV was 100% in laryngomalacia and TM.	the pulmonologist was not blinded. 2. Diffuse airway narrowing is difficult to detect in the VR images. 3. A selection bias may have occurred from excluding the patients with severe artifacts in the CT scan. 4. Small cohort of infants.	
Su SC, 2017	Prospective study	Children aged<18 years scheduled for having both FB (Flexible Bronchoscopy) and MDCT.	53 children evaluated for airway abnormalities: TM was confirmed in 37 at FB.	A Comparison of Virtual Bronchoscopy (VB) versus FB in the Diagnosis of TBM in Children. To determine sensitivity, specificity, PPV and NPV.	VB detected TM in 20patients. Sensitivity of 54.1% (95%CI 37.1–70.2), Specificity 87.5% (95%CI 60.4–97.8), and positive predictive value 90.9% (95%CI 69.4-98.4). VB cannot replace FB as gold standard for detecting TBM in children.	1. Preselection of patients with a diagnosis of TBM. 2. Duration of anesthesia was longer by the time FB occurred. 3. 7 children who underwent MDCT without sedation received gaseous anesthesia for FB.	Flexible Bronchoscopy

						4. Inability to standardized lung volumes and airway pressure during FB and VB.	
Deacon JWF, 2017	Retrospective study (Data were collected retrospectively by reviewing the medical record files)	Pediatric patients with TM, confirmed by rigid laryngobronchoscopy, over a 3,5-year period.	71 pediatric patients with TM: 28 had chest CTA.	To describe the clinical presentation of children with TM and to analyse the benefits to patient management of investigations used in the diagnosis and imaging of TM.	Rate of TM detection on CTA is 42,9%	Hospital records reviewed was variable and sometimes incomplete.	Rigid laryngobronchoscopy
Lee EY, 2010	Retrospective study (Retrospectively and randomly identify pediatric patients)	All pediatric patients who underwent paired inspiratory and expiratory MDCT studies for the evaluation of clinically suspected TM, on the basis of clinical signs and symptoms.	20 standard-dose and 20 reduced-expiratory dose, paired inspiratory-expiratory MDCT studies performed for the evaluation of suspected TM in paediatric patients (aged <18 years).	To assess the effects of radiation dose reduction on the assessment of the tracheal lumen on expiratory MDCT images of pediatric patients referred for evaluation for TM.	TM was diagnosed by CT in 7 patients who underwent standard-dose and 6 patients who underwent reduced-dose paired inspiratory-expiratory MDCT studies. CT results were concordant with the results of bronchoscopy in all 32 patients who underwent	1. Retrospective study. 2. Subjective grading of the confidence level in measuring the tracheal lumen. 3. Different machines used in the population.	Bronchoscopy

					both procedures. The radiation dose can be reduced by 23% while maintaining similar diagnostic confidence for assessment of the tracheal lumen compared to a standard-dose technique in pediatric patients.		
Javia L, 2016	Review	Do not describe papers search.					
Faust RA, 2001	Prospective, controlled study	Pediatric and adult patients, with respiratory symptoms scheduled for having both Endoscopy and cine-MRI.	A cohort of 10 pediatric patients, 10 adult patients, and 10 normal volunteers: underwent static MRI, as well as cine-MRI.	To investigate the feasibility of using cine-MRI techniques to dynamically image the human airway and to assess laryngeal and tracheal patency and function.	The imaging findings correlated with patient's endoscopy. TM was depicted in 8 pediatric patients. Airway cine-MRI has the potential to provide novel data regarding laryngeal and tracheal patency and function.	Small cohort of children.	Endoscopy
Faust RA,	Case series	Pediatric and adult	2 pediatric + 1	To apply cine-	Both techniques	Very limited	Bronchoscopy

