Research Article

Pulmonary Functions Test patterns in Cystic Fibrosis Patients in a Tertiary Care Center in Saudi Arabia

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Abstract

INTRODUCTION: *A specific physiologic measures that identified early lung disease in Cystic Fibrosis (CF) patients throughout the first years of life showed diminished values of forced expiratory volume at 0.75 seconds (FEV0.75) and forced expiratory flows between 25 and 75% of forced vital capacity (FEF25–75) across all age groups.*

OBJECTIVES: *To identify Pulmonary Functions Tests (PFT) patterns in our CF population and their severity.*

METHODS: *A retrospective chart review of all confirmed CF patients from the period 1st January 1984 - December 2018. All successful PFT tests that were done for all age groups during their follow-up period in the CF clinic were reported.*

RESULTS: *A total of 294 confirmed CF patients had their PFT done at the first visit and 199 patients had their PFT done at the last follow-up visit to our center. Of 294/199 patients who had proper PFT technique, 84 (29%)/93 (47%) had normal PFT, 79 (27%)/54 (27%) obstructive patterns, 33 (11%)/ 25 (13%) had restrictive pattern, 21 (7%)/14 (7%) had combined restrictive and obstructive component. In regard to the degree of severity: 91(41.55%)/50 (26.95%) had normal PFT, 42 (19.18%)/30 (16.1%) had mild degree, 29 (13.24%)/22 (11.8%) had moderate degree, 23(10.50%)/20 (11.98%) had moderate-severe degree and 25 (11.42%)/24 (14.37%) had severe degree, 9 (4.11%)/33 (19.76%) had very severe degree. Follow-up PFT collectively showed progression of disease severity in all parameters. There was a progressive reduction in all % predicted (FVC, FEV1, MMEF (75-25%) and PEF) values over the follow-up period of 7 years which showed a picture that favors obstructive or combined (obstructive and restrictive) patterns (P Value= <0.0001). FRC, RV and TLC values showed a progressive increase due to hyperinflation and air trapping (P Value= 0.085).*

In comparing PFT (1) with 219 patients and PFT (3) 186 patients, at last, follow up to 7 years period, there was a reduction of the normal PFT pattern from 91 (41.55%) to 50 (26.95%) patients respectively, and an increase of abnormal PFT of all types (P Value= <0.0001).

CONCLUSION: *PFT is an important tool to identify the progression of CF pulmonary disease. Physicians should monitor PFT changes regularly during their clinic follow-up visits to prevent progression.*

KEYWORDS: *Cystic Fibrosis, PFT, CFTR, FEV1, Obstructive lung disease, Restrictive Lung disease.*

1. Introduction:

During the past decade, advances in the early assessment of cystic fibrosis CF lung disease have led to an improved understanding of its pathophysiology, but many questions remained unanswered. The earliest airway abnormalities of focal, distal mucous plugging leading to peripheral airway dilatation **(**1-2**)**. Researchers have tried to identify early lung function changes in CF, but their study results have been difficult to interpret because of the small numbers of patients, lack of appropriate control data, and use of relatively insensitive methods. Recently, objective measures have been developed demonstrating that CF lung disease begins early, often before clinical manifestations **(**3-4**)**. Diminished physiologic measurements **(**3-5**)**, increased airway inflammation, and early infection **(**6-8**)** as well as developing bronchiectasis **(**7-8**)** have been demonstrated during early infancy. Longitudinal data during infancy have also shown that this reduction in lung function does not "catchup" even after initiation of treatment **(**4**)**. Despite these advances, the triggering factor for the cascade of events leading to early airway infection, inflammation, and flow limitation has not been entirely clear.

Castile et al 9 eloquently describe the evolution of lung function from infancy through the preschool years in children with CF compared with healthy control subjects. The longitudinal measures were performed using the raised-volume rapid thoracoabdominal compression technique and incentive spirometry and were carefully conducted based on standardized, published guidelines **(**9**)**.

