4.1 Clinical evaluation

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1. INTRODUCTION

- In a variable interval after birth (depending on the genotype and the phenotype) most CF patients develop destruction of the airways and lungs. This is due to decreased mucociliary clearance leading to retention of mucus in the airways and further damage of the lung through respiratory infections. Consequently, progressive respiratory failure with hypoxemia, exhaustion of the respiratory muscles and pulmonary hypertension may develop.
- It is essential to monitor the pulmonary function to determine the course of disease and to recognize pulmonary complications (such as bronchiectasis, colonisation with various pathogens, ABPA, bronchial hyperreactivity, atelectasis, pneumothorax, hemoptysis, respiratory failure) as soon as possible.
- In addition to getting an exact medical history, clinical status, spirometry and microbiological samples, several further investigations are recommended.

2. MEDICAL HISTORY AND CLINICAL STATUS:

- In general, the items noted in **Table 1** should be assessed at every visit

Table 1: Items to assess during clinical evaluations

Medical history
Symptoms
– Cough: frequency, dry or productive, any change
– Sputum: quantity, quality (color, viscosity, odor), any change
– Hemoptysis: amount, dark or bright colored, concomitant symptoms of exacerbation
– Dyspnea: in which situations, any change
– Wheezing: in which situations, trigger
– Chest pain: trigger, time course
– Exacerbation (e.g. fever, increased sputum production, increased cough, new infiltrates in chest imaging)
Therapy
– Current medications, dosing
– Inhalation technique, which device, care of the device
– Airway clearance technique, physiotherapy
– Physical activity
– Adherence
– Vaccination (influenza, *St. pneumoniae, B. pertussis*)

(continued)

Course of disease
– Exacerbations
– Recent antibiotics and response
– Recent changes of therapy and response
– Change of any symptom

Clinical status

– Vital signs: blood pressure, breathing rate, pulse rate, body temperature if fever suspected
– Oximetry (SpO_2-saturation) at room air
– Height and weight (Body mass index)
– Cyanosis
– Thoracic shape: e.g. increase in the anteroposterior diameter (barrel-shaped chest)
– Digital clubbing of fingers and toes
– Pulmonary auscultation

3. PULMONARY FUNCTION TESTS (PFTs)

- Pulmonary function tests (PFTs) play a central role in the clinical assessment of lung disease and they provide information about the longitudinal course, the stability or progression of the disease as well as the response to therapy.
- These tests are important instruments to orient therapeutic decisions.
- Usually the first change in lung function is an obstructive ventilatory defect. In more advanced disease, restrictive defects and progression to respiratory failure with hypoxemia and hypercapnia may develop.

3.1 Spirometry / Lung Clearance Index / Body plethysmography / Diffusing capacity / Arterial blood gas analysis (Table 2)

- PFTs should be performed according to the ATS/ERS guidelines.
- Although not specific to CF, some issues to consider particularly in this context are:
  - A recent pneumothorax or hemoptysis are considered relative contraindications for PFTs
  - Infectious control issues
- LCI is derived from Multiple Breath Washout (MBW) tests: it concerns the washout of an inert tracer gas from the lungs during tidal breathing. It provides a global measurement of ventilation heterogeneity and is considered an indicator of small airways disease. It is mainly used in pediatric patients (evaluation of early lung disease, when FEV_1 is still within normal range) and as an efficacy endpoint in clinical trials. Currently its use in adult CF patients is limited. The duration of the test is a limiting factor in clinical practice (it may be up to 30min in adults).

Table 2: Indications of Pulmonary Function Tests (PFTs)

Spirometry	– At every clinical visit (monitoring) – On suspicion of an exacerbation – Before, (during) and after treatment of an exacerbation – After change of treatment
Reversibility testing	– Newly developed obstructive syndrome in spirometry – Wheezing, chest tightness, dyspnea on exertion or after exposure to cold air – Clinical suspicion of hyperreactivity or allergic disease
Lung Clearance Index (LCI)	– Detection of ventilation heterogeneity – (mainly used in children)
Body plethysmography	– Annually – Suspicion or monitoring of restriction – Evaluation and documentation of hyperinflation (early sign of obstruction)
Diffusing capacity	– Annually – On suspicion of a gas exchange disorder
Arterial blood gas analysis	– On suspicion of a gas exchange disorder – Prescription and monitoring of long-term oxygen therapy (LTOT) – Prescription and monitoring of non-invasive ventilation (NIV)