2002		patients in respiratory distress underwent both bronchoscopy and cine-MRI.	adult patients underwent both bronchoscopy and cine-MRI.	MRI to evaluate patients with respiratory distress who exhibited tracheal compression at the level of the innominate artery.	confirmed TM in all cases, mainly at the level of the innominate artery. Cine-MRI provides extremely rapid acquisition for functional imaging of tracheal patency during the respiratory cycle, while it may provide additional insight into innominate artery compression syndrome.	cohort.	
Ciet P, 2014	Retrospective study (Retrospective image analysis)	Children suspected of having TBM underwent cine-MRI.	12 children underwent cine-MRI: TBM was diagnosed in 7.	To evaluate the feasibility of spirometer-controlled cine-MRI as an alternative to cine-CT.	TBM was diagnosed in 7, confirmed with bronchoscopy or chest CT. Spirometer controlled cine-MRI is a promising technique to assess TBM in children and has the potential to replace	1. Retrospective study. 2. Limited cohort.	Flexible Bronchoscopy or chest CT

					bronchoscopy.		
Rimell FL, 1997	Retrospective study (Study was based on a chart review)	Children with various distal airway disorders over a 3-year period, who underwent MRI for the evaluation of the airway.	49 children: 45 underwent both endoscopy and MRI, while14 underwent fluoroscopy as well.	To determine the role of MRI and how it relates to endoscopy as well as to other imaging modalities in the evaluation of pediatric airway disorders.	Discrepancies between MRI and endoscopy noted in 7, while 2 false negative results noted in fluoroscopy. Magnetic resonance imaging was the most accurate modality in defining extrinsic airway abnormalities. Fluoroscopy combined with barium swallow plays an important role as a screening examination.	1. Retrospective study. 2. No detailed description of TBM patients.	Bronchoscopy

QUESTION 6: LITERATURE REVIEW BRONCHOSCOPY

The role of bronchoscopy to diagnose and grade TB and TB

1st author, publication year	Setting; Study design	Inclusion criteria; Exclusion or definitions	Description of cohort	Main aim(s) of study	Primary findings relating to KQ	Main study limitation	Method of confirmation of TBM and type
Lee 2007	Case series	Children with MAVA referred for paired inspiratory-expiratory MDCT	N=5 mean age 4.1-mo (range 2 weeks – 6 months)	To assess technical feasibility of paired inspiratory-expiratory MDCT for evaluating TM among infants with MAVA	In patients who underwent bronchoscopy there was concordance between bronchoscopic findings and MDCT findings	1. Small number of patients 2. The technique require cooperation	FB, spontaneous breathing
Sanchez 2012	Case series	Children with a suspected airway abnormality and with clinical symptoms including stridor, chronic cough, recurrent pneumonia, persistent pulmonary infiltrates or atelectasis	22 children median age 33 months range 1-187. (4 with inspiratory, 2 expiratory and 8 biphasic stridor, 13 chronic wheeze, 8 cyanotic episodes)	To study sensitivity, specificity and predictive ratios of airway fluoroscopy compared with FB	TM was found in 21 children, fluoroscopy detected TM in 5 children. Airway fluoroscopy was poorly sensitive (23.8%) but highly specific (100%) and positive likelihood ratio was 8.6	Small cohort of children	FB
Lee 2013	Case series Retrospective study	Infants under 12 months old who underwent both chest CT and bronchoscopy within 1 week	17 patients mean age 2 months, range 1-11 months.	To evaluate the use of a non-breath held 3D-CT-bronchoscopy to detecting TM in infants	In 10 children TM was confirmed. Sensitivity was <75% in detecting laryngomalacia, TM and BM. Specificity and PPV was 100% in	1. 17 bronchoscopies were performed after CT and the pulmonologist was not blinded. 2. Diffuse airway narrowing is difficult to detect in the VR images. 3. A selection bias may	FB

