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Review

ECFS best practice guidelines: the 2018 revision

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Abstract

Developments in managing CF continue to drive dramatic improvements in survival. As newborn screening rolls-out across Europe, CF centres are increasingly caring for cohorts of patients who have minimal lung disease on diagnosis. With the introduction of mutation-specific therapies and the prospect of truly personalised medicine, patients have the potential to enjoy good quality of life in adulthood with ever-increasing life expectancy. The landmark Standards of Care published in 2005 set out what high quality CF care is and how it can be delivered throughout Europe. This underwent a fundamental re-write in 2014, resulting in three documents; center framework, quality management and best practice guidelines. This document is a revision of the latter, updating standards for best practice in key aspects of CF care, in the context of a fast-moving and dynamic field.

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In continuing to give a broad overview of the standards expected for newborn screening, diagnosis, preventative treatment of lung disease, nutrition, complications, transplant/end of life care and psychological support, this consensus on best practice is expected to prove useful to clinical teams both in countries where CF care is developing and those with established CF centres. The document is an ECFS product and endorsed by the CF Network in ERN LUNG and CF Europe.
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Keywords: Cystic fibrosis; Standards of care; Multidisciplinary management; Best practice; Guidelines; Consensus

Contents

1. Introduction

The clinical management of cystic fibrosis (CF) has long been of paediatric dominance. In the 1940s and 50s, when knowledge of the disease pathogenesis and availability of treatments were scarce, few patients entered adulthood [1]. Today this is no longer the case. In many countries, children account for less than half of the CF population, with the focus and burden of care gradually shifting towards adult care. This partly results from the understanding that the clinical spectrum of CF is wider than originally believed and the greater diagnostic consideration of phenotypes presenting in adulthood. However, there is no doubt that the outstanding attainments in survival predominantly stem from improvements in care. The establishment of multi-disciplinary centres, creation of large epidemiological datasets, emphasis on early diagnosis, together with important new treatments originated by dynamic pre-clinical and clinical research, have all been instrumental in the evolution of terrific care. Many adults with CF, some of whom have now lived beyond their own expectations, enjoy good quality of life and have jobs or are in further education. Some have families of their own. Yet despite this positive outlook, there remains considerable morbidity and early mortality in this group of patients - a situation particularly manifest in parts of Europe where available resources and facilities are limited [2–4]. Standards of care and campaigning for their implementation remain of capital significance.

The European CF Society (ECFS) has always held that delivering high quality care is paramount and published standards of care documents in 2005 [5] and 2014 [6]. The latter version introduced three distinct work packages; the requisite framework of the CF center [7], best clinical practice [8] and quality management in CF care [9]. Standards were established by achieving consensus amongst a broad spectrum of CF professional and stakeholders with the project being designed and coordinated by a dedicated ECFS core working group.

The 2014 publications were intrinsic to a larger project and in the subsequent years the Standards of Care Working Group brought forward other initiatives, including a survey on CF facilities across Eastern Europe [4] and two courses on quality improvement. It also recognized the importance of continually updating best practice standards. The time interval since the previous best practice document reflects fast-moving and dynamic developments in the field, for example, recommendations for adult CF care [3] and the expanded use of CFTR modulators [10].

In this revision and update of the 2014 Best Practice Standards [8] many of the original authors contributed together with new collaborators. A systematic review of the existing evidence available from the literature was performed. Whenever consistent results from well designed, well conducted clinical studies in CF populations were not available, recommendations developed by knowledgeable, multidisciplinary panels of experts and patient representatives were considered, discussed and where appropriate included in the document. The lead authors of the Newborn Screening and Early Specialist Care Chapter adopted a Delphi consensus methodology amongst the ECFS Neonatal Screening Working Group. Here, initial statements produced by the authors, were adapted in response to comments from the Delphi process. After several iterations, complete consensus was established for all statements.

The manuscript was ratified by the ECFS Board and patient representatives from CF Europe, and evaluated by three independent reviewers.

Whilst much of the structure and content of the 2014 version remains unchanged, there are important modifications including new areas and subjects covered, set out across seven chapters and précised in an executive summary.

2. Executive summary of major revisions and additions

2.1. Newborn screening and early specialist care

- Incidence declines, resulting from population carrier screening, should not impair the indication for a newborn screening programme.
- Factors in making the decision on whether to implement newborn screening should include available healthcare resources and the ability to provide a clear pathway to treatment.
- Infants with meconium ileus have an increased rate of false-negative newborn screening test results.
- Families of screened infants with a positive result should be informed of the function and achievements of CF research and made aware of opportunities for participation in clinical trials.

2.2. Diagnosis

- For mutations not characterized by CFTR2, other evidence to establish diagnosis may be considered, all requiring accompanying sweat chloride confirmation.
- Electrophysiological investigations (nasal potential difference, intestinal short circuit current measurement) should be undertaken in a centre with considerable experience of the procedure.

2.3. Treatment of lung disease

- Ivacaftor should be considered as part of the standard of care in patients with gating mutations.
- Ivacaftor has also shown efficacy in mutations with residual CFTR function.
- Lumacaftor combined with ivacaftor should be available as a treatment option for 508del/508del patients.

2.4. Nutrition and metabolic complications

- Fat soluble vitamin levels should be measured at least annually.
- Excessive doses of PERT may result in abdominal pain or constipation.
- When considering glucose assessment, a single abnormal oral glucose tolerance test requires confirmation with a second test. Some centres use continuous glucose monitoring as part of the diagnostic process.

2.5. Treatment of complications

- CF centers should have established protocols for desensitisation to allergies to antibiotics.
- Ivacaftor and the combination of lumacaftor/ivacaftor may cause hepatic impairment. When liver disease is present the dosing of these drugs may need adjustment.
- Drug-drug interactions, especially after the introduction of CFTR correctors and modulators, are complications clinicians should be aware of and when possible prevent by dose adjustment.
- Gastrointestinal malignancies are more prevalent in patients with CF than in the healthy population, with a higher yearly incidence in colorectal cancer and progression of adenomatous colorectal polyps to colorectal cancer. Screening for colorectal cancer is cost-effective, and should be started at an age of 40 years.

2.6. Transplantation and end-of-life issues

- Assessment and prioritisation of younger children with CF requires careful consideration with transplant teams who have a specific paediatric expertise.
- Ongoing regular contact should be established between the referring CF centre and the lung transplantation service about the health status of actively wait-listed patients.
- Potential risks of post-transplant complications in patients with active *Mycobacterium abscessus* infection need to be highlighted.
- The stress that transplantation assessment and being "wait-listed" can place on the patient and their family must be pro-actively assessed and managed.

2.7. Psychosocial care

- Recommendations for mental health screening, assessment and treatment are made in alignment with mental health guidelines in CF.
- The standard on "growing older with CF" has been expanded to consider living with end-stage disease to balance identifying and treating psychosocial problems with promoting psychological resilience.
- There are expanded details on supporting the CF Team and identifying key times of vulnerability.

3. Newborn screening and early specialist care

Kevin Southern (UK), Jurg Barben (CH), Anne Munck (FR).

There is clear evidence to support newborn screening (NBS) for CF. Early recognition provides the foundation for future management and prevents the delay in diagnosis that has affected many families in areas that do not screen [11]. Protocols should be designed to reflect the health service infrastructure and *CFTR* genetics of each population and minimise potential negative impacts. Please refer to the ECFS best practice guidelines on NBS and on the management of young infants with CF diagnosed through screening [12,13].

3.1. What population characteristics validate screening newborn infants for cystic fibrosis?

Health authorities need to balance the benefit/risk ratio of screening newborns for CF in their population. If the incidence of CF is <1/7000 births, careful evaluation is required as to whether NBS is valid. The protocol must be shown to cause the minimum negative impact possible on the population.

Incidence declines due to population carrier screening should not impair the indication for an early diagnosis programme as CF NBS and carrier screening have complementary roles and neither can replace the other [14]. Other factors in making the decision on whether to implement screening should include available healthcare resources and the ability to provide a clear pathway to treatment (see next question).

3.2. What health and social resources are minimally acceptable for newborn screening to be a valid undertaking?

Infants identified with CF through a NBS programme should have prompt access to specialist CF care that achieves ECFS standards. A NBS programme may be a mechanism to better organise CF services, through the direct referral of infants for specialist CF care. Countries with limited resources should consider a pilot study to assess the validity of NBS and the adequacy of referral services for newly diagnosed infants in their population.

3.3. What is an acceptable number of repeat tests required for inadequate dried blood samples for every 1000 infants screened?

The number of requests for repeat dried blood samples should be monitored and should be <0.5%. More than 20 repeats for every 1000 infants, is unacceptable (2%).

3.4. What is an acceptable number of false positive NBS results (infants referred for clinical assessment and sweat testing)?

Programmes should aim for a minimum positive predictive value of 0.3 (PPV is the number of infants with a true positive NBS test divided by the total number of positive NBS tests).