The specific physiologic measures that identify early lung disease throughout the first years of life showed diminished values of forced expiratory volume at 0.75 second FEV0.75 and forced expiratory flows between 25% and 75% of forced vital capacity FEF25–75 across all ages, FEV at 0.5 second FEV0.5 only differentiated children with CF from healthy controls during infancy, not during preschool years. This interesting finding likely reflects the predominance of the central airway component in the measure of FEV0.5 **(**10**)**. Because early CF lung disease is located in the distal airways, identifying longitudinal physiologic markers that best represent peripheral airway mucous plugging is critical for future therapeutic trials conducted at this young age group **(**10**)**.

Castile et al **(**9**)** reported that the presence of *Pseudomonas aeruginosa* P. aeruginosa infection, wheezing, and recent cough was independently associated with reduced lung function. In fact, lung function remained decreased even in those children with apparent eradication of *P.aeruginosa.* Lung damage may have provided a rich environment for the growth of *P.aeruginosa.* Nevertheless, the lack of improvement in lung function measures, despite aggressive treatment and apparent eradiation of *P.aeruginosa,* is concerning. This finding emphasizes the importance of employing preventative therapy.

Levine et al (11) found that the reversibility of obstruction decreases with age in CF due to increased bronchomotor tone and bronchospasm in early stages of the disease, which decreases as chronic inflammation and destruction of the airway wall increase over time. The wheezing phenotype was described in 25%of CF infants (12-15) and decreased Vmax FRCMaximal flow at functional residual capacity, normalized with metapropranolol has been demonstrated (16), suggesting the importance of increased bronchomotor tone and bronchoconstriction in CF airway obstruction at this age. Similarly, Sanchez et al showed that at least 40% of young children with mild CF already had moderate to severe nonspecific airway hyperreactivity, possibly due to subclinical lung damage, or related to an intrinsic feature of CF (16). Another study of 4480 young children with CF has shown that early childhood wheezing is common and associated with lower lung function in mid-childhood (17).

Levine et al (11) found that severe genotype associated with reversible airway obstruction suggests a possible role of chronic loss of CFTR in association with a hyper-contracted state. Indeed, recent studies have detected CFTR in smooth muscle, and functional studies suggest that CFTR may play a role in muscle relaxation. Another study discussed the interplay of likely direct effects of absent CFTR with progressive CF infection and inflammation upon airway smooth muscle proliferation and hyper-responsiveness (12).

The absence of CFTR may result in a hyper-contracted state of human airway smooth muscle as well (18-19). The commonality of smooth muscle changes in CF humans suggests an emerging role for CFTR in smooth muscle functioning and direct alterations in contractile signaling where CFTR is deficient. Airway hyperreactivity is common in CF and bronchodilator response is greater in those with positive methacholine MCh challenge test (12, 20-21). However, the basis for this response appears to differ from that in asthma. Mitchell et al (2)2 found a positive response to MCh in 51% of CF compared with 98% of asthmatic patients with different dose–response curves and time course suggesting different pathophysiologic mechanisms in each disease (22). There is evidence that in CF, as opposed to asthma, airway hyperreactivity is neurally mediated. Increased vagal bronchomotor tone was suggested as a possible mechanism by Van Haren et al (20) who demonstrated, that in CF, unlike in asthma, bronchodilation following exercise was correlated with a bronchodilator response to ipratropium bromide (20).

Levine et al (11) found that a majority of patients in his study were receiving long-term ICS therapy although significant benefit has not been conclusively demonstrated according to a Cochrane Database Systemic Review from 2014 (23). On the other hand, data from the Epidemiologic Study of CF has

demonstrated a significant reduction in the rate of FEV1 decline, with ICS use **(**24**)**. Other studies failed to find a significant change in FEV1 after ICS therapy **(**25**)**. Also, there was no difference in the number of respiratory exacerbations, days of intravenous antibiotic therapy, or days of hospitalization **(**24-27**)**. A study by Balfour-Lynn et al **(**26**)** based on the safety of ICS withdrawal rather than a prospective institution of ICS therapy, due to the large proportion of patients already on long-term therapy **(**26**)**. It should be noted that bronchodilator reversibility could have been masked in the patients on long-term ICS. Nevertheless, a third of patients with reversibility was not receiving ICS **(**26**)**.

As there is no study to show the PFT changes of CF population in Saudi Arabia, we carried out this study to identify its pattern in our population.

2. OBJECTIVES:

To identify Pulmonary Functions Tests PFT patterns in our CF population and its severity.

