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Care Recommendations for the Respiratory Complications of Esophageal Atresia-Tracheoesophageal Fistula The International Network of Esophageal Atresia, Respiratory Complications Working Group:

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ppul.24982.

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Running title: Respiratory Complications of Tracheoesophageal Fistula

Key words: Tracheoesophageal fistula; Tracheomalacia; Aspiration; Gastroesophageal reflux; Chronic bronchitis; Bronchiectasis

ABSTRACT

Tracheoesophageal fistula (TEF) with esophageal atresia (EA) is a common congenital anomaly that is associated with significant respiratory morbidity throughout life. The objective of this document is to provide a framework for the diagnosis and management of the respiratory complications that are associated with the condition. As there are no randomized controlled studies on the subject, a group of experts used a modification of the Rand Appropriateness Method to describe the various aspects of the condition in terms of their relative importance, and to rate the available diagnostic methods and therapeutic interventions on the basis of their appropriateness and necessity. Specific recommendations were formulated and reported as Level A, B, C based on whether they were based on “strong”, “moderate” or “weak” agreement. The tracheomalacia that exists in the site of the fistula was considered the main abnormality that predisposes to all other respiratory complications due to airway collapse and impaired clearance of secretions. Aspiration due to impaired airway protection reflexes is the main underlying

contributing mechanism. Flexible bronchoscopy is the main diagnostic modality, aided by imaging modalities, especially CT scans of the chest. Non-invasive positive airway pressure support, surgical techniques such as tracheopexy and rarely tracheostomy are required for the management of severe tracheomalacia. Regular long-term follow-up by a multidisciplinary team was considered imperative. Specific templates outlining the elements of the clinical respiratory evaluation according to the patients' age were also developed.

INTRODUCTION

Congenital tracheoesophageal fistula (TEF) is almost always (92% of cases) associated with esophageal atresia (EA) (commonly referred to as EA-TEF)[1] with an estimated incidence of approximately 1 in 3500-4500 live births [2,3].

The trachea and the esophagus share a common embryologic origin from an outgrowth of the foregut, the "lung bud", that appears around the fourth week of gestation. By the end of the fifth week a septum divides it in two parts and it separates from the foregut [4]. The TEF is caused by a defect in the septum that preserves the communication between the esophagus and the lower trachea. Rare variants include a communication between the esophagus and the right main stem bronchus or the connection of the trachea and esophagus at proximal and distal sites by two or even three fistulae[5].

Repair of the TEF consists of the separation of the esophagus from the trachea and closure of the defect of the tracheal wall. There is usually a visible "ridge" at the site of the repair and often a blind pouch that can be intermittently open (Image 1A). The

repair of the esophagus is far more complex, particularly if there is a long gap between the two atretic segments[6]. Despite the repair of the defect, the condition carries a very high morbidity primarily associated with the presence of severe tracheomalacia (TM) or tracheobronchomalacia (TBM). The complications of TEF are most prevalent and severe during the first few years of life but may last in varying degrees throughout life[7–18].

Improvement in the survival of infants born with EA-TEF has highlighted the need to optimally manage their symptoms, reduce morbidity, and improve quality of life. The International Network on Esophageal Atresia (INoEA), comprised of health professionals involved in the care of children with EA-TEF, published guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in EA-TEF and on the surgical management of long-gap EA[6,19,20]. The Respiratory Complications Working Group (RCWG) was formed at the invitation of the INoEA Steering Committee, to develop a similar framework for the management of the respiratory complications of TEF. The RCWG consists of 10 academic Pediatric Pulmonologists from Canada, Italy, Australia, and the USA, with experience in the diagnosis and management of infants and children with EA-TEF.

The document is intended for all health care professionals who are involved in the care of patients with EA-TEF in or outside the hospital setting. It may also be useful for the families of patients with EA-TEF in understanding the rationale behind the multiple diagnostic and therapeutic interventions that may be necessary throughout childhood and adolescence.

METHODS

The literature on the respiratory complications of TEF is based on small, single institution, retrospective case series and case reports. There are no systematic reviews or randomized controlled trials to formulate evidence-based guidelines on diagnosis and treatment. To address this deficiency the RCWG chose a modification of the RAND Appropriateness Method (RAM)[21] developed by the RAND Corporation–University of California Los Angeles, that helps synthesize the available empirical evidence using the collective experience of a panel of experts. The RAM approach has been widely used in the development of clinical practice guidelines, including in adult respiratory care[22], in primary pediatric care[23] and in rare pediatric conditions such as Duchenne Muscular Dystrophy[24–26].

The RAM rates diagnostic and therapeutic interventions on the basis of their "appropriateness" and "necessity". The appropriateness of an intervention is based on its known or expected medical benefit without consideration of any logistical or financial obstacles. Appropriateness does not automatically imply necessity (e.g. bronchoalveolar lavage is an appropriate diagnostic modality for the evaluation of pneumonia, but it is not necessary for every case of pneumonia). The "necessity" is based on whether a) the specific intervention has been deemed appropriate; b) there is reasonable expectation it will benefit the patient in a substantial way; c) according to prevailing standards of care, it would be inappropriate not to offer this intervention to the patient. The RAM enables individual expert opinion to be independently and anonymously expressed and identifies areas of agreement as well as of disagreement or uncertainty that are in need of further study.

The development of the recommendations consisted of the following steps (Figure 1):

Step 1. **Review of the literature and formulation of statements**. Questions relating to the domains of *Respiratory Physiology (RP), Diagnostic Methods (DM)* and *Therapeutic Interventions (TI)* for the management of respiratory complications in EA-TEF were generated by literature reviews limited to the English language. Each question was subsequently discussed and reformulated into specific statements during a face-to-face meeting. The agreed upon statements were entered into matrices containing clinical scenarios with a list of potential interventions in 3 areas: Respiratory Pathophysiology (RP) Diagnostic Methods (DM) and Therapeutic Interventions (TI).

Step 2. Rating of statements for "appropriateness". All statements were individually rated for appropriateness on an ordinal scale of 1-9 as follows: INAPPROPRIATE: ratings 1-3; UNCERTAIN: ratings 4-6; and APPROPRIATE: ratings 7-9. Pathophysiologic mechanisms were rated as "appropriate" according to the degree to which the statement was supported by generally acknowledged pulmonary physiology, currently available literature, and/or by the clinical experience of the responders. Statements in which all responses were in agreement i.e. within the same category were set aside whilst the remaining statements underwent a second and third round of rating. The results of each round were shared within the RCWG without identifying the responders.

Step 3. Rating of statements for "necessity". Necessity ratings were applied only to statements pertaining to Diagnostic Methods and Therapeutic Interventions and were rated on an ordinal scale 1-9 as follows: UNNECESSARY: 1-3; UNCERTAIN: 4-6;

NECESSARY: 7-9. The median, range and the mean (±SD) were calculated. In the final collation, the responses were classified as follows:

- **"Strong" agreement**: both the median and the mean values of the responses for a given item were within the highest category (7-9)
- **"Moderate" agreement**: both the median and the mean values of the responses for a given item were within the middle category (4-6)
- **"Weak" agreement**: The median value was in the lowest category (1-3) and/or the difference between the highest and lowest value was ≥ 3.

