Variables, Inclusion Criteria and Definitions used by the ECFSPR

List of 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

Therapy

Inhaled continuous hypertonic NaCl this year
Inhaled continuous antibiotic this year
Inhaled continuous bronchodilators this year
In Oxygen therapy this year
Use of rhDNase this year
Use of continuous azithromycin (or other macrolide) this year
Use of ursodeoxycholic acid this year
Use of pancreatic enzymes this year

Diagnosis

Diagnosis confirmed
Age at diagnosis
Type of sweat test
Electrolytes
Chloride value
Meconium Ileus
Neonatal screening

Complications

Allergic broncho-pulmonary aspergillosis this year
Diabetes: daily insulin treated this year
Pneumothorax requiring chest drain 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

Genotype

First mutation
Second mutation

Microbiology

Chronic *Burkholderia cepacia complex*
Nontuberculous mycobacteria this year
Chronic *Pseudomonas aeruginosa*
Chronic *Staphylococcus aureus*
Stenotrophomonas maltophilia this year

Follow-up

Date of best FEV_1 recorded this year
Value of best FEV_1 recorded this year
Value of best FVC recorded this year
Height measured at date of best FEV_1 (or in case of no FEV_1 last height of the year)
Weight measured at date of best FEV_1 (or in case of no FEV_1 last height of the year)

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)

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, then at least 2 of these should be fulfilled:

   a. DNA Analysis/Genotyping – two identified disease causing CF mutations;
   b. Transepithelial (Nasal) Potential Difference – 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 – 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 patient has not undergone sweat testing, record as "not done". If a sweat test is "not done" then two known genotype mutations must be reported.

i. Sweat Test: record the patient's sweat test;
ii. Electrolytes: Chloride concentration measurement is the preferred analysis;
iii. Chloride value: report the Chloride value in millimols per litre (mmol/L). If duplicate tests were carried out on the same day, report the highest positive value.

NOTE: The acceptable range for Chloride values is 1-170 mmol/L. Anyone who has a Chloride value above 170 mmol/L must be re-tested.

SPIROMETRY

The reason for recording data on spirometry values for the ECFSPR 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) might 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 all tests the spirometry should be performed according to the common ATS/ERS guidelines: (http://www.thoracic.org/statements/resources/pfet/PFT2.pdf).

Furthermore, for the values reported to the ECFSPR 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 sent to the ECFSPR, it is the value in litres of the highest available value of FEV_1% of predicted (according to local references) of the year which should be extracted;
   b. each patient's FVC and FEV_1 measurements 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_1 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 the percent of predicted values;
   e. only tests deemed valid according to ATC/ERS guidelines should be reported.

3. Calculation of percent of predicted values. A common set of reference values will be used:
   a. for male children 6-17 yrs and female children 6-15 yrs: Wang et al (1993);
   b. for male adults ≥ 18 yrs and females ≥ 16 yrs: Hankinson et al (1999);
   c. for children < 6 yrs no calculation of percent of predicted values will be performed because of lack of valid reference values.

   The definition group considered the issue of race-specific reference values and has 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. CFF registry committee task force to evaluate choice of spirometric reference equations for the national patient registry – summary and recommendations.
e. Hankinson JL, Odencrantz RJ, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respr Crit Care Med 1999;159:179-87.
f. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993;15:75-88.

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. they should be the values at the day of the recorded FEV_1.

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. Comparision 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.

CHRONIC INFECTION IN THE LOWER AIRWAYS

1. Chronic PA infection should be defined by the local physician in accordance with the modified Leeds criteria[a] and/or the presence of anti-pseudomonas antibodies[b]. Patient should be defined as chronically infected if he/she fulfils the criteria now or has done 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 positive, collected during the last 12 months. 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 using 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-Miskiewiscz, Dupont L et al. Evaluating the "Leeds criteria" for Pseudomonas aeruginosa infectionin a cystic fibrosis centre. Eur Resp J 2006;27:937-943.

c. Döring 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 BRONCHO-PULMONARY 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, 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.

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):

a. *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;
b. *Cirrhosis without Hypertension*: scarring of the liver relating to underlying CF;
c. *Liver disease without cirrhosis*: this includes fatty liver or viral hepatitis but not biliary cirrhosis.

PANCREATIC INSUFFICIENCY

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 ug/g.
Two determinations are mandatory: faecal fat excretion values of infants below 3 months are contradictory; causes of steatorrhoea, other than those which are pancreas-related, must have been excluded.

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

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

b. *Pancreatic sufficiency*
Faecal elastase ≥200 µg/g (twice) and Faecal fat normal (twice).*
*according to the definition above.

References:

a. 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.
b. 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.