Variables, Inclusion Criteria and Definitions used by the ECFSPR (from follow-up year 2021)

Variables

Demographics

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

Diagnosis status
Age at diagnosis
Sweat test type
Electrolytes type
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

First mutation (possible to record complex variants in cis)
Second mutation (possible to record complex variants in cis)

Maintenance Therapy

Inhaled continuous (≥ 3 months) hypertonic saline ≥3%
Inhaled continuous (≥ 3 months) Mannitol
Inhaled antibiotic this year - continuous (≥ 3 months) or on/off for a total of (≥ 3months)
Inhaled continuous (≥ 3 months) bronchodilators
Oxygen therapy ≥ 3 months during the year of follow-up (inc. 24h/day, night time, exercise). Does not need to be continuously but should be from a single prescription).
Use of continuous (≥ 3 months) non-invasive positive pressure ventilation (NIPPV)
Use of continuous (≥ 3 months) rhDNase this year
Use of continuous (≥ 3 months) Inhaled steroids
Use of continuous (≥ 3 months) Oral steroids
Use of continuous (≥ 3 months) azithromycin (or other macrolide) this year
Use of continuous (≥ 3 months) ursodeoxycholic acid this year
Use of continuous (≥ 3 months) pancreatic enzymes this year
Use of continuous (≥ 3 months) proton pump inhibitors (PPI)
Use of CFTR Modulator Therapy
Start and stop dates CFTR Modulator Therapy (start date & stop date x 2 per kind of modulator)
Sweat chloride values - before CFTR modulator & during CFTR modulator

Complications

Allergic broncho-pulmonary aspergillosis this year
Diabetes this year
Pneumothorax this year
Distal intestinal obstruction syndrome (DIOS)
Salt depletion this year
Liver disease this year
Haemoptysis major volume of expectorate > 250ml in a day.
Pancreatic status: faecal elastase
Pancreatic status: faecal fat
Occurrence of malignancy this year

Microbiology (*positive - chronic* or *positive - not chronic* options given for all pathogens)

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

Lung function and nutrition follow-up

Date of best FEV1* recorded this year
Value of best FEV1* recorded this year
Value of best FVC** recorded this year
Date of lowest LCI 2.5% this year
Value of lowest LCI 2.5% this year
Type of device used for LCI measurement
Height measured at date of best FEV1* (or in case of no FEV1, last height of the year)

Weight measured at date of best FEV1* (or in case of no FEV1, last height of the year)

*FEV1 of highest FEV1% predicted
**FVC at time of best FEV1

Transplant

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

Criteria and References used by the ECFS Patient Registry

1 Diagnosis / Reversal of Diagnosis: Criteria, References

i. Two sweat tests value > 59 mmol/L chloride: CF diagnosis accepted.

ii. One sweat test value > 59 mmol/L chloride + DNA Analysis/Genotyping – two identified disease-causing CF mutations in trans: CF diagnosis accepted.

iii. If the sweat value is less than or equal to 60 mmol/L chloride, or not reported, then at least 2 of the following must be fulfilled:

a. DNA Analysis/Genotyping: two identified disease-causing CF mutations in trans;
b. NPD (Transepithelial (Nasal) Potential Difference) or ICM (Intestinal current measurement): result consistent with a diagnosis of CF;
c. Clinical presentation: typical features of CF.

iv. **Diagnosis reversal***
CF diagnosis should be reversed if any of the following cases are true:

a. DNA Analysis: unable to identify any disease causing CF mutations;
b. NPD (nasal potential difference) &/or ICM (intestinal current measurement): result not consistent with diagnosis of CF;
c. Normal values from repeated sweat testing (confirm with the clinical team).

** See also ECFSPR SOP - Standard Operating Procedure - regarding reversal of diagnosis and previously submitted data (find it on the homepage of the data collection software ECFSTracker, together with other useful information).*

References (links)

1) ECFS best practice guidelines: the 2018 revision
2) European Cystic Fibrosis Society Standards of Care: Best Practice guidelines (2013)

2 Sweat Test: Parameters, Values to be reported, References

i. Diagnostic standards: the quantity of sweat should indicate an adequate rate of sweat production;

ii. a. The sweat sample should be processed immediately after sweat collection;
b. Chloride concentration measurement is the preferred analysis for Diagnostic sweat tests. For sweat tests in relation to CFTR modulator therapy, Chloride is the only accepted value;
c. Chloride value: report the Chloride value in millimols per litre (mmol/L). If duplicate tests were completed on the same day, for Diagnostic sweat tests, **report the highest positive value;**
d. A sweat chloride value >59 mmol/L is consistent with a diagnosis of CF;
e. A sweat chloride value <30 mmol/L makes the diagnosis of CF unlikely (However, specific CF causing mutations can be associated with a sweat test below 30 mmol/L).
n.b. *The acceptable range for Chloride values is 1-160 mmol/L.* ***Anyone who has a Chloride value above 160 mmol/L should be re-tested;***

iii. As already mentioned above, the ECFSPR will consider only Titration/Chloride values in analyses.

References (links)

1) ECFS best practice guidelines: the 2018 revision
1) European Cystic Fibrosis Society Standards of Care: Best Practice guidelines (2013)

3 Nutrition: Method, Values and Dates to be reported, References.

i. The height and weight reported to the ECFSPR should be from the same day as the reported FEV1 (of hightest FEV1% predicted of the year);

ii. If spirometry was not done, the last weight and height measurements of the year, and the date they were measured, should be recorded;

iii. Height and weight should be measured in accordance with EuroCareCF guidelines:
Weight: removal of outer clothing, shoes and socks;
Height: removal of shoes and socks, stadiometer - top of head in contact with head board, slight pressure.

iv. Z-scores for height, weight & BMI are calculated with the CDC reference values [Kuczmarski et al (2002)].