Step 4. **Formulation of the recommendations.** The recommendations were classified as Level A (based on strong agreement), B (moderate agreement) and C (weak agreement). The ratings on Necessity were formulated into specific recommendations presented in 10 sections (6 for Diagnostic Methods and 4 for Therapeutic Interventions) with their supportive evidence.

The methodology was presented for discussion to the membership of INoEA in its conference in in Sydney, Australia in 2016, whereas the findings and the basic recommendations were discussed in its conference in Rome, Italy in 2019. Representatives of several international patient and family organizations were also in attendance and provided input. Prior to its submission, the manuscript was reviewed by the members of the Steering Committee of the INoEA that includes specialists from different disciplines who also provided input.

RESULTS

A. RESPIRATORY PATHOPHYSIOLOGY

Respiratory complications in TEF are the result of several interacting anatomic and functional abnormalities (Figure 2), and they can be summarized as follows:

1. **Tracheomalacia:** Tracheomalacia in EA-TEF was identified as the main pathology that causes or predisposes to almost all other respiratory complications.[27] Tracheomalacia is caused by the anteroposterior collapse of the cartilaginous wall and especially by the intrusion of the posterior trachealis muscle into the lumen. This changes its appearance from the typical "Horseshoe arch" shape, to a flattened "crescent" shape (Images 1B & 1C). Bronchomalacia is often present as well (Image 1D).

Factors implicated in the development of TM include deficient tracheal cartilage at the level of the fistula, intrinsic cartilage weakness over longer tracheal segments due to *in-utero* compression from the dilated proximal esophageal pouch[14] and/or aberrant myoelastic development of the posterior membrane[27–29]. The lower (intrathoracic) trachea collapses mostly during exhalation, whereas the extrathoracic trachea collapses during inspiration. Further deterioration of the TM may ensue post-repair, from recurrent tracheal inflammation due to aspiration and infection, or due to tracheal wall weakness secondary to prolonged intubation and long-term mechanical ventilation.[27,28,30–33] Intermittent dilatation of the esophagus due to bolus obstruction can easily overcome the resistance of the weakened tracheal wall and cause its further collapse [34,35]. Complications attributed to TM are:

- Cyanotic spells: Early in infancy, patients can develop severe or even life-threatening airway obstruction associated with profound drops in oxyhemoglobin saturation and bradycardia (colloquially referred to as the TEF "death spells"). [34,36,37] The episodes tend to occur when there are increases in intrathoracic pressure (e.g. during crying or straining) that cause almost complete collapse of the tracheal lumen[37,38]The desaturation is more dramatic when there are anatomical communications (e.g. PDA, ASD, VSD) causing right-to-left shunt.

- **Chronic cough**: A dry barking cough (also described as "honking" or "brassy") is the trademark symptom of TM especially in infancy and childhood; this cough tends to decrease somewhat with age [8,18,39]. A chronic wet cough (often described as "smoker's cough") may develop in early childhood and can remain across the lifespan[40,41].

- Recurrent lower respiratory tract infections: Multiple episodes of pneumonia--especially during the first few years of life--are reported in as many as 50% of the children whereas intermittent or chronic bronchitis is reported by almost 2/3 of adults with EA-TEF.[9,11,13,15–18,41–46] Recurrent lower respiratory tract infections can lead to bronchiectasis, poor lung function, and lower quality of life in adulthood.[40,43,47]

- Chronic or recurrent "wheezing": Infants and young children with EA-TEF often produce a wheeze-like persistent harsh expiratory noise that is often misdiagnosed as "bronchiolitis" or "asthma", or in older patients as exercise induced asthma. The "wheeze" is produced by the collapse of the tracheal lumen and not by bronchospasm and therefore does not respond to bronchodilators.[11]

2. Impaired airway clearance: The narrowing of the tracheal lumen leads to retention of airway secretions whose clearance is further impaired by the loss of cilia on the respiratory epithelial cells at the fistula site[28,33,48]. The retention of secretions predisposes to colonization with bacterial organisms and progressive airway inflammation that may lead to irreversible lung damage, including bronchiectasis. Affected patients are likely to have recurrent or chronic wet cough often termed protracted bacterial bronchitis[49–51].

3. **Aspiration**: Recurrent aspiration is the result of anatomical and/or functional abnormalities and it is recognized as a cause or contributing factor of acute and chronic respiratory morbidity in various conditions[52–56]. The anatomical abnormalities consist of direct communications of the tracheobronchial tree and the alimentary tract (such as laryngeal clefts, tracheoesophageal or bronchoesophageal fistulae) and result in direct aspiration [12,52,53]. Direct aspiration can also result when one or both vocal cords are paralyzed in abduction.[57] The functional causes are due to predisposing conditions that allow liquids or solids near the larynx. Such factors include dysphagia and swallowing impairment (e.g. inability to or delayed bolus formation, pooling of secretions in the pyriform sinuses etc.), GER, and regurgitation of foodstuff that is stuck in the esophagus[58–61]. All of these factors can result in aspiration if the patient is also unable to protect the airways with laryngospasm and/or clear the trachea after laryngeal penetration using cough.

Regardless of the underlying mechanism, aspiration can exacerbate chronic airway inflammation, facilitate the colonization of the airways with bacteria, and expose the infants to allergens at an early age, potentially leading to atopy[62]. The ensuing chronic inflammation and recurrent infections may lead to the development of bronchiectasis and

severe impairment of the lung function consisting of lower airway obstruction with air-trapping as well as actual loss of lung volume[53,55,63,64].

4. Bronchiectasis: Bronchiectasis is one of the more serious pulmonary complications in patients with EA-TEF[9,11,43,65–70]. Although it is the end-result of other complications (especially recurrent LRTIs and aspiration), it becomes a specific entity by itself, becoming the source of even more infections and causing irreversible damage to the airways. Clinically, it is characterized by daily productive cough (even in the absence of an acute infection). Exacerbations are associated with increased purulent sputum production, frequently fever, dyspnea, and in advanced cases hemoptysis.[49,50] Because young children cannot expectorate, changes in the quality of the cough from dry to "wet" have been proposed as an alternative to changes in sputum production and appearance[47,49,50].

5. **Gastroesophageal dysmotility:** EA-TEF is characterized by multiple functional and anatomical gastroesophageal abnormalities that have been discussed in detail elsewhere.[19,59] In general, these abnormalities tend to be contributing or predisposing factors to the development of respiratory complications from the upper and/or lower airways.[58–61] Gastroesophageal reflux and/or esophageal regurgitation can cause chronic laryngeal irritation that may manifest itself as recurrent stridor and/or chronic hoarseness.[9,53,58,71] However, chronic stridor, especially if it is not accompanied by difficulty in breathing, should raise suspicions of vocal cord paralysis due to trauma of the recurrent laryngeal nerve during the repair[57,72]. Effects in the lower airways include tracheal compression from a dilated esophagus, and conditions that increase the risk of aspiration such as regurgitation, impaired swallow, and GER.