3. MATERIALS AND METHODS:

A retrospective chart review of all confirmed CF patients from the period 1st January 1984 - December 2018.

3.1 Definitions:

A patient with CF disease is defined as:

One who has a typical pulmonary manifestation and/or typical gastrointestinal manifestations GI and/or a history of cystic fibrosis in the immediate family in addition to sweat chloride concentration >60 mmol/ liter by the Wescor quantitative method, USA **(**28**)**.

1. Pathologic CFTR mutations on both alleles.
2. One who has typical pulmonary and gastrointestinal manifestations and borderline or normal sweat chloride CL level 30-60 mmol/L, and or pathologic CFTR mutations on both alleles.

3.2 PFT measurement:

Measures of lung volume and airflow are used to assess the degree of dysfunction in patients with CF and other chronic lung diseases. Forced vital capacity FVC, forced expiratory volume in the first second FEV1, and forced expiratory flow in the middle half of FVC are all measured by spirometry, a forced expiratory maneuver, which is relatively easy to perform by patients old enough to cooperate with a maximal inspiration, followed by a maximal hard expiration. Most children with CF are routinely tested one or more times a year from the age of 6 or 7 years. FEV1 is the variable that best reflects the status of lung function throughout CF lung disease 1° and is the best clinical predictor of death. FEF 25-75%

is thought to detect the earliest limitations of airflow in the small airways, and FVC reflects the reduction in functional lung volume as obstructive lung disease progresses. All pulmonary function tests for all patients in the study cohort were recorded in the Hospital secure computer CF database. No attempt was made to distinguish tests done for routine follow-up from those done when patients may have been ill. At each visit, at least three maximum expiratory maneuvers were performed, and the best maximal effort was selected from those producing a technically satisfactory tracing, according to criteria established by the American Thoracic Society throughout the study period. FVC, FEV 1, and FEF 25-75% from the selected effort were recorded in the database **(**29**)**. Percent of predicted values, based on height and sex, were used for all analyses **(**29**)**.

PFT studies were labeled as PFT 1: as first PFT where proper comprehension of PFT maneuvers are achieved. PFT 2: as PFT did at mid-period of follow up, and PFT 3: as PFT has done at last follow up period.

3.3 Severity of PFT:

The severity of any spirometry abnormality degree in this study was based on World Health Organization WHO guidelines 30 as the following:

- **Normal degree:** Forced Expiratory Volume in The First Second FEV1 equal or ≥ 80% predicted.
- **Mild degree:** FEV1 equal > 70-79% predicted.
- **Moderate degree:** FEV1 is 60-69% predicted.
- **Moderately severe degree:** FEV1 is 50-59% predicted.
- **Severe degree:** FEV1 is 35-49% predicted.
- **Very severe degree:** FEV1 is < 35% predicted.

3.4 Ethical considerations and Statistical Method:

After obtaining ethical approval from the research advisory committee. The Declaration of Helsinki and good clinical practice guidelines were followed. Data collection and data entry were supervised by the principal investigator. All data needed were obtained by a retrospective chart review. All data were stored in the pediatrics research unit, accessed only by the principal investigator and the assigned Clinical Research Coordinator. The entire patient's information is kept strictly confidential. Each patient was given a study number, and all patients' data were entered into the designated data sheet EXCEL without any patient's identification. The department of Biostatistics Epidemiology and Scientific Computing BESC carried out statistical analysis of the data.

3.5 Statistical Method:

Scale variables were summarized by means, standard deviations, or Medians and interquartile range IQR was appropriate. Categorical data were presented by frequencies and percentages. Paired T-test or Wilcoxon signed test was used to assess the differences between first and last PFT measurements. Chi-square was used to assess the relationships between PFT and mutations, while Mc Nemar's test was used to the difference in severity between the first and last observations. A (P-value of <0.05) was considered as the level of significance. Data were analyzed by JMP 15.0 from SAS. For continuous variables, mean, standard deviation and median were calculated using T-Test. Results were presented at a level of significance of (P-value < 0.05). All values were expressed in mean ± standard deviation SD.

