Published in final edited form as:

Pediatr Pulmonol. 2014 October ; 49(10): 960–970. doi:10.1002/ppul.22922.

Tracheomalacia is associated with lower FEV₁ and *Pseudomonas* acquisition in children with CF

Anthony J. Fischer, MD PhD¹, Sachinkumar B. Singh, MBBS MPH¹, Ryan J. Adam, MS², David A. Stoltz, MD PhD², Christopher F. Baranano, MD³, Simon Kao, MD⁴, Miles M. Weinberger, MD¹, Paul B. McCray Jr., MD¹, and Timothy D. Starner, MD¹

¹Department of Pediatrics, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242

²Department of Internal Medicine, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242

³Department of Otolaryngology, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242

⁴Department of Radiology, University of Iowa, 200 Hawkins Drive, Iowa City, IA 52242

Abstract

BACKGROUND—Tracheomalacia (TM) occurs in approximately 1 in 2,100 children. Because the trachea develops abnormally in animal models of cystic fibrosis (CF), we hypothesized this may also occur in children with CF, increasing their risk of TM.

PURPOSE—To examine the prevalence and clinical consequences of TM in children with CF.

METHODS—We studied children with CF born between 1995 and 2012. TM was defined as dynamic collapse of the trachea, and the severity was recorded as described in the chart. The effect of TM on patient outcomes, including FEV₁, CT changes, and acquisition of CF pathogens, was assessed using a longitudinal patient dataset.

RESULTS—89% of children with CF had at least one bronchoscopy (n = 97/109). 15% of these children had TM described in any bronchoscopy report (n = 15/97). Of the patients with TM, 8 had meconium ileus (p = 0.003) and all were pancreatic insufficient. *Pseudomonas aeruginosa* infection occurred 1.3 years earlier among children with TM (p = 0.01). Starting FEV₁ values by age 8 were diminished by over 18% of predicted for patients with TM. Life-threatening episodes of airway obstruction occurred in 3 of 15 patients with CF and TM, including one leading to death. Gender, prematurity, and hepatic disease were not associated with TM. No difference was observed in the frequency of bronchiectasis.

CONCLUSIONS—TM is significantly more common in infants and children with CF than in the general population and is associated with airway obstruction and earlier *Pseudomonas* acquisition.

Keywords

Tracheomalacia; Cystic Fibrosis; Bronchoscopy; Meconium Ileus; Pediatric; Infant; Airway; Obstructive Lung Disease

Introduction

Cystic Fibrosis (CF) is the most common lethal genetic disease of Caucasians with an incidence of approximately 1 in 3,000.¹ Tracheomalacia (TM), a disorder in which the tracheal cartilage is unable to prevent airway collapse from increased intrathoracic pressure during exhalation, is estimated to occur in 1 in 2,100 infants and toddlers.² The coexistence of CF and TM has been observed anecdotally in children³ and may result in prolonged respiratory symptoms despite antibiotic treatment of lower airway infection. A recent study using CT showed a high prevalence (69%) of TM in adults with CF.⁴ While some degree of TM and bronchomalacia occurs from chronic infection and inflammation, TM may be present congenitally in some patients. In fact, data from CF animal models including pig and mouse reveal tracheal abnormalities at birth.^{5,6} Currently, the prevalence of TM among children with CF is unknown. Our clinical experience suggested an increased rate of TM in infants and preschool children with CF who did not yet have bronchiectasis or chronic airway infection.

It is the standard-of-care at the CF Center at the University of Iowa to monitor for lower airway inflammation and infection by bronchoscopy; usually starting toward the end of the first year of life and then every 2 years until patients produce sputum. This provided a unique opportunity to estimate the prevalence of TM in early CF and to identify cases in which TM contributed to their disease progression.

We hypothesized that the prevalence of TM in young children with CF is higher than in the general population (i.e. > 1:2,100), that TM is congenital, and that TM is observed prior to the onset of chronic bacterial colonization or severe airway inflammation. We also hypothesized that TM negatively impacts CF disease course, including decreased initial lung function, increased acquisition of CF pathogens including *Staphylococcus aureus* and *Pseudomonas aeruginosa*, and earlier development of bronchiectasis. To test these hypotheses, we conducted a retrospective cohort study of children with CF followed at the CF Center at the University of Iowa to determine the prevalence of TM and the effects of TM on CF outcomes.