6. Associated congenital abnormalities. Although EA-TEF can be an isolated abnormality, in about 50% of patients it is part of syndromes involving multiple other organ-systems[3,73]. The most common include the VACTERL association (vertebral defects, anal atresia, cardiac defects, TEF, renal anomalies, and limb abnormalities), the CHARGE syndrome (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) and chromosomal abnormalities (including Down syndrome). Of special interest are associated abnormalities of the upper airways[74–77] as well as various cardiovascular anomalies[78–84]. All of these conditions increase the morbidity and, in the case of congenital heart disease, the mortality as well[85].

B. RECOMMENDATIONS ON DIAGNOSTIC METHODS

I. Evaluation of Tracheobronchomalacia
Level A Recommendations **Recommendation 1:** Flexible bronchoscopy is the gold standard for the evaluation of TBM **Recommendation 2:** Flexible bronchoscopy is recommended for unexplained wheezing or exercise intolerance **Recommendation 3:** Flexible bronchoscopy is indicated for all patients with a tracheostomy **Recommendation 4**: Rigid bronchoscopy is not a sensitive method for the evaluation of the severity of TBM
Level B Recommendations **Recommendation 5**: Multi-detector CT scan is an accurate method of assessing TBM **Recommendation 6**: Spirometry is a reliable way of assessing the severity of TBM in older children

Level C Recommendations
Recommendation 7: Tidal flow-volume loops are a reliable way of assessing the severity of

TBM in infants and toddlers

Flexible bronchoscopy is considered the gold standard for the evaluation of the presence and severity of TBM. Rigid bronchoscopy tends to underestimate the degree of the tracheal collapse because it "stents" the airway[51,86–88].

There was moderate agreement regarding the use of standard chest CT because it may not capture the dynamic changes of the tracheobronchial lumen that occur during the respiratory cycle (especially with cough). Inspiratory and expiratory dynamic multi-detector chest CT scans were considered superior because they are fast, relatively inexpensive, and provide additional and detailed information about the airways, the lung parenchyma, and the thoracic vasculature[51,87,89,90]. However, at the moment they may not be available in every hospital.

Maximal expiratory flow-volume curves (MEFVCs) can be often diagnostic of tracheomalacia[91], showing a characteristic flattening of the initial portion of the MEFVC (Figure 3A). Its disadvantage is that it can only be performed in children over 4-5 years of age, and it becomes less sensitive in older children and adolescents[44,92]. Infants can be evaluated with the raised-volume rapid thoracoabdominal compression (RVRTC) technique, which allows the performance of MEFVCs without the patient's cooperation but is labor intensive and usually requires sedation[93]. An alternative easy, non-invasive technique to evaluate flow-limitation is with tidal flow volume loops[94] (Figure 3B). However, it is not well standardized, and it may miss mild/moderate TBM. A significant

limitation of both techniques is that the necessary equipment (and expertise) are not available in many centers.

II. Evaluation of a Recurrent Tracheoesophageal Fistula
Level A Recommendations **Recommendation 8:** Combined endoscopy and bronchoscopy are the gold standard for the diagnosis of recurrent TEF
Level C Recommendations **Recommendation 9**: Barium swallow in prone/semi-prone position is the preferred radiographic method for the detection of recurrent TEF ***Recommendation* 10**: Pressure esophagogram is the preferred method for the detection of a small TEF

Recurrent TEFs occur in 5-10% of cases after primary repair[95–102], as a result of esophageal anastomotic leak, trauma from esophageal dilatations and/or airway infections. Higher rates have been reported[103,104], and they may be related in part to hospital expertise in managing the condition[101,103]. Interestingly, very low rates of recurrence have been associated with low gestational age[105]. The manifestations of recurrent TEF are potentially severe and include cough, choking and cyanosis during feeds, and recurrent pneumonias. Diagnosis is challenging and often delayed despite multiple investigations. There was strong agreement that recurrent TEFs are best diagnosed with simultaneous esophageal endoscopy and bronchoscopy, aided by the infusion of methylene blue on the tracheal or esophageal side and observing its appearance on the other side[97,106]. An esophagogram in prone or semi-prone position with contrast administered under pressure can be diagnostic and has the fewest false negative

results (compared with upper GI in supine or erect positions), but it may miss a TEF in the presence of an esophageal stricture[96,103,107,108]. Moreover, it is not a standard technique among radiologists, and therefore did not receive strong recommendation. This multidisciplinary approach is increasingly used to optimise outcomes in children with recurrent TEF[109,110].

III. Evaluation of Bronchitis and Pneumonia
Level A Recommendations **Recommendation 11**: The presence of a chronic wet cough requires further evaluation **Recommendation 12**: Children with more than one episode of lobar pneumonia should be evaluated for aspiration or underlying anatomical abnormalities **Recommendation 13**: Bronchoalveolar lavage is indicated for recurrent or persistent cough to rule out colonization of the airways by pathogens **Recommendation 14**: CT scan of the chest should be considered in cases of frequent respiratory infections **Recommendation 15**: CT scan of the chest is more useful as a baseline but not during an acute lower respiratory tract infection
Level B Recommendations **Recommendation 16**: Pneumonia in patients with EA/TEF should be confirmed by CXR
Level C Recommendations **Recommendation 17**: The threshold for obtaining CXR should be low because pneumonia in children with TEF may not be associated with fever **Recommendation 18**: CXR should be obtained in each episode of suspected pneumonia **Recommendation 19**: Chest CT should be considered in case of suspected pneumonia **Recommendation *20***: BAL should be considered in cases of suspected pneumonia **Recommendation 21**: Cultures from BAL should be obtained before starting antibiotics for suspected pneumonia **Recommendation22**: CBC with differential should be done only in cases of suspected pneumonia associated with fever

Based on the high risk for recurrent episodes of bronchitis and/or pneumonia in EA-TEF, the RCWG strongly recommended that chronic wet cough should be evaluated for underlying undiagnosed anatomic and/or functional abnormalities. The main evaluation includes a CT scan to determine the presence of chronic changes such as bronchiectasis[47,50], and a BAL to determine presence of colonization with bacterial and other pathogens as well as for evidence of aspiration(see also section V for the evaluation of aspiration). The threshold for repeating the investigations should be low because there is evidence that airway inflammation, bacterial bronchitis, and bronchiectasis may be present in young children with EA/TEF even when they are asymptomatic[9,45,65,110,111]. However, for patients with an established pattern it is not necessary to repeat the work-up for every exacerbation unless there is suspicion of new pathology. A CXR with each suspected episode of pneumonia may be useful to document how often a patient is having lobar pneumonia, which may, in turn, determine the necessity for further investigations.