4. RESULTS:

A total of 430 confirmed CF patients, 213/430 (49.54%) patients are males, and 217/430 (50.46%) are females. The majority 156 (36.53%) were from the eastern region, followed by the central region 100 (23.42%) **Table.1**.

Table (1). Demographic data of patients (430 patients):

Variable	**level**	**#(%)**
Gender	Male	213(49.54 %)
	Female	217(50.46%)
	Total	430
Region	East	156 (36.53%)
	West	77(18.03%)
	Central	100(23.42%)
	North	52(12.18%)
	South	42(9.83%)
	Total	427
Consanguinity	Any relation	163(38.02%)
	First cousin	194(45.04%)
	Not related	73(16.94%)
	Total	430
Number of Siblings	0	36(14.82%)/30(12.35%)
Male/female	1	62(25.51%)/66(27.16%)
	2	52(21.39%)/44(18.11%)

	3	40(16.46%)/48(19.75%)
	4	27(11.11%)/27(11.11%)
	5	16(6.58%)/15(6.17%)
	6	6(2.47%)/6(2.47%)
	7	2(0.82%)/6(2.47%)
	8	2(0.82%)/1(0.41%)
	Total	243/243
Family History Of CF	Yes	193(44.96%)
	No	237(55.04%)
	Total	430
Number of Sibling Affected Male/female	0	84(34.57%)/75(30.86%)
	1	110(45.27%)/133(54.73%)
	2	39(16.05%)/26(10.70%)
	3	6(2.47%)/9(3.70%)
	5	3(1.24%)
	7	1(0.41%)
	Total	243

Table 1: Number of cases.

Regarding parental consanguinity, 194/430 (45.04%) are first-degree cousins **Table.1**. One hundred ninety-three out of 430 (44.96%) have a positive family history of CF. Two hundred seventy-five out of 430 (63.79%) of males and 297/430 (69.13%) of females have from 1-3 siblings diagnosed with CF, and 71 (16.5%) have more than 3 siblings with CF diagnosis **Table.1**.

A total of 251/430 (58.37%) patients had their PFT done at the first visit at a mean age of 9.69 (5.18) years. The mean of Forced Vital Capacity FVC % Predicted 71.29 (23.88). FEV1 % Predicted 72.93 (27.6), FEV1/FVC ratio 85.02 (17.25). Maximal mid-expiratory flow between 25% and 75% MMEF 75-25% % Predicted 66.25 (41.9), Peak Expiratory Flow PEF % Predicted 73.8 (27.14), Functional residual capacity FRC % Predicted 128.1 (67.44), Residual Volume RV % Predicted 166.01 (92.66). Total Lung Capacity TLC % Predicted 92.19 (28.99). RV/TLC % Predicted 158.77 (71.89) **Table2**.

A total of 219/430 (50.93%) patients had their 2nd PFT done at the mid-period of follow-up visits at a mean age of 11.99 (5.57) years **Table 2**. Similarly, a total of 137/430 (31.86%) patients had their 3rd PFT done at the last follow-up visit at a mean age of 17.80 (7.17) years **Table 2**.

Variable	**PFT (1)**	**PFT (2)**	**PFT (3)**	**P. value PFT1/PFT2**	**P. value PFT1/PFT3**
Number of Patients	**N: 251**	**N: 219**	**N: 137**		
Age at PFT: Mean (SD)	9.69(5.18)	11.99(5.57)	17.80(7.17)		
FVC % Predicted Mean (SD)	71.29(23.88)	73.32(21.79)	64.35(23.38)	0.02	0.0001
FEV1% Predicted	72.93(27.6)	72.03(25.41)	60.03(25.27)	0.20	0.0001
(FEV1/FVC)	85.02(17.25)	83.11(16.1)	78.2(13.3)	0.0001	0.0001
MMEF (75-25%) % Predicted	66.25(41.9)	63.70(37.97)	56.68(35.62)	0.79	0.0001
PEF % Predicted	73.8(27.14)	65.82(32.72)	62.5 (25.2)	0.43	0.32
FRC % Pred.	128.1(67.44)	131.27(51.41)	149.62(40.87)	0.42	0.011
RV % Predicted	166.01(92.66)	180.92(88.86)	207.39(94.53)	0.27	0.024
TLC % Predicted	92.19(28.99)	93.67(19.98)	97.65(17.90)	0.135	0.006
(RV/TLC)	158.77(71.89)	162.92(70.22)	150.13(90.14)	0.085	0.019