Methods

A retrospective cohort of children with CF born between January 1, 1995 and October 31, 2012 and cared for at the University of Iowa Cystic Fibrosis Center (n=109) was studied. The study was approved by the Institutional Review Board of the University of Iowa. To calculate the prevalence of TM and compare outcomes of patients with and without TM, we included only active center patients who had at least one bronchoscopy at the University of Iowa. Children with CF-related metabolic syndrome were excluded. The diagnosis of CF was established using criteria published by the Cystic Fibrosis Foundation.⁷ The date of CF diagnosis was defined as birth for children with newborn meconium ileus or the date of diagnostic sweat testing or confirmatory genotyping for children without meconium ileus. Parameters collected included basic demographics to establish the diagnoses of CF and TM, as well as biometric measurements, bronchoscopy reports, problem list, and *CFTR* mutations.

We obtained measurements of bronchoalveolar lavage (BAL) fluid composition, including cell count and differential and quantitative bacterial culture as previously described.⁸ Microbiology data were recorded from quantitative sputum cultures or throat cultures obtained during regular visits to the CF Center. Spirometry was routinely performed at clinic visits for those children able to perform the maneuver. We recorded FEV₁, FVC, and FEF_{25–75} from each clinic visit and defined initial FEV₁ as the best percentage of predicted FEV₁ obtained by age 8. We also examined flow-volume loops for findings consistent with TM, including reduced peak expiratory flow rate or reproducible expiratory flow oscillations.⁹

From chest CT reports, we obtained presence of bronchiectasis, inhomogeneity of aeration, peribronchial thickening, or airway abnormalities. CT evidence supporting TM included abnormal tracheal circularity or tracheal deformation. Chest CT images were obtained directly from the medical record as de-identified .jpg files and imported into ImageJ. Volumetric data sets were imported into the Amira visualization software (Visualization Sciences Group, Burlington, MA) where the trachea was manually segmented and subsequently reconstructed for 3D visualization.

Flexible bronchoscopy was usually performed transnasally with a 3.8 mm Pentax bronchoscope on children sedated with intravenous midazolam and either propofol or fentanyl. On rare occasions (such as choanal stenosis), an oral approach was used. For one case (Patient 1), bronchoscopy was performed through endotracheal tube due to respiratory failure. Aside from this case, artificial airways, including laryngeal mask airway and endotracheal tube were not used. The diagnosis of TM was made by the bronchoscopist if there was dynamic airway collapse. The purpose of bronchoscopy was evaluation of inflammation and detection of airway pathogens rather than identifying TM. Therefore, patients were considered to have TM if the diagnosis was made during any bronchoscopy. We recorded the severity of TM as it was described in the procedure note. Selected bronchoscopic video files were imported into ImageJ, de-identified, and rendered as still images.

Data describing symptoms potentially related to TM were abstracted from discharge summaries, clinic notes, or histories and physicals. We recorded data related to the outcome of patients with CF and TM including operative reports and death notes, if applicable. When records were incomplete, families or local physicians were interviewed for clarification.

To identify CF-related conditions potentially associated with TM, we examined prescriptions for pancreatic enzyme replacement (to indicate pancreatic insufficiency). As a surrogate marker for CF-related liver disease, we noted the presence of any elevation in alanine transaminase greater than or equal to 100 U/L.

CFTR mutations were classified according to their predicted functional class (I – V).¹⁰ Novel mutations resulting in a premature stop codon, frameshift, or gross rearrangement of exon structure were classified as type I mutations. Other novel mutations were classified as unknown. The least severe mutation was identified for each patient as the mutation with the

highest functional class. TM, meconium ileus, and pancreatic sufficiency phenotypes were then correlated with mutation severity.

To examine potential associations of TM with CF pathogen acquisition, we used longitudinal culture data from CF clinic visits or hospitalizations. Per CF Foundation guidelines, patients with CF are scheduled 4 clinic visits per year and may have additional clinic visits at the time of illness. Respiratory culture reports from each patient were scored for the presence or absence of *S. aureus*, *P. aeruginosa*, mucoid *P. aeruginosa*, and *Haemophilus influenzae*. For this analysis, we did not distinguish between throat culture and BAL culture. The time to first acquisition of each pathogen was compared using Kaplan-Meier survival analysis, using cases of TM versus control patients with CF but no diagnosis of TM.

Standard methods of statistical analysis were applied using SAS version 9.3 (SAS Institute, Inc. Cary, NC). For comparisons between patients with and without TM, we used t-tests for normally distributed continuous variables, the Mann-Whitney-Wilcoxon test for ordinal or non-normally distributed continuous variables, and Fisher's exact test for categorical variables. Kaplan-Meier survival analysis was used to compare the time to acquisition of CF pathogens and bronchiectasis. *P* values less than 0.05 were considered significant, and there was no correction for multiple testing.¹¹

Results

109 patients diagnosed with CF were born during the study interval (Figure 1). 97 had at least one bronchoscopy performed in our center (89%). The median age at the time of initial bronchoscopy was 15 months, and the median number of bronchoscopies per patient was 2 (range 1 to 5). Of the patients who did not have a bronchoscopy, one patient's family declined consent, 2 did not have bronchoscopy because of young age, 3 were diagnosed with CF at an older age, and 6 were followed previously at other centers.