3.5. What is an acceptable number of false negative NBS results? These are infants with a negative NBS test that are subsequently diagnosed with CF (a delayed diagnosis)

a. Programmes should aim for a minimum sensitivity of 95%. Sensitivity is the number of true positive NBS results as a percentage of the total CF population (true positive and false negatives not including meconium ileus, see below).
b. Infants with meconium ileus (MI) have an increased rate of false negative NBS test results. This should have little impact on the timing of diagnosis which should be made clinically. However paediatric surgeons need to be aware of this situation. Sensitivity should be calculated and reported including with and without MI false negative infants.
c. Mechanisms should be in place for the collection of reliable long-term false negative data.

3.6. What is the maximum acceptable delay between a sweat test being undertaken and the result given to the family?

The sweat test should be analysed immediately and the result reported to the family on the same day.

3.7. What is the maximum acceptable age of an infant on the day they are first reviewed by a specialist CF team following a diagnosis of CF after NBS?

The majority of infants with a confirmed diagnosis after NBS should be seen by a specialist CF team by 35 days and no later than 58 days after birth. Programmes that are consistently missing these targets should undertake a protocol review and consider alternative strategies.

3.8. What is the minimum acceptable information for families of an infant recognised to be a carrier of a CF causing CFTR mutation after NBS?

a. Families should receive a verbal report of the result. They should also receive written information to refer to. Information should also be sent to the family Primary Care Physician.
b. The information should be clear that:

   i. The infant does not have CF.
   ii. The baby is a healthy carrier.
   iii. Future pregnancies for this couple are not free of risk of CF and the parents may opt for genetic counselling.
   iv. There are implications that could affect reproductive decision making for extended family members and the infant when they are of child bearing age.

3.9. What are the minimum acceptable standards for reporting a CF diagnosis following NBS to the family?

a. A CF Specialist should discuss the result in person with the parents.
b. The family should receive written information to read after the consultation. Information should also be sent to the family Primary Care Physician.
c. The family should have a clear understanding of short and long term plans with respect to the child's management.
d. Families of screened infants with a positive result should be informed of the function and achievements of CF research and made aware of opportunities for participation in clinical trials.

3.10. What are the minimal acceptable standards for the recognition and management of infants with an unclear diagnosis[1] following NBS?

a. The infant should be reviewed by a CF Specialist.
b. This may be in a CF clinic or a non-CF clinic, if local circumstances are appropriate.
c. Extended gene sequencing should be undertaken when one or no mutations are recognised.
d. Sweat testing should be repeated in a centre with considerable experience (> 150 sweat tests per annum) and sweat chloride measured by a standard method.
e. Families should receive clear verbal and written information about the current clinical status of the infant, as well as the plans for follow-up and assessments. It should be acknowledged that for many of these infants there may be uncertainty regarding clinical progress and possible future symptoms. Information should also be sent to the family Primary Care Physician. Infants should be managed as per the ECFS guidelines [15].

4. Diagnosis

Isabelle Sermet-Gaudelus (FR), Nataliya Kashirskaya (RU), Kevin Southern (UK).

It is mandatory to have a high standard of care for diagnostic evaluation in CF. Diagnostic confirmation is required for children and adults presenting with suggestive clinical features, but also in specific situations such as asymptomatic infants with a positive NBS test or a positive family history.

4.1. What are the requirements to undertake the diagnosis for CF? [17]

a. To be able to undertake sweat testing according to the standards described below.

[1] Definition; an infant with a repeatedly intermediate sweat test result, or an infant with two CFTR gene mutations (one of which has unclear phenotypic outcome) and a normal or intermediate sweat test result. An intermediate sweat test result is a sweat chloride value between 30 and 59 mmol/L [16]. The term CF Screen Positive, Inconclusive Diagnosis (CFSPID) is recommended as the designation for infants with an unclear diagnosis after NBS [16].

b. To be able to perform genetic testing for the most appropriate panel of *CFTR* mutations for the local population. Access to extended exon DNA analysis should be available when required.
c. Resources to undertake clinical assessment including assessment of respiratory condition (respiratory tract culture for CF-associated pathogens, age appropriate respiratory function testing and imaging), non-invasive evaluation of exocrine pancreatic function and sperm count in male adults.

4.2. What are the diagnostic criteria for CF? [17,18]

A positive NBS test result or clinical features suggestive of CF, including, but not restricted to, diffuse bronchiectasis; positive sputum cultures for a CF-associated pathogen (especially *P. aeruginosa*); exocrine pancreatic insufficiency; salt loss syndrome; and obstructive azoospermia in males and a sweat chloride > 59 mmol/L and/or two CF causing CFTR mutations in *trans*[2]

The term "mutation" is referred as a "pathogenic variant", according to the CFTR-2 database (http://www.CFTR2.org). For mutations not characterised by CFTR-2, other evidence may be considered, such as bibliographic data and other genetic databases (also see paragraph 4.6), all requiring accompanying sweat chloride confirmation.

4.3. What are the minimal standards for laboratories performing sweat tests? [19]

a. Sweat collection by experienced personnel (at least 150 sweat tests per annum) following national or international guidelines and subject to regular (at least annual) peer review.
b. Use of commercially available equipment approved for diagnostic use according to the national regulatory requirements or EU standards if no local ones are available.
c. Internal quality control (usually three samples) with acceptable limits of agreement for chloride before each sweat analysis.
d. Regular external quality assurance for the analyses according to national guidelines.
e. A high number of QNS (Quantity Not Sufficient) rates is a marker of technical issue. This necessitates renewing training for personnel experiencing sweat tests.

4.4. What are the diagnostic standards of a sweat test?

a. The quantity of sweat should indicate an adequate rate of sweat production (15μL for Macroduct™ tube system).
b. The sweat sample should be processed immediately after sweat collection.
c. A sweat chloride value >59 mmol/L is consistent with a diagnosis of CF.
d. 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. These include c.3718-2477C > T (3849 + 10kbC > T) and mutations associated with varied clinical consequence such as c.617T > G (L206W), c.1040G > A (R347H), and c.3454G > C (D1152H) [21].
e. Individuals with sweat chloride values in the borderline range (30–59 mmol/L) should undergo a repeat sweat test and further evaluation in a specialist CF Centre, including detailed clinical assessment and extensive CFTR gene mutation analysis [20].

4.5. What are the minimal standards for a laboratory performing mutation analysis for CFTR?

a. The laboratory should be able to reliably extract DNA from dried blood spot samples, whole blood (EDTA) or buccal swabs.
b. Samples should be analysed on a weekly basis to avoid significant delay.
c. The laboratory should partake in an external quality assurance exercise with at least annual certification.
d. The primary laboratory should be able to provide a limited *CFTR* mutation panel as a starting point that recognises at least one abnormal allele in >96% of the individuals with CF in the local population [22].
e. When only one mutation is recognised, extended exon DNA analysis (gene sequencing) should be available in the primary laboratory or a secondary laboratory to detect rare mutations and major deletions or duplications should be sought. The disease liability of variants detected by DNA sequencing should be validated against the CFTR-2 database.
f. Novel mutations or variants should be reported to locus specific databases in order to facilitate future interpretation of variants of unknown clinical significance.

4.6. What is a CF causing mutation?

a. A CF-causing mutation is a mutation that causes CF disease when found *in trans* with a known CF-causing mutation [23]. The diagnosis of CF is confirmed in patients with two CF-causing mutations identified in *trans* and classified in the CFTR-2 database (https://www.CFTR2.org) or other relevant information base. However, the absence of two CF-causing mutations after extended DNA testing in the presence of typical clinical or laboratory features of the disease, or abnormal CFTR bioassays (see paragraph 4.10), does not rule out CF.
b. Patients with "mutations of varying clinical consequence" require further evaluation in a Specialist CF Centre. Those include the mutations that result either in CF or in a CFTR-related disorder such as diffuse bronchiectasis, congenital bilateral absence of vas deferens (CBAVD), recurrent/chronic idiopathic pancreatitis.
c. Patients carrying mutations of unproven or uncertain clinical consequence also require further evaluation in a Specialist CF Centre.

[2] On rare occasions two mutations can occur on the same chromosome (called *in cis*). For this reason, it is important to check the parental origin of the mutations to ensure the mutations occur on separate chromosomes (*in trans*).

4.7. What are the minimal acceptable standards of care for reporting a diagnosis of CF to a symptomatic patient?

a. A positive CF diagnostic test result should be reported promptly (ideally within 24 hours after sweat result) by the CF physician.
b. The patient or parent/carer should receive clear written and verbal information about the disease and be provided with access to electronic media from the health service/national patient organization. Contact information on the appropriate CF Centre should be given (in accordance with treatment pathways for newly diagnosed CF in each country).
c. Genetic counseling should be offered and contacts for clinical genetic services provided. This will facilitate primary and secondary prevention of CF in affected families, including relatives who may have an increased disease risk.
d. An early follow-up appointment with the CF physician and the CF centre staff should be arranged to assess understanding (no more than one week). Contact information of the CF Centre should be given.
e. Patients and parents/carriers should receive advice on other information resources, in particular the internet.
f. At the initial diagnostic meeting, patients and parents/carriers should receive information about the model for future clinical care.
g. Patients and parents should receive information (including contact details) about the respective national CF patient organisation.