Table 2: PFT VALUES AT PRESENTATION AND AT FOLLOW-UP

FVC: Forced Vital Capacity, FEV1: Forced Expiratory Volume in One Second; FEV1/FVC: Forced expiratory volume in the first second/Forced vital capacity ratio. MMEF (75-25%): Maximal mid-expiratory flow between 25% and 75% of total force expiratory volume. PEF: Peak Expiratory Flow. FRC: Functional residual capacity. RV: Residual Volume. TLC: Total Lung Capacity, FRC: Functional Residual Capacity. TLC: Total lung capacity. RV/TLC: Residual Volume/Total lung capacity ratio. N: Number of cases. NA: Not applicable. SD: Standard deviation. PFT: Pulmonary Function Test. PFT(1): First Pulmonary Function Test. PFT(2): Pulmonary Function Test at Mid Period follow up. PFT(3): Pulmonary Function Test at Last follow up. L: Liters.

There was a progressive reduction in all % predicted FVC, FEV1, MMEF 25%-57% and PEF values over the follow-up period of 7 years which showed a picture that favors an obstructive or combined

obstructive and restrictive patterns (P Value= <0.0001) Table2. FRC, RV and TLC values showed a progressive increase due to hyperinflation and air trapping (P Value= 0.085), **Table2**.

In comparing PFT 1 with 219 patients and PFT 3 with 186 patients, at last, follow up to 7 years period, there was a reduction of the normal PFT pattern from 91 (41.55%) to 50 (26.95%) patients respectively, and an increase of abnormal PFT of all types (P Value= <0.0001), **Table 3**.

Table. (3): Comparison of types of PFT severity for PFT (1), PFT (2) and last follow up PFT:				
		TYPES Count Percentage %		
		PFT (1)	**PFT (2)**	**PFT (3)**
SEVERITIY	**Normal**	91 41.55%	63 32.3%	50 26.9%
	Mild	42 19.18%	49 25.1%	30 16.1%
	Moderate	29 13.24%	18 9.2%	22 11.8%
	Moderately severe	23 10.50%	19 9.7%	20 10.8%
	Severe	25 11.42%	28 14.4%	29 15.6%
	Very severe	9 4.11%	18 9.2%	35 18.8%
P-value: < 0.0001	**Total**	219	195	186

Table 3: PFT: Pulmonary Function Test. PFT (1): First Pulmonary Function Test.
PFT (2): Pulmonary Function Test at Mid Period follow up.
PFT (3): Pulmonary Function Test at Last follow up.

4. DISCUSSION:

Kraemer et al **(**31**)** studied the relationship between cystic fibrosis patients, the clinical manifestation, and lung function in 60 infants 33 females, 27 males with cystic fibrosis at the time of diagnosis age: 7.2 months; range: 0.8-23.8 months 31. Lung function was assessed by the infant's whole-body

plethysmography. Age at the time of diagnosis was independent of the genotype. Differences regarding lung function within the genetic groups are mainly related to pulmonary hyperinflation, measured by thoracic gas volume TGV, present in 8 of 9 infants with 3905insT, differentiating this frameshift mutation TGV of 7.0 (3.6) from the R553X mutation TGV 2.1 (4.6); ($p < 0.02$). It is concluded that the variable disease findings in infants with cystic fibrosis are clinically and functionally reflected by features already present at the time of diagnosis. The degree of pulmonary hyperinflation is, at least partly, influenced by the genotype **(**31**)**.

Our study did not include pediatric patients below 6 years of age due to inability to comprehend PFT maneuvers and we do not do infant PFT.

Our study has shown a progressive reduction in all FVC, FEV1, MMEF 25%-75% and TLC % predicted values over the follow-up period of 7 years which showed a picture that favors an obstructive or combined obstructive and restrictive patterns (P Value= <0.0001) **Table2**. In comparing PFT 1 with 219 patients and PFT 3 with 186 patients, at last, follow up to 7 years period, there was a reduction of the normal PFT pattern from 91 (41.55%) to 50 (26.95%) patients respectively, and an increase of abnormal PFT of all types (P Value= <0.0001), **Table 3**.

