

## Variables, Inclusion Criteria and Definitions used by the ECFSPR

### Variables

#### Demographics

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CF centre code  
Patient code  
Year of follow-up  
Date of birth (year and month)  
Gender  
Status of patient  
Cause of death  
Date of death

#### Diagnosis

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Diagnosis confirmed  
Age at diagnosis  
Sweat test type and value  
Electrolytes  
Chloride value  
Meconium Ileus  
Nasal Potential Difference (NPD)  
CF-typical NPD  
Date of NPD  
Intestinal current measurement (ICM)  
CF-typical ICM  
Date of ICM  
Neonatal screening

#### Genotype

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First mutation  
Second mutation

#### Therapy (this year)

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Inhaled continuous hypertonic NaCl  
Inhaled continuous Mannitol  
Inhaled continuous antibiotic  
Inhaled continuous bronchodilators  
In Oxygen therapy  
Use of continuous non-invasive positive pressure ventilation this year  
Use of rhDNase  
Use of continuous Inhaled steroids  
Use of continuous Oral steroids  
Use of continuous azithromycin (or other macrolide)  
Use of ursodeoxycholic acid  
Use of pancreatic enzymes  
Use of proton pump inhibitors  
Use of CFTR modulator therapy

## Complications

Allergic broncho-pulmonary aspergillosis this year  
 Diabetes treated this year  
 Pneumothorax this year  
 Distal intestinal obstruction syndrome (DIOS) this year  
 Salt loss syndrome this year  
 Liver disease this year  
 Haemoptysis major over 250 ml this year  
 Pancreatic status: faecal elastase  
 Pancreatic status: faecal fat  
 Occurrence of malignancy this year

## Follow-up

Date of best FEV<sub>1</sub> recorded this year  
 Value of best FEV<sub>1</sub> recorded this year  
 Value of best FVC recorded this year  
 Date of lowest LCI 2.5% recorded this year  
 Value of lowest LCI 2.5% recorded this year  
 Type of device for LCI measurement  
 Height measured at date of best FEV<sub>1</sub> (or in case of no FEV<sub>1</sub> last height of the year)  
 Weight measured at date of best FEV<sub>1</sub> (or in case of no FEV<sub>1</sub> last height of the year)

## Microbiology

Chronic *Pseudomonas aeruginosa*  
 Chronic *Staphylococcus aureus*  
 Chronic *Burkholderia cepacia complex*  
*Haemophilus influenzae* this year  
*Stenotrophomonas maltophilia* this year  
*Nontuberculous mycobacteria* this year  
*Achromobacter spp* this year  
 MRSA this year  
 Total days on iv antibiotics at home and in hospital  
 Total days on iv in hospital  
 Total days in hospital

## Transplant

Liver transplant  
 Year of latest liver transplant (if occurred before or during this year)  
 Lung transplant  
 Year of latest lung transplant (if occurred before or during this year)  
 Kidney transplant  
 Year of latest kidney transplant (if occurred before or during this year)  
 Other transplant

■ new variables, which will be collected with ECFSTracker vs 2 and included in the 2018 Annual Report.

## Inclusion criteria

Only patients who fulfil the diagnostic criteria below should be included the registry:

1. **Two sweat tests value > 60 mmol/L chloride:** CF diagnosis accepted.
2. **One sweat test value > 60 mmol/L chloride and DNA Analysis/Genotyping – two identified disease causing CF mutations:** CF diagnosis accepted.
3. **Sweat value less than or equal to 60 mmol/L chloride:**  
If the sweat value is less than or equal to 60 mmol/L chloride or not reported, then at least 2 of these should be fulfilled:
  - a. DNA Analysis/Genotyping – two identified disease causing CF mutations;
  - b. Transepithelial (Nasal) Potential Difference or Intestinal current measurement – study consistent with a diagnosis of CF;
  - c. Clinical Presentation – typical features of CF.
4. **Diagnosis reversal:**  
If the patient's CF diagnosis reversed during the year, identify the reason from the options listed:
  - a. DNA Analysis – unable to identify two disease causing CF mutations;
  - b. Transepithelial (Nasal) Potential Difference and/or Intestinal current measurement – study not consistent with a diagnosis of CF;
  - c. Repeat normal sweat testing – confirm with the clinical team.