4.8. What are the minimal standards of care and follow-up for a newly diagnosed patient?

A patient diagnosed with CF should have immediate access to a Specialist CF Centre that has the multi-disciplinary capacity to provide care that complies with the ECFS Standards of Care.

4.9. What are the minimal standards of care and follow-up for patients with symptoms suggestive of CF and intermediate sweat chloride values? [17]

a. A patient, with symptoms suggestive of CF of CF, with a sweat chloride concentration between 30 and 59 mmol/L, and either one or no CF causing mutations, should have access to a Specialist CF Centre for appropriate assessment. It is important that such patients have long-term care. Follow-up in a clinic other than a CF clinic may be acceptable in collaboration with a Specialist CF Centre.
b. Ancillary tests should be performed to detect pancreatic insufficiency (faecal pancreatic elastase), CBAVD in males, lung or sinus involvement, or by identifying an ion channel abnormality (see question 4.10).
c. These patients must be monitored carefully for development of any complications and appropriate therapy implemented.

4.10. Should a patient with unclear diagnosis have CFTR bioassay tests (nasal potential difference, intestinal current measurement)? [24]

Patients with an unclear diagnosis should be assessed by a Specialist CF centre. In cases with intermediate sweat test results, further electrophysiological investigations (nasal potential difference and intestinal short circuit current measurement), should be arranged if available. The analyses should be undertaken in a centre with considerable experience of these procedures.

5. Treatment of lung disease

Felix Ratjen (CA), Patrick Flume (US), Alan Smyth (UK).

Life expectancy in CF has improved dramatically in the last 4 decades [25]. However, the majority of CF patients still die of respiratory failure [26] and so slowing progression of lung disease is a primary aim of CF therapy. The basic defect of CF leads to failure of mucociliary clearance, mucus plugging and secondary infection, with pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Chronic infection (with neutrophil-driven inflammation) is punctuated by acute exacerbations, following which lung function may fail to return to baseline levels [27]. Meticulous daily management of lung disease, together with prompt, aggressive treatment of exacerbations are therefore essential to preserve lung function. Best practice in this area is discussed in this section.

5.1. Should initial or new bacterial infection with Pseudomonas aeruginosa be treated?

Left untreated, new infection with *P. aeruginosa* will progress to chronic infection, which is associated with worse lung function, worse nutrition, more pulmonary exacerbations and a higher mortality [28]. There is no clear evidence how quickly an eradication therapy should be commenced, but treatment should be started promptly (not >4 weeks from receiving a positive culture result). There is robust evidence that eradication treatment for *P. aeruginosa* is effective but no one regimen has yet been shown to be preferred because of superior efficacy [29]. Options include 28 days of tobramycin solution for inhalation (TIS) and up to 3 months of a combination of nebulised colistimethate and oral ciprofloxacin [30]. Follow-up cultures to document eradication after treatment are crucial.

5.2. How should chronic bacterial infection with P. aeruginosa be treated?

When eradication therapy has failed, the diagnosis of chronic infection is made and long term inhaled antibiotic therapy should be commenced [31]. USA guidelines recommend TIS on alternate months for patients over 6 years with chronic *P. aeruginosa*, irrespective of the severity of lung disease and continued indefinitely [32]. Whilst studies are lacking for children younger than 6 years, treatment at equivalent doses is also recommended in this age group. The licensed regimen

is 300 mg twice daily for 28 days, alternating with 28 days off treatment. A dry powder inhalation of tobramycin (TOBI Podhaler™) has been shown to be of equivalent efficacy [33]. Inhaled aztreonam lysine [34] is recommended as an alternative by both European and US guidelines. Colistimethate (2 MU twice daily) is used widely in Europe and is now also available as a dry powder preparation [35]. A specialist physiotherapist should advise on the timing of inhalational drugs and on appropriate inhalation techniques.

5.3. Is chronic maintenance therapy indicated to treat other bacteria?

Whilst individual patients may benefit from prolonged courses of antibiotics, there is currently little evidence to support chronic maintenance therapy for bacteria other than *P. aeruginosa*.

5.4. Is prophylactic therapy indicated to treat bacteria?

Prophylactic flucloxacillin for the first years of life to prevent infection with *Staphylococcus aureus* is endorsed by guidelines in some countries and recommended against in others; its use remains controversial [30]. There is no evidence to support prophylactic therapy for other bacteria.

5.5. Is physiotherapy an essential component of chronic maintenance therapy and is any form of airway clearance superior to others?

Chest physiotherapy to achieve airway clearance is advocated in UK [36] and US [37] guidelines and should be available to all CF patients. A recent head-to-head trial [38] has shown that conventional positive expiratory pressure (PEP) is superior to high frequency chest wall oscillation (which relies on expensive equipment). However, in most cases there is little evidence to support the use of one technique over another. The airway clearance technique should therefore be tailored to the individual [39]. Flexibility and appreciation of patient preference are essential when prescribing a suitable airway clearance technique [40]. The CF specialist physiotherapist should have a comprehensive knowledge of all techniques, CF pathophysiology, the rationale for alternative approaches and any contraindications to specific treatment techniques [39]. Exercise and physical activity should be integral to the overall physiotherapy management suggested for every individual with CF, irrespective of age and disease severity. Reduction in exercise capacity is associated with a decline in respiratory function and survival [41].

5.6. What are important components of treating patients during episodes of clinical deterioration?

5.6.1. Early recognition and treatment

Progression of CF lung disease is characterised by periods of stability and intermittent episodes of clinical deterioration, termed pulmonary exacerbations (PEX). There is no agreed definition of PEX but it is essential that these episodes are diagnosed and treated promptly. Patients experiencing a change in their symptoms that could represent a PEX need to have access to a specialised centre without delay. Necessary diagnostic tools for assessment of PEX include lung function measurements, microbiological testing and radiological tests. Treatment of a PEX usually requires antibiotics which can be administered orally, via inhalation and/or intravenously. If the patient needs hospital admission for intravenous antibiotic therapy it is important that this is not delayed.

5.6.2. Multidisciplinary care

Treatment of CF exacerbations does not rely on antibiotic therapy alone and requires a multidisciplinary approach. Patients should be reviewed regularly by a specialist physiotherapist who will adjust airway clearance and optimise aerosol regimens where appropriate. Patients often have a reduced appetite and require increased caloric intake during a PEX, due to higher metabolic demands. Access to a specialist dietician is crucial. Intravenous antibiotics should be selected with input from a pharmacist and infectious disease/microbiology specialist.

5.6.3. Antibiotic regimen

The pharmacokinetics of antibiotics differ between CF and non CF individuals and antibiotic dosages need to be adjusted according to disease specific guidelines (including higher doses in some cases) [42]. For *P. aeruginosa*, a combination of two or more antibiotics is recommended and, although evidence for choice of antibiotics and optimal treatment duration is lacking, 14 days of intravenous treatment is routine [43]. Some patients may benefit from longer therapy and this decision should be based on medical needs rather than resources and costs. Home intravenous antibiotic therapy is used in individual cases, but a home care programme needs to assure that all aspects discussed above are part of the treatment plan. Therefore hospital treatment remains the standard of care for most patients requiring intravenous antibiotic therapy.

5.6.4. Evaluating response to therapy

It is important to monitor lung function at the beginning and end of treatment of a PEX to guide decisions regarding treatment and its duration. Despite intensive treatment about 25% of patients experiencing a PEX requiring intravenous antibiotic therapy will have a persisting decline in lung function [27], emphasising the need for maintenance therapies to prevent exacerbations.

5.7. What are the recommended chronic maintenance therapies to maintain lung health?

A comprehensive review of this topic is beyond the scope of this document and is available elsewhere [32,44]. Airway clearance techniques, physical activity and nutritional support are important components in maintaining lung health; here we focus on drug therapy only.

5.7.1. Mucolytics

The only mucus degrading agent that has proven efficacy in CF is dornase alfa. Studies have demonstrated improvements in lung function and a reduction in PEX in patients regardless of disease severity [45]. Recent evidence from an analysis of a large data base suggests that dornase alfa reduces lung function decline [46]. Treatment effects are lost when treatment is ceased therefore long-term maintenance therapy is required. Other mucolytics, such as N acetyl cysteine, have not been proven to be effective in CF patients [47].

5.7.2. Hydrator therapy

Airways in CF are dehydrated and increasing the airway surface liquid can be accomplished with osmotic agents that are called hydrators. The mechanism of action differs from that of dornase alfa and both approaches are complementary. Hypertonic saline and mannitol are available as inhaled agents in Europe. Hypertonic saline (7%) has been shown to reduce PEX and marginally improve lung function in a systematic review [48]. Hypertonic saline is currently used in many patients with moderate to severe lung disease and is supported by guidelines [32]. Mannitol has been introduced more recently and improves lung function [49,50]. The drug is available as a dry powder formulation thereby reducing treatment time. Both agents act as irritants and require pre-treatment with a bronchodilator and initial tolerability testing.