In contrast to several other reports, Schaedel et al **(**32**)** found Patients with diabetes mellitus had a faster decline in FEV1 than patients without (P Value= 0.02). Also, patients with diabetes had a significantly steeper decline of FEV1 (P Value= 0.01), similar to those of all CF patients with diabetes. No difference was found between patients with and without liver cirrhosis (P Value=0.84). FEV1 is the variable of lung function that best reflects the progression of lung disease in CF, and impaired Vital Capacity VC is seen only in the late stages of the disease. His data also shown that CFTR genotypes associated with long-term pancreatic sufficiency have more benign lung disease and better pulmonary function. A significantly lower rate of chronic Pseudomonas colonization was found in patients with pancreatic sufficiency. No difference in the annual decline of FEV1 was found between Pancreatic Sufficient PS patients with and without PA colonization. He concluded that in patients with pancreatic sufficiency, no significant annual decline of lung function was observed, but those with *Pseudomonas* colonization may still be at risk for serious lung disease. An early diagnosis of patients in this group was advised. Risk factors that negatively affect lung function included pancreatic insufficiency and diabetes mellitus, in addition to chronic *Pseudomonas* colonization. He advised that patients with these characteristics should receive early and aggressive treatment and close monitoring at CF centers. The other conclusion is that the severity of lung disease varies in patients with the same CFTR genotype may suggest that other genetic, environmental, or immunological factors, as well as bacterial colonization and differences

in treatment, are important **(**32-34**)**.

Our study did not test the correlation of other morbid factors that may contribute to PFT abnormalities.

Hector et al **(**35**)** assessed the microbial colonization patterns and lung function parameters in 770 adolescent European German/Austrian CF patients in a retrospective study median follow-up time: 10 years. Colonization with P. aeruginosa and Methicillin-resistant Staphylococcus MRSA were most strongly associated with loss of lung function, while mainly colonization with *Haemophilus influenzae* was associated with preserved lung function. *Aspergillus fumigatus* was the only species that was associated with an increased risk for infection with P. aeruginosa. Microbial interaction analysis revealed three distinct microbial clusters within the longitudinal course of CF lung disease **(**35-41**)**.

Further studies are needed to assess PFT and microbiological colonization in our population.

5. CONCLUSIONS:

PFT is an important tool to identify the progression of CF pulmonary disease. Physicians should monitor PFT changes regularly during their clinic follow-up visits to prevent progression.

References

1.Davis SD, Fordham LA, Brody AS, Noah TL, Retsch-Bogart GZ, Qaqish BF, Yankaskas BC, Johnson RC, Leigh MW. “Computed tomography reflects lower airway inflammation and tracks changes in early cystic fibrosis”. Am J Respir Crit Care Med 2007;175:943–950.

2.Stick SM, Brennan S, Murray C, Douglas T, von Ungern- Sternberg BS, Garratt LW, Gangell CL, De Klerk N, Linnane B, Ranganathan S, et al. “Bronchiectasis in infants and preschool children diagnosed with cystic fibrosis after newborn screening”. J Pediatr 2009;155:623–628 e621.

3.Armstrong DS, Hook SM, Jamsen KM, Nixon GM, Carzino R, Carlin JB, Robertson CF, Grimwood K. “Lower airway inflammation in infants with cystic fibrosis detected by newborn screening”. Pediatr Pulmonol 2005;40:500–510.

4.Ranganathan SC, Dezateux C, Bush A, Carr SB, Castle RA, Madge S, Price J, Stroobant J, Wade A, Wallis C, et al. “Airway function in infants newly diagnosed with cystic fibrosis”. Lancet 2001;358:1964–1965.

5.Linnane BM, Hall GL, Nolan G, Brennan S, Stick SM, Sly PD, Robertson CF, Robinson PJ, Franklin PJ, Turner SW, et al. “Lung function in infants with cystic fibrosis diagnosed by newborn screening”. Am J Respir Crit Care Med 2008;178:1238–1244.

6.Davis PB. “The decline and fall of pulmonary function in cystic fibrosis: new models, new lessons”. J Pediatr 1997;131:789–790.