## Definitions according to the ECFSPR

### SWEAT TEST

If a sweat test was not performed on a patient, record “not done”. If a sweat test is “not done” then two known genotype mutations must be reported.

1. Sweat Test: record the patient's sweat test.
2. Electrolytes: Chloride concentration measurement is the preferred analysis.
3. Chloride value: report the Chloride value in millimols per litre (mmol/L). If duplicate tests were completed on the same day, report the highest positive value.

NOTE: The acceptable range for Chloride values is 1-160 mmol/L. Anyone who has a Chloride value above 160 mmol/L must be re-tested.

### SPIROMETRY

The purpose of recording data on spirometry values for the ECFS Patient Registry is to obtain standardised comparable data for comparison with other centres/countries and for use in specific epidemiological studies. Some of the conditions for this (see below) may not be met at every clinic visit for all patients. Therefore, for the purpose of the registry, only the spirometry tests fulfilling the criteria should be recorded/extracted for the ECFS Patient Registry. For all tests the spirometry should be performed according to the common ATS/ERS guidelines: ([www.thoracic.org/statements/resources/pfet/PFT2.pdf](http://www.thoracic.org/statements/resources/pfet/PFT2.pdf)).

Furthermore for the values reported to the registry the following criteria should be met

1. Pre-test:
  - a. date of birth, gender and height should be recorded for calculation of predicted values
  - b. all recorded spirometry tests should be pre-bronchodilator\* values
    - i. short-acting bronchodilators: at least 4 hours pre-test
    - ii. long-acting bronchodilators: at least 12 hours pre-test

\*This was decided according to the PortCF official definitions.
2. Reported values:
  - a. for values reported to national registries or to centres and extracted to the ECFSPR, the value in litres of the highest available value of FEV<sub>1</sub>% of predicted (according to local references) of the year should be extracted
  - b. each patient's FVC and FEV<sub>1</sub> measurement must be reported in litres (L), with up to two places to the right of the decimal
  - c. the FVC measurement must be greater than or equal to the FEV<sub>1</sub> measurement
  - d. for each reported spirometry value, the date of the test and the patient's height at that date should be reported in order to perform the calculation of percent of predicted values
  - e. only tests deemed valid according to ATS/ERS guidelines should be reported
3. Calculation of percent of predicted values:

A common set of reference values is used: Global Lung Function Initiative equations described by Quanjer PH et al. (Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343).

The ECFSPR Definition Group considered the issue of race-specific reference values and decided not to do this calculation and not to record race for European patients.

#### References:

- a) Miller et al. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338
- b) Miller et al. General considerations for lung function testing. *Eur Respir J* 2005; 26: 153–161
- c) Cystic Fibrosis Foundation Patient Registry User's Guide, Version 4.0. 2006
- d) Rosenfeld et al. Task Force to Evaluate Choice of Spirometric Reference Equations for the National Patient Registry: Summary and Recommendations. Cystic Fibrosis Foundation Registry Committee; 2005

## NUTRITION

Measurements: Weight and height are measured according to EuroCareCF guidelines:

- a. weight: removal of outer clothing, shoes and socks
  - b. height: without shoes and socks - stadiometer - top of head in contact with head board, slight pressure
  - c. it should be the value at the day of the recorded FEV<sub>1</sub>
- z-scores for height, weight and BMI will be calculated using the CDC reference values [Kuczmarski et al (2002)]

### References:

- a) Kromeyer-Hauschild K, Wabitsch M, Kunze D, Geller F, Geiss HC, Hesse V *et al.* Percentiles of body mass index in children and adolescents evaluated from different regional German studies. *Monatsschr Kinderheilkd* 2001; 149:807-818
- b) Lai H-C, Corey M, FitzSimmons S, Kosorok MR, Farrell M. Comparison of growth status of patients with cystic fibrosis between the United States and Canada. *Am J Clin Nutr* 1999; 69:531-538
- c) Public Use File BGS98, German National Health Interview and Examination Survey 1998, Robert-Koch-Institut, Berlin, Germany, 2000
- d) Wiedemann B, Paul KD, Stern M, Wagner TO, Hirche TO, on behalf of the German CFQA Group. Evaluation of body mass index percentiles for assessment of malnutrition in children with cystic fibrosis. *Eur J Clin Nutr* 2007; 61, 759-768
- e) Kuczmarski RJ, Ogden CL, Guo SS *et al.* 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat* 2002; 11(246): 1-190.