5.7.3. Antibiotic therapy

Airway infection in CF can be divided into early, intermittent and chronic infection. This scheme has been useful for *P. aeruginosa* infection (see paragraph 5.1) and may also apply to other bacteria. If eradication fails and chronic infection with *P. aeruginosa* develops, inhaled antibiotic therapy has proven efficacy to reduce pulmonary exacerbations, improve lung function and respiratory symptoms [31] and is therefore part of standards of care [30,32]. Inhaled antibiotic therapy should be administered as long term maintenance therapy with either single agent therapy or alternating therapy. Alternating different antibiotics is also used in patients deteriorating during months off antibiotics, even though the evidence for the efficacy of this approach is limited. The benefits of treatment outweigh the risks associated with the development of antimicrobial resistance which is often overcome by high topical antibiotic concentrations.

5.7.4. Macrolides

Macrolides are beneficial to CF patients likely due to their dual effect on infection and inflammation. Whilst not primarily efficacious against *P. aeruginosa*, there is evidence suggesting efficacy if the organism resides in biofilms, which is the case in chronic *P. aeruginosa* infection. Maintenance therapy with azithromycin has been shown to improve lung function and reduce PEX in chronically infected patients [51] and is part of recommended care [32]. A reduction in PEX has also been observed in younger patients not infected with *P. aeruginosa* [52]. Some concerns remain, regarding the durability of their effect and their impact on inducing resistance for other bacteria.

5.8. Is airway inflammation a target of chronic maintenance therapy and how should it be treated?

Inflammation is an important component of CF lung disease. CF airway inflammation is neutrophil dominated and common anti-inflammatory drugs such as corticosteroids, either systemic or inhaled, have no proven efficacy in CF patients, outside of treatment of concomitant asthma. High dose ibuprofen has been shown to reduce lung function decline in pediatric patients with preserved lung function [53]. Treatment requires monitoring of drug levels and despite these promising data it has not received widespread acceptance. Whilst other anti-inflammatory therapies are currently being studied, they are neither supported by sufficient evidence nor available for clinical care at the present time.

5.9. CFTR modulator therapy - which treatments address the underlying defect in CF?

Current treatment largely addresses the symptoms caused by the defective gene while CFTR pharmacotherapy aims to increase protein expression at the cell surface or its function with drug therapy [32]. Potentially this treatment strategy could make a difference in altering or even halting the disease process. Several drugs targeting specific classes of CFTR defects are currently being studied; to date two drugs have demonstrated clinical efficacy. Ivacaftor, a CFTR potentiatior studied initially in patients with the gating mutation G551D, showed enhanced ion transport reflected by reductions in sweat chloride concentrations but also improved clinical measures such as lung function and frequency of PEX [54]. A subsequent study including patients with other gating mutations confirmed these positive results [55]. The effect size of lung function changes exceeded that observed for any drug therapy available for CF patients to date. While gating mutations are only found in <5% of patients worldwide, ivacaftor is also a proof of principle demonstrating the potential impact of CFTR pharmacotherapy. In patients with gating mutations approved by regulatory agencies ivacaftor should be considered as part of the standard of care. Ivacaftor has also shown efficacy in mutations with residual CFTR function [56]. Lumacaftor, a corrector of intracellular trafficking of CFTR, when combined with the potentiator ivacaftor, has been demonstrated to improve lung function and reduce PEX in patients homozygous for the most common (508del) mutation [57]. The initial studies included patients 12 years and older, but positive treatment effects have also been reported in children 6 to 11 year of age [58]. While the observed effect size of treatment was smaller than for ivacaftor in gating mutations, this therapy should be available as a treatment option for 508del/508del CF patients.

5.10. How should fungal infections and severe/recurrent Allergic Bronchopulmonary Aspergillosis (ABPA) be treated?

ABPA is a well-characterised complication in CF patients and should be considered in any patient with clinical deterioration not responding to antibiotic therapy [30]. Diagnostic tests include allergy skin testing, measurements of serum IgE and IgE specific

to *Aspergillus*, and serum precipitins for *Aspergillus*. These tests need to be available to every CF care facility. Treatment is with oral prednisolone plus/minus antifungal therapy [30].

Aspergillus fumigatus, as well as other fungi, are commonly found in sputum of CF patients. The majority of these patients will not develop ABPA and the relevance of fungi beyond APBA in CF is not entirely clear. More recent evidence suggests that *A. fumigatus* may act as a pathogen in at least some CF patients [59]. Therefore, assessments of cultures in CF patients for fungi should be available.

5.11. How should we monitor lung disease?

a. A multi-disciplinary team is needed to assess and discuss all aspects of CF care.
b. Regular monitoring includes assessment of competence of airway clearance and inhalation technique and monitoring of adherence (see paragraph 9.4).
c. Clinical assessments should be performed at least every 3 months and at times of symptomatic deterioration [60].
d. As airway infection is a major driver of CF lung disease airway cultures should be obtained at every clinic visit [30].
e. The microbiological assessment needs to include specific culture media for the range of CF pathogens to ensure that relevant organisms are not overlooked.
f. CFTR modulator therapy requires safety monitoring that include liver function testing as the most commonly found laboratory abnormality, but also assessment for cataracts in children as well as monitoring of potential drug/drug interactions.
g. Lung function testing guides therapy and should be performed at every clinic visit in patients old enough to cooperate (usually 5 years and older) [60]. Tests for younger children are currently under development. Routine lung function testing should include spirometry performed according to ATS/ERS criteria [61] and testing pre- and post-bronchodilator should be available.
h. Chest X-rays are routinely performed on an annual basis in most CF centres as well as at times of clinical deterioration. Other imaging modalities, such as high resolution CT scanning, should be available as well, and are used routinely in some CF centres.

6. Nutrition and metabolic complications

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Nutritional status has a strong positive association with pulmonary function and survival in CF [62]. Attainment of normal growth in children and maintenance of adequate nutrition in adulthood, represent major goals for the CF team.

6.1. What are the goals for nutritional status in patients with CF?

Infants and children should grow normally, with infants achieving normal weight and height percentiles similar to the non-CF population by two years of age. Older children and adolescents should grow like healthy peers, with the aim of being at the 50th percentile for body mass index (BMI). In adults, absolute BMI should be maintained above 20 kg/m^2, ideally 22 kg/m^2 (females) and 23 kg/m^2 (males). All patients should have normal fat soluble vitamin and micronutrient status. Essential fatty acid status should be monitored, if the assay is available. Guidelines have been published on nutritional evaluation and management [5,13,63–71].

6.2. How do we monitor nutritional status in routine care?

Until growth ceases, accurate measurement of weight (kg), length or height (m), and head circumference (cm) (up to 2 years of age) should be made at each hospital visit. In adults, height should be measured annually. Measurements should be converted to BMI (>2 years) and compared to national reference charts. Special attention is needed for toddlers and adolescents due to rapid growth velocity. Fat soluble vitamins should be measured at least yearly to permit early detection of deficiency or excess [13,60,63–70,71–73].

6.3. How do we determine exocrine pancreatic insufficiency (EPI) and adequate pancreatic enzyme replacement?

Confirmation of EPI is required. Coefficient of fat absorption (CFA) is the “gold standard”, but is cumbersome.

Faecal pancreatic elastase-1 (FE1) is a simple and reliable marker from two weeks of age, in the absence of liquid stools.

Pancreatic sufficient patients should be monitored by annual FE1 during infancy and childhood and during periods of failure to thrive, weight loss or diarrhoea.

Pancreatic enzyme replacement therapy (PERT) adequacy is determined clinically, monitoring nutritional status, signs and symptoms of malabsorption and excessive appetite with poor weight gain. Excessive doses of PERT may result in abdominal pain and constipation. Guidelines for testing for EPI and dosing of enzymes are available [13,63–65,67–70,74].

6.4. What are the main strategies to provide preventive nutritional care?

CF centres should be familiar with the recommendations for age-appropriate dietetic advice to be directed by CF dietitians [5,13,60,63–68,70,74–77]. This includes:

a. Assessment of EPI and administration of PERT.
b. Selection of appropriate diet, with attention to a high fat intake.
c. Behavioural therapy to achieve positive mealtime experiences.
d. Providing sodium supplementation, when necessary, with special awareness in newborn screened infants.
e. Supplementing fat soluble vitamins, as indicated by laboratory testing.
f. Women with CF who plan their pregnancies should receive pre-conception advice to improve their nutritional status [75].

6.5. What factors should be evaluated in patients with poor growth?

Evaluation should be triggered by weight loss, decline in weight or length/height percentile (<2 years of age), decline in BMI percentile for age and gender (>2 years of age), poor linear growth (<18 years) or decline in BMI (>18 years). Early intervention is essential to avoid significant loss of weight or growth. Diagnosing the cause of malnutrition relies on a careful assessment and a multidisciplinary approach. Potential causes include insufficient food intake, excessive stool energy losses (inadequate PERT or poor adherence), *Giardia* infection, coeliac disease, hypercatabolism from pulmonary disease, vomiting or gastroparesis, glycosuria and psychological impacts of CF [13,63–65,67–70,74].