7.Jones M, Castile R, Davis S, Kisling J, Filbrun D, Flucke R, Goldstein A, Emsley C, Ambrosius W, Tepper RS. “Forced expiratory flows and volumes in infants. Normative data and lung growth”. Am J Respir Crit Care Med 2000;161:353–359.

8.Lum S, Stocks J, Castile R, Davis S, Henschen M, Jones M Morris MG, Ranganathan S, Sly PD, Tepper R. “ATS/ERS statement: raised volume forced expirations in infants: guidelines for current practice”. Am J Respir Crit Care Med 2005;172:1463– 1471.

9.Castile R, Filbrun D, Flucke R, Franklin W, McCoy K. “Adult-type pulmonary function tests in infants without respiratory disease”. Pediatr Pulmonol. 2000 Sep;30(3):215-27. doi: 10.1002/1099-0496(200009)30:3<215::aid-ppul6>3.0.co;2-v. PMID: 10973040.

10.Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. “Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on standards for infant respiratory function testing”. European Respiratory Society/ American Thoracic Society. Eur Respir J 2001;17:302–312.

11.Hagit Levine, Malena Cohen-Cymberknoh, Nitai Klein et al. “Reversible airway obstruction in cystic fibrosis: Common, but not associated with characteristics of asthma”. Journal of Cystic Fibrosis 2016;

12.McCuaig S, Martin JG. “How the airway smooth muscle in cystic fibrosis reacts in proinflammatory conditions: implications for airway hyperresponsiveness and asthma in cystic fibrosis”. Lancet Respir Med 2013;1: 137–47.

13.Eggleston PA, Rosenstein BJ, Stackhouse CM, Alexander MF. “Airway hyperreactivity in cystic fibrosis. Clinical correlates and possible effects on the course of the disease”. Chest 1988;94(2):360–5 Aug.

14.Kerem E, Reisman J, Corey M, Bentur L, Canny G, Levison H. “Wheezing in infants with cystic fibrosis: clinical course, pulmonary function, and survival analysis”. Pediatrics 1992;90(5):703–6.

15.Hiatt P, Eigen H, R Y, RS TT. “Bronchodilator responsiveness in infants and young children with cystic fibrosis”. Am Rev Respir Dis 1988;137: 119–22.

16.Sanchez I, Powell RE, Pasterkamp H. “Wheezing and airflow obstruction during methacholine challenge in children with cystic fibrosis and in normal children”. Am Rev Respir Dis 1993;147:705–9.

17.Ren CL, Konstan MW, Rosenfeld M, Pasta DJ, Millar SJ, Morgan WJ, et al. “Early childhood wheezing is associated with lower lung function in cystic fibrosis”. Pediatr Pulmonol 2014;49:745–50.

18.Meyerholz DK, Stolz DA, Namati E, Ramahandran S, Pezzulo AA, Smith AR, et al. “Loss of cystic fibrosis transmembrane conductance regulator function produces abnormalities in tracheal development in neonatal pigs and young children”. Am J Respir Crit Care Med 2010;182:1251–61.

19.Michoud M-C, Robert R, Hassan M, et al. “Role of the cystic fibrosis transmembrane conductance channel in human airway smooth muscle”. Am J Respir Cell Mol Biol 2009;40:217–22.

20.van Haren EH, Lammers JW, Festen J, van Herwaarden CL. “Bronchial vagal tone and responsiveness to histamine, exercise and bronchodilators in adult patients with cystic fibrosis”. Eur Respir J 1992 Oct;5(9):1083–8.

21.Mellis CM, Levison H. “Bronchial reactivity in cystic fibrosis”. Pediatrics 1978;6:446–50.

22.Mitchell, I., Corey, M., Woenne, R., Krastins, I. R. B., & Levison, H. (1978). “Bronchial hyperreactivity in cystic fibrosis and asthma”. The Journal of Pediatrics, 93(5), 744–748. doi:10.1016/s0022-3476(78)81070-1.

23.Balfour-Lynn IM, Welch K, Royal Brompton Hospital, London. “Inhaled corticosteroids for cystic fibrosis”. Cochrane Database Syst Rev 2014;10, CD001915 Oct 9.