					laryngomalacia and TM	have occurred from excluding the patients with severe artifacts in the CT scan	
Su 2016	Case series	Children aged <18 years scheduled for having both FB and MCDT, undertaken 30-min to 7-days of each other.	56 children median age 2.5 years, range 0.8-14.3 years.	To determine sensitivity, specificity, PPV and NPV of VB compared to FB in diagnosis TBM	VB cannot replace FB as gold standard for detecting TBM in children	1.Preselection of patients with a diagnosis of TBM 2. Duration of anesthesia was longer by the time FB occurred. 3. 7 children who underwent MDCT without sedation received gaseous anesthesia for FB 4. Inability to standardized lung volumes and airway pressure during FB and VB	FB
Carden 2005	Review	Do not describe papers search					
Snijders 2015	Review	Do not describe papers search					
Kugler 2014	Review	Do not describe papers search					
Masters 2009	Review	Do not describe papers search					
Wright 2003	Review	Do not describe papers search					
Austin 2003	Review	Do not describe papers search					
Fraga 2016	Review	Do not describe papers search					
Yie Tan 2011	Review	Do not describe papers search					

Nemes 2014	Review	Do not describe papers search					
Masters 2008	Prospective case control study	Children with CRS of cough, stridor or wheeze present for > 3 weeks who underwent FB.	Patients:116 children (77 male), 81 with TM, median age 2.1 years, range 0.2 -17.3 years. Controls: 31 healthy children	Prospectively examine relationship between TM lesions and their respiratory illness profile	The RR of illness frequency was 2.1 (95% CI 1.3 to 3.4) and of significant cough 7.2 (95% CI 1.01 to 27.22) for the malacia group while the CARIFS day 1 score was 1.66 (95% CI, 1.1 to 2.56) compared to control subjects. Malacia type and severity of lesions were not associated with increased rates of illness or worse clinical profile	1. The tools for the bronchoscopic measurement. 2. Clinical illness outcome scales. 3. Sample size	FB under sevofluorane general anesthesia. End expiratory airway images were recorded 10 mm from the object and were measured using histogram mode technique.
Majid 2014	Prospective observational pilot study	Adult patients with suspected TM	10 adult patients (median age 65 years, 6 female) with suspected TM	To test inter and intra observer agreement (23 pulmonologist) of dynamic FB data estimating the degree of TB collapse obtained at five different sites during exhalation or excessive dynamic airway collapse.	Inter and intra observer correlation coefficients were: PT 0.85 (0.002) and 0.92 (<0.001); MT 0.68 (0.03) and 0.82 (0.004); DT 0.89 (<0.001) and 0.95 (<0.001); RMSB 0.72 (0.02) and 0.8 (0.02); LMSB 0.92 (<0.001) and 0.96 (<0.001).	1. Video images that are susceptible to distortions 2. Lumen size was estimated by antero-posterior diameter and not quantitatively measured by cross-sectional area. 3. Small number of adult patients	Dynamic FB
Asai 2001	Case report	A child who presented airway	A 22 month old child with an	Description of a case of airway obstruction with	Obstruction due to TBM during	One case	FB

		obstruction due to TM during emergence from anesthesia.	erythematous lesion on the right arm scheduled for resection of the cutaneous lesion under anesthesia with sevoflurane	hypoxia during emergence from anesthesia due to unexpected TBM	emergence from anesthesia		
Oh 2002	Case report	A child who presented unexpected TM after beginning of the operation	A 12 yr old boy with MS who was scheduled for a spine fusion operation because of scoliosis under general anesthesia	Description of a case of TM in a child with MS who undergo surgery for scoliosis	Obstruction due to TM after beginning operation	1. One case 2. No description of general anesthesia	FB
Okuda 2000	Case report	A child who presented airway obstruction during induction and after anesthesia	A 1 yr old girl with suspected congenital TM scheduled for FB under GA with secifluorane	Description of a case of TM who undergo FB for a suspected congenital TM	Obstruction during during induction and after GA	1. One case	FB
Eastwood 2002	Case series	Adult patients recruited from those undergoing minor surgical procedures not involving the head or neck and suitable for GA administered via a face mask	16 adult subjects while supine and spontaneously breathing on nasal positive airway pressure	To measured collapsibility of upper airways in spontaneously breathing during inhalational anesthesia with isofluorane in order to examine the site and mechanism of collapse and the influence on them of anesthetic depth	Isoflurane anesthesia is associated with decreased muscle activity and increased collapsibility of the upper airway	1. Small number of patients 2. Difficulties in the application of the technique	LFT
Eastwood	Case series	Adult patients	12 white adult	1. To determine	Increasing depth of	1. Small number of	LFT