IV. Evaluation of Bronchiectasis
Level A Recommendations **Recommendation 23**: A negative CXR does not rule out the presence of bronchiectasis **Recommendation 24**: The presence of bronchiectasis can be best evaluated by low radiation chest CT without contrast **Recommendation 25**: Chest CT should be considered in cases of chronic irreversible changes on CXR
Level C Recommendations **Recommendation26**: CXR should be obtained annually in all children with TEF regardless of their clinical status **Recommendation27**: Chest CT should be obtained annually in all children with TEF regardless of their clinical status

Bronchiectasis is defined as an abnormal dilatation of the bronchial tree and it is one of the more serious pulmonary complications in patients with EA-TEF[65,66,112]. A ratio >0.8 of the bronchial & arterial lumens in a chest CT is considered diagnostic[50]. The finding of "tramlines" and/or of "signet ring" sign opacities in plain radiographs are typical of bronchiectasis but their absence does not rule out the diagnosis[113,114]. Monitoring of disease progression is best achieved with a low-dose high resolution chest CT because it may reveal airway changes that can be prevented from progressing if treated early and aggressively[9,50,65,110].

Radiation exposure from chest CT evaluations remains a concern, especially for young children. High-resolution ultrashort echo time (UTE) magnetic resonance imaging (MRI) completely eliminates radiation exposure[115], whereas modifications in the technique of the dual multidetector CT (MDCT) allow scanning of the pediatric lungs in less than 1 sec and with markedly lower dose of radiation than a regular CT scan[116]. Neither technique requires sedation. However, the techniques are not readily available in every hospital and therefore they are not recommended at this point.

V. Evaluation of Possible Aspiration
Level A Recommendations **Recommendation 29**: Multiple episodes of lobar pneumonia should be evaluated for aspiration or possible underlying anatomical abnormalities **Recommendation 29**: Rigid bronchoscopy is indicated for the evaluation of a possible laryngeal cleft

Level B Recommendations **Recommendation 30**: BAL is indicated in cases of suspected aspiration
Level C Recommendations **Recommendation 31**: Asymptomatic children with EA/TEF who have positive cultures in BAL should be evaluated for possible aspiration **Recommendation 32**: In infants with TEF, the CXR may show characteristic changes consistent with aspiration **Recommendation 33**: Chest CT should be considered in cases of known or highly suspected chronic aspiration **Recommendation 34**: Presence of lipid laden macrophages in BAL of children without acute or chronic lung disease is suggestive of aspiration **Recommendation 35**: Modified Barium Swallow should be performed in all patients prior to initiating oral feedings

Patients with EA-TEF are predisposed to aspiration and the possibility should be investigated in cases of recurrent pneumonia. Conditions to be ruled out include undiagnosed occult communications (e.g. laryngeal cleft and/or undiagnosed fistulae)[18,59–61,74–76,117] or functional abnormalities such as impaired swallowing, vocal cord dysfunction and esophageal dysmotility that predispose to aspiration. Laryngeal clefts in particular can be found in almost 20% of the cases of EA-TEF, and rigid airway endoscopy with probing of the posterior glottis is the gold standard for its diagnosis[118,119].

Presence of contrast material in the tracheobronchial tree after a contrast study (e.g. upper GI series) or foodstuff seen in the trachea of a patient with tracheostomy are definitive of the diagnosis but rather "accidental" findings. Direct visualization of the swallowing with videofluoroscopy or flexible laryngoscopy are the most commonly used clinical modalities that can provide a definitive diagnosis when positive but do not rule out the

diagnosis when negative[52,120,121]. Chest radiographs and especially CT scans of the chest are useful in documenting the presence and extent of the lung damage but they are not pathognomonic of aspiration.

Bronchoalveolar lavage is widely used for the diagnosis of aspiration on the basis of the presence of lipid laden macrophages (LLM) in the BAL[122]. The assumption is that normally there are no lipid molecules in the BAL, therefore their presence is evidence of aspiration of exogenous lipids[122,123]. However, lipid molecules are also released as part of cell death. Therefore lipid-laden macrophages can be found in conditions causing acute or chronic damage to the airways independent of aspiration (e.g. pneumonia, Cystic Fibrosis)[124,125]. Of other potential biologic markers, the most promising is pepsin, but its use has not yet been standardized[126,127]. A detailed approach to the investigation of gastroesophageal abnormalities predisposing EA-TEF patients is provided in the INoEA gastroesophageal guidelines statement[19].

VI. Evaluation of Cyanosis
Level A Recommendations **Recommendation 36**: An echocardiogram should be performed in infants with EA-TEF who develop episodes of severe cyanosis in order to rule out anatomical shunts
Level B Recommendations **Recommendation 37**: Chest CT with contrast should be performed when a vascular anomaly is suspected.

Intermittent acute profound cyanosis in patients with EA-TEF is usually due to near complete collapse of the trachea. However, the possibility of an anatomical shunt has to be ruled out because congenital heart malformations associated with right-to-left shunts

(such as valve atresia, Tetralogy of Fallot, anomalous pulmonary venous return, and septal defects or patent ductus arteriosus) are present in more than one quarter of the patients[80,84] and they are independent predictors of survival[128]. For children with no history of congenital heart disease an echocardiogram is useful in order to investigate for presence of vascular abnormalities such as right-sided or double aortic arch, and aberrant right or left subclavian arteries that may complicate the clinical presentation by causing or exacerbating the degree of tracheomalacia[37,78,80,81,129]. Definitive confirmation will require a CT-angiogram or an MRI/MRA or cardiac catheterization.

RECOMMENDATIONS ON THERAPEUTIC INTERVENTIONS

VII. Management of Tracheobronchomalacia
Level A Recommendations **Recommendation 38**: Non-invasive Positive Pressure Ventilation is useful in children with severe TBM **Recommendation 39**: Tracheostomy may be necessary for TBM associated with severe cyanotic episodes and/or respiratory failure **Recommendation 40**: Custom-made long tracheostomy tube and positive pressure support maybe necessary for severe TBM
Level B Recommendations **Recommendation 41**: Aortopexy is a safe & effective way to treat severe TBM **Recommendation 42**: Posterior tracheopexy than aortopexy is preferable for severe TBM **Recommendation 43**: Bethanecol could be considered in cases of severe TBM

Infants with mild TM can be successfully extubated after the repair of the EA-TEF and do not require any ventilatory or other support. They often remain symptomatic with recurrent or persistent symptoms (such as “barking” cough and coarse wheeze), which tend to be amplified during episodes of upper and/or lower respiratory tract infections. Tracheomalacia tends to improve over time due to the increase in diameter of the tracheal lumen and a reduction in airway collapsibility that minimize the degree of obstruction

relative to lumen size. However, it is a slow process that even under the best circumstances continues for years.

Patients with severe (especially extensive) tracheomalacia (with or without bronchomalacia) may have severe, potentially life-threatening symptoms due to the almost complete tracheal collapse, and they are likely to require some type of ventilatory support[130–133]. Such support is usually needed immediately after extubation following the surgical repair of the EA-TEF, but may be needed for weeks or months afterwards. Patients without lung disease and/or respiratory muscle weakness respond well to non-invasive positive airway pressure (continuous positive airway pressure (CPAP) or Bi-Level Positive Airway Pressure (PAP)) that prevents the complete collapse of the tracheal lumen. High flow nasal cannula (HFNC) is a newer modality that has been shown to be effective and safe[71,134–136].