3.2 Pulse oximetry/Capnography/Sleep studies

- Overnight oximetry is used for the detection of nocturnal hypoxemia. The number of desaturations per hour may raise suspicion for sleep apnea, which should be confirmed with a sleep study.
  - About 18% of CF patients with stable, moderate to severe disease suffer from nocturnal desaturations.
  - Chronic inflammation and nasopharyngeal obstruction may contribute to the development of obstructive sleep apnea.
- Oximetry and/or capnography are recommended in symptomatic patients (e.g. abnormal saturation at rest, decreased sleep quality, frequent awakenings or morning headaches). Oximetry during exacerbations may help adapt short-term oxygen therapy **(Table 3)**.

Table 3: Indications of oximetry, capnography and sleep studies in CF

Oximetry	– $SatO_2$ at every clinical visit – Monitoring of disease progression – Nocturnal oximetry: suspicion of nocturnal hypoxemia or monitoring during nocturnal oxygenotherapy – Monitoring of LTOT overnight – Monitoring of short-term oxygen therapy during exacerbations
Capnography	– Suspicion of hypercapnic respiratory failure – Initiation and monitoring of NIV
Sleep Studies	– Suspicion of sleep apnea – Adaptation of NIV

3.3 Six-minute walk test (6MWT), 3-minute step test (3MST) and cardiopulmonary exercise testing (CPET)

- Exercise testing in subjects with CF is recommended to evaluate exercise tolerance and to detect hypoxemia on exertion **(Table 4).**
- 6MWTand 3MST
  - are non-invasive
  - reflect daily activity better than cardiopulmonary exercise testing (CPET) on a cycle ergometer.

Table 4: Indications of 6MWT, 3MST and CPET

6MWT,3MST,CPET	– Evaluation of exercise tolerance – Establishment of an exercise training program – Detection of hypoxemia on exertion – Evaluation in case of cor pulmonale – Efficacy assessment of therapeutic interventions

4. IMAGING STUDIES

- Chest radiography (CXR) and chest computed tomography (CT-scan) are both used to detect and monitor structural lung damage in CF.
  - Currently, chest CT-scan is the most sensitive tool for the diagnosis and monitoring of lung alterations such as bronchiectasis, small airway disease, etc.
    - Paired inspiratory/expiratory CT-scans help visualize air-trapping and mosaic patterns
    - CT-pulmonary angiography is often required in cases of hemoptysis
  - **In most cases, CT-scan is performed with minimal radiation protocols (except when CT-pulmonary angiography is indicated)**.

- **Table 5** summarizes the indications and our recommendations for performing imaging studies in adult CF patients **(see also Chapter "*Annual assessment*")**. Briefly:
  - Annual CXR are NOT recommended for all patients routinely.
  - At initial patient evaluation (e.g. at transition from pediatric care, or at diagnosis for patients diagnosed in adulthood) a paired inspiratory/expiratory low dose (**minimal radiation protocol)** chest CT-scan without contrast medium is proposed.
  - A low dose chest CT-scan is recommended every 2-3 years.

- Currently, MRI of the chest is not routinely done for the evaluation of lung disease in CF, but may be promising.

Table 5: Indications of imaging studies

Plain chest radiography (CXR)	– When clinically indicated, e.g. suspicion of pneumonia, pneumothorax
Chest CT-scan (low dose)	– When clinically indicated, e.g. suspicion of atelectasis, small pneumothorax, non-tuberculous mycobacterial (NTM) infection and other alterations, which are difficult to see in plain chest films – Evaluation before transplantation
Paired inspiratory/expiratory Chest CT-scan (low dose)	– At initial patient evaluation – When clinically indicated, e.g. suspicion of bronchiolitis and small airways disease*[1]
CT-pulmonary angiography*[2,3]	– Localization of bleeding site in major hemoptysis – Suspicion of pulmonary embolism

*[1] **See also Chapter "*Small airways disease*"**

*[2] CT-pulmonary angiography should not delay embolisation in cases of life-threatening hemoptysis **(see also Chapter "*Hemoptysis*")**

*[3] In case of iodine-based contrast media allergy, useful information can be found in the following addresses
- http://www.acr.org/Quality-Safety/Resources/Contrast-Manual (ESUR guidelines)
- http://geiselmed.dartmouth.edu/radiology/pdf/ACR_manual.pdf

5. MICROBIOLOGY

- Airway cultures should be done at every clinical visit (at least every 3 months) and during respiratory exacerbations.
  - Specific examination of *B. cepacia complex* should be routinely included in sputum culture (performed by most microbiology laboratories collaborating with CF centers).
  - Screening for non-tuberculus mycobacteria (NTM) should be conducted
    - at least annually
    - before starting azithromycin

  Note: the frequency of controls should be increased in cases of NTM positivity or decline of lung function.