2005		recruited from those undergoing minor surgical procedures not involving the head or neck	volunteers	the effect of varying concentrations of propofol on upper airway collapsibility and the mechanisms responsible for it. 2. To identify the effects of anesthesia on central respiratory drive to upper airway dilator muscles 3. To determine whether a sufficient dose of propofol could produce complete flaccidity of the upper airways	propofol anesthesia is associated with increase collapsibility of the upper airway	patients 2. Difficulties in the application of the technique	
Hillman 2009	Case series	Adult healthy volunteers	9 healthy adult volunteers	To determine how upper collapsibility changes during slow stepwise induction on anesthesia with propofol	The progression of effects during slow stepwise induction of anesthesia with propofol does not occur in smooth continuity but disproportionate changes in upper airway collapsibility in a	1. Small number of patients 2. Difficulties in the application of the technique	LFT

					narrow propofol concentrations in each subjects		
Masters 2005	Case series	1.Reliability testing: children who had undergone FB for chronic cough 2. In vivo measurement: children who undergone FB for protracted or chronic cough and or wheeze	1. Reliability testing: 18 children, median age 30 months, range 2-127 months 2. In vivo measurements: 35 children > 3 months of age.	1. To describe a new method to define and measure airway lumen using a FB and a computer software. 2. Describe intra and inter-observer reliability, validation and application of the technique 3. Compare airway size measurements using different methodologies.	1. Validation results showed very high levels of agreement of measurements at all distance 2. Good inter and intra observer reliability 3. The cross sectional area assessed at low light intensity is more likely to be representative of the true cross sectional area than that captured at normal operating light	Factors that govern tissue reflectance and absorption of light during the respiratory cicle while under anesthesia can be compounded by the physical effects of the instruments, the type of light, airway suctioning, and disease processes	FB and computer
Okazaki 2004	Case series	Infants with and without TM	Cases: 8 infants with TM Controls: 4 infants without TM	Static pressure/area relationships of the trachea in infants with TM were obtained and tested if the relationship quantitatively describes collapsibility of the trachea	Tracheal collapsibility of infants with TM can be quantitatively assessed by the static pressure/area relationship of the trachea	1. Insufficient control of tracheal smooth muscle tone that could be influenced by anesthesia 2. Overestimation of the lower airway pressure area because the collapsibility site may have shifted to the endoscope tip with the pressure decrease 3. Difficult to estimate	FB and LFT

						the relative contribution of tracheal stenosis because the method only assesses collapsibility of the trachea 4. Deformation of endoscopic image is inevitable for obtain a wide angle view 5. Small number of patients	
Loring 2006	Case series	Adult patients referred to FB for suspected TBM	Patients: 80 adult patients (34 men), mean age 63 year, range 29-94 years Controls: 4 adult healthy volunteers (2 men, age range 33-47 years)	To quantify central airway collapsibility and relate it to expiratory flow limitation in patients with TBM	In TBM central airway collapse is not closely related to airflow obstruction and expiratory flow limitation at rest often occurs in peripheral airways without central airway collapse.	1. Small number of patients 2. The trachea transmural pressure may have been affected by the presence of the bronchoscope and local anesthetic solution 3. The method may overestimates airway size and underestimates airway narrowing	FB and LFT
Negerncham (2015)	Case series. Retrospective study	Infants who had esophageal atresia who underwent MDCT as preoperative evaluation of TBM prior to artopexy	18 children (8 male), median age 8 months, range 1month-11 years.	To compare MDCT with intraoperative FB in the assessment of TBM in children who had esophageal atresia	MDCT is highly accurate and reliable non invasive modality for evaluating TBM	1. MDCT depends on patient cooperation. 2. Radiation exposure	MDCT and RB
	Review						