References

1) 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.
2) Lai H-C, Corey M, FitzSimmons S, Kosorok MR, Farrell M. Comparision of growth status of patients with cystic fibrosis between the United States and Canada. Am J Clin Nutr 1999; 69:531-538.
3) Public Use File BGS98, German National Health Interview and Examination Survey 1998, Robert-Koch-Institut, Berlin, Germany, 2000.
4) 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.
5) 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.

4 Spirometry: Criteria, Method, Values to be reported, References.

The ECFS Patient Registry collects data on spirometry values to obtain standardised data for comparison with other centres/countries and for use in specific epidemiological studies. **n.b.** Some of the conditions for this (see below) may not be met at every clinical visit for all patients and, for the ECFSPR, only spirometry tests fulfilling the criteria should be recorded by centres/submitted by the National Registries. **All spirometry tests should be carried out in accordance with the ATS/ERS guidelines** (www.thoracic.org/statements/resources/pfet/PFT2.pdf).

For the spirometry values reported to the ECFSPR the following criteria should be met:

i. Pre-test preparation

a. 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.

b. Date of birth, gender and height should be recorded for calculation of predicted values. In addition, the ECFS Patient Registry asks for the weight to be measured at the same time, and recorded.

***** *In accordance with the official criteria of PortCF.*

ii. Values to report:

a. FEV1 in litres: must be the FEV1 in litres (to 2 decimals) of the **highest FEV1% predicted of the year**, in accordance with local reference values;
b. The FEV1 and FVC measurements must be reported in litres (L), to max 2 decimal points;
c. FVC in litres: must be the FVC measured at the same time as the FEV1 of the highest FEV1% predicted of the year and it must be greater than or equal to the FEV1 measurement.
d. For the reported spirometry values, the date of the test and the patient's height and weight at that date should also be recorded in order to calculate the percent of predicted values and other values;
e. Only tests deemed valid according to ATS/ERS guidelines to be reported.

iii. Calculation of percent of predicted values:

a. A common set of reference values - the Global Lung Function Initiative equations (See (a) below) - is used for calculations;

b. n.b. The ECFSPR Definitions Group has considered the issue of race-specific reference values. The decision was to not record race for European patients for the moment and therefore not to calculate race-specific values. This may change in the future.

References

1) 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).
2) Miller et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319–338.
3) Miller et al. General considerations for lung function testing. Eur Respir J 2005; 26: 153–161.
4) Cystic Fibrosis Foundation Patient Registry User Guide, Version 4.0. 2006.
5) 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.

5 Chronic infection in the lower airways: Definition, References.

i. Chronic Pseudomonas aeruginosa infection: A patient should be considered chronically infected if the modified Leeds criteria are met - (a) below - and/or anti-pseudomonas antibodies are detected - (b) below.
A 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 that the status has changed.

a. Modified Leeds criteria - chronic infection: >50% of the samples (sputum/other) collected during the last 12 months should be positive; at least 4 samples collected.

b. Significantly raised levels of anti-pseudomonas antibodies according to local laboratories.

ii. Chronic infection with other gram-negative or gram-positive bacteria should meet the same criteria as described above.

References

1) 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
2) Proesmans M, Balinska-Miskiewiscz, Dupont L et al. Evaluating the "Leeds criteria" for Pseudomonas aeruginosa infection in a cystic fibrosis centre. Eur Resp J 2006;27:937-943.
3) 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.

6 Allergic Bronchopulmonary Aspergillosis (ABPA): Diagnostic criteria, References

i. 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;

ii. Total IgE > 500 IU/ml;

iii. Positive skin prick test for Aspergillus antigen (> 3 mm), or positive specific IgE for A. fumigatus.

iv. Either:
a). Precipitins to A. fumigatus, or in vitro demonstration of IgG antibody to A. fumigatus;
or
b). 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

1) Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, Denning DW, Crameri 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

7 Liver Disease: Definitions

The ECFSPR has adopted the definitions for Liver Disease used by the Cystic Fibrosis Registry in the UK. 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 related to underlying CF;
- **Liver disease without cirrhosis**: this includes fatty liver or viral hepatitis but not biliary cirrhosis.

8 Pancreatic Status: Pancreatic Insufficiency, References

i. **Indcator of Pancreatic Insufficiency - Faecal Fat** (2 determinations are mandatory)

a. Young children: Stool fat (van de Kamer) > 4-5 g/d;

b. Children older than 10 years and adults: Stool fat (van de Kamer) >7g/d and/or faecal pancreatic elastase-1 < 200 ug/g.

Please note

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

ii. **For the ECFSPR, pancreatic status will be assessed as follows:**

- 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).

** Refer to 9.8.i.a and 9.8.i.b above*

References

1) 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.
2) 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.

9 Salt Loss Syndrome: Definition and Reference

Primary metabolic alkalosis with blood pH > 7.45, serum sodium < 130 mmol/l and serum chloride < 90 mmol/l (all 3 of these to be manifest).

Reference

1) Fustik S, Pop-Jordanova N, Slaveska N, Koceva S, Efremov G. Metabolic alkalosis with hypoelectrolytemia in infants with cystic fibrosis. Pediatr int 2002; 44: 289-92.

10 Transplantation: Indications

i. For patients who had a transplant during the year of follow up*:

a. Use the best FEV1 before transplantation;

b. Record therapy, complications and microbiology from before transplantation.

ii. For patients who had a transplant before the current follow-up year:

a. Record all available information.

*Direct Data Entry Hospitals (not National Registries): if a patient is transferred to a different hospital for transplant and that hospital submits data to the ECFSPR, the transplant centre must not re-register the patient. The Core Data will be transferred through the data collection software to the transplant centre.