## DEFINITION OF CHRONIC INFECTION IN THE LOWER AIRWAYS

1. Chronic PA infection should be defined by local physician according to modified Leeds criteria<sup>a</sup> and/or anti-pseudomonas antibodies<sup>b</sup>. Patient should be defined as chronically infected if he/she fulfils the criteria now or has done so in recent years and the physician has no reason to think the status has changed:
  - a. modified Leeds criteria, chronic infection: >50% of the sputum samples, collected during the last 12 months were positive. At least 4 sputum samples during that period;
  - b. and/or significantly raised anti-pseudomonas antibodies according to local laboratories.
2. Chronic infection with other gram-negative bacteria should be recorded by the same criteria as above.

### References:

- a) Lee TWR, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic *Pseudomonas aeruginosa* in cystic fibrosis patients. *J Cystic Fibrosis*
- b) Proesmans M, Balinska-Miskiewicz, Dupont L *et al.* Evaluating the "Leeds criteria" for *Pseudomonas aeruginosa* infection in a cystic fibrosis centre. *Eur Resp J* 2006;27:937-943.
- c) Doring G, Conway SP, Heijerman HG, *et al.* Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. *Eur Respir J* 2000;16:749-767.

## ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

Diagnostic criteria:

1. Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, change in pulmonary function, or increased sputum production) not attributable to another etiology.
2. Total IgE > 500 IU/ml.
3. Positive skin prick test for *Aspergillus* antigen (> 3 mm) or positive specific IgE for *A. fumigatus*.
4. Either:
  - a. precipitins to *A. fumigatus* or in vitro demonstration of IgG antibody to *A. fumigatus*;
  - b. or new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (characteristic changes) that have not cleared with antibiotics and standard physiotherapy.

### References:

Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, Denning DW, Cramer R, Brody AS, Light M, Skov M, Maish W, Mastella G; Participants in the Cystic Fibrosis Foundation Consensus Conference. Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. *Clin Infect Dis.* 2003 Oct 1;37 Suppl 3:S225-64.

## LIVER DISEASE

We adopt the definitions for Liver Disease used by the UK Registry. These definitions discriminate patients with severe liver disease (with portal hypertension) from milder cases (cirrhosis without portal hypertension).

*Cirrhosis with Hypertension*: scarring of the liver related to underlying CF, typically in a biliary pattern.

Severe liver disease may include portal hypertension and/or hypersplenism.

*Cirrhosis without Hypertension*: scarring of the liver relating to underlying CF.

*Liver disease without cirrhosis*: this includes fatty liver or viral hepatitis but not biliary cirrhosis.

## PANCREATIC STATUS

Definition:

Stool fat (van de Kamer) > 4-5 g/d in young children, > 7g/d in children above 10 yrs and adults and/or faecal pancreatic elastase-1 < 200 µg/g.

Two determinations are mandatory. Faecal fat excretion values of infants below 3 months are contradictory. Other than pancreatic causes of steatorrhoea must have been excluded.

Pancreatic status will be assessed at the registry level, according to the following:

*Pancreatic insufficiency*: Faecal elastase <200 µg/g (twice) and Faecal fat high\* (twice);

*Pancreatic sufficiency*: Faecal elastase ≥200 µg/g (twice) and Faecal fat normal\* (twice).

\*according to definition above

*Salt loss syndrome* (salt depletion, Pseudo-Barter):

Primary metabolic alkalosis with blood pH > 7.45, serum sodium < 130 mmol/l and serum chloride < 90 mmol/l.

### References:

- Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HGM, Robberecht E, Döring G. Nutrition in patients with cystic fibrosis. A European consensus. *J Cystic Fibrosis* 2002; 1:51-75.
- Walkowiak J, Nousia-Arvanitakis S, Henker J, Stern M, Sinaasappel M, Dodge JA. Invited review: Indirect pancreatic function tests in children. *J Pediatr Gastroenterol Nutr* 2005; 40:107-114.
- Reference: Fustik S, Pop-Jordanova N, Slaveska N, Koceva S, Efremov G. Metabolic alkalosis with hyponatremia in infants with cystic fibrosis. *Pediatr int* 2002; 44: 289-92.

## TRANSPLANTATION

We advise to record information of patients after transplantation, and to use the best FEV1 of the year, therapy and complications before transplantation in the year of transplantation.