24.Pasta DJ, Rasouliyan L, Wagener JS, Konstan MW, Morgan WJ, Scientific Advisory Group, et al. ‘Relationship between inhaled corticosteroid therapy and rate of lung function decline in children with cystic fibrosis”. J Pediatr 2008;153(6):746–51 Dec.

25.Nikolaizik WH, Schoni MH. “Effect of inhaled corticosteroids on lung function of cystic fibrosis patients – a prospective study”. Eur Respir J 1994;7: 430S.

26.Balfour-Lynn IM, Lees B, Hall P, Phillips G, Khan M, Flather M, et al. "Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis". Am J Respir Crit Care Med 2006;173(12):1356–62.

27.De Boeck K, De Baets F, Malfroot A, Desager K, Mouchet F, Proesmans M. "Do inhaled corticosteroids impair long term growth in prepubertal cystic fibrosis patients?" Eur J Pediatr 2007;166(1):23–8.

28.LeGrys VA. "Sweat testing for the diagnosis of cystic fibrosis: practical considerations". Journal of Pediatrics. 1996; 129:892–7.

29.Corey, M., Edwards, L., Levison, H., & Knowles, M. (1997). "Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis". The Journal of Pediatrics, 131(6), 809–814. doi:10.1016/s0022-3476(97)70025-8.

30.Pellegrino, R. (2005). "Interpretative strategies for lung function tests". European Respiratory Journal, 26(5), 948–968. doi:10.1183/09031936.05.00035205.

31.Kraemer, R., Birrer, P. & Liechti-Gallati, S. "Genotype-Phenotype Association in Infants with Cystic Fibrosis at the Time of Diagnosis". Pediatr Res 44, 920–926 (1998).

32.Schaedel C, de Monestrol I, Hjelte L, Johannesson M, Kornfält R, Lindblad A and et al. "Predictors of deterioration of lung function in cystic fibrosis". Pediatr Pulmonol. 2002 Jun;33(6):483-91. doi: 10.1002/ppul.10100. PMID: 12001283.

33.de Gracia J, Mata F, Álvarez A, et al "Genotype-phenotype correlation for pulmonary function in cystic fibrosis". Thorax 2005;60:558-563.

34.Stoltz DA, Meyerholz DK, Welsh MJ. "Origins of cystic fibrosis lung disease". N Engl J Med 2015;372:351–62.

35.Hector Andreas, Tobias Kirn, Anjali Ralhan, Ute Graepler-Mainka, Sina Berenbrinker, Joachim Riethmueller. "Microbial colonization and lung function in adolescents with cystic fibrosis". Journal of Cystic Fibrosis 15 (2016) 340–349.

36.Ramsey KA, Ranganathan S, Park J, Skoric B, Adams AM, Simpson SJ, et al. "Early respiratory infection is associated with reduced spirometry in children with cystic fibrosis". Am J Respir Crit Care Med 2014;190:1111–6.

37.Mayer-Hamblett N, Rosenfeld M, Gibson RL, Ramsey BW, Kulasekara HD, Retsch-Bogart GZ, et al. "Pseudomonas aeruginosa in vitro phenotypes distinguish cystic fibrosis infection stages and outcomes". Am J Respir Crit Care Med 2014;190:289–97.

38.Doring G, Flume P, Heijerman H, Elborn JS, Consensus SG. "Treatment of lung infection in patients with cystic fibrosis: current and future strategies". J Cyst Fibros 2012;11:461–79.

39.Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, Elborn JS, LiPuma JJ, et al. "Antibiotic management of lung infections in cystic fibrosis". I. the microbiome, methicillin-resistant Staphylococcus aureus, gram-negative bacteria, and multiple infections. Ann Am Thorac Soc 2014;11:1120–9.

40.Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, Elborn JS, LiPuma JJ, et al. "Antibiotic management of lung infections in cystic fibrosis". II. Nontuberculous mycobacteria, anaerobic bacteria, and fungi. Ann Am Thorac Soc 2014;11:1298–306.

41.Muhlebach MS, Heltshe SL, EB P, MB M, Thompson V, Kloster M, et al. "Multicenter observational study on factors and outcomes associated with different MRSA types in children with cystic fibrosis". Ann Am Thorac Soc 2015.

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