MDCT**:** multidetector CT, MAVA: mediastinal aortic vascular anomalies, TM: tracheomalacia, BM: broncomalacia, VR: volume rendering, TBM: trachea bronchomalacia, CRS: chronic respiratory symptoms, RR: relative risk, TB: tracheobronchial, DAC: dynamic airway collapse, PT: proximal trachea, MT: mild

trachea, DT: distal trachea, RMSB: right main stem bronchus, LMSB: left main stem bronchus, MS: Marfan syndrome, GA: general anesthesia, LFT: lung function testing, RB: rigid bronchoscopy

QUESTION 8
Respiratory physiotherapy systematic search

Search terms

Tracheomalacia OR bronchomalacia OR tracheobronchomalacia OR malacia OR tracheal abnormalities OR tracheal diseases

AND

Physiotherapy OR physical therapy OR physical therapy modalities OR airway clearance OR positive pressure and physiotherapy

Exercise tolerance OR exercise therapy

Administration inhalation OR nebulisation OR saline solution hypertonic OR deoxyribonuclease I OR nebulised dornase alfa OR nebulised hypertonic saline

Tracheomalacia and physiotherapy

Title	Authors	Journal, Date	DOI/PMID	Type	Language	N
Interventions for primary (intrinsic) tracheomalacia in children	Masters IB, Chang AB.	The Cochrane Library 2005, Issue 4	10.1002/14651858.CD005304.pub2	Systematic review	EN	0 studies
Interventions for primary (intrinsic) tracheomalacia in children.	Goyal V, Masters IB, Chang AB.	Cochrane Database Syst Rev. 2012 Oct 17;10:CD005304	10.1002/14651858.CD005304.pub3	Systematic review	EN	1 study
Recombinant human DNase in children with airway malacia and lower respiratory tract infection	Boogaard R, de Jongste JC, Vaessen-Verberne AA, Hop WC, Merkus PJ.	Pediatr Pulmonol. 2009 Oct	10.1002/ppul.21073	RCT	EN	40
Positive expiratory pressure to enhance cough effectiveness in tracheomalacia	Sirithangkul S, Ranganathan S, Robinson PJ, Robertson CF.	J Med Assoc Thai. 2010 Nov;93 Suppl 6:S112-8.	21280523	Observational case-control study	EN	40
Effect of continuous positive airway pressure on forced expiratory flows in infants with tracheomalacia	Davis S, Jones M, Kisling J, Angelicchio C, Tepper RS.	Am J Respir Crit Care Med 1998;158:148–152	10.1164/ajrccm.158.1.9711034	Observational prospective study	EN	6
Paediatric chronic suppurative lung disease: clinical characteristics and outcomes	Goyal V, Grimwood K Marchant JM, Masters IB, Chang AB.	Eur J Pediatr. 2016 Aug;175(8):1077-84	10.1007/s00431-016-2743-5	Retrospective study	EN	22 (41% TM)
Tracheomalacia and Tracheobronchomalacia in Children and Adults	Carden KA, Boiselle PM, Waltz DA, Ernst A.	Chest. 2005 Mar;127(3):984-1005.	10.1378/chest.127.3.984	Review	EN	
Primary bronchomalacia in infants and children	Finder JD	J Pediatr. 1997 Jan;130(1):59-66	9003852	Retrospective study	EN	17