There is concern that non-invasive PAP in the immediate post-repair period increases the risk of air leak in the area of the repaired TEF, or damage to the esophageal anastomosis[137]. However, in practice the various forms of PAP/HFNC have been used safely[138] and the RCWG felt that the risk of respiratory decompensation in the immediate post-operative period, outweighs the theoretical risks of non-invasive PAP. The situation is more problematic for infants who may need prolonged continuous support because in many countries (including the US) the non-invasive types of ventilation are not approved for continuous use in the home environment.

Aortopexy has been used successfully for TM due to compression of the anterior tracheal wall (e.g. compression by the innominate artery)[139]. However, in EA-TEF the tracheal

occlusion is caused mostly by the intrusion of the posterior tracheal wall into the tracheal lumen. Thus a posterior tracheopexy (pulling of the posterior tracheal membrane with sutures that are secured onto the anterior longitudinal spinal ligament) has been suggested as a more definitive treatment. The technique has been modified to include aortopexy of the descending aorta that is often causing severe compression of the posterior wall of the left main stem bronchus [36,71,130,139–144]. These techniques are still very much dependent on specific surgical and institutional expertise and the evidence about their long-term effectiveness is still scant. Even the timing of the procedure varies, with some centers performing these procedures at the time of the initial repair of the EA-TEF, while other consider them only for severe persisting malacia not responding to non-invasive PAP. Thus, they did not receive a strong recommendation by the RCWG. However, it was recognized that they could become the standard of care in the future.

For patients who have repeated, life threatening cyanotic episodes despite non-invasive PAP, and are not candidates for surgical repair, a tracheostomy provides a secure airway that can be used with or without positive pressure support[145]. Because most TEFs are located near the carina, a regular tracheostomy tube that extends only to the middle trachea may not prevent the collapse of the lower trachea. Therefore a custom made tube that extends to the lower trachea may be necessary (these tubes may also provide enough stenting of the main stem bronchii)[146].

The use of tracheal (and/or bronchial) stents for the management of severe TBM was recently reviewed by the European Respiratory Society[147]. Theoretically, stents would be the “ideal” solution to the problem of severe TBM. However, they are rarely used in infants because of lack of size-appropriate stents, stent migration, difficulty of removal,

and most importantly, because of the need to replace them with a bigger stent as the trachea grows.

Bethanecol is a synthetic muscarinic stimulant that has been used in certain cases of tracheomalacia. Stimulation of the muscarinic receptors in the airways should normally produce bronchospasm, but it seems to actually "open" an airway that is floppy due to malacia by increasing the trachealis muscle tone. There are no RCTs on its use but in a small series it appeared to be safe [148].

VIII. Antibiotic Therapy
Level A Recommendations **Recommendation 44**: The threshold for considering antibiotics should be lower in children with EA-TEF **Recommendation 45**: Azithromycin may be useful in children with recurrent respiratory infections and presence of bronchiectasis
Level B Recommendations **Recommendation 46:** Antibiotic therapy is indicated for asymptomatic children with positive cultures for bacteria in BAL **Recommendation 47:** Antibiotics should be given only in patients who have respiratory symptoms and radiographic changes
Level C Recommendations **Recommendation 48**: Antibiotics should be given only in patients who are febrile and have elevated white blood count

The retention of secretions due to poor airway clearance, and the high prevalence of recurrent, aspiration that promotes the colonization of the lower airways with organisms from the oropharynx, predispose children with EA-TEF to recurrent LTRIs[9,12,17,149]. There was strong agreement that these factors justify the lower threshold for initiating antibiotics with the development of symptoms such as increased "wet" cough (even

without fever) or when cultures from BAL are positive for bacterial pathogens even in the absence of symptoms.

Borrowing primarily from the experience in patients with Cystic Fibrosis[150–152], there was a borderline strong agreement on the use of prophylactic azithromycin due to its antimicrobial and anti-inflammatory properties for patients with chronic symptoms, especially those with documented bronchiectasis[153,154]. However, there was only moderate agreement on using antibiotics in asymptomatic children who have positive BAL cultures especially with organisms are considered to be "normal" oral flora.

There are no systematic studies on the exact organisms that may colonize the airways of patients with EA-TEF, but it is reasonable to assume that they are colonized by the same organisms found in children without EA-TEF who have chronic wet cough (such as *Haemophilus influenzae, Staphylococcus aureus and Streptococcus pneumoniae, Moraxella Catarrhalis)*[50,70,114]*, as well as* anaerobic organisms due to possible aspiration. Most of these organisms are usually sensitive to amoxicillin/clavulanic acid that is recommended for the treatment of chronic cough[155].

IX. Health Maintenance and Prevention
Level A Recommendations **Recommendation 49**: Children with EA-TEF should be followed by a specialized interdisciplinary team **Recommendation 50**: Children with EA-TEF should be evaluated at least annually **Recommendation 51**: Routine evaluation should continue throughout childhood and adulthood **Recommendation 52**: Annual Influenza vaccination is indicated for children with EA-TEF

Level B Recommendations
Recommendation 53: Anti-RSV prophylaxis is indicated for infants with EA/TEF under 12 months of age
Recommendation 54: Airway clearance techniques should be instituted in asymptomatic children with positive cultures in BAL.

Historically, patients with EA-TEF had little follow-up by specialists once they recovered from the initial repair. However, longitudinal studies in adult survivors of EA-TEF highlighted the high prevalence of respiratory complications across the lifespan[44,46]. Early detection and management of respiratory complications may prevent irreversible structural lung disease and loss of lung function[11,16,18,156].

The RCWG strongly recommends systematic follow-up by multidisciplinary teams that include pulmonologists, gastroenterologists, otolaryngologists, pediatricians and thoracic surgeons, as well as dieticians, physiotherapists, speech-language pathologists or occupational therapists, and social workers [2,19,20,110,127,157–159]. Some centres have also included diagnostic and interventional radiologists and an intensivist[160]. Special emphasis is given to have regular evaluation and follow-up by psychologists because of growing concern about the long-term effect of EA-TEF on the quality of life of the patients and their families [161–164].

This approach allows the timely identification of multisystem treatable abnormalities, better care coordination and increase safety by reducing the number of exposure to general anesthesia[156]. For the family, it decreases the number of visits to the hospital and the associated facility charges. This results into higher family satisfaction, while it remains cost effective for the hospitals[109,165,166].

The RCWG strongly agreed that patients with EA-TEF should receive all recommended mandatory vaccinations as well as the annual influenza vaccine. There was only moderate agreement on the need for RSV prophylaxis possibly reflecting different policies that exist in each country regarding this intervention.