6.6. What are the options for interventional nutritional care?

Interventions should be tried stepwise for a limited period of time or until nutritional status is optimised, depending on the severity of malnutrition and the age of the patient. Avoid spending too much time on a single strategy if it is not producing results.

a. Anticipatory guidance. Reinforcement of adherence to diet, sodium and enzyme recommendations, using behavioral intervention for dysfunctional feeding issues in toddlers and young children [78] or motivational interviewing in older patients.
b. Moderate malnutrition. Oral supplements should be used as additional calories in a time-limited trial or temporarily as meal replacement for ill patients. Temporary nasogastric (NG)/nasojejunal (NJ) feeds may be useful.
c. Severe malnutrition. Enteral feeding via NG or gastrostomy tubes usually improves and maintains nutrition in a patient with CF.
d. Other therapies: Cyproheptadine and growth hormone are not part of routine management. Parenteral nutrition is only appropriate when enteral nutrition is impossible or fails.
e. Nutritional rehabilitation can take 3–6 months, so if being used pre-operatively should start well ahead of an anticipated operation (e.g. organ transplantation) [63–65,69,70,76].

6.7. When and how do we screen for diabetes mellitus?

All CF patients who have not been diagnosed with diabetes/CF-related diabetes (CFRD) including those who may have had gestational diabetes should be screened during a period of clinical stability using the standard WHO protocol annually from age 10 years. A single abnormal oral glucose tolerance test (OGTT), requires confirmation with a second test. Some centres now use continuous glucose monitoring as part of the diagnostic process [79,80]. Refer to the published guidelines for additional detail. Published guidelines [81–83] suggest more frequent screening with fasting/post-prandial glucose and/or OGTT in the following situations: pulmonary exacerbation, initiation of glucocorticoids, enteral tube feeding, planning for pregnancy, during pregnancy, planned organ transplantation and where there are symptoms of diabetes.

6.8. What is the current management of CFRD?

Care of patients with CFRD should adhere to standards of care for all individuals with diabetes; specific variations required for patients with CF are outlined below [81–83]. Patients with CFRD require care from a multi-disciplinary management team with experience in CFRD and in communication and consultation with the CF team. It is recommended that CFRD be treated with insulin, not oral diabetic agents. Glucose control may be challenging during pulmonary exacerbations, requiring more frequent monitoring and increased insulin. CF nutritional guidelines apply to CFRD patients. Modification of calorie, fat, protein, or salt intake as a result of the diagnosis of diabetes is not appropriate. Monitoring for complications of CFRD is similar to that for other forms of diabetes. CF patients with impaired glucose tolerance (IGT) must be monitored closely, particularly when ill, as they may need insulin therapy intermittently [79].

6.9. Should patients be screened for CF bone disease and if so how and which factors are involved in the prevention of reduced bone mineral density?

Low bone mineral density (BMD) is a common complication in adolescent and adult patients and can occur in children as clinical status declines. Routine screening for reduced BMD using dual energy X-ray absorptiometry (DXA) scans from the age of eight to ten years is recommended, as detailed in published guidelines [84–86].

Centres should be familiar with the factors contributing to development of reduced BMD in CF and how to reduce these risks. The most common risk factors include: pulmonary infections, poor nutritional status and lack of weight bearing exercise, delayed puberty, glucocorticoid treatment, hypogonadism, and vitamin D, calcium and vitamin K deficiencies [84–86].

6.10. What is the current management of reduced bone mineral density?

Known risk factors should be minimised and dietary intake of calcium and vitamin D should be optimised to enhance bone health. The use of bisphosphonates should be considered on an individual basis, taking bone mineral density, low trauma fracture history and transplant status into consideration [84–86].

7. Treatment of complications

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7.1. Pulmonary complications

Patients with CF may develop a variety of complications which, although infrequent, occur commonly. The CF centre

should be well-prepared in their management. The following offers standards of diagnosis and management for these complications as well as resources for additional guidance.

7.1.1. What is the best way to manage pneumothorax in patients with CF?

Pneumothorax is a complication occurring more commonly in patients with more severe obstructive airways disease [87]. The CF centre should have a high suspicion for this complication in the patient with acute chest pain and shortness of breath and be able to make the diagnosis using radiologic studies (i.e. chest X-ray, chest CT). Management guidelines have been published [88]; the centre should be able to provide basic treatment (i.e. chest tube, pain control). For those patients who may need more complicated procedures (e.g. VATS), the centre should have pre-agreed referral process with Thoracic Surgery Services where additional novel strategies may also need to be considered [89].

7.1.2. What is the best way to manage hemoptysis in patients with CF?

Hemoptysis is a common complication and may range in severity from scant to massive, defined as >240 mL/d or >100 mL/d for several days [90]. Management guidelines have been published [88]. The centre should give the patient and family clear guidance about when to call, if hemoptysis occurs, and should be able to provide the recommended therapies. For severe bleeding, the centre should have access to interventional radiology (e.g. bronchial artery embolization) and/or thoracic surgery.

7.1.3. What is the best way to manage respiratory failure in patients with CF?

The natural history of CF lung disease is progression to advanced stage airways obstruction and eventual respiratory failure. The centre should recognise progression to this stage and have discussions about lung transplant and advanced healthcare directives (see Chapter 8). The need for supplemental oxygen should be assessed in the patient with advanced stage lung disease ($FEV_1 < 40\%$ predicted) both at rest and with exercise [76]. Ventilatory support (e.g. non-invasive ventilation) should be provided in accordance with the patient's wishes for palliation of dyspnea [60]. The centre should be able to assess symptoms and the need for opiates to relieve dyspnea and pain associated with advanced stage disease [91–93].

7.2. Liver and pancreas complications

7.2.1. What is the best way to manage liver disease in patients with CF?

Many pancreatic insufficient (PI) CF patients will have evidence of liver disease ranging in severity from very mild biliary fibrosis to end-stage cirrhosis. CF related liver disease (CFLD) is a biliary cirrhosis that usually presents before age 20 years and can lead to portal hypertension and hepatic failure [94]. The centre should monitor all patients with routine physical examination and periodic liver enzyme testing. Guidelines on the use of ultrasonography, ursodeoxycholic acid ("Urso"), and when to consider a liver biopsy, are available in published guidelines [94–97].

Patients with portal hypertension should be referred to a gastroenterologist/hepatologist for screening endoscopy and management of complications of pulmonary hypertension. Routine management of CF patients with cirrhosis should include immunization against hepatitis A and B viruses, avoidance of NSAIDs and hepatotoxic agents (e.g., alcohol) and monitoring of the functional status of the liver (i.e. coagulation, albumin). Recently, CFTR modulators and correctors have been introduced. Ivacaftor and the combination of lumacaftor/ivacaftor may cause hepatic impairment. When liver disease is present the dosing of these drugs needs adjustment [98]. The centre should have a pathway for referral to a liver transplant program, for those patients with advanced stage liver disease leading to hepatic failure.

7.2.2. What is the best way to manage cholelithiasis in patients with CF?

Cholelithiasis is not always symptomatic [99]. The centre should be suspicious when evaluating the patient with nonspecific abdominal pain and nausea. The centre should have access to ultrasonography and HIDA scan for assessment of the gallbladder. For symptomatic gall stones, ursodeoxycholic acid is ineffective and surgical referral is usually necessary [100].

7.2.3. What is the best way to manage pancreatitis in patients with CF?

Pancreatitis is a less common complication in the CF population, but troublesome in some CF individuals with pancreatic sufficiency [101]. Recurrent acute pancreatitis may contribute to the transition from pancreatic sufficiency to insufficiency in CF. The presentation may be a non-specific abdominal pain, so there should be high suspicion when seeing a patient with recurrent, unexplained pain and associated nausea and vomiting. The centre must be able to evaluate with standard laboratory testing (i.e. amylase, lipase) and imaging (e.g. ultrasonography, CT, or MRI). Management principles are no different than those for non-CF pancreatitis. However, acute pancreatitis is associated with severe dehydration and in the CF population this may be more severe, demanding attention to rehydration and electrolyte monitoring. Recently developed CFTR correctors and potentiators may play a role in the treatment of recurrent pancreatitis as they stimulate bicarbonate and fluid secretion in the pancreas [102].

7.3. Gastrointestinal complications

7.3.1. What is the best way to manage gastro-oesophageal reflux disease (GORD) in patients with CF?

GORD occurs commonly in patients with CF, affecting over 36% [26]. The centre should be aware of the signs and symptoms of GORD and be able to provide, if necessary, appropriate diagnostic testing (i.e., impedance and pH probe, upper endoscopy) and treatment [103–107].

7.3.2. What is the best way to manage constipation in patients with CF?

Constipation has a slow onset with reduced frequency of stooling [108]. It is common in CF and may be exacerbated by use of narcotics. Most of the time constipation responds to hydration therapy, stool softeners or laxatives (e.g., polyethylene glycol). Enemas are rarely needed [106,107,109].