LITERATURE REVIEW Tracheomalacia and physiotherapy							
1st author, publication year	**Setting; Study design**	**Inclusion criteria; Exclusion or definitions**	**Description of cohort**	**Main aim(s) of study**	**Primary findings related to KQ**	**Main study limitation**	**Method of confirmation of TBM**
Finder, 1997	Retrospective	not specified	N = 17, mean age = 38 mo (range 3 mo - 17 y) with bronchomalacia	To determine the natural history of primary bronchomalacia	All patients had physiotherapy. All patients aged more than 5 years had exercise limitation	Descriptive study	Bronchoscopy
Goyal, 2012	Systematic review	RCTs related to symptoms associated with primary or intrinsic TM	1 study examined about role of rDNase	To evaluate the efficacy of medical and surgical therapies for children with intrinsic (primary) TM	No RCTs identified about role of physiotherapy	Related to symptoms rather than the impact of physiotherapy	not specified
Davis, 1998	Cross-sectional	TM=50% tracheal narrowing at bronchoscopy	N = 6, mean age 6.8 mo (range 3-10 mo) with moderate to severe TM; Controls: N = 5, mean age 6.4 mo	In infants with TM, to determine whether the increase in V'max FRC with CPAP could be explained by the increase in FRC with CPAP (0, 4, 8 cm H_20)	continuous positive expiratory pressure (CPAP) increases maximal expiratory flow at functional residual capacity secondary to increasing lung volume	Small cohort	Bronchoscopy
Sirithangkul, 2010	Observational case-control study	Incl. children with OA/TOF with corrective surgery; Excl. complex congenital abnormalities (spinal deformity, congenital heart disease or neurological impairment)	N = 40, mean age 12.5 y (range 8 - 18 y); Controls: N = 21, mean age 13.1 y	To determine the effectiveness of increasing levels of PEP during coughing to enhance expiratory flow and improve efficiency of the cough in children with TOF	Children with TOF: PEP=5: +18.8% increase CEF25-75 PEP=10: +11.7% increase CEF25-75 PEP=15: +0.5% increase CEF25-75 PEP=20: -2.4% decrease CEF25-75 Controls: PEP=5: -3.1% decrease CEF25-75 PEP=10: -6.3% decrease CEF25-75 PEP=15: -22.2% decrease CEF25-75 PEP=20: -19% decrease CEF25-75	CEF25-75 were calculated from cough flow-volume curve	History, clinical symptoms

LITERATURE REVIEW QUESTION 9: STENTS

1st author, publication year	Study design	Number of patients	Type(s) of stent	Outcome (survival at time of report)	Complications	Attempted stent retrieval	Main study limitation
Soong 2018	retrospective	unclear (>21)	BEMS	unclear for TBM patients	tracheal perforation at time of stent removal, granulation tissue, infection, stent fracture	optional	data combined with stenting for other indications
Sztano 2016	retrospective	3	absorbable	2/3, 67%	stent fragmentation, infection, airway obstruction	required for complications	small series presented as review of complications
Anton-Pacheco 2016	retrospective	3	absorbable	3/3, 100%	granulation tissue	no	small series
de Trey 2016	retrospective	15	BEMS, absorbable	11/15 (73%)	stent fracture, infection, airway obstruction	optional (28%)	data combined with stenting for vascular compression
Anton-Pacheco 2008	retrospective	19	BEMS, silicone (Dumon™, Polyflex™)	unclear for TBM patients	stent migration, granulation tissue, infection	optional	data combined with stenting for other indications
Yang 2006	retrospective	3	not stated	1/3 (33%)	not stated	1/3	small series, poor description of patients
Airway Reconstruction team 2005	retrospective	2	BEMS	2/2 (100%)	not stated	unclear	small series
Valerie 2005	retrospective	14	BEMS	13/14 (93%)	death during stent removal	9/14 (64%)	small series
Geller 2004	retrospective	9	BEMS	5/9 (55%)	airway haemorrhage, infection	no	small series
Nicolai 2001	retrospective	4	BEMS, SEMS	1/4 (25%)	pneumomediastinum, difficult stent removal, granulation tissue, stent	yes	small series

					collapse with coughing		
Furman 1999	retrospective	2	BEMS	1/2 (50%)	granulation tissue	no	small series
Filler 1998	retrospective	8	BEMS	8/8 (100%)	granulation tissue	6/8 (75%)	small series
Tsugawa 1997	retrospective	2	SEMS	2/2 (100%)	stent too short	1/2 (50%)	small series, experimental device (not available for clinical use)
Santoro 1995	retrospective	3	BEMS	1/3 (33%)		no	small series
Mair 1990	retrospective	2	SEMS, plastic polymer	1/2 (50%)	infection	no	small series, experimental device (not available for clinical use)