How often the patients need to be evaluated by the entire team depends on the special needs of the patients and the feasibility of assembling such a large team in each institution[162]. Acknowledging that such a team may not be feasible in smaller institutions, let alone in clinics or doctors' offices, the RCWG developed a list of the essential elements for the follow-up of patients with EA-TEF (Tables 1A, 1B & 2)

Level A Recommendations **Recommendation 55.**: Airway clearance techniques should be instituted in asymptomatic children with positive cultures in BAL.
Level B Recommendations **Recommendation 56**: A trial of medical anti-GER therapy is useful in children with persistent respiratory symptoms **Recommendation 57*:*** Bronchodilators should not be used because they may worsen the airway collapse
Level C Recommendations **Recommendation 58**: Mucolytics should be used routinely to facilitate airway clearance **Recommendation 59**: Inhaled steroids should be used routinely due to presence of chronic airway inflammation **Recommendation 60**: Inhaled steroids should be used in cases of suspected pneumonia **Recommendation 61**: Systemic steroids should be used in cases of suspected pneumonia **Recommendation 62**: Fundoplication may be required for chronic respiratory symptoms and

Virtually all therapies used in patients with EA-TEF are directed to specific problems/symptoms and are based on empiric evidence. The RCWG rated the following:

Airway Clearance: There was strong agreement that age appropriate airway clearance techniques (e.g. manual chest physiotherapy, High Frequency Chest Wall Oscillation, Positive Expiratory Pressure valve) should be used routinely to aid the clearance of secretions not only for patients who are symptomatic but for those who are asymptomatic as well. There are no studies comparing these techniques in the EA-TEF population (or in tracheomalacia in general). Therefore, the selection relies on the availability of the various devices, and on institutional practices[167–169]. The Positive Expiratory Pressure valve technique may be particularly helpful in patients with tracheomalacia and/or bronchiectasis, by stenting collapsible airways open and aid airway clearance[170].

Anti-GE Reflux therapy: The association of GER with respiratory morbidity and the effectiveness of empiric anti-GER treatment remain highly controversial[58,61,171]. This is in part, due to the fact that respiratory symptoms from the upper and/or from the lower airways can be caused by miniscule amounts of refluxate and as a result the usual diagnostic studies for GERD may likely be within the normal range. The RCWG did not address in detail the management of GER, GERD and aspiration because they have been recently reviewed in detail in the INoEA Consensus Guidelines on Gastrointestinal Complications of EA-TEF[19,171]. However, a moderate agreement was reached on trying empirically anti-GER therapy for patients with persistent respiratory symptoms based primarily on the fact that the prevalence of GER is very high in EA-TEF[52,172].

Bronchodilators: The use of bronchodilators in EA-TEF remains controversial. On one hand there is evidence of increased airway hyperreactivity among patients with EA-TEF that warrants the use of bronchodilators[15,68]. Albuterol is also being used to improve mucociliary clearance[173]. On the other hand, chronic "wheezing" in patients with EA-TEF is often caused by the collapse of the tracheal lumen that cannot be prevented or reversed with bronchodilators. Moreover, the overrelaxation of the tracheobronchial smooth muscle may actually worsen the obstruction (Figure 3A)[174]. Thus, although, a trial with bronchodilators for symptomatic children is warranted, the RCWG does not recommend β_2-agonists as standard therapy for EA-TEF. However, ipratropium bromide (an anticholinergic agent) has been shown to be associated with improved symptoms in children with TM (possibly due to decreased effect on the tracheobronchial muscle tone and/or by reducing the amount of secretions) and it may be considered as an alternative of albuterol[175]..

Inhaled corticosteroids (ICS): The role of steroids in TBM is rather controversial and there was weak agreement on their routine use because the inflammation in EA-TEF tends to be neutrophilic and therefore less likely to respond to steroids[63]. Furthermore, there is some evidence that chronic use of high doses of ICS may actually cause or exacerbate existing tracheomalacia[176]. Thus of the routine use of ICS should be reserved for documented or highly suspected airway hyperreactivity.

Mucolytics: Mucolytic agents (Dornase alpha, hypertonic saline, N-Acetylcysteine) are often used in patients with tracheomalacia on the assumption that the impaired airway clearance probably results in the accumulation and possibly thickening of secretions. Dornase alpha and hypertonic saline are commonly used in the management of cystic

fibrosis-related chronic bronchiectasis, but their effect in non-CF bronchiectasis is not as well defined[177]. Thus, the RCWG did not support its routine use.

DISCUSSION

Guidelines are intended to review systematically the available evidence, rate its validity, and distill the findings into easy to understand recommendations that practitioners can follow. Many different methodologies have been developed for this purpose[21,178,179] The GRADE method (Grading of Recommendations Assessment, Development and Evaluation)[179], has been recently adopted by a number of professional organizations for the development of guidelines, but we did not choose it because it relies heavily on RCTs and systematic observational studies that are not available in the literature on EA-TEF.

We developed our recommendations on the basis of the Rand Appropriateness Method[24–26], offered certain important advantages for the type of evidence we had available such as: a) the responders do not have to accept positions they do not agree with, in order to reach a consensus; b) disagreements are not suppressed, thus reflecting more accurately the uncertainties and variability that exist in the actual clinical practice; c) each item is rated by all responders, and their responses carry the same weight (thus preventing a single issue (or a single person) from dominating the process; d) the anonymity of the responses allows the participants to express their opinions more freely; and e) it provides timely feedback by communicating the results of each round to the responders, allowing them to compare their responses to others and potentially adjust them.

Our recommendations were based on the strength of the agreement among the RCWG members. Thus, Level A recommendations refer to unanimous adoption of specific

interventions and care practices. Level B & C recommendations reflect both the lack of evidence and actual controversies on a specific topic, as well as the different areas of expertise, skill mix, resource availability and hospital culture among the RCWG's representative institutions. This differs from other consensus based methods that assign different weight on the evidence depending on the design of the study, its size, the type of analysis etc.)[180].

As diagnostic methods improve and therapeutic interventions become more precise, it is likely that many of the current recommendations will have to be revised. In the meantime, the document provides a common approach for the evaluation and management of these complex patients at levels that can be provided by most practitioners and institutions. It may also serve as the basis for multicenter collaborations that will eventually provide a higher level of evidence.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contribution of Dr. Michael Rutter and Dr. Marlene Soma for their input in the development of the original statements. We would also like to thank Drs. Frederic Gottrand, Christophe Faure, Luigi dall' Oglio, and Usha Krishnan for their critical review of the manuscript.

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LEGENDS - FIGURES

Figure 1. Schematic presentation of the methodology for the development of the recommendations on the diagnosis & management of the respiratory complications of EA-TEF.