7.3.3. What is the best way to recognize and manage distal intestinal obstruction syndrome (DIOS)?

The symptoms of DIOS have acute onset with right lower quadrant pain [108]. Complete and incomplete DIOS have been described [109]. The centre should be able to recognize these complications and have standard protocols for diagnosis and treatment based upon published recommendations [60,107,108,110]. Patients may respond to oral rehydration combined with stool softeners, but more severe cases may require IV hydration, nasogastric aspiration, and enemas. For patients who fail such conservative therapies, referral to a gastroenterologist with knowledge of DIOS is essential. Pancreatic enzyme replacement therapy should be re-evaluated in patients with DIOS [106,107]. Delayed arrival at hospital after the initial symptoms causes significant morbidity. Medical treatment may fail only in cases of complete DIOS. Although surgery is the ultimate resource [111] the centre should have surgeons who know about this CF complication.

7.3.4. What is the best way to prevent fibrosing colonopathy (FC)?

This is an uncommon complication. At present, the only clear recommendation to prevent FC is to use the appropriate dose of pancreatic enzymes, not increase enzyme dose without clear indication and not exceed 10,000 lipase units/kg/day total enzyme dose [112–115].

7.3.5. What is the best treatment for appendiceal mucocele?

Ultrasonography will aid the diagnosis [116]. In case of symptoms, appendectomy with resection of the appendix edges and resection of the caecal tip will avoid risk of recurrence.

7.3.6. What is the best way to manage small intestinal bacterial overgrowth (SIBO) in patients with CF?

SIBO is suspected when patients have diffuse or peri-umbilical abdominal pain, excessive bowel gas, diarrhea, nausea and malabsorption despite adequate enzyme intake. Risk is higher in patients who have had previous intestinal surgery or are using narcotics. Although many non-invasive diagnostic procedures have been used, there is no golden standard test to demonstrate SIBO [107,117]. It is recommended that diagnosis be made by a clinical therapeutic trial of metronidazole [118]. Treatment includes cyclical administration of oral antibiotics effective in the GI lumen, pre- and probiotics, laxatives and prokinetic drugs [107]. Due to differences in studies design and outcome measures, scanty evidence exists on the effects of probiotics supplementation in SIBO [119].

7.3.7. What is the best way to manage meconium ileus (MI) in patients with CF?

MI is a neonatal emergency best handled at a centre familiar with CF and where a pediatric surgeon with expertise in MI is available. Early referral to a centre familiar with both non-surgical and surgical management is essential [120–122]. Complicated MI is more severe, more difficult to treat, and may require prolonged hospitalization. Post-operative management may require a centre familiar with management of short bowel. MI does not predispose to later development of DIOS, however children with MI have a higher rate of surgery for DIOS [111].

7.3.8. Is there an increased risk for GI malignancies in patients with CF?

In patients with CF, gastrointestinal malignancies are more prevalent compared to the healthy population. Several studies show a higher yearly incidence in colorectal cancer and progression of adenomatous colorectal polyps to colorectal cancer [123–126]. A recent study shows that screening for colorectal cancer is cost-effective and should be started at an age of 40 years [127].

7.4. Other complications

7.4.1. What is the best way to manage medication toxicities?

The treatment of CF lung disease can result in complications due to the treatment and toxicity related to medications, especially aminoglycosides (e.g. nephro-, oto-, and vestibular toxicity) [128]. Drug-drug interactions, especially after the introduction of CFTR correctors and modulators, are complications clinicians should be aware of and when possible, be prevented by dose adjustment. The inclusion of a specialized pharmacist in the CF team is important. The centre should utilise standard protocols for therapeutic drug monitoring when using aminoglycosides and follow recommended treatment dosing [30]. When using intravenous (IV) aminoglycosides, there should be strict avoidance of NSAIDs to avoid nephrotoxicity. The centre should perform assessment for ototoxicity using audiology testing for patients who have hearing loss or tinnitus, or as part of a routine screening assessment. The centre should also have access to a clinician experienced in vestibular assessment.

7.4.2. What is the best way to manage nephrolithiasis in patients with CF?

Nephrolithiasis is common in CF patients [129]. The centre should be aware of the signs and symptoms associated with nephrolithiasis and be able to evaluate by urinalysis and CT-IVP. The metabolic disorder causing kidney stones should be determined, given the high frequency of enteric hyperoxaluria [130]. Fluid intake to maintain a high urine output combined with a low-oxalate and high-calcium diet is appropriate for patients with kidney stones [130,131]. The centre should have access to a specialist nephrologist, urologist and interventional radiologist for complicated nephrolithiasis.

7.4.3. What is the best way to manage arthropathy in patients with CF?

Arthralgias are common symptoms in CF patients [26] but arthropathy remains poorly understood. The centre should be aware of this problem. Treatment with analgesics and anti-inflammatory agents may be needed. Glucocorticoids and disease-modifying anti-rheumatic drugs may be considered in refractory cases in consultation with a rheumatologist who has knowledge of CF [132].

7.4.4. What is the best way to manage sinus disease in patients with CF?

Chronic sinusitis with or without nasal polyposis is common in patients with CF and occurs already in early childhood [26,133]. The centre should routinely evaluate sinus disease and offer recommended treatment, recognizing that this could be a source for lower airways infection [134]. It should have access to diagnostic testing (i.e., CT sinus) and an otolaryngologist experienced with CF-related sinus disease. Recently developed CFTR correctors and potentiators may ameliorate sinonasal disease [135].

7.4.5. What is the best way to manage allergic disease in patients with CF?

With the exception of ABPA (discussed in paragraph 3.10), allergic disease is not increased in CF patients and can be managed similarly to non-CF patients with allergies. Patients can develop allergies to antibiotics (especially beta-lactams) that increase the risk of potentially life-threatening reactions and can complicate medical treatment in patients with advanced lung disease and frequent exposure to parenteral antibiotics [136,137]. Hospitalisation at the start of treatment in patients 'at risk', should be considered to improve safety [138]. The centre should be aware of signs and symptoms of possible allergic response to treatment and stop that therapy accordingly. Following allergologists' advice, the centre should have established protocols for desensitization should that therapy be important and with no other treatment options [137,139–142]. Written instructions on the emergency treatment of allergic reactions should be provided to patients self-administering intravenous antibiotics at home [139].

7.4.6. What is the best way to avoid complications that result from chronic indwelling intravenous (IV) catheters in patients with CF?

An indwelling catheter should be placed in accordance with the patient's wishes if difficulties exist in performing IV treatment. The centre should have access to professionals experienced in the placement of indwelling catheters (e.g. Midline catheters, peripherally inserted central catheters [PICCs], Port-A-Cath). Only trained individuals should be able to access the indwelling catheter, using standardized protocols in infection control and maintenance of the catheter. Common complications of catheters include vascular problems (e.g. infection, thrombus, SVC syndrome) [143–144]. The centre should be keenly aware of the signs and symptoms of catheter-related complications and be able to perform proper testing including blood cultures, ultrasonography and contrasted radiology studies to assess infections and vascular occlusion. Intravascular catheter-related infections should be managed according to published guidelines [145,146].

7.4.7. What is the best way to address pregnancy in a CF patient?

Pregnancy can complicate the management of women with CF. The centre should always inquire about possible pregnancy when assessing women who may be fertile, especially when considering additional medications that are contraindicated in pregnancy. The pregnant CF patient should always be considered a high-risk pregnancy because of the potential pulmonary and nutritional/metabolic complications and should be seen by an obstetrician experienced in high-risk cases. Management recommendations for pregnant CF patients have been published [75].

7.4.8. What is the best way to address infertility in a CF patient?

Females with CF can become pregnant and those with good lung function and nutrition are likely to complete the pregnancy. In less well females there is the possibility of reduced fertility, and they should be referred to specialists in fertility services if there is a perceived inability to become pregnant. Most (98%) CF males will be azoospermic and should be informed of this finding at an appropriate age. Sperm analysis should be offered to those patients interested in knowing their status. Patients should receive proper counseling regarding fertility options including assisted reproductive techniques.

8. Transplantation and end-of-life issues

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Transplantation is an established therapy for end-stage lung and liver disease in patients with CF. Referral to transplant services is enhanced by the CF team having an understanding of the processes leading to a successful transplant. In some patients, transplant is not a suitable treatment option or does not occur for various reasons such as death occurring prior to suitable donor organs becoming available. Effective management of the end-of-life is vital and requires attention to communication, symptom control and a multi-disciplinary approach to care, including expertise in palliative care.

Outcomes for people with CF undergoing lung transplantation have continued to improve and with 10-year survival rates approaching 50% [147] and even exceeding this in single-centre reports [148]. These standards include a series of questions about the approach to transplantation assessment and end-of-life care, utilising available published evidence and guidelines. For a detailed review of all facets of the topic see "Practical guidelines: Lung transplantation in patients with cystic fibrosis" prepared by the European Centres of Reference Network for Cystic Fibrosis (ECORN-CF) Study Group [149] and the ECFS End-of-life Care Guidelines [150].

8.1. What are the important determinants for timing of listing for lung transplantation in patients with CF?

The lead time for assessment and waiting for suitable donor lungs is variable but can be in excess of two years. Factors associated with increased mortality, and where referral for transplantation assessment is recommended [151] are:

a. FEV_1% of ≤30 predicted
b. Rapid decline, particularly female and younger patients.
c. Oxygen therapy for hypoxaemia.
d. Hypercapnia.
e. Frequent exacerbation that respond poorly to intravenous antibiotics.