TM was documented in 15 of the 97 patients (15%). One patient was diagnosed with TM prior to CF and one patient was diagnosed with TM and CF on the same visit. One patient was diagnosed with TM at the time of second bronchoscopy (patient 10). The incidence of new cases of TM in patients with CF has been stable over time. Of the 15 patients, 7 were born between 1995 and 2000, 3 between 2001 and 2006, and 5 between 2007 and present. There was additionally one patient who had a complete tracheal ring in the mid-trachea. Of the 6 patients previously cared for at other centers, one had been diagnosed with TM by bronchoscopy at the prior center. Patients with CF and TM were generally young when diagnosed with TM (median age of diagnosis was 16 months) and all but one had chronic cough (Table 1).

The percentage of tracheal collapse was estimated in 8 of the 15 patients and all of these had >50% collapse. 6 of the 8 patients had 80 – 90% tracheal collapse. TM was categorically graded in the other 7 patients and ranged from very mild to mild. Dynamic collapse of the trachea with tidal breathing can result in contact between the anterior and posterior walls of the trachea, as shown for a 9 month old patient with CF (Figure 2). There was no explicit

documentation of airway collapse secondary to cough in the bronchoscopy reports examined. 6 of the 15 patients with TM had no bronchoscopy subsequent to the diagnosis of TM. 4 of 9 patients had TM re-demonstrated on followup bronchoscopy.

Chest CT was performed for 11 of the 15 patients with TM. Tracheal abnormalities were visible on CT for 6 patients. A 3-dimensional rendering of a chest CT of a 7 month old patient with CF (patient 11) showed marked flattening of the mid-trachea (Figure 3A). Rotational views of this trachea can be viewed in a supplemental video. Similarly, a chest CT of a 5 year old patient with CF who had been diagnosed with TM at another center (patient 16) shows abnormal tracheal circularity (Figure 3B). This patient had similar symptoms of chronic cough, noisy breathing, and apneic spells.

Pulmonary function testing was completed for 11 of the 15 patients with TM. Large airway obstruction was apparent on spirometry (reduction in peak expiratory flow rate or oscillations on peak flow) for 5 patients (Supplemental Figure). One patient (patient 11) had infant pulmonary function testing using the raised volume rapid thoracoabdominal compression technique that was consistent with TM. There was expiratory flow limitation at a very low applied extrathoracic pressure, as would be expected to occur with TM.

Conditions associated with tracheomalacia

Of the patients with TM, all were pancreatic insufficient and 8 had meconium ileus (relative risk 4.1, $p = 0.003$ by Fisher's exact test). Gender, prematurity, and CF liver disease were not associated with TM. There was a similar age at first bronchoscopy and no significant difference in sweat chloride concentration between groups (Table 2).

There was wide variation in BAL fluid neutrophil count and in the bacteriology results (Table 1). TM was observed in 4 cases of patients with $<25\%$ neutrophils, and in 5 cases where *S. aureus*, *P. aeruginosa*, and *H. influenzae* were not isolated. There was no difference in BAL fluid neutrophil percentage between patients with and without TM (Table 2).

Patients with TM had lower initial FEV₁ than patients without TM (18.5% lower median FEV₁ % predicted) (Table 2). The median age of diagnosis of bronchiectasis was not statistically different between groups (9.7 years in patients with TM and 9.9 years in patients without TM). There were also no differences in earlier signs of small airway disease including air trapping and peribronchial thickening.

CFTR Genotype-Phenotype Correlation

Patients with CF and TM generally had more severe *CFTR* mutations. 14 of the 15 patients with CF and TM had at least one copy of the F508 mutation and 11 were homozygous for F508 (Table 2). No patients with CF and TM carried class III, IV, or V mutations of *CFTR*. This pattern was similar to the meconium ileus phenotype and in stark contrast with pancreatic sufficiency (Table 3).

Pathogen acquisition in patients with TM

Time-to-event analysis was completed for first acquisition of common CF pathogens. There was no difference in the acquisition of *S. aureus* or *H. influenzae*. For the full cohort, the median age at first positive culture for *H. influenzae* was 1.5 years and *S. aureus* was 2.2 years. The time to acquisition of *P. aeruginosa* was earlier for patients who had a diagnosis of TM (Figure 4). The median age of first *P. aeruginosa* infection was 1.3 years in patients with TM, and 2.6 years in patients without TM ($p = 0.01$). There was also earlier acquisition of mucoid *P. aeruginosa*, a surrogate for chronic *Pseudomonas* infection ($p = 0.04$).