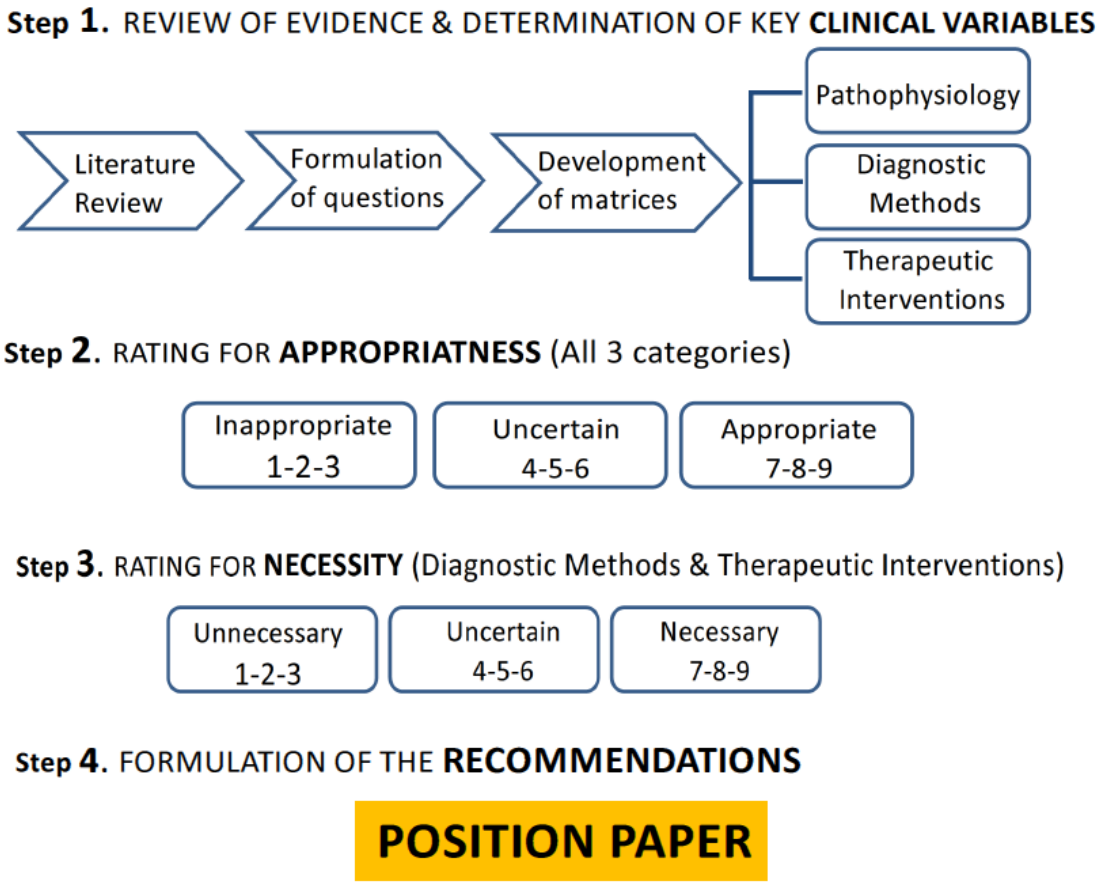


Figure 2. Schematic diagram of the pathophysiology of the respiratory complications of TEF.

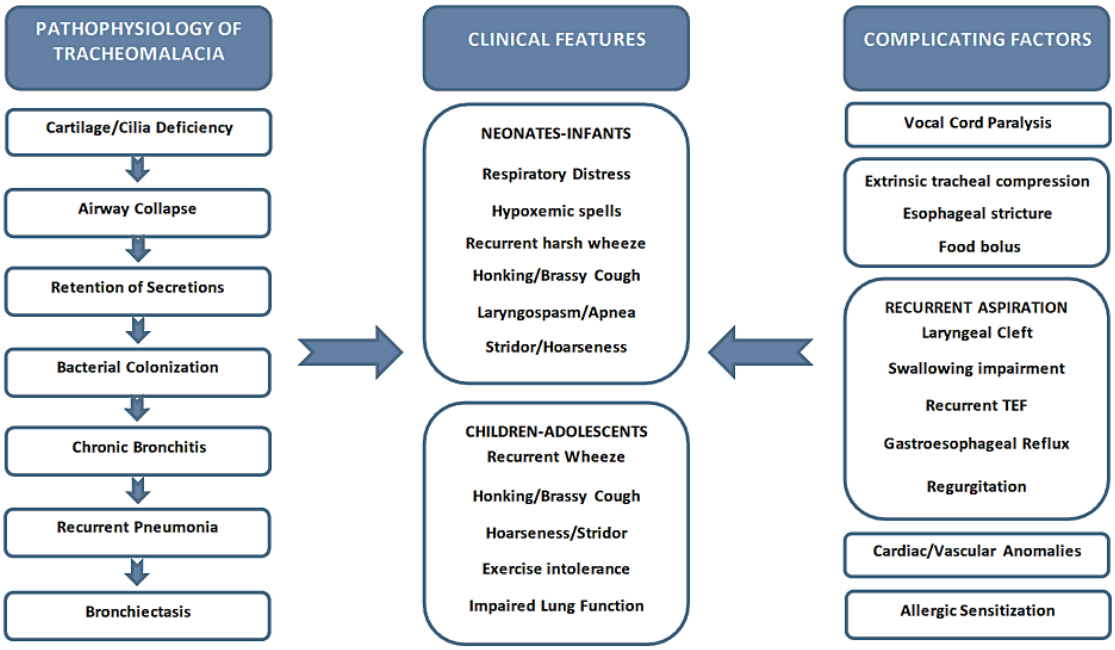
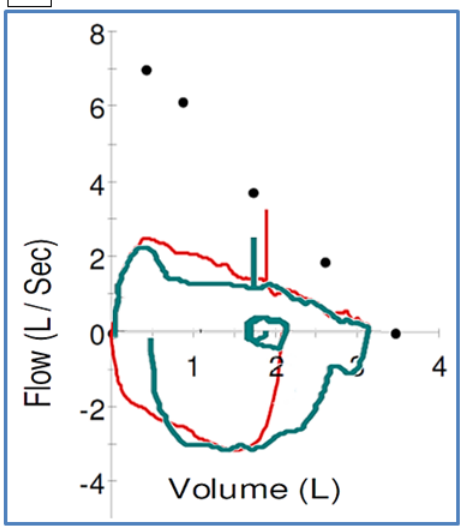


Figure 3A. MEFVCs in a child with EA-TEF and tracheomalacia. **Red line (Baseline)**. The flow-volume curve is concave consistent with significant lower airway obstruction. The partial collapse of the trachea affects the initial portion of the MEFVC causing greater decrease in the FEFmax and the FEF_{25} than on the FEV_1.. The inspiratory flow-volume loop is normal. **Green line (post-bronchodilator):** There is more extensive flattening of the MEFVC reflecting increased collapse of the trachea and major bronchii due to overrelaxation of the airway smooth muscle. The inspiratory flow-volume loop remains normal.

3B. Tidal flow-volume loop in an infant with significant tracheomalacia. The flattening of the expiratory tidal loop is due to the collapse of the trachea on expiration, while the inspiratory flow-volume loop is normal. The ratio of the maximal expiratory to the maximal inspiratory flow (ME/MI) that is normally approximately 1, is only 0.3. The tidal inspiratory and expiratory volumes are not affected.