Earlier referral should be considered in patients with refractory pneumothorax and recurrent massive haemoptysis [152]. Increased survival, limited donor availability and differences in organ allocation schemes have led to prediction models of mortality/survival which assist with decisions for prioritising patients for transplantation [153,154]. There remain barriers to referral for transplant assessment including physicians' perception of suitability and difficulty in predicting timing of assessment, and socioeconomic factors [155–157]. The complexities of timing transplantation-referral require close liaison with the transplant service. This will also help patients' process complex information and make informed choices. If in doubt about the optimal timing for referral for an individual patient it is better to consider an earlier referral.

Regular and detailed communication with the Transplant Service is vital to allow regular updates of the clinical progress of all wait-listed patients. One recent analysis based on the US CF Foundation Patient Registry of predictors of non-referral for transplant assessment included low socio-economic status, older age and *B. cepacia* complex sputum culture [155].

Assessment and prioritisation of younger children with CF requires careful consideration with transplant teams who have a specific paediatric expertise [158]. Children often have poorer pre-transplant clinical status and have a higher incidence of post-transplant infections and diabetes [159].

8.2. What clinical features increase the risk for dying on the lung transplant waiting list?

Priority for transplantation [152,160,161] should be given to CF patients with:

a. Oxygen-dependent respiratory failure.
b. Chronic hypercapnia.
c. Pulmonary hypertension [162,163].
d. Under-nutrition - especially female patients.

The limited donor pool determines the number of possible transplants. National policies optimise the efficiency of donor-organ allocation differently, depending on donor identification systems and practical/geographical logistics. Prioritisation of urgent cases is managed at a national level [164,165]. Aggressive approaches to nutritional restoration should be considered in all under-nourished patients being considered for lung transplantation.

8.3. What are the important patient variables, which may prevent active listing for lung transplantation in CF?

Exclusions for lung transplantation [151] include:

a. Malignancy within 2 years. A disease-free period of 5 years is generally required. Consideration for cutaneous and some urogenital cancers may be given.
b. Untreatable dysfunction of another major organ (e.g. heart, liver, kidney).
c. Chronic extra-pulmonary infection (e.g. hepatitis B, hepatitis C, HIV).
d. Severe skeletal deformity.
e. Prolonged poor-adherence or irregular clinic attendance.
f. Untreatable psychological condition/s limiting ability to participate with therapies.
g. Lack of consistent social support system.
h. Substance addiction (e.g. alcohol, tobacco, within previous 6 months).

Most transplant services do not assess patients with chronic *Burkholderia cenocepacia* and/or *Mycobacteria abscessus* (*M. abscessus*).

The impact of *M. abscessus* infection remains unclear, with recent studies reporting higher rates of post-transplant infection requiring intensive therapy but not necessarily increased mortality [166,167], *M. abscessus* is often associated with increased morbidity following transplantation. Careful consideration about suitability for listing includes the presence of smear positive sputum status and presence of multi-resistant *M. abscessus* [168].

Other infections (e.g. multi-resistant *Pseudomonas aeruginosa*, *Scedosporium* species *and Clostridium difficile*) are influenced by local transplant unit policy and experience and require detailed discussion.

Combined 'liver/lung' or 'lung only' transplantation both require careful consideration in patients with advanced lung disease and portal hypertension [169]. CF may be associated with worse outcomes following liver transplantation than for other indications [170–172].

Re-transplantation may be considered in specific circumstances in some transplant recipients [173].

8.4. What complications of CF are important to prioritise prior to lung transplantation?

Optimising nutritional status is a priority for wait-listed patients, but should not be a strong factor in delaying the listing process [161].

CFRD is present in 40–50% of patients at assessment and develops post-transplant in another ~20% of patients. Increased mortality, infection and rejection-related hospitalisation have

been reported in patients with CFRD at transplantation [174,175]. Optimising control of CFRD is important whilst wait-listed [175,176].

Chronic kidney disease (CKD) occurs in many adults with CF and where practical, limiting exposure to nephrotoxic drugs pre-transplant should be considered [177]. The impact of long-term systemic use of aminoglycosides before transplantation on post-transplant renal function is uncertain [178]. Calcineurin inhibitors, hypertension and CFRD have been associated with CKD following transplantation.

Osteoporosis (24%) and osteopaenia (38%) is reported in patients with CF [179]. Bisphosphonate therapy may be required to maintain and improve bone health pre-transplantation.

Systemic corticosteroids are required in some patients with advanced lung disease (e.g. ABPA). Limiting daily dose of prednisolone to <15 mg/day is thought to assist in healing and reducing post-operative infection risk although – if higher doses are needed – this should not exclude the patient from transplantation and reduce post-operative infection risk and limit further reduction in bone density [180].

Although transplant programmes around the world have varying guidelines and timelines, individuals presenting with alcohol or substance abuse/dependency are evaluated to determine suitability. Recommendations are then made regarding rehabilitation and counselling prior to listing, or as a condition of listing. Improving conditioning by pulmonary rehabilitation or a structured exercise programme is considered important for patients who are actively waitlisted. In some instances patients sign a contract pledging not to use alcohol or any illicit or addictive substances agreeing to unlimited, random drug and/or alcohol screening both while awaiting and following transplantation.

Psychologically it is vital to help patients maintain hope and counter demoralisation or exhaustion. Patients awaiting transplantation and their families report that waiting is the most distressing aspect of the transplant experience. Pre-transplant care should involve interventions aimed at managing stress [181].

8.5. Under what circumstances should invasive ventilation be considered in patients with CF?

The role of invasive ventilation for patients with end-stage pulmonary disease is controversial and associated with poor outcomes [182].

Consideration should be made for patients who develop respiratory failure in the setting of an acute precipitant and where recovery is anticipated (e.g. massive haemoptysis, pneumothorax, influenza, post-operative care) [182,183].

Transplantation from the ventilator is associated with higher early mortality [184] and is only offered in highly selected cases and not by all transplant services. Usually this only occurs in patients who have completed transplant work-up prior to ventilation.

Some transplant services consider transplantation in patients who have required Extra Corporeal Membrane Oxygenation (ECMO) for severe respiratory failure. Case reports have suggested excellent outcomes [185–187]. Close communication between the CF Team and the Transplant Service is mandatory prior to ECMO initiation. ECMO and veno-venous lung assist devices have been successfully used to bridge to lung transplantation [188].

8.6. What therapeutic modalities are important in the palliative care of the patient with CF?

Early discussions (including the potential for transplantation) to allow time to psychologically adjust and carefully consider options is required, particularly as misunderstanding is common. The physician should initiate a conversation about end-of-life care with the patient and family and should involve the multidisciplinary team. Significant psychological intervention can be required (e.g., management of anticipatory grief and work with family members) [189].

Symptoms that frequently require control include dyspnoea, chest pain, headaches, fatigue and poor sleep quality [190]. The use of narcotic analgesic, anxiolytics, airway clearance support, psychological strategies, oxygen and non-invasive ventilation support are important [92,150,191]. Whilst palliative care should be integrated into routine care of the patient with CF [192], teams should also have ready access to support from palliative care colleagues to optimise symptom control, when required [190,193,194].

The balance between effective, active treatments, whilst providing adequate symptom control, can be difficult especially in patients waiting for transplant [190,195]. In a clinical setting of rapid decline where a person is preparing for transplantation, there is a need to address end-of-life issues as part of the medical management. Incorporating both active and palliative management may be required in such circumstances [181].

Even if transplant is an option, the course of CF can be changeable and it may be difficult to predict end-of-life. Advance care planning allows individuals and their CF team to 'hope for the best, but plan for the worst'. Advance care planning is a process of discussion between the patient, CF team and, if requested, family members and/or friends. Discussions allow concerns, requests or wishes about future care to be expressed and recorded.

Symptom control does not preclude lung transplantation, however close communication between CF and Transplant teams is vital [190].

The death of a patient can have a significant effect on other patients and staff at the centre. Support of other patients with CF and staff members should be offered [190].

8.7. What factors are important in deciding on the location of care for the dying person with CF?

Patients' and families' wishes should be key to making decisions about where to manage the dying patient and where practical, measures taken to assist facilitating these wishes [196]. The support available at home to optimally manage all symptoms is a key consideration (e.g., providing airway clearance support, the availability of timely symptom control).

Patients may prefer to have care by staff that they know well in a familiar environment [197] and in many cases, prefer to receive care in hospital [190,198].

Active management of patients to maximise symptom control often continues and potential for conflict between active management and optimising control symptoms needs to be carefully considered.

Communication between all team members, community healthcare team (including primary care), the patient and the family are vital.

8.8. How should CF-specific complications be managed following recovery from lung transplantation?

After lung transplant, management of complications of CF remains important (e.g. CFRD, osteoporosis, DIOS). In many cases, the transplant service manages the complete care of the patient. However, the CF centre should be available to support where assistance is desired. Psychosocial input is required to address psychopathology (e.g. drug-related psychosis, post-traumatic stress reactions).