Clinical characteristics of patients with CF and TM

Patients with CF and TM generally presented with chronic cough (14/15 patients), worse during the daytime and markedly worse with viral infection. Stridor was reported in one patient. Wheezing was reported in five patients. The response to albuterol and corticosteroid treatment was variable and the response to antibiotics was generally favorable.

Life threatening episodes of airway obstruction were seen in 4 infants with CF and TM. The most severely affected patient suffered an apneic arrest at 2 months of life despite administration of CPAP and required intubation. Bronchoscopy and cine CT revealed severe TM and bilateral bronchomalacia. Because of inability to maintain respiration off of a ventilator, bilateral bronchial stents were placed. The patient ultimately died at 3 months following multiple complications. Another patient had 3 episodes of bradycardic arrest while in hospital and an aortopexy was performed at 5 months of age. He continues to have abnormal pulmonary function testing with blunted peak expiratory flow secondary to TM (Supplemental Figure), but aortopexy resulted in substantial improvement in respiratory effort and elimination of a loud expiratory noise.

Discussion

The data presented here show that TM is prevalent in children with CF and that TM is associated with more severe manifestations of CF. The prevalence of TM in children with CF (15%) is much higher than would be expected from the 1:2,100 rate estimated in the general pediatric population.² Similar rates of TM have recently been reported in two other centers.^{12,13} In contrast to the prevalence of TM identified by bronchoscopy, a recent study of 20 children with CF utilizing an acoustic reflection method did not identify association of CF and TM.¹⁴ TM becomes more common in adults with CF, with a 69% prevalence estimated by one recent study.⁴

The most important associations with TM in children with CF were their decreased initial FEV₁ values and significantly earlier acquisition of *P. aeruginosa*. Possible mechanisms linking TM to decreased FEV₁ and acquisition of *P. aeruginosa* are listed below.

Model 1. TM is an acquired consequence of airway infection

Patients with the most impairment in CFTR function have relatively greater deficit in host defense. This results in more frequent infections, proteolytic airway destruction, and a more rapid decline in pulmonary function. Following repeated infections, patients acquire

secondary TM. This model is supported by the high prevalence of TM in adults with CF.⁴ Neutrophilic inflammation in the early stages of cystic fibrosis increases the risk of airway dilation and bronchiectasis, likely mediated by enzymes such as neutrophil elastase.^{15,16} Tracheal deformation by cough could also increase acquisition of TM. TM was reported in 15% of children with respiratory symptoms examined in one tertiary care center¹⁷, and TM coexists with chronic bronchitis in adults.¹⁸ Furthermore, the prevalence of TM may correlate with underlying disease severity.^{18,19} These observations illustrate the principle that acquired TM can occur in patients with frequent cough and worsen over time.

Model 2. TM contributes directly to airway obstruction and infection

Morphologic abnormalities of the trachea interfere with airway clearance due to tracheal collapse. This directly worsens peak expiratory flow, decreases airway clearance, and increases the risk of pathogen acquisition. This model is supported by the fact that CF animal models including pig and mouse have abnormalities in tracheal development.^{5,6} The observation of abnormal tracheal circularity was also verified in young children with CF.⁶ Abnormalities of tracheal cartilage could increase deformability and predispose to airway collapse. In this study, we show evidence that TM is present at very early time points, preceding chronic lower airway infection. We did not identify differences in BAL neutrophil percentage between patients with and without TM, implying that inflammation alone was an unlikely explanation for TM. The data in this study suggest that TM is present at birth in a subset of patients. Thus, TM may be part of a spectrum of CF-related congenital abnormalities including meconium ileus, obstruction of the pancreatic duct, and obstruction of the vas deferens.

Model 3. TM, airway obstruction, and infection are inter-related

TM can occur congenitally in some patients and impair clearance. Congenital TM may worsen over time following infection and pulmonary clearance subsequently deteriorates. Model 3 represents a combination of Models 1 and 2. It is probably the most realistic situation given the current data, with TM present congenitally in a subset of patients and subsequent worsening of airway malacia due to chronic airway inflammation.

The relationship between meconium ileus, early respiratory symptoms, and CF disease progression was recently identified.¹⁶ We found that TM was associated with meconium ileus, suggesting perhaps these abnormalities share a common mechanism or occur at the same stage of fetal development. These disorders both tended to occur in children with more severe *CFTR* alleles (Table 3), and our most severely affected patient with TM had meconium ileus and two Class I *CFTR* mutations (G542X and 3659delC). Patients with meconium ileus may have diminished pulmonary host defense due to less residual *CFTR* activity. This deficit would then allow for earlier infection and subsequent acquisition of secondary TM, similar to Model 1 above. However, TM and associated airway abnormalities on CT appeared prior to chronic airway infection or bronchiectasis. We hypothesize that TM, like meconium ileus, is a congenital phenotype observed in patients with the least residual *CFTR* activity. *CFTR*, by controlling fluid and electrolyte transport, may be an important gene product influencing primordial airway and gut formation during fetal development.