A



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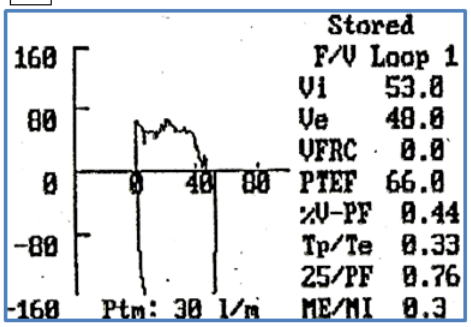

LEGENTS - IMAGES

Image 1. Tracheoesophageal fistula & Tracheobronchomalacia: (A) TEF post repair. Note the ridge on the posterior tracheal wall above the carina as well a visible pouch (the pouch is often closed); **(B)** At rest, the mid-trachea maintains its characteristic "horseshoe" shape; **(C):** Severe obstruction of the trachea lumen and change in its shape due to the intrusion of the posterior membranous wall into the lumen during cough; **(D):** Almost complete occlusion of the Right Main Stem Bronchus during cough

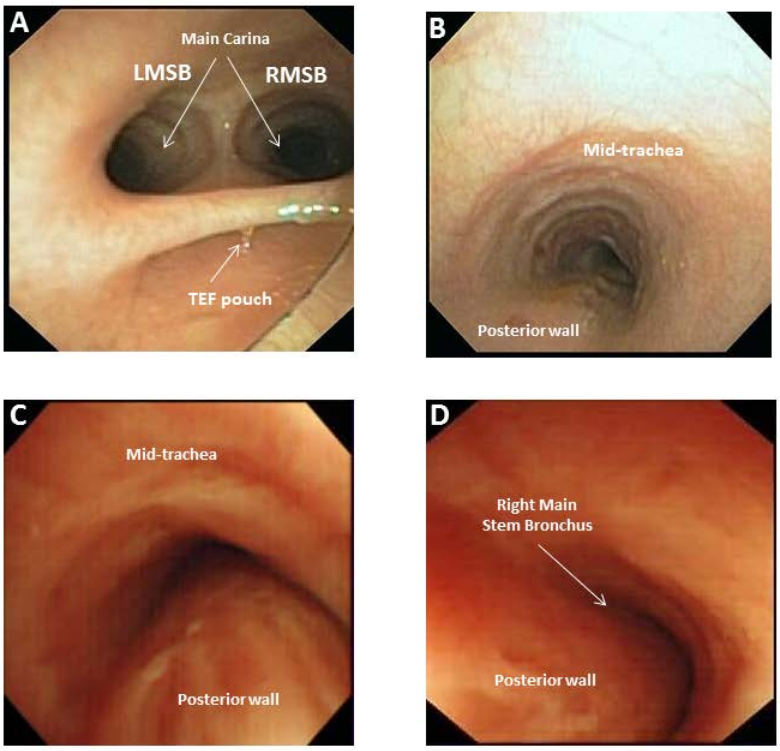

Table 1A. Respiratory Evaluation - INITIAL VISIT

EA-TEF type	**Type A; Type B; Type C; Type D; Type E ("H-type")**
Upper airway anomalies	• Laryngeal cleft; choanal atresia
Cardiac anomalies	• VSD, PDA, TOF, other
Musculoskeletal anomalies	• Vertebral, rib & limb abnormalities
Gastrointestinal anomalies	• Imperforated anus, duodenal atresia, malrotation
Renal & Urologic anomalies	• Renal agenesis, horseshoe kidney, hypospadias
Genetic abnormalities	• VACTERL; Trisomy 13, 18, 21; CHARGE; Feingold; Pallister-Hall; Anophthalmia-esophageal-genital syndromes
Surgical History	• Age at repair; Type of surgical repair • Evaluation of trachea, larynx, vocal cords • Surgical and/or medical complications • Tracheopexy, aortopexy, tracheostomy
Respiratory Symptoms	• "Breath holding" spells with or without color change • Cough and/or wheezing without respiratory infection • Recurrent pneumonia

Respiratory Support	• Invasive & non-invasive ventilation (duration) • Supplemental oxygen (duration) • Tracheostomy
Gastrointestinal symptoms & complications	• Esophageal strictures / Esophageal dilatation • Aspiration (Choking/coughing while eating/drinking • Gastroesophageal reflux and/or Regurgitation (gagging/choking not associated with eating
Feeding History	• Route of feeding (oral, NG/ND tube); G-tube; G-J tube) • Growth: Body Mass Index (%ile)
Adjunct therapies	• Anti-GER • Chronic antibiotics • Inhaled Bronchodilators and/or steroids • Mucolytics • Airway clearance

VSD: ventricular septal defect; PDA: Patent Ductus Arteriosus; TOF: Tetralogy of Fallot; NG: nasogastric; ND: nasoduodenal; G-tube: gastrostomy tube; G-J tube: Gastro-jejunal tube; GER: Gastroesophageal reflux

Table 1B. Respiratory Evaluation - FOLLOW-UP VISIT

Interim surgical and/or medical complications	• **Esophageal dilations** • **Aspiration/Pneumonia**

Respiratory support (chronic)	• Tracheostomy • Chronic invasive/non-invasive ventilation • Need for supplemental oxygen
Respiratory symptoms (chronic)	• "Breath holding" spells with or without color change • Cough and/or wheezing without respiratory infection • Recurrent pneumonia • Exercise intolerance
Feeding History	• Route of feeding (oral, NG/ND tube); G-tube; G-J tube)
Gastrointestinal complications & symptoms	• Esophageal strictures / Esophageal dilatation • Aspiration (choking/coughing while eating/drinking) • Gastroesophageal reflux and/or Regurgitation (gagging/choking not associated with eating)
Growth	• Body Mass Index (%ile)
Medications & adjunct therapies	• Anti-GER • Chronic antibiotics • Inhaled Bronchodilators and/or steroids • Mucolytics • Airway clearance

VSD: ventricular septal defect; PDA: Patent Ductus Arteriosus; TOF: Tetralogy of Fallot; NG: nasogastric; ND: nasoduodenal; G-tube: gastrostomy tube; G-J tube: Gastro-jejunal tube; GER: Gastroesophageal reflux

Table 2. Suggested diagnostic tests for patients with TEF according to their age

TEST	INFANT	CHILD	ADOLESCENT
Bronchoscopy (flexible & rigid)	**Yes**	**prn**	**prn**
Pulmonary Function Testing	**(?)[1]**	**Yes**	**Yes**
Modified Barium Swallow / Videofluoroscopy / FESS study	**Yes[2]**	**prn[3]**	**prn[3]**
Chest X-ray	**Yes**	**prn**	**prn**
Chest CT	**(?)[4]**	**Yes[5]**	**Yes[5]**
Upper-GI Endoscopy	**Yes**	**prn**	**prn**
Echocardiogram	**Yes**	**prn**	**prn**

1: Moderate or weak support because equipment are not readily available everywhere; **2**: before oral feedings are introduced; **prn**: as needed; **3**: for suspected aspiration; **4**: multidetector CT for evaluation of tracheomalacia & with contrast for vascular abnormalities; **5**: for detection and/or follow-up of bronchiectasis