TBM = tracheobronchomalacia; BEMS = balloon-expandable metal stent; SEMS = self-expanding metal stent

LITERATURE REVIEW: QUESTION 9 - SURGERY

1st author, publication year	Setting; Study design	Inclusion criteria	Description of cohort	Main aim(s) of study	Primary findings relating to KQ	Main study limitation	Method of confirmation of TBM and type
Jennings 2014	Retro-spective cohort	children with TM who underwent aortopexy	N=41 median age-7.5 mo (range 1-136)	To determine the outcomes among three different surgical approaches for performing an aortopexy	The partial sternotomy technique had the most reliable resolution of symptoms and no recurrence requiring reoperation.	Variation in patient populations, ages at operation, surgical teams, use of intraoperative bronchoscopy to assess results.	Flexible bronchoscopy, spontaneous breathing
Briganti 2006	Retro-Spective cohort	children with esophageal atresia-tracheoesophageal fistula presenting segmentary TM	7 children Mean age: 25.2 mo (range 2-103)	Usefulness of preoperative imaging by dynamic fiberoptic bronchoscopy and spiral multilayer computed tomography with 3-dimensional reconstruction	Dynamic fiberoptic bronchoscopy and CT scans allowed us to describe 3 morphological variations of thoracic TM	Short series of cases	Flexible bronchoscopy and CT scan with 3-D reconstruction
Filler 1992	Retro-Spective cohort	children with esophageal atresia tracheoesophageal fistula (EA-TEF) who underwent surgery for severe tracheomalacia	32 children	Surgical outcomes of aortopexy	Aortopexy provides long-term relief of severe symptoms of tracheomalacia associated with EA-TEF in almost all affected children		Chest x-ray, esophagogram, and bronchoscopy.
Morabito 2000	Cohort	children with significant symptoms of TM undergoing aortopexy and/or tracheopexy	16 children	Surgical outcomes of aortopexy and/or tracheopexy	Sustained tracheal improvement and resolution of the life-threatening features of TM		Bronchoscopy (type undefined)
Arnaud	Case study	Children with TM	4 children	To review initial experience	All patients were relieved of	larger and	Bronchoscopy

2014		and EA/TEF undergoing thoracoscoic aortopexy		with thoracoscopic aortopexy.	their symptoms, and no recurrence was noted.	prospective study with a longer follow-up to confirm these preliminary results, needed	
Shieh 2017	Retro-spective cohort	Children undergoing posterior tracheopexy for tracheomalacia with posterior intrusion	98 patients median age of 15mo (IQR 6-33months)	To review patient outcomes of posterior tracheopexy for tracheomalacia	Tracheomalacia scores on bronchoscopy improved significantly in all regions of the trachea and bronchi ($p<0.001$). 9.2% had persistent airway intrusion requiring reoperation, usually with aortopexy.		Flexible bronchoscopy with standardized dynamic airway evaluation by anatomical region
Morrison 2015	Case study	3 children with severe TBM treated with a 3D-printed personalized bioresorbable medical device	3 children	Assess the application of 3D printing technology to produce a personalized medical device for treatment of TBM	These infants no longer exhibited life-threatening airway disease and demonstrated resolution of both pulmonary and extra-pulmonary complications of their TBM.	This report was not designed for definitive testing of device safety. Further patient accruement and analysis under a US/ FDA-enabled clinical trial will be necessary.	Bronchoscopy and CT scan with multiplanar reconstruction

PATIENT AND PARENT PERPECTIVE

HTTPS links to internet sources

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