The individual cases illustrate the potential for TM to cause morbidity and mortality in infants and toddlers with CF, including multiple episodes of life threatening airway obstruction. Symptoms of TM in children with CF included noisy breathing and chronic “barky” cough similar to previous descriptions of airway malacia in the non-CF population.^{20,21} Symptoms in these patients generally occurred prior to the onset of substantial bacterial infection, inflammation, or airway remodeling. TM may complicate common viral infections in early childhood by decreasing airway clearance of the increased mucus production that occurs distal to the malacia. Bacteria may then more readily proliferate as appears to occur in protracted bacterial bronchitis.⁸

This study is limited by its retrospective, single-centered design. Because the purpose of bronchoscopy was not identifying TM, there may be underdiagnosis of TM in our cohort. This is because the standard practice for bronchoscopy in children with CF involved deeper levels of sedation than would be used for investigation of suspected airway malacia. The diagnosis of TM at the time of bronchoscopy is influenced by the degree of sedation.²² Indeed, one patient in this study was not diagnosed with TM on the initial procedure despite symptoms in infancy suggestive of TM. This patient had a deeper level of sedation documented on the first bronchoscopy at age 2 than on the subsequent procedure at age 6. Patients who are heavily sedated may not breathe deeply enough to observe dynamic airway collapse. Similarly, increased airway pressure delivered through an artificial airway (endotracheal tube or laryngeal mask airway) can stent open the airway and prevent the diagnosis.

Clinical Implications

TM should be considered in infants and pre-school age children with CF who have persistent cough unresponsive to antibiotics. The occurrence of apneic spells in infancy should also raise suspicion for an airway disorder. Infants with CF and TM developing acute respiratory symptoms may benefit from positive pressure ventilation (CPAP or BiPAP), as these interventions can stent open proximal airways and relieve respiratory distress. Because bronchodilators relax airway smooth muscle, they may paradoxically worsen respiratory distress due to airway collapse from decreased airway smooth muscle tone.²³ Patients receiving bronchodilator therapy should be observed closely for the nature of the clinical response. Since airway malacia may predispose children without CF to bacterial bronchitis,⁸ lower respiratory infections (including *P. aeruginosa*) may occur earlier or more frequently in children with both CF and TM. TM is likely to decrease airway clearance, an important part of therapy for CF. Aggressive mucolytic therapy may be of benefit for such patients. Huff-coughing may improve airway clearance because it has lower peak expiratory flow than harsh coughs, reducing the tendency for tracheal collapse. We report one case where aortopexy was used successfully for severe TM associated with continuous increased work of breathing. Although that patient clinically benefited from the surgical procedure, he still has functional evidence of TM by spirometry (supplemental figure). Other recent approaches to management of localized segments of airway malacia include customized absorbable stent placement.²⁴

Future Directions

Because many patients with TM also had had CT abnormalities of the trachea, new radiologic methods may offer alternatives for identification of TM that are less invasive than bronchoscopy.^{25,26} However, further comparisons of the sensitivity of these tests relative to flexible bronchoscopy are needed, optimally in prospective studies. Another method that may prove helpful in diagnosing TM is the use of simultaneous esophageal and tracheal manometry during bronchoscopy, allowing direct measurement of the pressure needed for tracheal collapse.¹⁹ Although there are surgical options for TM, there is no consensus yet about medical management of TM. The association of airway malacia with bacterial bronchitis⁸ suggests that antibiotics (either inhaled or systemic) may benefit children with CF and TM. In this study, we did not identify earlier development of bronchiectasis in patients with TM. Prospective studies are needed to further examine the effects of TM on bronchiectasis and other aspects of lung disease progression. The observation of congenital TM in CF raises further questions about the role of *CFTR* in airway development, and animal models of CF could help elucidate the underlying mechanisms or identify new therapeutic targets.

Conclusions

We have identified TM as a common co-morbidity of infants and children with CF. It appeared most commonly in children with other severe manifestations of CF such as meconium ileus and was not observed in pancreatic sufficient patients. TM was associated with some features of disease progression, including reduced initial lung function and earlier acquisition of *P. aeruginosa*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Julie Davis, RRT for assisting with bronchoscopies and Joseph Zabner, MD for helpful comments.