- Specimens:
  - Preferred: spontaneous sputum after mouth rinsing.

- Alternative: provoked sputum with hypertonic saline, provoked sputum after physiotherapy or sports, throat swab after coughing.
- Bronchial aspiration and bronchoalveolar lavage (BAL) are not routinely done in adults but are considered in special situations such as:
  - New or increased symptoms of infection with no identifiable pathogens and no response to antibiotic treatment.
  - Identification of NTM.
  - Monitoring after lung transplantation.

- Fast transport to microbiology laboratory to avoid contamination with saprophytes.
- Information on the ''diagnosis of CF'' and ''recent or current use of antibiotics'' should be transmitted to the laboratory.
- Microscopic evaluation to differentiate sputum from saliva. In general, sputum samples having the following criteria are unlikely to be contaminated by oropharyngeal flora:
  - $<$10 squamous epithelial cells per field (low-power 10x lens, total magnification 100x) and $\geq$ 25 neutrophils per low-power field or
  - a ratio of neutrophils to epithelial cells $>$5:1

  Note: When reporting the number of squamous epithelial cells in a qualitative way:
  (+) corresponds to 1-10 epithelial cells per field (good quality sputum sample)
  (++) corresponds to 11-25 epithelial cells per field
  (+++) corresponds to more than 25 epithelial cells per field (poor quality sample containing saliva)
- In CF, in the absence of a ''good quality'' sputum sample, salivary samples or throat swabs may still offer some information concerning the presence of bacterial pathogens.

6. BRONCHOSCOPY

- Bronchoscopy is not routinely performed in adult CF patients **(Table 6)**.
- There is no evidence for BAL-guided antimicrobial therapy in adults. But there are several clinical situations where diagnostic or interventional bronchoscopic techniques are recommended.
- Special attention should be paid on the increased bleeding risk due to hyperplastic bronchial arteries.

Table 6: Indications of diagnostic bronchoscopy

Diagnostic Bronchoscopy	– Suspicion of central mucous plugging causing atelectasis despite optimal conservative treatment – Sampling for pathogens in special situations – To determine the bleeding site in specific conditions (rarely necessary, it should not delay bronchial artery embolisation)* – Surveillance and suspicion of rejection after lung transplantation

* **See also Chapter *''Hemoptysis''***

7. REFERENCES

1. www.cysticfibrosis.org.uk.
2. Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2005;4:7-26.
3. Smyth AR, Bell SC, Bojcin S, et al. European Cystic Fibrosis Society Standards of Care: Best Practice guidelines. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2014;13 Suppl 1:S23-42.
4. Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care: consensus conference report. Chest 2004;125:1S-39S.
5. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. The European respiratory journal 2005;26:319-38.
6. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. The European respiratory journal 2005;26:948-68.
7. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. The European respiratory journal 2005;26:720-35.
8. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. The European respiratory journal 2005;26:511-22.
9. Young AC, Wilson JW, Kotsimbos TC, Naughton MT. The impact of nocturnal oxygen desaturation on quality of life in cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2011;10:100-6.
10. Loeve M, van Hal PT, Robinson P, et al. The spectrum of structural abnormalities on CT scans from patients with CF with severe advanced lung disease. Thorax 2009;64:876-82.
11. Pye A, Hill SL, Bharadwa P, Stockley RA. Effect of storage and postage on recovery and quantitation of bacteria in sputum samples. J Clin Pathol 2008;61:352-4.
12. Jain K, Wainwright C, Smyth AR. Bronchoscopy-guided antimicrobial therapy for cystic fibrosis. Cochrane Database Syst Rev 2013;12:CD009530.
13. Cooper BG. An update on contraindications for lung function testing. Thorax 2011;66:714-23.
14. Kent L, Reix P, Innes JA, et al. Lung clearance index: evidence for use in clinical trials in cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society 2014;13:123-38.
15. Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. The European respiratory journal 2013;41:507-22.