Even when patients are in good physical health post-transplant they can face challenges regaining their previously social roles, for example as family members and partners. Other stressors include financial problems (including loss of benefits), employment, or education. Additionally, individuals can feel stressed by the need to maintain a change in lifestyle (e.g. regular activity, healthy eating, alcohol and tobacco abstinence) and strict adherence to their treatment regimen (e.g. timely intake of medication, frequent follow-up appointments, dietary restrictions, and infection prophylaxis). Psychosocial interventions may also be required to support both the patient and family members throughout this time.

9. Psychosocial support

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Living with CF can be emotionally and physically challenging for people with CF and their relatives. The condition and its treatment influence the ability to deal with normal tasks of daily living and unexpected life events. Good psychosocial care is now well-integrated into the CF team and there is a substantial body of literature that establishes the essential elements of the psychosocial role [60,199,200]. The focus of this chapter is to set out the key psychosocial issues and make recommendations for appropriate management. Effective behavioural interventions for feeding behavior problems in toddlers and young children are addressed separately in Chapter 6 (6.6). End-of-life issues are addressed in Chapter 8.

9.1. What are the core elements of supporting parents in the first year, post-diagnosis?

Diagnosis of CF for the majority is by newborn screening which aims to minimise morbidity and mortality. Yet potential disadvantages must be recognised and addressed [12]. Diagnosis of CF is traumatic, especially in an otherwise healthy infant. Parents can experience disbelief and dissociation from the diagnosis and baby, which can last well beyond the first few weeks [199]. Preventative counseling and emotional support must be offered to assess parents' (i) understanding of information, (ii) reactions to diagnosis and, (iii) coping style, support needs and resources.

Parents need to engage in education about their child growing up with CF, ensuring a balance between managing a complex health condition and enabling their child to grow with good self-esteem. Families should be hopeful that their child will enter adulthood having a good quality of life (QoL) with achievements similar to non-CF peers. Key tasks are to advise on:

a. Establishing treatment with baby's daily-routine.
b. Helping parents accept and administer treatment.
c. Communicating to family and friends about the medical condition.
d. The availability of psychosocial follow-up for parents if required including couple counselling.
e. Available financial support/benefits/allowances and other sources of support.
f. Navigating on-line and social media sites to ensure accurate acquisition of information about CF and new therapies.

9.2. In what ways should mental health problems be prevented, identified and addressed?

Rates of depression and anxiety symptoms in people with CF and parents were established in 2014 [201] with elevated scores associated with worse adherence, QoL and outcomes. In response, the International Committee on Mental Health (ICMH-CF) published guidelines on preventing, assessing and treating depression and anxiety [202].

The CF team needs to screen annually for mental health symptoms in people with CF (≥12 years) and parents of children and young people with CF. The guidelines describe psychometric screening and follow-up pathways [202]. Where there is no integrated psychologist, referral to mental health agencies should be considered. A CF team psychologist should also assess annually for other significant or emerging emotional health difficulties and for health management problems (see ECFS Standards of Care; Centre Framework for access to psychological professionals [7]).

Psychological intervention, when required, needs to be supported with consideration of the practical, social, educational and vocational needs of the patient and their caregivers [203].

9.3. How do we promote psychosocial resilience at key transition points and address potential associated psychosocial vulnerability?

Transitions relate to significant changes in developmental and personal prospects and challenges for people with CF, and the sense of responsibility these imply.

Key transition points are:

a. Parental adaptation to diagnosis.

b. Commencement of schooling; nursery, primary and secondary.
c. Parental- to self-guided treatment.
d. Transition of care from paediatric to adult services.
e. Entering the workplace or further education.
f. Loss of independence (e.g., retirement, loss of activities and functioning, increased reliance on intrusive treatments and carers, and facing transplantation).
g. End-of-life care.

Psychosocial resilience is broadly an ability to recover from negative events with an absence of lasting emotional disturbance. It is multi-factorial, the elements of which are not all amenable to change [204]. The primary focus should be to increase psychosocial support and foster hope (primarily by paediatric preparation of patients for fulfilling adult lives and increasing self-efficacy and control). Emotional vulnerability should be addressed pro-actively at each transition point.

9.4. What are the core components in addressing adherence, particularly to nebulised therapies?

Improving adherence, particularly to nebulisers, is a key challenge for the prevention of disease-progression. Successful psychosocial intervention is determined by (i) the team ethos to patient care, (ii) forming partnerships with patients to increase their motivation and, (iii) identifying barriers and actively supporting patients' efforts to increase treatment.

a. Teams must endorse a collaborative, nurturing and holistic approach to adherence, based on effective information-giving and empathic communication. Open discussion leads to facilitating care that is individually meaningful and accounts for patient involvement and making informed choice. Teams should discuss adherence at every visit, with psychosocial professionals supporting team-members' efforts to engage patients in conversation using active-listening skills.
b. Persuading patients with chronic sub-optimal adherence does not work. Psychosocial professionals must lead on efforts to address perceptual or emotional barriers to adherence in patients unwilling to acknowledge problems or who lack motivation [205].
c. Some techniques are effective but their use depends on the developmental stage of the patient (e.g., simplifying and regulating treatments where possible, addressing concerns about treatment, reinforcement scheduling and problem-solving). Clinical trials of interventions and e-application developments are ongoing.

9.5. What are the main components to supporting patients diagnosed in adolescence/adulthood?

CF diagnosed beyond childhood may arise for a range of reasons. Patients may often be angry and/or overwhelmed by information (diagnosis, prognosis, infertility) and technical aspects of CF. A more flexible and individualised approach to clinical management is needed for the patient, which differs from the routine care provided to those diagnosed in early childhood. Emphasis must be placed on prognosis, personal support, fertility issues, and reviewing what CF knowledge patients may have acquired and from where (some sources being misleading) [206,207].

9.6. Disordered eating and body image problems in patients impact on treatment and prognosis. What are the key components in addressing these?

Competing demands of CF management, including monitoring of nutritional status emphasising weight gain within cultures that promote ‘thinness’, contribute to confused attitudes towards eating. Disordered eating and body image problems have been reported in people with CF [208].

The approach to nutritional management needs to take account of the patient's attitudes towards eating, shape and personal appearance, rather than focus simply on calorie intake and weight gain. Assessment of nutritional intake should include questions on the above and diet plans incorporating healthy eating ideas.

Educational programmes should be available to inform people with CF about digestion, calorie consumption and energy usage in CF. Health professionals working with people with CF should be equipped to identify disturbed eating behaviours allowing early detection and joint intervention between dietitian and psychologist.

9.7. How should we tackle the key psychosocial issues of adulthood and growing older with CF?

Key issues of adulthood and older age are (i) that the normal tasks of adulthood are compounded by CF, (ii) making complex decisions (e.g. vocational plans, becoming a parent, or treatment decisions), (iii) coping with deterioration in health and loss of mobility and independence, as well as new complications/diagnoses (e.g., CFRD) and (iv) living with end-stage disease, considering transplantation and/or engaging in end-of-life care (see Chapter 6). Challenges of growing older with CF can lead to, for example, increased anxiety and depression, low self-esteem and relationship difficulties. CF teams must be aware of the likelihood of demoralisation occurring as a consequence of multiple health problems. This resembles, but is different to depression in personal impact and treatment [209].

Key approaches are (i) being pro-active during routine clinics and annual review can help identify emotional, practical and social support requirements (e.g., employment, fertility, risk-taking behaviours). Patients tend not to initiate discussion of these issues [210,211], (ii) early identification of psychological difficulties affords prevention, (iii) promoting positive coping strategies is a key part of supporting emotional adjustment in CF and fostering resilience may be particularly important [212] and, (iv) referral to a CF team psychosocial professional or external specialist mental health services.

Integrated approaches by psychosocial and other CF professionals, allows highly specialised interventions for complex problems related to ageing with CF.

9.8. What are the core aspects of training and supporting the MDT in developing psychosocial skills?

a. All CF team members need good skills in several areas including compassionate communication, effective information giving and recognising and responding to emotional distress.
b. Some CF team members will require training in more specific skills such as breaking bad news, recognising significant psychopathology and referring appropriately, including to emergency psychiatric services.
c. At the next level of psychological support some trained and accredited staff may use approaches such as problem-solving, relaxation training, desensitisation to painful procedures and psychological "first aid" following difficult life events or traumatic experiences.
d. Specialist mental health professionals in CF teams (e.g., clinical psychologists or psychiatrists) can provide a range of well-established therapies and strategies through the diagnosis/formulation of complex emotional health or health management issues.

The CF team psychological professional also has an important role in developing the skills and support of other CF staff in these areas (e.g., via training and supervision). CF team members can at times experience stress and CF teams need mechanisms in place to support such emotionally demanding work. Elements such as team meetings following particularly distressing events including deaths of patients, and opportunities for "reflective practice" about complex issues have been shown to be helpful in other specialties [200]. An effective system for regular screening for psychological distress and other CF-related problems also needs to be in place in all CF services.

Conflict of interest

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