Funding source: This study was supported by the Division of Pediatric Allergy, Immunology, and Pulmonary Medicine at the University of Iowa Children's Hospital

Abbreviations

BAL	Bronchoalveolar lavage
CF	Cystic Fibrosis
TM	Tracheomalacia

References

1. O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet*. 2009; 373(9678):1891–1904. [PubMed: 19403164]

2. Boogaard R, Huijsmans SH, Pijnenburg MW, Tiddens HA, de Jongste JC, Merkus PJ. Tracheomalacia and bronchomalacia in children: incidence and patient characteristics. *Chest*. 2005; 128(5):3391–3397. [PubMed: 16304290]
3. Walker W, Head C, Legg J, Connett G. Primary tracheomalacia and persistent wheezing in cystic fibrosis during infancy. *Journal of bronchology & interventional pulmonology*. 2011; 18(2):161–163. [PubMed: 23169087]
4. McDermott S, Barry SC, Judge EE, Collins S, de Jong PA, Tiddens HA, McKone EF, Gallagher CC, Dodd JD. Tracheomalacia in adults with cystic fibrosis: determination of prevalence and severity with dynamic cine CT. *Radiology*. 2009; 252(2):577–586. [PubMed: 19508990]
5. Bonvin E, Le Rouzic P, Bernaudin JF, Cottart CH, Vandebrouck C, Crie A, Leal T, Clement A, Bonora M. Congenital tracheal malformation in cystic fibrosis transmembrane conductance regulator-deficient mice. *The Journal of physiology*. 2008; 586(13):3231–3243. [PubMed: 18450781]
6. Meyerholz DK, Stoltz DA, Namati E, Ramachandran S, Pezzulo AA, Smith AR, Rector MV, Suter MJ, Kao S, McLennan G, Tearney GJ, Zabner J, McCray PB Jr, Welsh MJ. Loss of cystic fibrosis transmembrane conductance regulator function produces abnormalities in tracheal development in neonatal pigs and young children. *American journal of respiratory and critical care medicine*. 2010; 182(10):1251–1261. [PubMed: 20622026]
7. Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, Durie PR, Legrys VA, Massie J, Parad RB, Rock MJ, Campbell PW 3rd, Cystic Fibrosis F. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *The Journal of pediatrics*. 2008; 153(2):S4–S14. [PubMed: 18639722]
8. Kompare M, Weinberger M. Protracted bacterial bronchitis in young children: association with airway malacia. *The Journal of pediatrics*. 2012; 160(1):88–92. [PubMed: 21868031]
9. Vincken WG, Cosio MG. Flow oscillations on the flow-volume loop: clinical and physiological implications. *The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology*. 1989; 2(6):543–549.
10. Green DM, McDougal KE, Blackman SM, Sosnay PR, Henderson LB, Naughton KM, Collaco JM, Cutting GR. Mutations that permit residual CFTR function delay acquisition of multiple respiratory pathogens in CF patients. *Respiratory research*. 2010; 11:140. [PubMed: 20932301]
11. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990; 1(1):43–46. [PubMed: 2081237]
12. Poreddy SR, S SM, Murray C. Comparison Of CT Scan With Bronchoscopy For Detection Of Tracheobronchomalacia In Young Children With Cystic Fibrosis. *American journal of respiratory and critical care medicine*. 2013; 187(A1173)
13. Wyatt CA, B L, Wood RE. Higher Prevalence Of Tracheomalacia In Pediatric Patients With Cystic Fibrosis. *Am J Respir Crit Care Med*. 2013; 187:A1173. 2013;187(A1173).
14. Leboulanger N, Louis B, Corvol H, Ramirez A, Fodil R, Lofaso F, Fauroux B. Evaluation of the trachea and intrathoracic airways by the acoustic reflection method in children with cystic fibrosis. *Respiratory physiology & neurobiology*. 2012; 181(1):74–78. [PubMed: 22326722]
15. Davis SD, Ferkol T. Identifying the origins of cystic fibrosis lung disease. *The New England journal of medicine*. 2013; 368(21):2026–2028. [PubMed: 23692172]
16. Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, Murray CP, Stick SM, Investigators AC. Risk factors for bronchiectasis in children with cystic fibrosis. *The New England journal of medicine*. 2013; 368(21):1963–1970. [PubMed: 23692169]
17. Jacobs IN, Wetmore RF, Tom LW, Handler SD, Potsic WP. Tracheobronchomalacia in children. *Archives of otolaryngology–head & neck surgery*. 1994; 120(2):154–158. [PubMed: 8297572]
18. Carden KA, Boisselle PM, Waltz DA, Ernst A. Tracheomalacia and tracheobronchomalacia in children and adults: an in-depth review. *Chest*. 2005; 127(3):984–1005. [PubMed: 15764786]
19. Loring SH, O'Donnell CR, Feller-Kopman DJ, Ernst A. Central airway mechanics and flow limitation in acquired tracheobronchomalacia. *Chest*. 2007; 131(4):1118–1124. [PubMed: 17426218]

20. Masters IB, Chang AB, Patterson L, Wainwright C, Buntain H, Dean BW, Francis PW. Series of laryngomalacia, tracheomalacia, and bronchomalacia disorders and their associations with other conditions in children. *Pediatric pulmonology*. 2002; 34(3):189–195. [PubMed: 12203847]
21. Weinberger M, Abu-Hasan M. Pseudo-asthma: when cough, wheezing, and dyspnea are not asthma. *Pediatrics*. 2007; 120(4):855–864. [PubMed: 17908773]
22. Wood RE. Pitfalls in the use of the flexible bronchoscope in pediatric patients. *Chest*. 1990; 97(1): 199–203. [PubMed: 2403897]
23. Panitch HB, Keklikian EN, Motley RA, Wolfson MR, Schidlow DV. Effect of altering smooth muscle tone on maximal expiratory flows in patients with tracheomalacia. *Pediatric pulmonology*. 1990; 9(3):170–176. [PubMed: 1980538]
24. Zopf DA, Hollister SJ, Nelson ME, Ohye RG, Green GE. Bioresorbable airway splint created with a three-dimensional printer. *The New England journal of medicine*. 2013; 368(21):2043–2045. [PubMed: 23697530]
25. Goo HW. Free-breathing cine CT for the diagnosis of tracheomalacia in young children. *Pediatric radiology*. 2013
26. Tan JZ, Crossett M, Ditchfield M. Dynamic volumetric computed tomographic assessment of the young paediatric airway: Initial experience of rapid, non invasive, four-dimensional technique. *Journal of medical imaging and radiation oncology*. 2013; 57(2):141–148. [PubMed: 23551770]

Figure 1.

Study flow diagram. 109 patients born between January 1995 and October 2012 were followed at the University of Iowa CF center. 97 patients had at least one bronchoscopy. 15 of those patients were diagnosed with TM. Subsequent group comparisons were made between patients with and without TM.

Figure 2.

Bronchoscopy findings of TM in a 9 month old patient with CF (Patient 14) who was sedated with midazolam and propofol and spontaneously breathing. A series of still images of the distal trachea are shown through one respiratory cycle. The anterior and posterior walls and the left and right main bronchi are labelled. The anterior and posterior walls meet in panel 9 during the expiratory phase as indicated by arrowheads.

Figure 3.

A. A 7 month old CF patient (patient 11) with chronic cough and noisy breathing had a chest CT. 2 mm axial CT cuts were reassembled into a 3 dimensional rendering of the trachea, showing long segmental flattening of the trachea with anterior-posterior diameter between 3–4 mm. **B.** A 5 year old boy with CF diagnosed with TM at another center (patient 16) had a chest CT that showed mild bronchiectasis and marked irregular circularity of the trachea. At right is a magnified region of interest containing the trachea.

Figure 4.

A. Kaplan-Meier analysis of time to first acquisition of *P. aeruginosa* and **B.** mucoid *P. aeruginosa*. Patients with TM are compared to patients who had bronchoscopy but were not diagnosed with TM. Censored data points (indicated by a small vertical line) represent patients who have no further data after a given age. Patients with TM develop infection with *P. aeruginosa* and mucoid *P. aeruginosa* earlier than patients without TM. The results are both statistically significant ($p = 0.01$ for first *P. aeruginosa* and $p = 0.04$ for mucoid *P. aeruginosa*).

Table 1

Clinical features of children with CF and TM

Patient	Age at Diagnosis		Year TM diagnosed	Preceding Symptoms	TM Severity	BAL %Neutrophils	BAL culture log ₁₀ CFU/mL			Supporting Evidence ^d	CFTR Genotype	Meconium Ileus
	CF	TM					<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>H. influenzae</i>			
1 ^b	0 mo	1 mo	1996	Apneic spells, positive pressure dependence	80% collapse, bilateral BM	92%	none	none	none	CT	G542X/3659delC	yes
2	13 mo	14 mo	1998	Chronic cough	mild	25%	none	none	none	none	F508/2184delA	no
3 ^c	3 mo	2 mo	1998	Chronic cough, wheezing, apneic spells	80% collapse, left BM	0%	3	none	none	PFT, CT	F508/ F508	no
4	8 mo	2 yr, 8 mo	1999	Chronic cough, sleep disturbance	50–75%	70%	3.6	5.3	none	PFT	F508/3659delC	no
5	13 mo	15 mo	2000	Chronic cough, FTT	mild	86%	5	4.2	none	none	F508/N1303K	no
6	0 mo	8 mo	2000	Chronic cough	>50% collapse, left BM	12%	none	4.5	none	none	F508/ F508	yes
7	13 mo	13 mo	2001	Chronic cough, FTT	90% collapse, bilateral BM	74%	none	none	none	PFT, CT	F508/ F508	no
8	0 mo	16 mo	2005	Chronic cough, choking spells	not quantified, bilateral BM	73%	6.5	none	none	none	F508/ F508	yes
9	0 mo	4 yr, 1 mo	2005	Chronic croupy cough	not quantified	58%	6.5	none	none	none	F508/ F508	yes
10	0 mo	6 yr, 3 mo	2009	Croupy cough, apneic spells	90%	67%	7	none	5.6	PFT, CT	F508/ F508	yes
11	1 mo	11 mo	2010	Noisy breathing, apneic spells	90%	4%	none	none	none	Infant PFT, CT	F508/ F508	no
12 ^d	2 mo	15 mo	2011	Chronic cough	mild	1%	3	none	none	none	F508/ F508	no
13 ^d	0 mo	14 mo	2011	Chronic cough	mild	6%	none	none	none	none	F508/ F508	yes
14 ^d	0 mo	9 mo	2013	Chronic cough, FTT	90%	94%	none	none	none	none	F508/ F508	yes
15 ^d	0 mo	10 mo	2013	Cough only with colds	very mild	67%	none	none	none	none	F508/c.1022_1023insTC	yes
16 ^e	0 mo	9 mo	2005	Chronic cough, apneic spells	severe	NA	NA	NA	NA	PFT, CT	F508/ F508	Yes

^aPFT evidence supporting a diagnosis of TM included decreased peak expiratory flow rate or reproducible peak flow oscillations. CT evidence supporting TM included abnormal tracheal circularity or tracheal deformation.

^bpatient died in infancy

^cpatient treated with aortopexy for severe TM

^dpatients did not have CT scan or PFT

^ediagnosed at another CF center, bacteriology and cell count data not available

Abbreviations: TM – Tracheomalacia, CF – Cystic Fibrosis, FTT – failure to thrive, BM – bronchomalacia, BAL – bronchoalveolar lavage fluid, PFT – pulmonary function test, mo – month, yr – year

Table 2

Conditions associated with TM in children with CF

Frequency	TM present			TM absent			RR	CI	p ^a
	n	%	n	%	Total	%			
Total patients	15	15%	82	85%	97				
Female	4	27%	41	50%	45	46%	0.4	0.14 – 1.22	0.158
F508 First allele	14	93%	80	98%	94	97%	0.4	0.08 – 2.38	0.399
F508 Second allele	10	67%	45	55%	55	57%	1.5	0.56 – 4.13	0.572
Pancreatic insufficiency	15	100%	75	91%	90	93%	–	–	0.367
Meconium ileus	8	53%	13	16%	21	22%	4.1	1.69 – 10.1	0.003
ALT 100	3	20%	17	21%	20	21%	0.95	0.32 – 2.89	0.95
Prematurity	2	13%	13	16%	15	15%	1.3	0.52 – 3.36	1.00

	Median	IQR	Median	IQR	p ^b
Age at 1 st bronchoscopy, mo	14	9.5 – 34	15.5	9 – 18	0.42
BAL % Neutrophils	62 n = 14	3 – 82	32 n = 77	16 – 68	0.62
Starting FEV ₁ , % of predicted ^c	95.5 n = 8	91 – 109	114 n = 51	105–123	0.01
Highest ALT	67	57–86	55	37–91	0.30

	Mean	SD	Mean	SD	p ^d
Sweat chloride, mEq/L	103.4 n = 10	± 23.4	101.0 n = 62	± 20.0	0.82

^a Calculated using Fisher's exact test^b Calculated using Mann-Whitney Wilcoxon test^c Defined as best percentage of predicted FEV₁ prior to age 8.^d Calculated using Student's T-test

Abbreviations: BAL – bronchoalveolar lavage fluid, CI – confidence interval, IQR – interquartile range, RR – relative risk, SD – standard deviation

Table 3

Correlation of *CFTR* genotype with different CF phenotypes

Phenotype	Functional Class of Least Severe <i>CFTR</i> Mutation						Total
	I	II	III	IV	V	Unknown	
TM	1	14	0	0	0	0	15
MI	2	16	0	0	1	2	21
PS	0	0	0	1	2	4	7
Total	2	81	2	1	5	6	97

Abbreviations: TM – Tracheomalacia, MI – Meconium Ileus, PS – Pancreatic sufficiency